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THE MEDICINAL VALUE OF THE SOUTHERN AFRICAN ASTERACEA

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THE MEDICINAL VALUE OF THE SOUTHERN AFRICAN ASTERACEAE

by

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ABSTRACT

This dissertation comprises a literature study on the medicinal value of the southern African Asteraceae. It includes data on the medicinal uses of the Asteraceae species, chemical compounds isolated, the pharmacological action of extracts and in some cases the active compounds isolated from the extracts of species of Asteraceae.

One of the objectives of this dissertation was to validate the use of indigenous Asteraceae species in traditional medicine. This was difficult to achieve due to a lack of pharmacological and chemical information on the southern African Asteraceae. From the little data available, a remarkable correlation between the pharmacological action of the plants and the traditional uses, was observed. Many species used for eye and skin diseases contain the phototoxic (antibiotic only in UVA light) compounds polyacetylenes and thiophenes. Polyacetylenes are common in the Asteraceae.

Although the Asteraceae contains a wide range of secondary compounds, only a few pharmacologically active compounds have been identified. It is evident that much work is still needed in this field.

UITTREKSEL

Hierdie dissertasie is 'n literatuurstudie oor die medisinale waarde van die Asteraceae van suidelike Afrika. Data oor medisinale gebruike, chemiese verbindings, die farmakologiese effek van ekstrakte, en in sommige gevalle die aktiewe bestandeel van spesies van die Asteraceae is versamel.

Een van die oogmerke van die dissertasie was om die waarde van die gebruik van die inheemse Asteraceae in tradisionele medisyne te bevestig of te weerlê. Die gebrek aan informasie oor die farmakologie en aktiewe chemiese bestanddele van die Asteraceae, het dit egter moeilik gemaak om die oogmerk te bereik. Uit die beperkte inligting beskikbaar, is daar wel 'n korrelasie tussen die farmakologiese effek van die plant en die tradisionele medisinale gebruik, opgemerk. Baie van die plante wat gebruik word vir oog- en velsiektes, bevat fototoksiese stowwe soos poli-asetilene en tiopene. Fototoksiese stowwe is antibioties wanneer dit blootgestel word aan UV-A lig. Poli-asetilene kom algemeen voor in die Asteraceae.

Die Asteraceae bevat 'n wye reeks sekondêre metaboliete, maar ten spyte daarvan is slegs 'n paar farmakologies aktiewe bestanddele geïdentifiseer. Daar bestaan nog 'n groot behoefte aan verdere navorsing in hierdie veld.

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CONTENTS

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

It is estimated that between 12 and 15 million South Africans still depend on traditional herbal medicine from as many as 700 indigenous plant species. (Meyer *et al.* 1996) The millions of people that still rely on traditional medicines can benefit from the scientifically founded knowledge of the pharmacological activity of the plants used in traditional medicine. The Traditional Medicines Programme (TRAMED) is currently compiling a primary health care booklet for Traditional Healers with information on the different plant species, plant parts, application and dosage recomended for various ailments.

The utilization of knowledge in ethnobotany can lead to the development of indigenous new drugs that can be used in Western medicine. The limited spectrum of antibiotics and the increasing resistance of organisms against drugs emphasise the need for different medication. The appearance of new diseases like AIDS further necessitates new remedies to be developed.

The Asteraceae is one of the largest and probably one of the most advanced plant families and occurs throughout the world (Phillipson *et al.* 1995). The name Compositae is synonymous with the name Asteraceae, but Asteraceae is usually the preferred name. Some Asteraceae species from other parts of the world have long been used in folk medicine. Plants such as *Chamomilla*, *Cynara* and *Silybum* have been applied for their therapeutic use owing to their antihepatotoxic, choleretic, spasmolytic, anthelmintic, antiphlogistic, antibiotic or antimicrobial activity. New screening methods and isolation techniques have made it possible to elucidate the mode of action of old drugs and thereby reintroduce them into modern therapy. Many structures, discovered for the first time in this family, have served as models for the synthesis of biologically active compounds (Wagner 1977). New drugs are currently being developed from other Asteraceae species, for example artemisinin, a new antimalarial agent that was isolated from *Artemisia annua* found in the far East and it is in the process of being licensed as a medicine in several tropical countries (Phillipson *et al.* 1995).

Many species of the southern African Asteraceae are also used extensively in traditional medicine. *Artemisia afra* is the most common plant stocked by Witwatersrand muti traders (Williams 1996). However, little work has been done on the ethnopharmacology of the local species of Asteraceae.

1.1.1 Ethnopharmacology

The science of pharmacognosy is concerned with the examination of species of plants, animals and other life forms for the purpose of isolating new substances responsible for observed biological effects (Delaveau 1981).

Valuable leads to new and potentially useful medicinal agents may be derived from traditional or folk medicine (Delaveau 1981). There are, however, several problems when using data from traditional or

folk medicine in pharmacognosy. Much ethnopharmacological data exist for treatment of external remedies such as dermatologic, digestive, respiratory, urinary and genital diseases; but rarely do we find applications concerning cardiology and endocrinology. African traditions, for example, deal with swelled abdomen without specifying the digestive, urogenital or peritoneal syndrome, which might have infectious or cancerous origins (Delaveau 1981). However, a search for anti-infective or antimalarial agents would probably benefit from an ethnobotanical focus, because native cultures in the tropics have long had to deal with these disease states. On the other hand, AIDS is a relatively new human disease as far as we know, and there are no known established ethnobotanical treatments for this disease. Similarly, many cancers are not readily identifiable in native cultures, although ethnomedicinal agents have been identified for some cancerous states such as melanomas (Cardellina & Boyd 1995). Traditional medicine is often accused of being unsatisfactory in diagnosis and inadequate in pharmacology; there is often a lack of standard dosage.

Iwu (1993) states that the art of healing is part of African religion; there is a peculiar unity of religion and life that is characteristically African. All creatures and objects are believed to possess some psychic quality in them. If a sick person is given a leaf infusion to drink, he drinks it believing not only in the organic properties of the plant, but also in the magical or spiritual force imbibed by nature in all living things, and also the role of his ancestors, spirits and gods in the healing processes. The medicine men are very knowledgeable in the medicinal uses of local plants, but they employ such herbs for far more uses than for the treatment of diseases; they provide charms to neutralize the effects of the enemy's charms, ward off evil spirits and intercede between the community and the gods. Spirits are usually blamed for most misfortunes and diseases (Iwu 1993).

In considering the medicinal and toxic flora of Africa, it is necessary to realize that there is a considerable belief in magic among Africans. As a result there is often no clear division in the African mind between rational and magical remedies. The belief in magic is a supernatural explanation for many mundane happenings and is the essence of ordinary life among Africans (Watt 1967).

The success of traditional African healers in treating stress related ailments is more often attributed to the counseling skills of the healers and to the use of herbal remedies as placebos, rather than the bioactivity of the plants involved (Hutchings & Van Staden 1994).

While not condemning the metaphysical side of healing, this dissertation focuses on the chemical substances in the medicinal plants and their proven pharmacological effect.

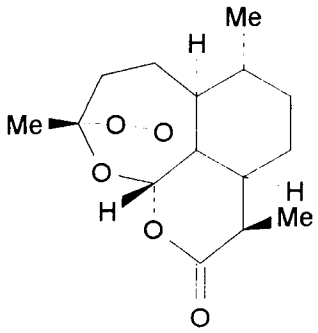
1.1.2 Drugs obtained from higher plants.

In the United States of America, the American public paid about $3 billion for prescription drugs that were extracted from higher plants in 1973. Of the 1 532 billion prescriptions dispensed during that year, 25.2% contained one or more constituents from higher plants. A total of 76 different chemical compounds of known structure, derived from higher plants were represented in the prescriptions. Of these, only seven are commercially produced by synthesis. This does not imply that they have not been synthesized, but it is more economical if it is commercially extracted from natural sources.

Ninety-nine (99) different crude plant drugs, or types of extracts from crude plant drugs were found to be present in the prescriptions analysed (2.5% of the total). Plant-derived chemical compounds can also be used as building blocks for semi-synthetic derivatives. Steroids, mostly derived from diosgenin, and alkaloids were the most commonly-encountered pure compounds from higher plants used as drugs in 1973 in the USA. Farnsworth & Bingel (1977) reports that less than 5% of new structures, isolated from higher plants as determined from a 1975 literature study, were reported to have been evaluated for any type of biological activity. (Farnsworth & Bingel 1977)

The Periwinkle, *Catharanthus roseus* (L.) G.Don from Madagascar is the source of two alkaloids, vincaleukoblastine (vinblastine) and vincristine (leukocristine) (Iwu 1993). Vincristine and vincaleukoblastine continue to be the two most important antitumor agents in the clinicians armamentarium. (Cordell 1977) Vinblastine is used in the treatment of Hodgkin's disease and choriocarcinoma. Vincristine is administered in the treatment of childhood leukemia and breast cancer (Iwu 1993).

Artemisinin was isolated by the Chinese scientists in the early 1970's from the Chinese medicinal herb *Artemisia annua* which is used for the treatment of malaria. Artemisinin has proven to be an effective drug for the treatment of cerebral malaria. Artemisinin and its derivatives have been used for antimalarial chemotherapy in more than 1.5 million patients. The synthesis of artemisinin involves numerous steps and the yields are low, hence the drug is extracted from the plant (Phillipson *et al.* 1995).



Artemisinin, an unusual sesquiterpene containing an endoperoxide moiety.

The importance of artemisinin and its derivatives is currently highlighted because they are the only effective treatment for some drug resistant malaria in the Thai-Burmese and Thai-Cambodian border regions. The Chinese have developed artemether (a methyl ether derivative) for major drug use and their products have been licensed as medicines in China, Burma, Brazil, Thailand and Zimbabwe. Rhone-Poulenc Rorer has developed Paluther (artemether), for oral, intramuscular and intravenous use (Phillipson *et al.* 1995).

Phillipson *et al* (1995) have investigated the ability of the plant tissue cultures of *Artemisia annua* to produce artemisinin. Although artemisinin was not produced, extracts of the tissue cultures did possess activity against *Plasmodium falciparum in vitro*. The active compounds were identified as the flavonoids artemetin, chrysoplenetin, chrysoplenol D and circilineol but they were not as active as

artemisinin. They have also shown that artemetin and another flavonoid from *A. annua*, casticin act synergistically against *Plasmodium falciparum in vitro* in concentration in which they exhibit no antiplasmodial activity. The flavonoids have no activity against *P. falciparum* at concentrations of 5×10^{-6}M but they had a potentiating effect on artemisinin. The maximum potentiation was obtained with chrysoplenol D, which is the most abundant flavonoid in *A. annua*, however it is not known whether these *in vitro* results have any significance clinically in the traditional clinical use of the herb. The ability of *P. falciparum* to develop resistance to drugs used clinically is a major problem in malaria therapy. In order to minimize this problem clinicians may use drugs in combination, particularly if the combined drugs have a potentiating effect on each other, e.g. combinations of artemisinin and its derivatives with mefloquine have potentiating effects *in vivo* with drug sensitive and drug resistant strains of *P. berghei* (Phillipson *et al.* 1995).

However the majority of plant products with activity, will never become clinical agents because they are either not sufficiently active, insufficiently selective, too toxic or not economically viable. Nevertheless they may lead to semisynthetic or synthetic analogues and should also help to further our knowledge of the mode of action (Phillipson *et al.* 1995).

1.1.3 Problems with pharmacological screening and bioassays:

Many biologically active substances with antibiotic, antifertility, insecticidal, moluscicidal, anti-inflammatory agents can be easily identified in a bioassay. However, several pitfalls exist in the design and application of a bioassay technique. Even if the active principle is potent, its concentration may be low in crude drug samples, and its detection might be difficult. Occasionally the active constituents are unstable and might decompose during the cause of extraction. Furthermore, in crude and complex extracts, the activity of an agent might be enhanced by synergistic forces so as to provide a false indication of potent activity. Quite often, the bioassay procedure fails to provide a clue as to the chemical makeup of the active principles in crude extracts (Delaveau 1981).

Failure to duplicate pharmacological results obtained with extracts from one lot of plant material with an extract from subsequent lots of plant material is a real problem (Farnsworth & Bingel 1977). There may be variations between different populations, different growth stages and even growth conditions. It might even be due to failure to collect the same specimen.

False negative results may be obtained in pharmacological screens. A logical explanation could be that the active compound(s) was (were) present in insufficient quantity or that other compounds in the extracts antagonized the effects of the active compound(s) (Farnsworth & Bingel 1977).

It is possible that a compound might exhibit one type of activity at a lower dose and an opposite type of activity at a higher dose; i.e. compounds can be anti-estrogenic at low doses and estrogenic at high doses.

Most of the natural products have been examined for activity *in vitro* and in many cases against a single organism. There are some discrepancies between *in vitro* and *in vivo* correlation, for example, berberine is inactive against *Entamoeba hystolica in vitro*, but is active *in vivo*. In addition to seeking novel drugs from natural products, it is important to understand the mode of action and to verify the efficacy of the plant extracts which are used in traditional medicines. Highly potent lipid-soluble compounds isolated on the basis of classical fractionation techniques may not be present to any great extent in aqueous extracts which are used medicinally (Phillipson *et al.* 1995).

Some compounds may be converted *in vivo* to more active or less active compounds. Aqueous teas of *Brucea javanica* (Simaroubaceae) have been compared for their activities against *Plasmodium, in vitro* and *in vivo* and it has been suggested that polar glycosidic quassinoids are converted *in vivo* to lipophilic potentially active quassinoids. (Phillipson *et al.* 1995)

Plants may contain several compounds, each of which displays different pharmacological activities. The Syringa tree (*Melia azadirach*, Meliaceae) contains limonoids, some of which are active against protozoa, but they also contain polysaccharides which have anti-inflammatory and antitumor activity as well as peptidoglycans and phenolics which activate polymorphonuclear leukocytes. Compounds which have direct antiprotozoal activity may also have other effects in humans, for example, the alkaloid emetine stimulates the immune system. There is a considerable lack of knowledge concerning the effects of total extracts which may act by more than one mechanism and in which different compounds may potentiate or antagonize the activity (Phillipson *et al.* 1995).

1.2 OBJECTIVES OF THE LITERATURE STUDY

Research is being done on medicinal plants for the following reasons:

1. Millions of South Africans still depend on traditional herbal medicine from as many as 700 indigenous plant species (Meyer *et al.* 1996).
2. There is a great need for new drugs because of the problem of resistance of organisms against drugs currently being used as well as a limited spectrum of activity.
3. The appearance of new diseases like AIDS further necessitates new remedies to be developed.
4. New screening methods and isolation techniques have made it possible to elucidate the mode of action of old herbal medicines and thereby reintroduce them into modern therapy (Wagner 1977).
5. In our present overwrought age, there has been a revival of interest in phytotherapy, in which natural substances play an important part in the regeneration and healing of the human organism. "Aromatherapy" is one branch of phytotherapy, which takes advantage of the antibacterial, antifungal, antiseptic, tranquilizing, palliative, disinfecting and insecticide effects of essential oils (Héthelyi *et al.* 1989).

To assist researchers in their decision of further research projects it is essential to know the extent of the research already done. The purpose of this dissertation is :

1 To give an overview on the work already done on the pharmacological activity of the Asteraceae of southern Africa.

2 To point out where the shortcomings in ethnopharmacological research on the Asteraceae are.

3 To establish priorities for further study. It may even be possible to predict which species may give positive results.

4 To draw a conclusion about the validity of the use of certain plant species in traditional medicine.

1.3 STRUCTURE

The dissertation comprises a literature study of relevant scientific papers published in scientific journals, on the medicinal value of the southern African Asteraceae. The majority of the information on the southern African Asteraceae is compiled in Chapter 5: Database of the medicinal uses of the Asteraceae. The genera are arranged in alphabetical order.

Chapter 1, the Introduction, gives the motivation for the study, as well as the background, the objectives and the scope of the thesis.

Chapter 2 looks at the subject from a medical point of view. The emphasis is on the various medicinal uses and economic importance of the Asteraceae species from all over the world. The various ailments for which these species are used elsewhere may possibly shed some light on the use of Southern African species.

Chapter 3 deals with the chemistry of the compounds isolated from the Asteraceae. Different groups of chemical compounds are mentioned in scientific literature. Some authors used only extracts of the plant material to be assayed or tested, but in most cases, they have also identified a chemical compound responsible for the pharmacological action of the extract. In other cases, different chemical compounds were isolated without any mention of their pharmacological action. Chapter 3 gives an overview of the different classes of chemical compounds which are characteristic of the Asteraceae with their respective pharmacological actions.

Chapter 4 gives an overview of the chemotaxonomy of the Asteraceae. If species or genera which are closely related contain similar chemical compounds, then it follows that related taxa could be used for the same or similar ailments.

Chapter 5 is a database on the medicinal value of the Southern African Asteraceae. It includes data on the various medicinal uses of Asteraceae species, chemical compounds isolated from these species, the pharmacological action of extracts, and in some cases the active compounds isolated from the extracts. All the data were compiled from scientific journals and other publications. This chapter also includes the unpublished research results of work done by the pharmaceutical company, Noristan.

Chapter 6 is the Discussion. The extent of the research done on the Southern African Asteraceae is discussed and priorities for further study are mentioned. The validity of the traditional medicinal use of these plants is also evaluated.

Chapter 7 gives a summary of the dissertation.

Two appendices have been included. Appendix 1 is a diagram of the pathways of phospholipid-derived inflammatory mediators. Some of these mediators have been mentioned in Chapter 5. In view of the multi-disciplinary nature of the dissertation a glossary, appendix 2, was included. The abbreviations used in chapter 5 is explained in the glossary.

1.4 SCOPE OF THE THESIS

The study was limited to the Asteraceae of southern Africa. Introduced species and cosmopolitan weeds have also been included. Mention was made of commercial crop species like the sunflower with its medicinal uses, but the literature study was not comprehensive with regard to the chemical composition and the medicinal uses in other parts of the world.

Most of the ethnobotanical information wase found in two sources. They are Watt & Breyer-Brandwijk (1962) and the Traditional Medicine Database. The pharmaceutical company, Noristan, compiled a database on the plants used in traditional medicine in South Africa. The database was recently handed over to the Traditional Medicines Programme (TRAMED) of the Medical School at the University of Cape Town. Other sources were also used and it was updated by data published in scientific journals. This ethnobotanical information on the medicinal uses of the plant species was used as point of departure for the literature study.

The literature search was conducted by means of a computer search. The database used for the search was the Science Citation Index and an international database, the Dialog Service from the Knight-Ridder Information Inc. The keywords used with the Science Citation Index were; (medicinal or antimicrobial, or antiviral or antifungal or antibacterial or antitumor or anticancer or cancer or anti-inflammatory or antibiotic) and (Compositae or Asteraceae or Helichrysum) and (southern Africa or southern African)". The results however, were disappointing. The key words "southern Africa or southern African" were very seldom used in the title or abstract. It was decided therefore to do the search without the key words " and (Southern Africa or southern African)". The search resulted in a list of titles or abstracts of papers. It then had to be determined from the titles or abstracts if the species mentioned were indigenous to southern Africa. This was done with the aid of a list of species of southern Africa (Arnold & De Wet 1993). Watt & Breyer-Brandwijk (1962) was also used as a reference for several introduced species not listed in the species list of Southern Africa that were used medicinally in Southern Africa.

It was found that the pharmacological activity of the plant species was not covered adequately by the above mentioned keywords. In addition, in many cases the plant family to which the plant species

belongs was not mentioned in the title or abstract, only the generic name. It was therefore decided to use the generic names as keywords as well. The search was repeated, using only the generic names as key words. Since many genera are apparently not used medicinally, only the generic names mentioned in Watt & Breyer-Brandwijk (1962) were used as key words.

The Science Citation Index has only been available on CD ROM since 1981. The search was conducted as mentioned above. The bound form of the Science Citation Index was used for the years before 1981. The keywords used were the generic names of the Asteraceae mentioned in Watt & Breyer-Brandwijk (1962). The search in the Science Citation Index went only as far back as 1975.

A problem with using the botanical names as keywords is that some of the names could have changed. Using the botanical names that appear in Watt & Breyer-Brandwijk (1962) pose the problem that some of the names could have changed and would not appear in more recent literature. An example to illustrate this is *Artemisia maderaspatana* L. This plant was previously known as *Grangea maderaspatana* (as in Watt & Breyer-Brandwijk (1962)) but this name would not be found in the more recent literature. Alternatively, using the recent names (as found in Arnold & De Wet (1993)) would mean having to check if the names have changed. The older literature would use *Grangea maderaspatana* L. and not *Artemisia maderaspatana*. This may have resulted in an incomplete search. When it was determined that the name had changed, the old and the new names were used as keywords.

Noristan pharmaceutical company has developed a comprehensive database of plants which are used medicinally. The database comprises about 1200 plant species. The database was developed by means of interviews with local people. It contains information about the indication (use), the relevant body part, the population group that use the plant, the part of the plant used and the method by which it is applied. Where available, it also contains references of papers on the chemistry and pharmacological effect of the plant. It contains data of about 91 genera of the Asteraceae. Recently the control of the database was transferred to the Traditional Medicines Programme (TRAMED) at the University of Cape Town. Data of the medicinal use of relevant species and references to papers on their chemistry and pharmacology were collected from the reference cards of this database. The relevant data was incorporated in the study and the references were used to find papers that could be used in the study.

Noristan had also done research on the pharmacological action of extracts of selected plants species. The bulk of this data was never published. Most of the relevant data of the screening was incorporated in this study. The majority of the results of the screening of species of the Asteraceae did not justify further work on the isolation and identification of the active compounds and possible development of it as a medicine. However, in some cases the active compounds were isolated and identified. For example, caespitin, a phloroglucinol derivative, was isolated and identified from *Helichrysum caespititium* (DC.) Harv (Dekker *et al.* 1983).

Other relevant information was followed up in order to collect as much data as possible. The references quoted in a paper were sometimes used to find new sources of information. Searches were also done for papers or books quoted. Due to the multi-disciplinary nature of the subject the results of the search for quoted authors were not as promising as hoped for, despite the cross referencing done.

The data collected was arranged in Chapter 5 according to the botanical species. The genera were arranged alphabetically. The species belonging to the same genera were placed alphabetically under the heading of the generic name. For each species, the ethnobotanical data (uses), the chemical composition and the pharmacological action were grouped together where possible. Although the data was arranged according to the botanical species, Chapter 3, "The chemistry of the Asteraceae" looks at it from the point of view of the active chemical compounds and Chapter 2 focuses on the pharmacological effect or medicinal use of Asteraceae species.

CHAPTER 2: USES OF ASTERACEAE SPECIES

Despite the fact that the Asteraceae is one of the largest plant families, comprising about 900 genera and 17 000 species, it is the source of relatively few products of economic and medicinal importance. Wagner (1977b) reported that only about 30 plant species are employed as crude drugs and no more than about 20 well defined pure substances are commercially available, or used therapeutically. Only 16 drugs are found in pharmacopoeias (Wagner 1977b). It would seem, however, that species of the Asteraceae of Africa (especially Southern Africa) have not been included in this survey.

2.1 ANTIPHLOGISTIC AND SPASMOLYTIC AGENTS

The true chamomile, *Matricaria chamomilla*, is one of the oldest pharmaceutical plants. Aqueous and alcoholic extracts have been used since antiquity, internally and externally, for their anti-inflammatory and wound-healing activity. For a long time the only known active principle was the blue azulene compound. It is produced from matricin during steam distillation. More recently, other substances have been found which possess even greater activity than azulene (Wagner 1977b).

2.2 ANTIHEPATOTOXIC AND CHOLERETIC AGENTS

The best known example is the fruits of *Silybum marianum*. It was listed as a liver remedy in the "Materia Medica" of Dioscorides, who lived in about A.D. 50. It protected the liver against the action of trinitrotoluene and carbon tetrachloride (Wagner 1981). Drug preparations of the flavonoid-rich *Helichrysum arenarium* have also been used in folk medicine as anti-choleretic and as remedy for liver diseases (Dombrowicz *et al.* 1992).

2.3 CYTOTOXIC (ANTICANCER) AGENTS

Plants have been used in the treatment of cancer for over 3500 years, but it is only since 1959 that a concerted systematic effort has been made to screen crude plant extracts for their inhibitory activity against animal tumor systems (Cordell 1977). The availability of modern, refined methods for testing anticarcinogenic agents has encouraged the systematic search for cancerostatic agents amongst natural products (Wagner 1977). The Natural Products Drug Development Program of the National Cancer Institute has found over 3000 species of plants which were reported to be used as some form of cancer treatment (Cassady, Chang & Mclaughlin 1981). Although natural products which exhibit anticancer activity represent an enormous variety of chemical structures (Cordell 1977), a large number of the active plant-derived compounds were found to be sesquiterpenes from the Asteraceae (Cassady, Chang & Mclaughlin 1981).

Many of the sesquiterpenoids in the Asteraceae, chiefly lactones from the germacranolide, guaianolide, pseudoguaianolide and elemanolide class, are especially active. The therapeutic use of these sesquiterpene lactones have hitherto been prevented by their relatively high toxicity. Attempts

to increase the activity of the molecule by chemical modification have so far been unsuccessful (Wagner 1977). Molelephantinin from *Elephantopus mollis* shows WM activity (Walker intramuscular carsinosarcoma), ambrosin from *Hymenoclea salsola* exhibits P-388 activity and eupahyssopin from *Eupatorium hyssopifolium* was active in the WM system. All three of the above compounds are germacranolides isolated from members of the Asteraceae. The common sneezewood, *Helenium autumnale* var. *montanum* (Asteraceae) has afforded helenalin, a sesquiterpene lactone which shows activity in the PS WM and B-16 melanoma system (Cordell 1977). Vernolepin, isolated from *Vernonia hymenolepis* (Asteraceae) exhibits in vitro toxicity (KB) and *in vivo* tumor inhibitory activity against Walker intramuscular carcinosarcoma (Kupchan et al. 1968). There have been many approaches to synthesize vernolepin, but only one of these has been carried through successfully (Cordell 1977).

The diterpenes have recently been a very interesting source of structurally new antitumor agents, some of exceptional promise. *Podocarpus* species in the family Taxaceae have yielded novel diterpenoid tumor inhibitors, podolide and nagilactone C (Cordell 1977).

Lignans have been of interest in the treatment of cancer since 1942 and extensive studies have been made of derivatives of podophyllotaxin, particularly glycosides (Cordell 1977).

The largest and most diverse group of compounds exhibiting anticancer activity are the alkaloids. They include some of the major alkaloid groups, pyrrolizidine alkaloids, isoquinoline alkaloids, benzophenanthridines, monomeric indole alkaloids, dimeric indole alkaloids and others (Cordell 1977). However, only the pyrrolizidine alkaloids occur in the Asteraceae. Alkaloids of the pyrrolizidine type from *Senecio* and *Crotalaria* species are potent hepatotoxins, but, as with phorbol esters, at lower doses antileukemic activity was observed. Thus monocrotaline has been obtained as the antitumor principle from *Crotalaria spectabilis* and *C. assamica*. Its antitumor effects were traced to an inhibition of cell multiplication (Cordell 1977). Combined administration of cyclophosphamide and methanolic extracts of *Senecio chrysanthemoides*, *S. densiflorus* and *S. jacquemontanus* led to the prolonging life span of S180 (ascitic) tumour bearing mice (Indap & Gokhale 1986). Tumour inhibiting action is shown by three groups of compounds related to pyrrolizidine alkaloids; by some alkaloids themselves; by indicine N-oxide (and possibly related compounds); and by pyrrolic alkylating agents. Indicine N-oxide, the active principle of extracts of *Heliotropum indicum*, is the only pyrrolizidine alkaloid which has ondergone clinical trials as an anticancer drug (Mattocks 1986).

Another cytotoxic principle has been found in the flavone and flavonol di- and trimethyl ethers of *Eupatorium perfoliatum* and *E. semiserratum*. The active flavonoids all have a methoxy group in position 6 (Wagner 1977). The antineoplastic and cytotoxic properties of some flavonoids could be attributed to the inhibition of mitochondrial enzymes by the flavonoid constituents (Hodnick *et al.* 1986). For example, quercetin which has been shown to inhibit the growth and proliferation of malignant cells and tumor promotion, also inhibits the activities of several enzymes including cAMP-independant protein kinases, Ca2+ -phospholipid-dependent protein kinase, and tyrosine protein kinases associated with mammary tumours (Srivastava & Chiasson 1986).

2.4 ANTIMICROBIAL AGENTS

Antimicrobial agents represent a group of drugs which have made the greatest impact on curative medicine. However, there is a growing prevalence of antimicrobial resistance among pathogens (Conradie & Straughan 1988). Antimicrobial agents include antibacterial, antifungal, antiviral and antiprotozoal agents. Antibiotics are usually secondary metabolites of micro-organisms. One of the principle drugs for systemic fungal infections is amphotericin B, a polyene (polyine) antibiotic (Conradie & Straughan 1988).

It has been shown that about 60% of essential oils possess antifungal and 35% antibacterial properties. The essential oil of the herb *Santolina chamaecyparissus* Linn, indigenous to the Mediterranean regions, was found to be effective in controlling candidiasis both *in vivo* and *in vitro* (Suresh *et al.* 1995).

Some of the polyacetylenes from the Asteraceae possess remarkable bacteriostatic and fungistatic properties. Bacteriostatic activity is also exhibited by the many phenolic carboxylic acids that occur in the Asteraceae, e.g. caffeic acid and chlorogenic acid. Part of the bacteriostatic activity of *Echinaceae* preparations, which are used pharmaceutically, is due to a complex depside, consisting of dihydroxy-phenol-ethanol, caffeic acid, 1 mol rhamnose and 2 mol glucose (Wagner 1977b).

Garcia *et al.* (1990) screened 30 Argentine medicinal plants for antiherpetic activity. Five species, all belonging to the Asteraceae, showed clear antiviral activity.

2.5 ABORTIVE, OXYTOCIC AND ANTI-FERTILITY AGENTS

Some species of the Asteraceae are widely used for their abortive, oxytocic and anti-fertility properties (Watt & Breyer-Brandwijk 1962). *Aspillia mosambicensis* (Oliv.) Wild, *Sphaeranthus* sp. *Vernonia amygdalina* Delile, *Vernonia tigna* Klatt, *Grangea maderaspatana* (L.) Poir, *Dicoma zeyheri* Sond. and *Acanthospermum australe* (Loefl.) Kuntze are a few of the species used in this regard.

2.6 GASTROINTESTINAL DISORDERS

Gastrointestinal disorders are one of the major health problems in developing countries. In Mexico, plants with astringent properties are particularly valued to treat diarrhoea and dysentery. Bitter, aromatic and bitter-aromatic plants are especially employed to treat gastrointestinal cramps and pain. Frequently tannin containing drugs are used to treat diarrhea and dysentery (Heinrich *et al.* 1992).

2.7 INFLAMMATORY CONDITIONS AND HEADACHES

Feverfew (*Tanacetum parthenium*) has been used as a herbal remedy for inflammatory conditions and migraine since ancient times and there is recent evidence of its effectiveness in migraine. (Hayes & Foreman 1987) Extracts of Feverfew inhibit secretion of granular contents from platelets

and neutrophils and this may be relevant to the therapeutic value of Feverfew in migraine and other conditions. The herb is also reputed to be of value in conditions such as arthritis and psoriasis. Groenewegen *et al.* (1986) have analyzed an extract of Feverfew and identified several compounds with anti-secretory activity. They isolated sesquiterpene lactones possessing a α-methylene butyrolactone unit (Groenewegen *et al.* 1986). An extract of the plant Feverfew produces a dose-dependent inhibition of histamine release from rat peritoneal mast cells stimulated with anti-IgE or the calcium ionophore A23187 (Hayes & Foreman 1987).

2.8 ECONOMIC IMPORTANCE OF MEMBERS OF THE ASTERACEAE

Many of the substances isolated from the family are toxic or show other significant physiological activity, and this may be one reason why plants of the Asteraceae are rarely used in human diets or for animal fodder. The lettuce, is however a regular item in human diets. Unlike the wild relatives of the lettuce (*Lactuca sativa*), the bitter compounds, lactucin and lactupicrin, are largely absent from the cultivated varieties. Other species used for food include *Helianthus tuberosus* L. (Jerusalem artichoke), *Cynara scolymus* L. (globe artichoke), *Cichorium endiva* Willd. (endive) and *Cichorium intybus* L. (chicory) (Heywood, Harborne & Turner 1977).

The most generally useful economic plant of the Asteraceae, however, must be the sunflower, *Helianthus annuus*. It is widely cultivated as an oil seed crop, but is also a good source of seed protein. The oil is a valuable food, with a good balance of dietary fatty acids, and has even been employed beneficially in the treatment of human cancer (Heywood, Harborne & Turner 1977). The Safflower, *Carthamus tinctorius*, better known as a source of a yellow dye in the flowers, is another oil crop. Safflower oil is a drying oil, its highly unsaturated character is due chiefly to its content of linoleic acid (up to 75% of the total fatty acids). It is used as salad oil and pharmaceutically in vitamin preparations (Wagner 1977b).

2.8.1 Polysaccharides

Roots and rhizomes, in particular those of *Inula* species, the tubers of the *Dahlia* and *Helianthus* species, the roots of *Taraxacum officinale*, *Arctium lappa*, Pyrethrum and *Cichorium* species are characterized by a great abundance of inulin. Inulin consists of approximately 20-30 fructose units and has a molecular weight of 3000-5000. The fructofuranose units are joined by 1,2-linkages. Since inulin is cleaved by the body into D-fructose (fructofuranose), it is tolerated better than other carbohydrates by diabetics. Plants containing inulin, or inulin itself are therefore used for the preparation of diabetic bread. Furthermore, inulin is the starting material for the technical preparation of fructose (Wagner 1977b).

2.8.2 Spices and flavouring agents

The rich accumulation of essential oils and other terpenoids in certain composites is responsible for the use of various members such as tansy, (*Tanacetum vulgare*), Wormwood (*Artemisia absinthium*) for flavouring foods or liqueurs (Heywood, Harborne & Turner 1977). Vermouth wines are prepared

predominantly from *Artemisia pontica* L. Since absinthe liqueurs are prepared predominantly form Oleum Absinthii, they contain considerable quantities of thujone. In large doses this is very toxic and can lead to chronic poisoning. For this reason their preparation is prohibited in Germany and Switzerland (Wagner 1977b).

2.8.3 Sweet substances

Whereas bitter substances are fairly widely distributed in the Asteraceae, only one plant is known to produce a sweet material. The plant, *Stevia rebaudiana* Bertoni grows in Paraguay and has been used for along time by the natives for sweetening bitter drinks. The sweetening action is due to a diterpene glycoside, known as stevioside. It is 300 times sweeter than sucrose (Wagner 1977b).

2.8.4 Bitter substances

Although bitter substances occur fairly widely in the Asteraceae, only *Artemisia absinthium* and *Cnicus benedictus* are important in the pharmacy and food industries. The bitter taste of *A. absinthium* is due to the guaianolides, absinthin and anabsinthin and cnicin is the bitter principle in *Cnicus benedictus*. The pharmaceutical usefulness of these bitter drugs is due to their stimulation of stomach secretion, which is the result of reflex nervous activity. Furthermore, the release of gastrin causes an increase in stomach activity. The motor action of the intestine and the bile and pancreatic secretion are therefore also increased. The liqueur, absinthe, is classed with gentian as a bitter drug that causes a marked increase in the salivary flow (Wagner 1977b).

2.8.5 Insecticides

The dried flowers of *Chrysanthemum cinerariaefolium* Vis. have been used for a long time as fly repellent. The insecticidal activity is due to the presence of the following six components: pyrethrin I and II, cinerin I and II, and jasmolin I and II. Other compounds with insecticidal activity have been obtained from species of Echinaceae, *Chrysanthemum*, *Heliopsis* and *Anacyclus*. They are isobutylamides of long chain simple unsaturated fatty acids or acetylene fatty acids. They possibly act as natural protective agents or resistance factors for the plant against insects attack (Wagner 1977b).

2.8.6 Cautchouc

Two plants of the family Asteraceae, *Taraxacum bicorne* (=Kok Saghyz) Rodin and *Parthenium argetatum* L. yield caoutchouc (rubber) (Wagner 1977b).

2.8.7 Toxic substances

The vegetative parts of the flowers of *Senecio* were approved in antiquity as folk remedy for inflamed wounds, stomach trouble, worms, and illness of the liver and bile system. Toxic pyrrolizidine alkaloids have been isolated from *Senecio* plants. *Senecio* cause a loss of many cattle and horses and is known as Molteno disease in South Africa. Other toxic species include *Geigeria*, *Eupatorium* and *Xanthium* (Watt & Breyer-Brandwijk 1962).

CHAPTER 3: CHEMISTRY OF COMPOUNDS ISOLATED FROM THE ASTERACEAE

Several classes of compound are characteristic of the Asteraceae, notably the terpenoid-based sesquiterpene lactones, the fatty acid derived polyacetylenes and the polysaccharide fructans. Composites, are exceptionally rich, both in the range of secondary compounds present (Table 1) and also in the number of complex structures known of any one class. (Heywood *et al.* 1977)

The combined occurrence of sesquiterpene lactones, acetylenic compounds and inulin-type fructans is almost characteristic of the Asteraceae. Triterpenes and flavonoids are present in every member of the family (Hegnauer 1977).

Table 1: Classes of chemical compounds (Heywood *et al.* 1977)

Class of compound	Location and biological activity
Present in all tribes	
1. Inulin-type fructans	storage organs
2. Fatty acids	seed oils
3. Sesquiterpene lactones	mainly in leaves
4. Pentacyclic triterpene alcohols	as esters in fruit pericarps, and in lipids generally
5. Caffeic acid esters	leaves; cynarin is diuretic
6. Methylated flavonoids	leaves and flowers (as yellow pigments)
Present in most tribes	
7. Acetylenic compounds	roots and leaves; antimicrobial activity
	leaves and fruits
8. Essential oils, including phenolic monoterpenes	leaves
9. Cyclitols	leaves and flowers
10. Coumarins	--
Present in few tribes	
11. Rubber (poly-isoprene)	roots and stems
12. Pyrrolizidine alkaloids	leaves, toxic
13. Triterpene acids	free in flowers; combined with sugar (as saponin) in leaves
14. Diterpenes	all tissues
15. Cyanogenic glycosides	leaves and fruit; toxic
16. Anthoclor pigments	yellow flowers
17. Chromenes	leaves and roots; insecticidal
18. Fatty acid amides	roots; insecticidal

3.1 POLYACETYLENES, THIOPHENES AND PHOTOTOXICITY.

Both polyacetylenes and thiophenes are classified as photosensitizers, their toxic effects being enhanced by exposure to light. Fifteen years after the discovery of the nematocidal activity of the two thiophene derivatives α-terhienyl and 5-(3-buten-1-ynyl)-2,2'-bithienyl isolated from the roots of the common marigold (*Tagetes*), their nematocidal activities were found to be tremendously enhanced by light. Daniels, a dermatologist, used *Candida* to screen plant materials brought to his clinic by patients suffering from phytodermatitis. The method used by Daniels is relatively simple and rapid and involves placing small parts of the plant material on agar plates spread with living *Candida albicans* and incubating one set of plates in the dark and the other in long wave UV light. Plant materials which caused a halo on growth inhibition after incubation in near UV (300-400 nm), but not after dark incubation, were termed phototoxic (Towers 1980). The discovery of antibiotic properties of plant extracts has often led to the identification of polyacetylenes as the compound responsible for this activity (Towers 1980).

Acetylenes (or polyacetylenes) are an unusual group of naturally occurring hydrocarbons which have one or more acetylenic groups in their structures. Over 900 polyacetylenes are known as plant products, most have additional functional groups and are either alcohols, ketones, acids, esters, aromatics or furans. Thiophenes differ from acetylenes in containing sulfur and characteristically have one or more thiophene substituents. Many thiophenes have acetylenic substituents (Harborne & Baxter 1993).

Polyacetylenes are characteristic of the Asteraceae and Apiaceae but are also present in at least a dozen other families of flowering plants as well as in certain basidiomycetous fungi (Towers 1980). The acetylenes from all but one of the families of higher plants are predominantly aliphatic, by contrast, the Asteraceae are crowded with "curled up" compounds, i.e. compounds which are aromatic, furanoid, thiophenic or spiroketal. Ten of the 26 structural types are confined to the Antemidae and three other types are so far restricted to the Inulae. Some of the heterocyclic polyacetylenes, such as thiophenes, have been found in the majority of tribes (Sørensen 1977).

The Asteraceae are the best studied family and most of the known natural acetylenes have been isolated here. More than 1100 species out of 267 genera from the Asteraceae have been studied. They are present in all 13 tribes. However, the amount of structure variation is extremely wide. Especially rich in acetylenes are the tribus Heliantheae, Anthemideae and Cynareae (Bohlmann, Burkhardt & Zdero 1973).

Most of the work on naturally occurring acetylenes has been done by Prof. F. Bohlmann from the institute of Organic Chemistry of the Technical University, Berlin. The book **Naturally Occurring Acetylenes**, by F. Bohlmann, T. Burkhardt & C. Zdero gives an overall summary of the current (1971) knowledge of all the naturally occurring acetylenes. It also contains a comprehensive overview of the distribution of the acetylenes.

Often particular polyacetylenes are localized within a particular region or organ in a given species. (Towers 1980) Polyacetylenes and thiophenes tend to be found more regularly in root tissues than in aerial parts of plants (Harborne & Baxter 1993). Many polyacetylenes are stored in the roots and the polyacetylene content of some plants is also known to change quantitatively and qualitatively with the growing season (Towers *et al.* 1977). In those cases where labeled polyacetylenes have been studied, they have been rapidly metabolized, with a half-life of 1-2 days (Sørensen 1977). Acetylenic compounds are much more labile than most other plant substances and they can only be isolated successfully from fresh plant material (Heywood, Harborne & Turner 1977).

Camm et al. (1975) tested the roots, leaves and flowers of 80 species of Asteraceae for phototoxic activity against *Candida albicans*. Many genera showed activity, especially in the roots. No active genera were found in the tribe Chichorieae. Chemotaxonomic evidence and preliminary chemical data suggest that the compounds are polyacetylenic in nature. It may also be noted that the tribe Chicorieae is poor in polyacetylenes (Camm *et al.* 1975).

Bacteriostatic and fungistatic activity of simple acetylene derivatives has been clearly demonstrated and the notorious unstable tridecapentaynene has been shown to be an effective antibiotic against a number of micro-organisms including *Candida albicans*. Some polyacetylenes are antibiotic as well as phototoxic. Towers *et al.* (1977) reported a correlation between phototoxicity and the reported occurrences in plants of (a) tridecapentaynene or (b) thiophene derivatives such as α-terthienyl or (c) matricaria ester. For example, *Tithonia*, *Gnaphalium*, *Bidens* and *Vernonia* have been reported to contain tridecapentaynene and were shown to be phototoxic. Species of *Bidens*, *Tagetes*, *Centaurea* and *Schkuhria* contain thiophene compounds and representative species of these genera were found to be phototoxic. Matricaria ester is a common constituent of species of *Baccharis* and species of *Baccharis* tested were found to be phototoxic (Towers *et al.* 1977).

Studies have implicated this class of compounds as active constituents in Asteraceae used in folk medicine. In a survey of 42 species of Asteraceae used in traditional medicine to treat skin diseases, 20 species were found to be phototoxic or antibiotic, and their activity correlated with the presence of polyacetylenes or thiophenes. (Towers & Champagne 1977)

A number of well-known fungi and bacteria were tested against some polyacetylenes. Many of these compounds were found to be phototoxic to fungi and bacteria with the exception of *Pseudomonas fluorescens* which remained unaffected by any of them including tridecapentaynene. *Escherichia coli* and *Proteus vulgaris*, the two other gram negative bacteria, were unaffected by most of the polyacetylenes although they reacted strongly to tridecapentaynene. A greater incidence of phototoxic and antibiotic activities was exhibited by these compounds against the gram positive organisms tested (Towers *et al.* 1977).

Most of the polyacetylenes tested were phototoxic to *Candida albicans* although there were a few exceptions, for example, tridecatetraynediene was negative whereas a positional isomer was positive (Towers *et al.* 1977).

Certain acetylenes such as the fish poisons ichthyothereol (the active principle of *Ichthyothera terminalis)* and its acetate have no light requirement for their toxic behaviour. However, many of the acetylenes of the Asteraceae require UV-A light (320-400nm) for their toxicity or other biological activities. For example, the nematocidal effects of α-terthienyl (α-T) are enhanced many times under UV-A light. With photosensitizing acetylenes, toxicity extends to a wide range of organisms including bacteria, fungi, algae, higher plants, protozoans, nematodes, insects and mammalian cells. Phototoxic acetylenes are also particularly effective against membrane-bound viruses *in vitro* (Towers & Champagne 1977).

The mechanism of phototoxic action of these compounds is unknown, but it seems to be different from the polyene antibiotics. Sterols are effective in 'protecting' fungi from the effects of these antibiotics, which interfere with the membrane structure. However, when plates of agar were coated with cholesterol ($10\mu g/cm^2$) before the addition of *Candida*, there did not seem to be any protection of the yeast from the phototoxic activity. Furanocoumarins, such as psoralen, when applied to human skin cause damage in the presence of long-wave UV light (320-370nm), but not in the dark. This phototoxicity has been well examined in plants and with chemicals obtained from the families Rutaceae, Umbelliferae and others which are rich in furanocoumarins. Furanocoumarins are not known from Asteraceae (Camm *et al.* 1975).

α-Terthienyl can evoke photodermatitis, evidenced by erythema and long-lasting hyperpigmentation in human and guinea pig skin. Polyacetylenes on the other hand do not induce hyperpigmentation at low concentrations. There is a strong correlation between photodynamic activity and carcinogenicity. Thus a strong photosensitizer may be suspected of being carcinogenic. Neither α-terthienyl nor the polyacetylenes appear to be mutagenic, however. They do not induce an increase in the frequency of chromosome aberrations or of sister chromatid exchanges in Syrian hamster cells whereas 8-methoxypsoralen does so to a marked extent. These are in agreement with other experiments which indicate that furanocoumarins react with DNA whereas the acetylenes and thiophene compounds do not (Towers 1980).

The biological role of acetylenes and thiophenes are most likely as toxins in either plant-animal or plant-plant interactions. Thiophenes are noted especially for their nematocidal activities (Harborne & Baxter 1993).

If the mode of action of polyacetylenes is similar to that of xanthotoxin, by the light mediated cross-linking of double-stranded DNA, then two reaction sites in the molecule are required. α-Terthienyl in the presence of long wave UV can evoke photodermatitis in human skin (Towers *et al.* 1977).

3.1.1 Thiophenes

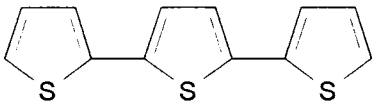
α-Terthienyl and related thiophenes, powerful photodynamic compounds occur in a number of medicinal species of the Asteraceae such as *Tagetes* and *Eclipta*. Many of the biological activities of these plant species may be ascribed to the thiophenes which occur in them. α-Terthienyl and other thiophenes show pronounced phototoxic activity against a diversity of fungi, including the pathogenic yeast *Candida albicans*, gram positive bacteria, and to a lesser extent gram-negative bacteria. α-Terthienyl is also phototoxic to membrane-bound viruses such as herpes virus, murine cytomegalovirus (MCMV), and Sinbid virus, but not the membraneless T4 phage. Photosensitized viruses penetrated mouse cells effectively but the viral DNA could not replicate and late viral proteins were not synthesized. Of an array of 31 naturally occurring and synthetic thiophenes, 20 were photoactive against MCMV and 25 were able to photoinactivate Sinbid virus (Towers & Champagne 1977).

Terthiophenes have been found in many species of the Asteraceae family. Their biological activities, including antiviral activities, invariably require long-wavelength (320-400nm) ultraviolet radiation, UVA. A number of carboxylic acid derivatives of the photoactive terthiophene, α-terthienyl, were found to possess impressive UVA-dependent activity against the human immunodeficiency virus (HIV-1); but only when assayed in the absence of serum, indicating that the latter contained interfering components. Good antiviral activity required a high rate of singlet oxygen production, in accordance with previous observations on thiophenes. Partition coefficients indicate that these terthiophenes are quite lipophilic; this increases their affinities for the lipophilic domains of proteins, and this is illustrated by the observation that αT appears to bind to albumin. This may be what happened in the case of the carboxylic acid derivatives of αT, since they displayed relatively little or no anti-HIV activity when the reactions were conducted in the presence of serum, whereas they generally showed impressive anti-HIV activity in its absence (Hudson *et al.* 1994).

Two thiarubrines (dithiacyclohexadienes), which were isolated recently from species of Asteraceae, were investigated for light-mediated antiviral activity against HIV-1. Both compounds (thiarubrines A and D) showed good anti-HIV activity, in micromolar concentrations, which was dependent upon UVA radiation. They showed no antiviral activity in the dark, and only weak visible light mediated activity, despite the significant absorbance of these compounds in the 480nm region. The resulting inactivated virus was unable to replicate in cell cultures, as indicated by the loss of cytopathogenicity, the absence of cells expressing HIV-1 antigens and lack of production of HIV-1 p24 protein. Although this antiviral activity was not as efficient as that shown by the photoactive plant thiophene, α-terthienyl, both thiarubrines demonstrated increased activity when the serum component of the virus stock was reduced. This suggested that a component of bovine serum interfered to some extent with the anti-HIV activity (Hudson *et al.* 1993).

Several lines of evidence indicate that the target of α-T involves membranes and probably membrane proteins and does not involve DNA, in contrast to other phototoxic furanocoumarins. α-T, unlike other polyacetylenes is able to photosensitize human skin *in vivo*. It caused dose dependent

erythema, edema, crustin, erosion and inhibition of hair growth when administered topically to guinea-pig epidermis and dermis and irradiated for one hour. As α-T does not exhibit mutagenic or carcinogenic activity, it may provide a safer alternative to psoralens for the photochemotherapy of psoriasis and other cutaneous diseases. However, guinea pigs also display a type IV or delayed contact allergic sensitivity to α-T in the absence of photosensitizing light, which may compromise the compound's usefulness (Towers & Champagne 1977).

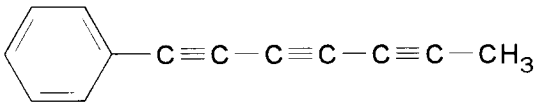


α-Terthienyl

3.1.2 Phenylheptatryine

The use of *Bidens* species, particularly *Bidens pilosa*, as sources of antibiotics can be explained by their abundant production of antifungal, antibacterial and antiviral phenyl acetylenes, e.g. phenylheptatryine (PHT). As with the thiophenes, many polyacetylenes and in particular PHT show potent phototoxic activity against filamentous fungi, various yeasts including *Candida albicans*, gram-positive bacteria including *Staphylococcus* and *Streptococcus* and to a lesser extent gram negative bacteria. Trematode bacteria are killed by 0.3ppm PHT even without photosensitizing light. Membrane bound viruses including MCMV, Sindbis virus, the fish virus IHNV (infectious hematopoietic necrosis virus), and the bacterial virus PM2 are susceptible to photoinactivation by PHT, but the membraneless T4 phage and IPNV (infectious pancreatic necrosis virus) are resistant. PHT-treated MCMV did not have cross-links or extra single strand breaks, and the genome and proteins of the inactivated virus penetrated the nuclei of susceptible cells normally. However, cells infected with the inactivated virus did not synthesize late viral protein, RNA or viral DNA. The PHT-induced damage must involve some early function of the virus which is normally required for replication to occur (Towers & Champagne 1977).

PHT may deserve further attention as a topical antibiotic: like α-T, it is not carcinogenic or mutagenic and it is active against a similar array of organisms. However, it does not induce photodermatitis in man, and there is no evidence to implicate it as a contact allergen (Towers & Champagne 1977).



Phenylheptatriyne (PHT)

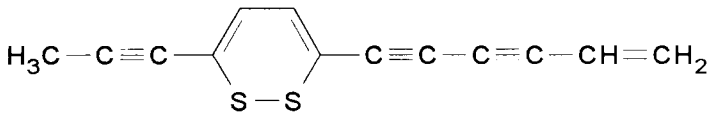
3.1.3 Thiarubrines

The red acetylenes, also known as the thiarubrines, are sulfur heterocycles restricted to ten genera of the Asteraceae, including *Aspilia* which is important in the traditional medicine of African countries. Thiarubrine A is strongly antibiotic against *Candica albicans*, *Saccharomyces cereviseae*, *Bacillus subtilis*, *E. coli* and *Mycobacterium phlei* and is markedly phototoxic to *Staphylococcus albus* and *Streptococcus faecalis*. The phototoxic activity appears to be more significant at low thiarubrine

concentrations. When tested against *Aspergillus fumigatus* and *C. albicans*, thiarubrine A is comparable to the antibiotic Fungizone and is more effective than Amphotericin B. The soil nematode *Coenorhabditis elegans* is killed by exposure to 5ppm thiarubrine in the dark or 0.03ppm thiarubrine in conjunction with 30 min irradiation, which suggest a basis for its traditional use as stomachic (Towers & Champagne 1977).

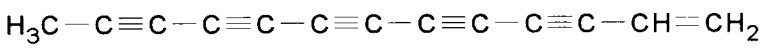
The antiviral activity of thiarubrine is similar to that of α-T. However, thiarubrine is also toxic to mammalian cells, causing mitotic inhibition of Chinese Hamster ovary cells at 2.0 ppm in the dark of 0.12 ppm in the light. This toxicity is abolished by the addition of an S9 microsomal activation mix, suggesting that thiarubrine might be less toxic *in vivo* (Towers & Champagne 1977).

Oral doses of thiarubrine (40-60μg) significantly reduced the severity of *C. albicans* infection in mice. When the thiarubrine was injected intraperitoneally, it was toxic; the degree of toxicity appeared to be correlated with the level of *Candida* infection, i.e., control mice survived 100μg injected thiarubrine but mice previously injected with an amount of $1.5x10^5$ *C. albicans* succumbed to 40μg thiarubrine. Obviously, any clinical use of this compound would have to be based on oral administration (Towers & Champagne 1977).

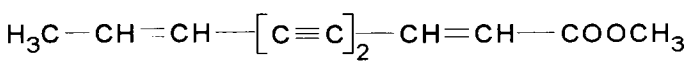


Thiarubrine A

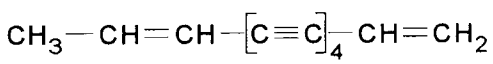
Pentaynene is undoubtedly the most common of all Asteraceae acetylenes, but it has never been found in the Anthemidae or Astereae. Tridecapentaynene has been found in 10 of the 13 tribes, and is only absent in the Senecioneae, Astereae and Anthemidae. The very frequent occurrence of the matricaria ester - inclusive of analogues and derivatives - in the Astereae and Anthemidae confirms the relationship between these two tribes. Polyacetylenes occur only in three genera of the Senecioneae, namely: *Arnica*, *Doronicum* and *Gamolepis*. Relatively few members of the Asteraceae possess the ability to synthesize phenyl rings from acetylenic precursors. They are the Heliantheae, Anthemideae and Cynareae, but are common within the first two tribes. Thietanones have so far been found to be restricted to the tribe Arctotideae, subtribe Gorterinae. (Sørensen 1977)



Pentaynene (trideca-1-mono-3,5,7,9,11-pentayne)



Matricaria ester



Tridecadiene-(1,11)-tetrayne-(3,5,7,9)

Good bactericidal and fungicidal activity are also shown by the acetylenes trideca-1-mono-3,5,7,9,11-pentayne and trideca-1,11-diene-3,5,7,9-tetrayne. The various thymol ethers isolated are also implicated in the bactericidal activity of the *Arnica* root drug. Fungistatic activity is also exhibited by the polarization of the triple bond and with the lipid solubility. The bactericidal activity increases with the hydrophylic nature of the compound. (Wagner 1977)

3.1.4 Amides

Isobutyl amides of long-chain fatty acids with characteristic olefinic and acetylenic unsaturation patterns are restricted to members of Anthemideae and Heliantheae. Many of these constituents have a pungent taste and possess insecticidal properties. Examples are pellitorin from roots, leaves and anthodia of *Anacyclus pyrethrum* DC., spilanthol (=affinin) from anthodia of *Spilanthes oleraceae* Jacq and echinacein from roots of *Echinacea angustifolia* DC. These insecticidal amides are generally present in plants as complex mixtures of isomers and homologues. The active isobutylamides have C_{10}, C_{11}, C_{12}, C_{14} or C_{18} polyunsaturated fatty acids. A trans-double bond in position 2 and a dimethylene interruption between the two systems of unsaturation seems to be essential for pungency and insecticidal activity (Hegnauer 1977).

3.2 TERPENOIDS

Terpenoids are largely water insoluble acyclic and cyclic compounds with five to several hundred carbons. Included in this group are the essential oils, the steroids and large polymers such as rubber (Ting 1982).

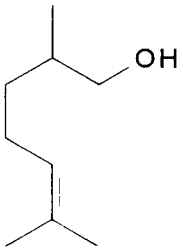
Table 2: Types of terpenoid compounds (Sticher 1977)

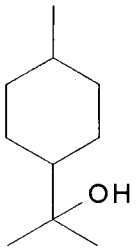
Type	Number of isoprene units	Occurrence/example
Hemiterpenes	1	Combined with some other type of compound, e.g. coumarins, quinones etc.
Monoterpenes	2	Essential oils, iridoids
Sesquiterpenes	3	Essential oils, bitter principles
Diterpenes	4	Resin acids, phytol, vitamin A, gibberellins
Triterpenes	6	Sterols, steroids, saponins
Tetraterpenes	8	Carotenoids
Polyterpenes	n	Rubber, gutta

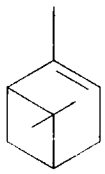
3.2.1 Monoterpenoids

Monoterpenes are the major components of oils obtained by steam distillation of plant material. Characteristically, they are volatile, insoluble in water and usually fragrant. Usually they have 10 carbons, because they are derived from two isoprene units. The monoterpenoids may be acyclic, monocyclic (with one ring), or bicyclic (with two rings) (Ting 1982).

Acyclic Monocyclic Bicyclic







Geraniol α-Terpineol α-Pinene

The biological, pharmacological and therapeutic activity of monoterpenes is very closely connected to that of the essential oils. Various essential oils and essential oil drugs are used as skin stimulants, antiphlogistic agents, expectorants, stomachics, arminatives, diuretics, antiseptics and disinfectants etc. But the most common use of the volatile oil drugs as well as of the separated oils is for flavouring purposes. Volatile oils are employed as flavours for food and confections and in the spice, perfume and cosmetic trades, as well as in pharmacy, where they are often used as flavouring agents to mask the disagreeable taste of certain medicines (Sticher 1977).

Antiseptic, disinfectant, anthelmintic properties: At one time various essential oils and their constituent terpenoids were applied in combating infections, particularly in those of bronchial and urinary tracts, and in preventing sepsis of burns and wounds. Since the advent of the sulfanomides and the antibiotics, terpenoids have seldom been used for such purposes. However, some monoterpenes still find extensive application as disinfectants. Since phenol was often used for the comparison of the efficacy, the carbolic acid coefficient shows how much a compound is more efficacious than phenol. Thymol is about 20 times more antiseptic than phenol. Thymol and carvacrol are still used extensively in mouth washes, the various monoterpenoids are incorporated in tooth-pastes, in which their mild antiseptic properties coupled with their rubefacient action on the gums are beneficial. Among the monoterpenoids, ascaricole especially has found clinical use as anthelmintic agent. Several essential oils and their monoterpenoids possess insect-repellent properties. The best known example is citronellal, which enjoyed a reputation as a mosquito-repellent before the introduction of superior synthetic agents (Sticher 1977).

Irritant, skin stimulant, expectorant, diuretic properties. Many of the simpler terpenoids are characterized by the possession of irritant properties. Certain essential oils may still be used as counter -irritant and as rubefacients in the form of embrocations or liniments. They produce the initial feeling of warmth and smarting, which is often followed by a mild local anesthesia, making them valuable in antipruritic preparations. Similar preparations are used to relieve rheumatic pain and neuralgia and in the treatment of the common cold and bronchitis. Monoterpenoids containing essential oils are also used as inhalants with expectorant and cough stimulant properties due to their mild irritation of the bronchial glands. Certain essential oils are used as diuretics because they produce irritation of the kidneys (Sticher 1977).

Sedative, carminative, spasmolytic properties. Some essential oils with monoterpenoids act on the central nervous system with stimulating, sedative or narcotic effects. Essential oils with sedative activity are valerian oil, calamus oil and lavender oil (Sticher 1977).

The accumulation of monoterpenes appears to be associated in may cases with glandular structures ("oil glands") (Francis 1971). Monoterpenes may also be present in non-steam distillable forms, for example the cyclopentanoid monoterpenes are normally present in plant tissue as their β-D-glucosides (iridoids). Compounds including the β-D-glucosides of geraniol, berol, thymol etc. were isolated (Sticher 1977).

3.2.2 Sesquiterpenoids

Sesquiterpenoids are volatile terpenoids composed of three isoprene units having 15 carbons. They may be acyclic, monocyclic or bicyclic. The main occurrence of sesquiterpenes is in plant essential oils (Herout 1971). Some act as phytohormones (abscisic acid represent in principle an "inhibitory" hormone). A role in plant growth regulation has also been ascribed to some other sesquiterpenoids, nevertheless, their importance and distribution is much more limited than those of abscisic acid. An example is xanthinin present in many species of *Xanthium* which shows antagonism against auxin. Others have pronounced antifeeding effects on insects and act as juvenile hormone mimics (mainly the farnesane-type compounds). A similar "self defence" against insects and wood -decaying fungi is exerted by these substances for preservation of the heartwood (Herout 1971).

3.2.3 Sesquiterpene lactones

Sesquiterpene lactones are a natural class of sesquiterpenoids, which are chemically distinct from the other members of the group through the presence of a γ-lactone system (Harborne & Baxter 1993). From a botanical point of view, the bitter lactones may be interpreted as components of essential oils which have been rendered non-volatile by oxidation (Hegnauer 1977).

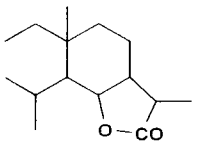
Sesquiterpene lactones are characteristic constituents of the Asteraceae but also occur sporadically in other angiosperm plants. These bitter substances often contain as major structural feature an α,β-unsaturated-γ-lactone, which in recent studies has been shown to be associated with anti-tumor, cytotoxic, antimicrobial and phytotoxic activity. They are known to poison livestock, to act as insect feeding deterrents and to cause allergic contact dermatitis in humans (Rodriguez 1976).

At least 3000 lactones have been described, the majority of them from the Asteraceae (Harborne & Baxter 1993). Sesquiterpene lactones are common constituents of most genera of the Asteraceae, with the exception of the evolutionary "advanced" tribe, the Tageteae (Rodriguez *et al.* 1976). They have also been reported as occasional constituents in 16 other angiosperm families. They are found in the aerial parts of the plant, chiefly in the leaves and in the flowering heads in concentrations of about 5% of the dry weight and are often located in the leaf trichomes or in the surface wax. They usually occur in mixtures of up to 15 different sesquiterpene lactones. There are also infraspecific variations in the *Artemisia* and *Ambrosia* (Harborne & Baxter 1993). In taxa of *Artemisia*, the

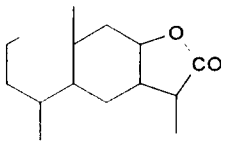
lactone content may vary from winter to summer. Lactones are rarely found in the stems and roots (Rodriguez *et al.* 1976).

Sesquiterpene lactones are colourless, bitter, relatively stable, lypophilic constituents which are biogenetically derived from *trans*, *cis* farnesyl pyrophosphate. The major types of lactones resulting from enzyme mediated cyclisations are classified primarily on the basis of their carbocyclic skeletons as; germacranolides, guaianolides, pseudoguaianolides, eudesmanolides, eremophilanolides and xanthanolides. The suffix "olide" refers to the lactone group. The α,β-unsaturated lactone is either cis-or trans-fused to the C_6-C_7 or C_8-C_7 positions of the carbocyclic skeleton. Structural modifications of the basic terpene skeleton involve the incorporation of an epoxide ring, hydroxyl groups (generally esterified), and/or a 5-carbon acid, such as tiglic or angelic acid. Some sesquiterpene lactones also contain covalently bound halogen atoms.

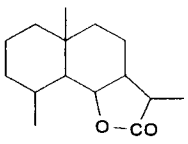
An individual plant species generally yields only one skeletal type, with oxidative variations on that skeleton. In genera having wide-ranging geographical distributions, a given species may exhibit considerable infraspecific variation in its sesquiterpene lactone structures (Rodriguez *et al.* 1976).



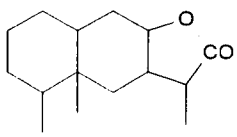
Elemanolides



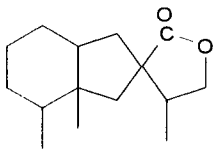
Seco-eudesmanolides



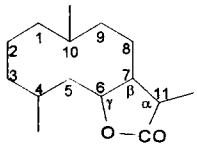
Eudesmanolides



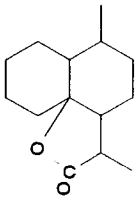
Eremophilanolides



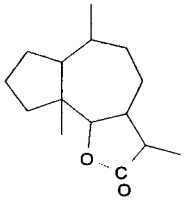
Bakkenolides



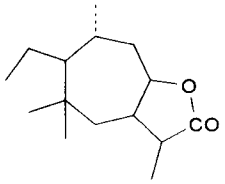
Germacranolides



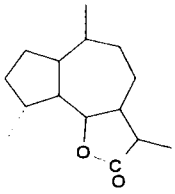
Cadinolides



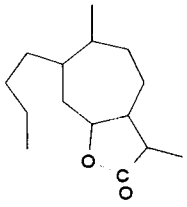
Ambrosanolides



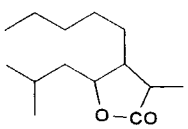
Seco-helenanolides



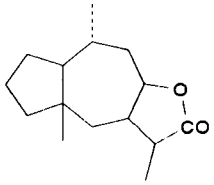
Guaianolides



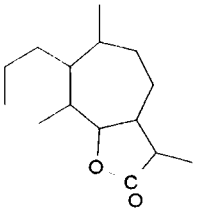
Xanthanolides



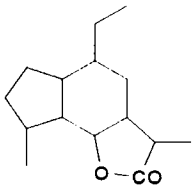
Seco-germacranolides



Helenanolides



Seco-ambrosanolides



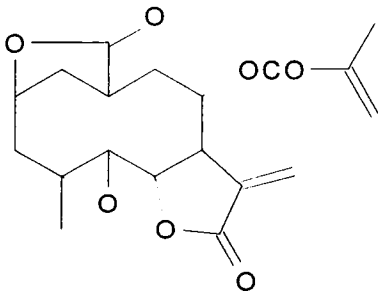
Chrymoranolides

(Rodriguez *et al.* 1976)

They are lipid soluble crystalline substances, isolated from dried plant material by extraction into methylene dichloride and separation on silica gel columns. (Harborne & Baxter 1993)

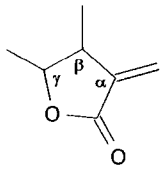
3.2.3.1 Biological activity of Sesquiterpene lactones.

Antitumor and cytotoxic activity. Plant extracts that exhibit antineoplastic (anticancer) activity have received considerable attention lately. The Natural Products Drug Development Program of the National Cancer Institute has found over 3000 species of plants which were reported to be used as some form of cancer treatment. A large number of the active plant-derived compounds were found to be sesquiterpenes from the Asteraceae. A majority of the hundreds of compounds in this class which have been evaluated are cytotoxic and exhibit no *in vivo* activity. This group includes compounds such as centaurepensin, which is the cytotoxic constituent of *Centaurea solstitialis.* On the other hand a small group of these compounds exhibit significant *in vivo* activity. These are a series of polyfunctional germacranolides including elephantopin isolated from *Elephantopus elatus* (Cassady, Chang & Mclaughlin 1981).



Elephantopin (Cassady, Chang & Mclaughlin 1981)

In a study of the structure-activity relationship, it was found that all the known cytotoxic sesquiterpenes contained a lactone function; all but one of these were α,β-unsaturated and the α-ethylenic link was exocyclic in every case. The presence of a C_{11}-C_{13} exocyclic double bond conjugated to the γ-lactone was essential for cytotoxicity. Compounds having endocyclic double bonds gave unstable cysteine adducts and were inactive. However, sesquiterpene lactones which incorporated a cyclopentenone, or α-methylene lactone (in addition to the α,β-methylene-γ-lactone) appeared to produce enhanced cytotoxicity. Non of the monofunctional sesquiterpenes containing only an α,β-unsaturated ester or cyclopentenone displayed significant activity.



α-Methylene-γ-lactone, a major functional group for biological activity in diverse compounds.

However, it was found that bakkenolide A, a β-methylene-α-lactone (which does not have an O=CH-CH=CH_2 - system) gave results against cells derived from human carcinoma. Other structural parameters must therefore be taken into consideration when evaluating the cytotoxic potential (Rodriguez *et al.* 1976).

Microbial growth-inhibitors (antibiotics). Some sesquiterpene lactones have been shown to possess antibacterial, antifungal, antihelminthic properties. Some examples are the germacranolides, mikanolide and dihydromikanolide which inhibit the growth in culture of a bacterium *Staphylococcus aureus* and also of the yeast *Candida albicans* and parthenin which inhibit sporangial germination and zoospore mobility in *Sclerospora graminicola*, but not of *Aspergilus flavus* (Rodriguez *et al.* 1976).

The biological activity of parthenin and other sesquiterpene lactones containing an exocyclic methylene γ-lactone moiety is ascribed to their high reactivity forming Michael addition adducts with nucleophiles such as thiol groups which are present in a number of enzymes and proteins. Surprisingly, parthenin acetate which contains both the exocyclic methylene, γ-lactone and the cyclopentenone A ring were less active. Antiplasmodial activity is therefore thought to be due to nucleophilic attack at C-2 and/or C-13 (Phillipson *et al.* 1995).

Giesbrecht *et al.* (1985) tested 12 sesquiterpene lactones from the Asteraceae for their antimicrobial action. Nine of the twelve lactones tested, inhibited the growth of one or more of the microorganisms tested. The effectiveness of the lactones did however, not correlate with the presence or absence of either α-methylene-γ-lactone residue or a cyclopentone ring, which have been implicated by other investigators as essential for inhibitory activity.

Towers *et al.* (1977) tested 65 sesquiterpene lactones for phototoxicity against *Candida albicans.* Only glaucolide G was phototoxic, and mikanolide, glaucolide B and ψ-ivalin were antibiotic.

Chemoprophylaxis by lactones in schistosomes. The wood oils of two Brazilian trees (Asteraceae) contain lactones (eremanthine, colstunolide) that inhibit skin penetration by cercariae of the trematode *Schistosoma mansoni.* It was suggested that the activity of schistomicidal lactones may be related to inhibition of sulphydryl groups in cercarial enzymes (Rodriguez *et al.* 1976).

Allergic contact dermatitis. Over 80 sesquiterpene lactones were used in patch tests to determine their allergic potential, and the presence of an α-methylene group, exocyclic to the γ-lactone, was shown to be the principle immunochemical requisite for the production of dermatitis. Allergic and contact dermatitis from *Parthenia hysterophorus*, an introduced weed in India, has become an important dermatological and public health problem. Parthenin, a pseudoguaianolide, was found to be the major allergen in *P. hysterophorus*. All known allergenic sesquiterpene lactones contain an exocyclic α-methylene function which may conjugate with sulphydryl groups of proteins in cells by a Micheal-type addition to form complete antigens capable of producing cell-mediated contact allergic reactions (Rodriguez *et al.* 1976).

Insect feeding deterrents. Experimental evidence that sesquiterpene lactones provide resistance to insect feeding has been demonstrated by a study of *Vernonia* (Rodriguez *et al.* 1976). Feeding experiments were conducted on *Spodoptera eridania*, *S. frigiperda*, *Diacrisia virginia*, *Trichoplusia ni* and *S. ornithogalli.* Supplementing the agar medium with glaucolide A, the major lactone in various species of *Vernonia*, resulted in greatly reduced larval feeding; feeding was inversely proportional to the concentration of glaucolide A.

Vertebrate poisoning. Livestock poisoning from foraging on bitter-tasting plants of the Asteraceae is well known (Watt & Breyer-Brandwijk 1962). Vomiting disease in sheep has been noted on sheep grazing on *Geigeria* which contain vermeerin. It was suggested that the lactone toxicant may alter the microbial composition of the rumen and thus affect vital metabolic functions. Plants containing lactones, when eaten by dairy cattle, impart a bitter taste to their milk.

Plant growth inhibitors (Phytotoxins). A variety of sesquiterpene lactones of different skeletal types, have been reported to show plant growth regulatory activity (Rodriguez *et al.* 1976). Vernolepin, from *Vernonia hymenolepis*, inhibits growth (20%-80%) of wheat coleoptile sections. Increasing amounts of auxin reduced the inhibitory effect of vernolepin. Alantolactone was shown to be a potent inhibitor of seed germination and seedling growth.

Anti-inflammatory activity. The anti-inflammatory drugs ethacrynic acid and N-ethylmaleimide have been shown to bind to sulfhydryl groups. Cysteine, a sulfhydryl-donating compound, reversed the anti-inflammatory activity of these agents, indicating that sulfhydryl groups participate in the inflammatory process. In addition, the sulfhydryl-binding properties of drugs, e.g., salicylates and indomethacin were related to their anti-inflammatory activity. It was also shown that sulfhydryl and disulfide interactions are altered in rat arthritis, human connective tissue and anti-inflammatory drug therapy (Rodriguez *et al.* 1976).

Mechanisms of action studies with sesquiterpene lactones showed that the α-methylene-γ-lactone and cyclopentenone moieties undergo Micheal-type addition with L-cysteine, glutathione and a number off cell enzymes. Metabolic studies with sesquiterpene lactones in mammalian cancer cells demonstrated that these agents are potent inhibitors of the lysosomal enzymes, oxidative

phosphorylation and protein synthesis and that they significantly elevate cellular cyclic AMP levels. A number of clinically useful anti-inflammatory agents have similar effects on cell metabolism. Moreover, certain sesquiterpene lactone-producing plants, such as *Eupatorium formosanum*, have been used as anti-inflammatory herbal remedies as well as antipyretic drugs (Hall *et al.* 1979).

In this light, 29 sesquiterpene lactones and related compounds were tested for anti-inflammatory activity in rats (Hall *et al.* 1979). In the edema-induced carrageenan inflammation screen, the α-methylene-γ-lactone moiety of the sesquiterpene lactones was required for inhibitory activity. The 6-hydroxy group of helenalin was also required for potency. The same structures were required for the inhibition of the writhing reflex. 2.5mg/kg of helenalin given twice, caused 72% inhibition, but it afforded no activity against induced hyperpyrexia in rats. In the hot plate test, which more closely relates to narcotic analgesic activity, it was inactive at 20mg/kg. The writhing reflex test, which is more closely related to inflammation pain, showed that helenalin caused 93% reflex inhibition. In the chronic adjuvant arthritic screen, compounds containing the α-methylene-γ-lactone moiety, the β-unsubstituted cyclopentenone ring, and the α-epoxycyclopentenone system afforded significant inhibition at 2.5mg/kg/day. Helenalin caused a greater than 60% inhibition of induced adjuvant arthritis in rats. The sesquiterpenes were marginally effective against induced pleurisy. The sesquiterpene lactones caused a slight, but significant, increase in serum immunoglobulin in mice. T-lymphocyte production seemed to be depressed, with helenalin having the best effects. The mitogenic affects of helenalin would explain the immunostimulant effects on B cells. Substances of T-cells, e.g., lymphotoxin, migration inhibition factor (MIF), and blastogenic factor were found in the synovial fluid of patients with rheumatoid arthritis. For these reasons, immunosuppressors e.g. azathioprine, cyclophosphamide, D-penicillamine and gold are used. Whether elevated T-cell responses are due to the primary pathogenisis of chronic arthritis, or to secondary changes in the disease state, e.g. response against phagocytic products or vasoamine release, is not known. Thus the sesquiterpene lactones offer an alternative to the current anti-inflammatory therapy. The dose required for antiarthritic activity is relatively low compared to marketed drugs. No deleterious side effects were observed with these agents from the limited tests performed. The sesquiterpenes had no effects on fertility in mice at 6 mg/kg/day. No teratogenic or congenital abnormalities were noted in the viable fetuses. It had no estrogenic effects on immature female rats. After 3 weeks of drug administration in rats, no gastric or duodenal bleeding or ulcerogenic effects were noted. White and red blood cell counts were within normal control limits, and the heatocrit values were also normal. No abnormal CNS effects were observed in any of the animals being administered drugs. Sesquiterpene lactones at equivalent doses had no effect on liver aerobic respiration (Hall *et al.* 1979).

3.2.3.2 Mechanism of action of sesquiterpene lactones.

The following structural configurations are the principal requirements for biological activity:

1. The presence of an exocyclic methylene conjugated to a γ-lactone.
2. The presence of a functional group, such as an epoxide, hydroxyl, chlorohydrin, unsaturated ketone or O-acyl adjacent to the α-CH_2 of γ-lactone which can enhance the reactivity of the conjugated lactone toward biological nucleophiles.

The inhibitory activity of the sesquiterpene lactones result from the presence of highly electophilic functional groups. These selectively alkylate by Micheal-type addition to sulphydryl proteins, specifically thiol groups in the presence of other nucleophiles (Rodriguez *et al.* 1976).

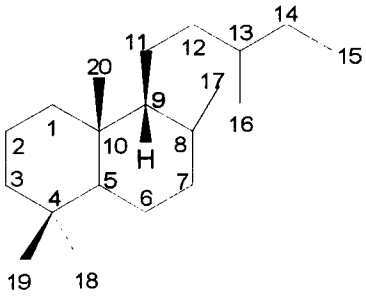
Pharmacological testing of medicinal plants and isolation and identification of the active constituents have been done mainly on plants that have a wide distribution. Very little work has been done on localized southern African species. However, Ferdinand Bohlmann identified many compounds in these plants, of which the activities now need to be determined.

3.2.4 Diterpenoids

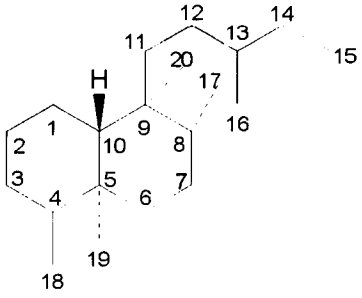
Diterpenoids are 20-carbon compounds considered to be derived from four isoprene residues. They are not volatile and may be either acyclic or ring compounds (Ting 1982). The presently known diterpenoids of the family belong to four main classes:

Bicyclic diterpenoids

- Regular: The labdane-monooloxide type; represented in the family by the "normal" and *ent*(enantio) series.
- Rearranged: Clerodane-type; cis- and trans-clerodane derivatives occur in composites.



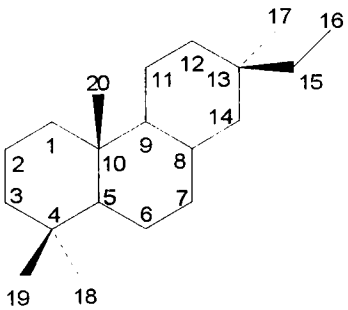
Labdane



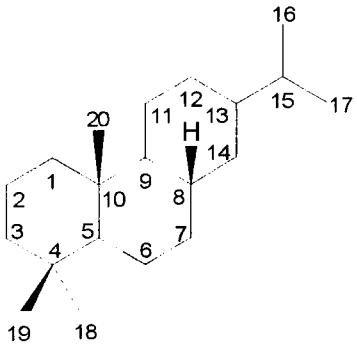
ent-Clerodane

Tricyclic diterpenoids

- Pimarane-type; occurring in composites as derivatives of sandracopimarene ("normal") and of (-)-pimarene (*ent*-series).
- Abietane-type



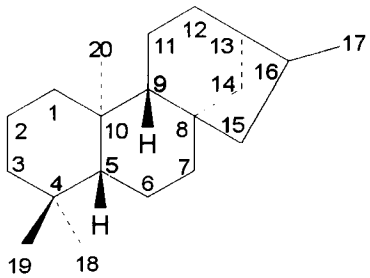
Pimarane



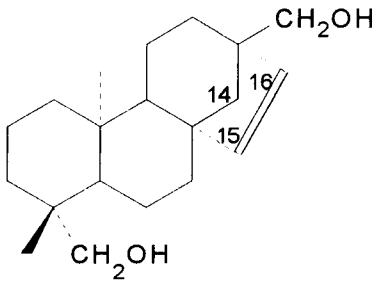
Abietane

Tetracyclic diterpenoids

- Kaurane-type; represented only by (-)-kaurene derivatives (*ent*-series)
- Stachane-type; represented only by (+)-stachene derivatives (*ent*-series).



Kaurane-type



Stachane-type

Pentacyclic diterpenoids

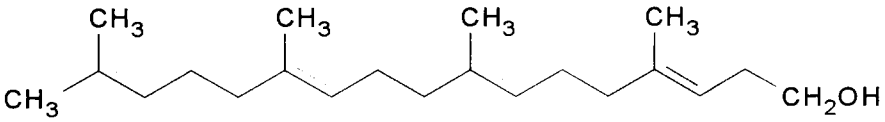
-Trachlobane-type.

A series of bitter furanoid clerodane-type compounds possess strong antifeeding properties against insects. The labdane-type sclareols of *Nicotiana glutinosa* prevents rust diseases (Hegnauer 1977).

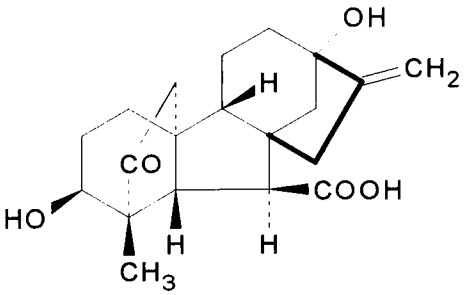
Diterpenoids occur predominantly free, ersterified or glycosylated, depending on the taxa concerned and on the plant parts where accumulation takes place (Hegnauer 1977).

Two groups of diterpenoids can be distinguished which have a carboxylic acid function in addition: the resin acids and gibberellins. A number of diterpenoids are very toxic. Diterpenes are usually isolated from plants as optically active solids which exist in both the normal and antipodal stereochemical configurations. They are separated by thin-layer or column chromatography on silica, using solvents such as petroleum-ether or chloroform (Harborne & Baxter 1993)

Acyclic diterpenoid



Geranylgeraniol - the biogenetic precursor of diterpenes.

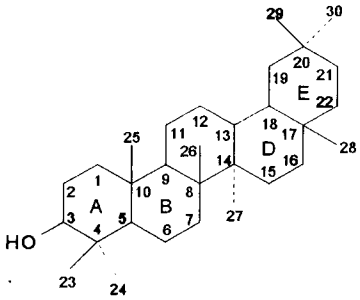


Gibberellin GA_3 (MacMillan 1971)

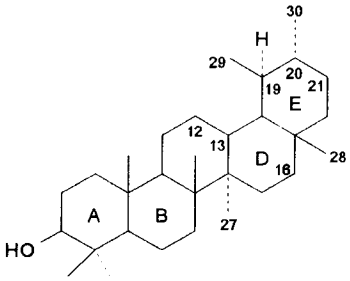
The biological activity of diterpenoids ranges from the bitter principles through antibiotics, insecticidal compounds and tumor inhibitors to the gibberellin plant growth hormones (Sticher 1977).

3.2.5 Triterpenoids

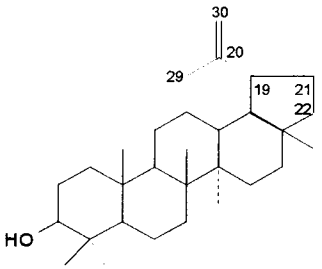
Asteraceae are triterpene accumulators. Monols and diols of the oleanol (1), ursanol (2), and lupeol (3) type are most characteristic of the family. They occur free or, more frequently, esterified with acetic acid or fatty acids in the lipid fractions of the roots, stems, flowers and fruits and, in Cichorieae, in latices (Hegnauer 1977).



1



2



3

Esters of triterpene monols may account for the often large amounts of unsaponifiable matter in "seed" oils of the Asteraceae; they are however, derived from the pericarp part of the fruits (Hegnauer 1977).

Triterpenoids are complex 30-carbon compounds that may be acyclic or tetracyclic. Squalene is a precursor in steroid biosynthesis. Triterpenoid glycosides fall within the group that includes saponins and cardiac glycosides. They are frequently surface-active compounds and many are poisonous to vertebrates. Perhaps those from *Digitalis purpurea* are the best known. (Harborne & Baxter 1993) Plant sterols are triterpenoids with an additional methyl group. They are quite common in the plant kingdom. Virtually all have a hydroxyl group at position C-3. Common sterols found in plants are cholesterol, stigmasterol in the soybean and spinasterol in spinach (Harborne & Baxter 1993).

3.2.5.1 Saponins

Saponins are a group of plant glycosides in which water-soluble sugars are attached to a lipophilic steroid (C27) or triterpenoid (C30) moiety. This hydrophobic/hydrophilic asymmetry means that they have the ability to lower the surface tension, and are soap-like. They form foam in aqueous solution and cause hemolysis of blood erythrocytes. They are toxic to cold-blooded animals but not generally to warm-blooded animals. They have been identified in more than 100 plant families. Saponins are found in all parts of the plant, with some concentration in root, foliage or seed. They are regularly present in many pasture legume species, and are responsible in part for the condition of bloating in ruminant animals (Harborne & Baxter 1993).

Saponins are toxic to insects and molluscs, and some of the most useful natural agents for controlling schistosomiasis snails are saponin in nature. Antifungal activity is present and they may aid plants to resist microbial infection. From the medicinal viewpoint, the most widely used saponins are the ginsenosides of ginseng, which are reputed to prolong human life and aid survival to stress (Harborne

& Baxter 1993). The formation of precipitates with cholesterol in alcohol is also referred to as a characteristic nature of saponins. Crude drugs which contain saponins are generally used for their detergent properties, and some of them which give less irritating effects with oral administration are employed as expectorant and antitussive agents (Shibata 1977).

The saponins are classified chemically in two groups: steroidal saponins and triterpenoid saponins on the basis of chemical structures of their aglycones or sapogenins. In general, steroidal saponins are known to be more important as the starting materials for the synthesis of steroid hormones and related medicines than the direct use as remedies, whereas the triterpenoid saponins have been shown to possess biological and pharmacological activities which would be developed to some medical uses (Shibata 1977).

Triterpenoid saponins generally taste bitter; a few can be very sweet (glycyrrhizin) (Harborne & Baxter 1993). Licorice (liquorice), the root of *Glycyrrhiza glabra* contain glycyrrhin which has anti-inflammatory activities, inhibits ulcers and reduces the blood cholesterol level by promoting the excretion of cholesterol, but it stimulated the biosynthesis of cholesterol in the rat liver (Shibata 1977). Saponins are found in all tribes of the Tubuliflorae. Saponins are known for their hemolytic affects.

Saponins can be quantified after acid hydrolysis by a colour reaction using Liebermann-Burchard (sulfuric acid and acetic anhydride) or Carr-Price (antimony chloride) reagent. They are separated by high performance liquid chromatography, and then characterized by proton and carbon-13 NMR spectral analysis (Harborne & Baxter 1993).

Steroid saponins are related to cardiac glucosides. They are used as detergents, foaming agents in fire extinguishers, and as fish poisons. Fish are dazed or killed by saponin but are not rendered inedible, since saponins are not toxic to humans, presumably because when taken orally, they are not absorbed by the gut. Diosgenin, isolated from *Dioscorea* roots, is well known as a starting material for the partial synthesis of sex hormones used in contraceptive pills, e.g., progesterone (Harborne & Baxter 1993).

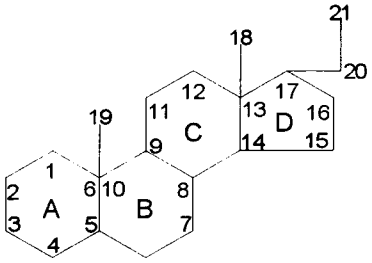
3.2.5.2 Phytosterols

Steroids are chemical substances with 4 interlocking C-rings. Adrenal steroids, corticosteroids, sex hormones, D vitamins and cholesterol are all steroids.

Sterols were mainly considered to be animal products, but increasing number of such compounds have been detected in plant tissues. Three phytosterols, sisterol, stigmasterol and campesterol are ubiquitous in higher plants. Sisterol and several similar derivatives are recognised as essential components of plant cell membranes. They also play an important role in plant cell growth. Phytosterols are structurally distinct from animal sterols in having an extra methyl or ethyl substituent in the side chain. The discovery of certain animal sterols in plant tissues is therefore very intriguing. The human female sex hormone, oestrone, for example has been found in trace amounts in date

palm seed, while the male hormone, testosterone, is present in the pollen of Scots pine. A large number of insect moulting hormones, known as phytoecdysones have been uncovered in plants. They appear to represent a novel defence system of plants for protection against insect predation, since they have damaging effects on insect feeders (Harborne & Baxter 1993).

Phytosterols are formed in plants from squalene and they can be detected in plant extracts using thin layer chromatography followed by spraying with antimony chloride in chloroform. These sterols are further characterized and quantified by gas chromatography of their trimethylsilyl ethers (Harborne & Baxter 1993).



A steroid (Harborne & Baxter 1993)

3.3 ALKALOIDS

Alkaloid bearing plants have long been known in the Asteraceae. The Senecioneae produce pyrrolizidine-type ester alkaloids, Heliantheae (*Eclipta*, *Zinnia*) synthesize nicotine, nornicotine and anabasine and the genus *Echinops* (Cardueae) produce echinopsine. From other taxa, alkaloid-like substances such as the diterpene alkaloids from *Inula royleana* DC. (Inulaeae) and betaines (betaine, chrysanthemine, achillein and moschatine) have been reported (Hegnauer 1977).

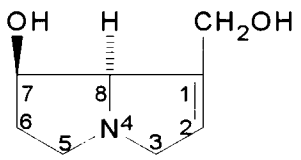
3.3.1 Pyrrolizidine alkaloids

The pyrrolizidine alkaloids are probably the most poisonous single group of alkaloids. They are hepatotoxic and cause death and liver damage to humans and livestock (Harborne & Baxter 1993). Pyrrolizidine alkaloids are found in a number of taxonomically widely separated plant families; the Boraginaceae, Asteraceae and Leguminosae. Within the Asteraceae, pyrrolizidine alkaloids are restricted to two tribes, the Eupatorieae and the Senecioceae. The major occurrence of these alkaloids is in plants of the cosmopolitan genus *Senecio*; probably all 1500 species contain them in varying amounts (Robins 1977).

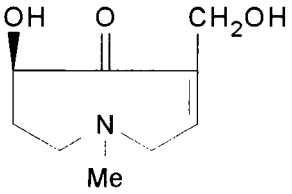
Chemically the pyrrolizidines are readily distinguished by the presence of a fused 5-membered ring system, which has a bridge nitrogen shared between the two rings (Harborne & Baxter 1993). Pyrrolizidine alkaloids are composed of a base portion (necine), esterified either with one or two acids (necic acids), or with a dicarboxylic acid to form a macrocyclic compound with both hydroxyl groups on the necine. The most abundant representatives are retrorsine, senecionine and senciphylline. Alkaloids often occur as N-oxides in the plant especially during the growing and flowering period.

Senecio plants with N-oxides of pyrrolizidine are more palatable and so more readily consumed by livestock, with consequent toxic effects often delayed in onset.

The most common necine in the Senecionae is retronecine, often accompanied by othonecine (Robins 1977).



Retronecine



Othonecine

The necic acids vary more in composition, containing 5 to 10 carbons. The acids are mostly considered to be derived from terpenes. The double bond in the pyrrolizidine moiety and the intact ester structure appear to be essential in causing liver damage. Compounds which have 10 carbon atoms in a cyclic ester, are effective and those having 9 carbon atoms in the cycle, such as monocrotaline, have in addition a pronounced effect on the lungs. Of the alkaloids with the cyclic esters and the open esters, the di-esters are more effective than the mono-esters. The cyclic ester compounds, in the form of N-oxides, are also effective in causing liver lesions while alkaloids, with reduced double bond in the ring, and their hydrolysis products are inactive. For example, platyphylline differs from senecionine only by the absence of the double bond in the pyrrolizidine moiety and consequently produces, even in lethal doses, no effects on the liver as seen with senecionine. It has been shown that regeneration of the liver from the toxic effects may be followed by hyperplasia of the liver cells or the formation of tumour-like masses, showing the character of hepatomas (Watt & Breyer-Brandwijk 1962).

Zhao *et al.* (1989) investigated 20 Chinese medicinal herbs of the Asteraceae for the presence of pyrrolizidine alkaloids. They found that the alkaloid content varied in the different batches of plant material bought from the same store at different times. This was especially marked with *Eupatorium* species; the amount of pyrrolizidine alkaloid varied by a factor of five in four batches of *E. japonicum* (Zhoa *et al.* 1989).

For a pyrrolizidine alkaloid metabolite to have acute pneumotoxicity, the presence of an ester group appears to be essential; but the often complex acid moiety of the natural alkaloid is not necessary (Mattocks 1986).

There is evidence that protein synthesis is inhibited in rat liver by chronic pyrrolizidine alkaloid intoxication. Retrorsine (49mg/kg), given to rats intragastrically, inhibits the incorporation of radioactive leucine into liver and plasma protein within 1 hour (Mattocks 1986).

Pyrrolizidine alkaloids and their derivatives do not generally have exceptional pharmacological effects, although a variety of actions have been recorded. These effects are produced by a wide

variety of structures, and are not directly associated with the cytotoxicity shown by many pyrrolizidine alkaloids, although pharmacological actions of pyrrolizidine alkaloid metabolites might play a part in some aspects of pyrrolizidine alkaloid-induced lung and heart damage (Mattocks 1986). Platyphylline, riddelline, senecionine and seneciophylline were tested with rat ileum; they inhibit smooth muscle and have anticholinergic activity. Platynecine esters have local anesthetic, hypotensive, cardiac depressant and spasmolytic action (Mattocks 1986).

Mutagenicity and cell tests have been done on some pyrrolizidine alkaloids and source plants. The non-hepatotoxic alkaloids were inactive (platyphylline was inactive in a mutagenicity test with *Drosophila*, and rosmarinine was inactive in the cell transformation test) while the hepatotoxic alkaloids were active in most tests done. For example, retrorsine was positive in all three tests done (Salmonella ("Ames") test, mutagenicity in *Drosophila* and cell transformation test) (Mattocks 1986).

The most characteristic chronic effect of hepatotoxic pyrrolizidine alkaloids in the liver of animals is to induce the development of greatly enhanced hepatocytes, often called megalocytes; this is a consequence of a powerful *antimitotic* action exerted by the compounds on the liver (Mattocks 1986).

The powerful toxicity of many pyrrolizidine alkaloids to animals, the striking cytotoxic, mutagenic and antimitotic effects make it desirable that these compounds should be tested for both carcinogenic and anticancer activity (Mattocks 1986).

In spite of early doubts, it is now generally accepted that some pyrrolizidine alkaloids, and plants containing them, are *carcinogenic* to experimental animals (chiefly rats), and they are listed among the few carcinogens known to occur in higher plants. They are not powerful carcinogens. Generally, chronic dosing schedules have been the most successful in producing tumours. Regardless of the route of administration, whether given orally or injected by various routes, tumours have most frequently appeared in the liver and not in the site of injection of topical application of the alkaloid. This sternly suggests that the proximate carcinogens are metabolites formed in the liver. Mattocks (1986) reported that the data available were insufficient to enable relationships to be established between the types of tumours seen in livers of rats given pyrrolizidine alkaloids and the molecular structure of the pyrrolizidine alkaloids. A common factor is that they are all esters of unsaturated necines and capable of being metabolized to pyrrolic esters in mammalian liver (Mattocks 1986).

There has recently been an increase in interest in the potential *antitumour* activity of pyrrolizidine alkaloids and their derivatives because of their cytotoxic and antimitotic properties although their hepatotoxicity would seem to present an obstacle to their therapeutic usefulness. However, the saturated alkaloid retusine is active in the mouse sarcoma 180, Walker carcinoma 156 and Lewis lung carcinoma 615 test systems. These results appear to show that an unsaturated necine ester is not essential for antitumour activity. It now appears likely that this activity may be expressed through at least two unrelated mechanisms involving on the one hand the antimitotic effects of pyrrolic metabolites and on the other an unknown mechanism associated with some alkaloid N-oxides.

Indicine N-oxide, the active principle of extracts of *Heliotropium indicum*, is the only pyrrolizidine alkaloid which has undergone clinical trials as an anticancer drug (Mattocks 1986).

Tumour inhibiting action is shown by three groups of compounds related to pyrrolizidine alkaloids: by some of the alkaloids themselves; by indicine N-oxide (and possibly related compounds); and by pyrrolic alkylating agents. In the last category, those which have lower alkylating reactivity, and are therefore the most stable *in vivo*, are the most effective. This has been exploited in a series of synthetic analogues (Mattocks 1986).

3.4 PHENOLICS

3.4.1 Flavonoids

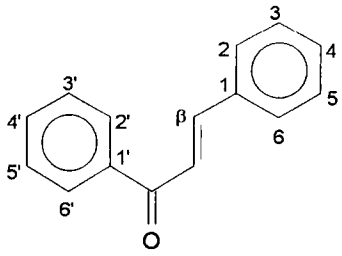
Flavonoids are universal in green land plants (Hegnauer 1977). The Asterales produce a phenomenal array of flavonoids. The flavonols kaempferol and quercetin are common as well as polymethoxylated flavonoids including compounds with 6- or 8-hydroxyl/methoxyl substitutions (Giannasi 1988). The common flavones apigenin and luteolin are widely distributed; they are represented by their glycosides. The frequent occurrence of 6-hydroxylated compounds such as scutellarein (6-hydroxyapigenin), the methylation of flavonoids and the relatively frequent occurrence of chalcone glycosides are somewhat distinctive for the family. Methylated flavonoids occur free or as glycosides. Several of these compounds have cytotoxic properties. The chalcone glycosides are flower pigments in the genera *Bidens*, *Carthamus*, *Coreopsis* and *Helichrysum* where they are often accompanied by the corresponding aurones or flavanones (Hegnauer 1977).

Anthochlor pigments are found mainly in the Coreopsidineae (found in 28 of the 30 genera sampled). The anthochlors produced fall in two groups: (1) A-ring phloroglucinol-based (Cardueae, Eupatorieae, Inuleae) and (2) A-ring resorcinol-based (Heliantheae, Lactuceae) (Giannasi 1988).

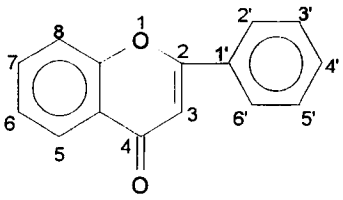
Unusual flavonoids in the family include the *flavonolignans* of *Silybum marianum*, the *Helichrysum* flower pigment and the isoflavonoids wedelolactone (*Eclipta*, *Wedelia*), demethylwedelalactone and its 7-glucoside (*Wedelia*) (Hegnauer 1977).

The production of externally accumulated flavonoid aglycones is known to occur preferentially in taxa that exhibit secretory structures that excrete further lipophilic natural products (notably terpenoids) (Wollenweber & Mann 1989). Significant correlations between flavonoid chemistry and plant geography were found in the *Senecio radicans* complex (Glennie *et al.* 1971).

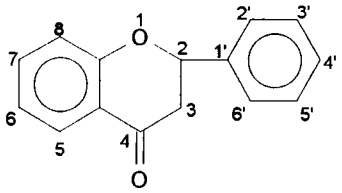
Phytochemicals from almost all classes of chemical compounds have been implicated in plant chemical defence. Flavonoids are found in almost all higher plants and are believed to confer some protection on their parent plants. Some flavonoids are feeding attractants, while others act as feeding deterrents for insects. Other flavonoids are insect growth inhibitory or even toxic (Kubo & Hanke 1986).



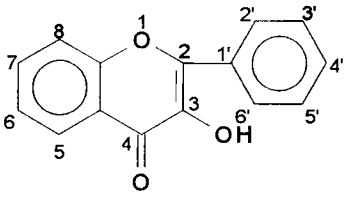
Chalcone



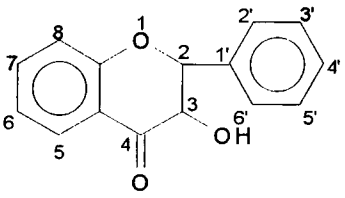
Flavone



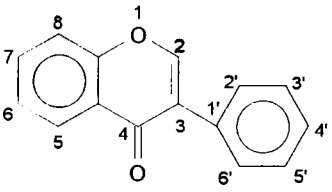
Flavanone



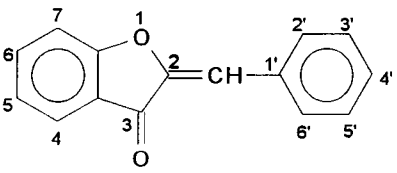
Flavonol



Dihydroflavonol



Isoflavone



Aurone

Some members of the flavonoid group of compounds have been known to possess anti-allergic, anti-inflammatory, antitumor, spasmolytic, antianginal, anti-ulcer, anti-hepatotoxic and antimicrobial effects (Gábor 1986).

The actions of the flavonoids on cells are as varied as the flavonoid compounds themselves and the cell types which are affected by them. The cell membrane is often the first organelle to respond to a stimulus or drug action, and the plasma membrane associated enzymes such as phospholipases. ATPases and methyltransferase are affected by certain flavonoids. Flavonoid-induced changes in cell free fatty acid levels, Ca^{2+}, Na^{+} and K^{+} transport, and cAMP levels may be expected to affect biochemical sequelae and cell activation. Within the cell, cyclooxygenase (CO), lipoxygenase (LO), protein kinase, and cyclic nucleotide phosphodiesterases (PDE) are affected by flavonoids, with resultant effects on prostoglandin (PG), leukotriene, cAMP and cGMP levels and protein phosphorylation. Flavonoid effects on RNA polymerase, and the estrogenic activity of some flavonoids suggest a far reaching influence of flavonoids on cell biochemistry (Laychock 1986).

A major action of flavonoids on cells concerns fatty acid mobilization and metabolism. Phospholipase A2 (PLA2) is primarily responsible for the hydrolysis and release of arachidonic acid (AA) from membrane phospholipids, and quercetin has been reported to inhibit this enzyme. Flavonoids such as cirsiliol, silybin, quercetin and (+)-catechin, possessing anti-oxidant activity have been reported to

inhibit LO and/or CO activity with varying degrees of effectiveness. Flavonoids can also inhibit 12-HETE and 5-HETE biosynthesis. (Appendix 1)

3.4.1.1 Flavonols & flavones:

The position of O-methylation may be crucial for the biological activity of flavonols and flavones e.g. 3-methylation of flavonols enhances antiviral properties. Flavones and flavonols of leaf waxes and plant exudates nearly always occur in the free state, without glycosylation, and often in methylated form. The flavonoid glycosides are usually located in the leaf or flower in the cell vacuole. (Harborne 1986) For activity against insects, flavone and flavonol aglycones require at least two hydroxyl substituents. Growth inhibition of *Pseudomonas maltophilla* and *Enterobacter cloacae* was observed in all flavone and flavonol aglycones with 3'-,4'-dihydroxyl groups and in all aglycones that had orthodihydroxyl groups at other positions (Hedin & Waage 1986).

Antiviral activity: It was already reported as early as 1947 that several plant flavonoids have antiviral properties. Most of the investigations were carried out with the flavonoles quercetin and morin, which have been shown to inhibit virucidal activity against enveloped viruses including herpes simplex type 1 (HSV), respiratory syncytial virus, pseudorabies, parainfluenza type 3 and Sindbis viruses, but not against non-enveloped viruses as poliomyelitis, Mengo and adenoviruses (Vlietinck *et al.* 1988).

From an antiviral evaluation, only 3-methoxyflavones exhibit pronounced antiviral activities at non-cytotoxic concentrations against picornaviruses, except for Mengovirus. Picornaviruses represent a large family of single-stranded RNA viruses. They consist of the rhinoviruses (of which there are over 120 serotypes), the enteroviruses comprising polio, coxsackie A and B, ECHO, and five unclassified enteroviruses, including hepatitis A. Rhinoviruses are responsible for approximately 50% of the common cold infections and cause mild localized infections of the upper respiratory tract. The enteroviruses cause a broad spectrum of clinical illnesses ranging from mild upper respiratory ailments to more sever diseases such as aseptic meningitis, muocarditis and poliomyelitis, resulting in greater morbidity and mortality for the pediatric population (Vlietinck *et al.* 1988).

It has been shown that the antiviral flavonoids, which are active exclusively against human rhinoviruses such as 2'-hydroxy-4'-ethoxy-4,6'-dimethoxychalcone and 4',6-dichloroflavan act through a different mode of action as the 3-methoxyflavones (Vlietinck *et al.* 1988).

With so many immunodistinct serotypes the chances of developing a multivalent vaccine for rhinovirus, the major agent for the common cold, are remote. The herpes virus is reactivated in spite of an immune response. Natural flavonoids with antiviral activity have been known for nearly 40 years. They include derivatives of chalcones, flavones and flavans. The aglycone seems to be required, for example rutin, a glycoside of quercetin is inactive. Hydroxylation at the 3-position appears to be a prerequisite for activity also. The antiviral activity of quercetin has been frequently demonstrated against several viruses and compared with other flavones. Compared with acyclovir (IC_{50} 0.1-1.0μM) quercetin is about 100-fold less active. The mechanism studies have revealed

compounds which may bind to viral nucleic acid, interact to the polymerase region and bind to the virus capsid proteins (Selway 1986). Flavonoids, depending on specific structural features possess both anti-infective and anti-replicative activity against some DNA (herpes simplex type 1 (HSV-1)) and DNA (respiratory syncytial virus (RSV), parainfluenza virus type 3 (Pf-3), polio) viruses.

It is also well recognized that naturally occurring flavonoids affect the response of many different cell types to a variety of stimuli including antigen (and other secretogogue)-induced release of histamine from basophils and mast cells, the generation and effector function of lysosomal enzymes from polymorphonuclear leukocytes together with inhibition of superoxide anion generation, amongst other effects. There is a corresponding relationship between basophil activation/secretion and virus infection of tissue culture monolayers (Middleton, Faden *et al.* 1986).

Anti-inflammatory and anti-allergic properties: A number of flavonoids with anti-inflammatory effects have been discovered recently. Hypolaetin-8-glycoside also displays anti-ulcer activity. A chromone derivative with anti-allergic activity of significant importance is the therapeutically valuable sodium chromoglycate (chromolyn sodium). Orally effective chromone derivatives have also been produced recently. Baicalein, a plant flavonoid that inhibits lipoxygenase, deserves mention. Flavonoids which inhibit lipoxygenation will at least reduce the cellular component of inflammation. Quercetin has been shown to inhibit the 5-lipoxygenase pathway of the arachidonic acid metabolism. At a concentration of 50μM, most flavonoids, including flavone, chrysin, phloretin, flavanone, apigenin and kaempferol inhibit cyclooxygenase activity (Gábor 1986).

Flavonoids, particularly quercetin, are inhibitors of allergic (IgE-mediated) mediator release from mast cells and basophils. Flavonoids exhibit a wide range of effects on the arachidonic acid metabolism *in vitro* depending on the particular compound under study. A number of flavones and flavanones with hydroxyl groups at the 4', 3, and 7 positions were potent inhibitors of 5-LO (Welton *et al.* 1986).

Effects on basophil histamine release and other secretory systems: Various flavonoids have been shown in a number of systems to influence the secretory process, most frequently as inhibitors. Quercetin, kaempferol and myrecetin were all found to inhibit the stimulated release of mast cell histamine and a variety of flavonoids inhibited neutrophil lysosomal enzyme release. In an *in vitro* model of human immediate-type, Ig-E dependent hypersensitivity disorders, e.g. hay fever and asthma, quercetin inhibited antigen-stimulated human basophil histamine release. The inhibitory effect of flavonoids on secretory processes is not limited to basophils and mast cells. A number of flavonoids are capable of inhibiting stimulated rabbit lysosomal enzyme release. Superoxide anion production was also reduced by quercetin. Inhibition of platelet aggregation and secretion by certain flavonoids has also been observed. Immunoglobulin secretion from mitogen-stimulated human breast milk B lymphocytes is also affected by several flavonoids (Middleton 1986).

Extracts from medicinal plants used in folk medicine for the treatment of thyroid hormone related diseases were found to act as potent inhibitors of iodothyronine deiodinase (ITH-D) both *in vitro* and

in vivo. On a broad survey on the active principle(s) of the constituents of these plants various phenolic secondary metabolites, especially flavonoids were found to act as potent inhibitors of rat liver microsomal ITH-D with efficiencies equal to or higher than that of synthetic ITH-D inhibitors. The most potent inhibitors among naturally occurring flavonoids are the aurones (Koehrle *et al.* 1986).

Inhibition of lens aldose reductase: possible attenuation of diabetic complications: Aldose reductase, as the name implies, catalyzes the reduction of various aldoses to the corresponding sugar alcohols, utilizing NADPH as the co-substrate. In a subsequent reaction, the sugar alcohol may be oxidized to a keto sugar, the reaction being catalysed by a polyol dehydrogenase, requiring NAD as the co-substrate. The two reactions constitute the familiar polyol pathway.

Glucose + NADPH $\xrightarrow{\text{Aldose reductase}}$ Sorbitol + NADP

Sorbitol + NAD $\xrightarrow{\text{Polyol Dehydrogenase}}$ Fructose + NADH

Aldose reductase was first discovered in seminal vesicles, but has since then been found to be present in many other tissues such as the retina, blood vessels, cornea, lens, brain, liver, red blood cells, kidney, sperm, etc. However, it has been most extensively studied in the lens. Excessive amounts of sorbitol was found in the lenses of rats rendered diabetic by alloxan. The accumulation of these high levels of sugar alcohols precedes the formation of cataracts. This led to the concept that aldose reductase plays a central role in the pathogenisis of sugar cataracts in experimental animals. The systemic administration of aldose reductase inhibitors results in a delay or even a cessation of the cataractous process. Flavonoids are the most potent inhibitors of aldose reductase. To date, all flavonoids tested inhibit aldose reductase. Varma (1986) listed structure activity relationships. The effect of flavonoids against polyol synthesis in biological situations is lower than that *in vitro*. The bio-effectiveness, however, is yet significant and was apparent in many subsequent studies. The structure of sorbinil, an aldose reductase inhibitor presently under clinical trial, is similar to that of coumarins (Varma 1986).

Anticonvulsants and anti-epileptics: Carbamazepine and phenacemide, in common with all other established anti-convulsant drugs tested, have been shown to inhibit the activity of the enzyme, aldose reductase, purified from ox brain. This has led to the suggestion that modifications in brain aldehyde metabolism may be relevant to the physiological action of anti-convulsants and that inhibition of aldose reductase *in vitro* may provide a simple screening test for potential anti-epileptic drugs. (Whittle & Turner 1981)

Flavonoids have been shown to inhibit a variety of adenine nucleotide requiring enzymes, for example ATPases, cyclic nucleotide phosphodiesterases, malate dehydrogenase and hexokinase as well as aldose reductase. A number of flavonoids have been shown to have anti-asthmatic activity and to produce coronary vasodilation. They have been used clinically in the treatment of venous insufficiency (Whittle & Turner 1981).

In addition to flavonoids previously shown to be aldose reductase inhibitors, four water-soluble flavonoids were also tested. These are hydroxyethyl-substituted analogues of quercetin and rutin. All the flavonoid compounds tested were shown to be effective inhibitors of ox brain aldehyde reductase. Quercetin and morin are the most potent inhibitors yet reported with K_i values below 1μM. It is interesting to note that the potency of inhibition is opposite to that reported for lens aldose reductase, for which quercitrin is the most potent inhibitor. There appears to be no simple correlation between flavonoid structure and potency of inhibition, although some generalisations can be made. The addition of a 7-hydroxyethyl residue also considerably decreases the inhibitory effects of quercetin, but a similar substitution on the rutin molecule has little or no effect. Further substitutions on other hydroxyl groups also have relatively little effect. (Whittle & Turner 1981)

The flavonoids exhibited no anti-convulsant effects in the mouse maximal electro-shock test, which may partly be due to problems of absorption with these compounds. Water-insoluble flavonoids (e.g. quercetin, morin) are known to be poorly absorbed from the alimentary tract. In the case of the water-soluble flavonoids, which are known to be absorbed from the gut (e.g. 7-hydroxyethylquercetin) it is probable that they are unable to cross the blood-brain barrier. (Whittle & Turner 1981)

Anti-cancer: Flavonoids possess cytotoxic and antineoplastic properties. Flavonoids have been shown to inhibit a wide range of enzymes, including mitochondrial electron transport. Inhibition of mitochondrial enzymes by flavonoid constituents may contribute to their cytotoxic and antineoplastic activities (Hodnick *et al.* 1986).

Quercetin has been shown to inhibit the growth and proliferation of malignant cells and tumor promotion. Quercetin also inhibits the activities of several enzymes including cAMP-independant protein kinases, Ca2+ -phospholipid-dependent protein kinase, and tyrosine protein kinases associated with mammary tumors (Srivastava & Chiasson 1986).

The cytochrome P450-dependent monooxygenase enzyme system is widely recognized for its role in the metabolism of drugs and other foreign compounds (xenobiotics). A number of flavonoids have marked effects on the cytochrome P450-dependent monooxygenase system, including the induced synthesis of specific cytochrome P450 isozymes and the activation or inhibition of these enzymes depending on the relative amounts of the various cytochromes P450 that are present in the microsomes used (Wood *et al.* 1986). Bromination of the 4'-position of the flavone markedly enhanced the inducing properties while the methoxy groups had little or no effect on the inducing activity whereas the addition of hydroxyl groups or saturation of the 2-3 double bond abolished activity. The pretreatment of mice with 7,8-benzo-flavone can markedly inhibit the carcinogenic activity of certain hydrocarbons applied 24h later. The observed antitumorigenic activity could be due to the increased rate of hydrocarbon detoxification (Wood *et al.* 1986).

Hydroxylation of benzo[a]pyrene catalysed by human liver microsomes is inhibited by polyhydroxylated flavonoids. The order of inhibition, from the strongest to the weakest, was

quercetin, kaempferol, morin and chrysin. The hexahydroxylated flavonoid, myricetin was the most active inhibitor (Wood *et al.* 1986).

Flavonoids have been shown to increase skin capillary resistance, i.e. they prevent the rise in capillary permeability. Flavonoids inhibit platelet adhesion, aggregation and secretion. Flavonoids seem to influence various steps both in coagulation and fibrinolysis. Some of these effects could be beneficial while others could play a part in toxic effects involving trombosis, vessel damage and inflammation. Flavonoids modify some parameters affecting blood rheology: they lower erythrocyte adhesion and aggregation and accelerate sedimentation rate, lower blood viscosity , and increase blood filterability.

Flavonoids can inhibit various stages thought to be involved in the initiation of atherosclerosis: endothelial damage, leukocyte activation, platelet adhesion, aggregation and secretion. Flavonoids also can lower serum lipids and cholesterol. Similarly, flavonoids have been shown to inhibit several individual aspects of blood vessel wall interactions involved in the initiation of thrombosis, such as endothelial cell damage, and activation of leukocytes and platelets (Beretz & Cazenave 1988).

3.4.1.2 Coumarins

Coumarins are derivatives of benzopyran and are widely distributed in plants and essential oils. They are used as fragrance components in perfumes, toothpastes and tobacco products. Coumarins are pharmacologically active and have been used in the treatment of a diverse range of diseases, such as brucellosis, burns, rheumatic disease and even cancer (Ochocka *et al.* 1995).

The 700 or more plant coumarins can all be derived from the parent compound coumarin itself, which has a characteristic odour of newmown hay and which occurs widely, usually in bound form. There are three major classes; the simple hydroxycoumarins such as esculetin, the furanocoumarins and the pyranocoumarins. Furanocoumarins have been reported as phytoalexins (antifungal agents) in the Umbelliferae and the Asteraceae. Furanocoumarins are more biologically active than simple coumarins. They exhibit phototoxicity (porphyrins and the psoralens), many are allergenic, they exhibit a range of toxic effects on insects, though some are able to detoxify them. To mammals and humans, the most dangerous coumarins are the aflatoxins, which are hepatotoxic (Harborne & Baxter 1993). Other effects include; growth effects on plants, antibiotic activity (particularly associated with novobiocin) and anticoagulant activity. They are also diuretic, molluscocidal, have and anticholerostatic activity, are estrogenic, hypnotic, antispasmodic, rodenticidal, anti-atherosclerotic and are vasodilators. The cis-arrangement of the molecule is a structural requirement for effective prolongation of the anticoagulent effect (Schwarting 1977).

Coumarins are aromatic lactones, have characteristic ultraviolet spectra, and can be identified on the basis of spectral and chromatographic measurements (Harborne & Baxter 1977).

3.4.2 Tannins

Tannins are polymeration products of phenolic compounds. They account for the discoloration of injured plant tissues. An excellent example is the browning of potato tubers when they are cut and exposed to air. They will link to animal-skin proteins and render them resistant to decay, a process called tanning. Many healthy tissues have tannins present, but more frequently they are synthesized when injury causes cellular disruption, which brings into contact polyphenol oxydases and phenolic substances such as gallic acid, chlorogenic acid, caffeic acid and the flavonoids. Oxidation of the latter phenolic compounds by polyphenol oxidases produces quinone products, which polymerize and form tannins. The tannins will bind to proteins, and if the proteins are enzymatic, activity is reduced or completely inhibited (Ting 1982).

There are two main groups of tannins, hydrolyzable tannins and condensed tannins (proanthocyanidins). The hydrolyzable tannins can be hydrolyzed with hot hydrochloric acid into component phenolics and sugars, of which they are polymeric esters. Commercial tannin (tannic acid) is a mixture of gallic acid and gallic acid esters of glucose. Condensed tannins are largely polymeric condensation products of catechin (flanan-3-ol) and flavan-3,4-diols (Ting 1982).

Tannins may deter herbivores from predation. They may also deter micro-organisms, either by increasing resistance against pathogens, or by protecting essential tissues such as wood against decay (Scalbert 1991).

Tannins were shown to inhibit the growth of many filamentous fungi. The minimum inhibitory concentration (MIC) is usually higher than 0.5g/l and often reaches 10-20g/l. Germination of *Crinipellis perniciosa* spores is inhibited at a tannin level of 0.15g/l. Yeasts seem to be more resistant. Some species are inhibited at a tannin concentration of 25g/l, whereas others require levels as high as 125g/l. The MIC for bacteria is usually lower and can vary between 0.012 and 1g/l (Scalbert 1991).

Tannins are ligands which may form soluble or insoluble complexes with many polymers such as proteins and polysaccharides. To ascertain if tannin toxicity is due to these characteristic properties, their toxicity is often compared to that of simpler phenols such as catechol, pyrogallol, gallic acid, catechin and other flavanols. An increase in protein binding efficiency with M_r, of protoanthocyanidins has commonly been observed. However, in some instances the toxicity of tannins is no higher than that of catechin, although catechins have a very poor affinity for proteins. It appears that if tannins are more toxic than related phenols to some species, this difference cannot be generalized to all microorganisms (Scalbert 1991).

The bactericidal activity against *Xanthomonas phaseoli* of phenols such as catechol and caffeic acid is greatly enhanced upon oxidation by peroxidase. Oxidized phenols may react with sulphydryl groups of enzymes and form covalent linkages with them. An increase of M_r through oxidative

polymeration could also contribute to increase the efficiency of binding proteins through non-covalent linkages (Scalbert 1991).

Mechanisms of tannin toxicity.

- *Astringency: enzyme inhibition and substrate deprivation.* The astringent character of tannins may induce complexation with enzymes and substrates. Many microbial enzymes were found to be inhibited when raw culture filtrates or purified enzymes were mixed with tannins: cellulases, pectinases, xylanases, peroxidases, laccases or glycosyltransferases. This may explain the reduction of virulence of viruses such as *Herpes simplex* virus by tannins. The astringency of tannins may also explain the reduction of larvicidal activity of bacteria such as *Bacillus thuringiensis*, through interaction with their endotoxins. It has not been established which of the two mechanisms, inhibition of extracellular enzymes or depravation of substrates is effectively involved in tannin toxicity (Scalbert 1991).

- *Action on membranes.* Tannic acid at low concentration (less than 1 mg/l) inhibits oxidative phosphorylation by mitochondria of blowfly flight muscle. Inhibition of the electron transport system was also observed on rat liver mitochondria with a tannic acid concentration of 50mg/l; integrity of the membranes was affected at twice this concentration. The action on bacteria could be similar to that of related synthetic phenols such as diphenyl (e.g. *o*-phenyl-phenyl) and diphenylalkane (e.g. hexachlorophene) compounds which have found wide application as disinfectants (Scalbert 1991).

- *Metal ions deprivation.* Another mechanism might involve complexation with metal ions by tannins. Biological systems, including microorganisms, are highly dependent on the metal ion status of the environment. Depletion of metal ions through precipitation was postulated as mode of fungicidal action of hydrogen sulphide which would form insoluble metal sulphides. Tannins might exert their antimicrobial action through a similar mechanism. Indeed, most tannins have more than two *o*-diphenol groups in their molecule, which can form chelates with many metal ions such as ferric or cupric ions (Scalbert 1991).

Several microorganisms have however evolved to withstand high concentrations of tannins. Despite the antimicrobial properties of tannins, many microorganisms can grow and develop on tannin rich materials for example some moulds develop easily on the surface of tannin rich woods such as European oak. Several detoxification mechanisms may contribute to the explanation: Microorganisms may secrete outside the cell, polymers with a high affinity for tannin with which they will combine. Tannins will thus become unavailable for combination with other molecules such as microbial enzymes, which are essential for the growth of the microorganism. However, few enzymes such as tannases or invertase and α-amylase are known to maintain full activity in the presence of high concentration of tannins. Oxidation of tannins by polyphenoloxidases has also been inferred in studies of their detoxification. Another possible way for microorganisms to deter tannin defences of plants may be related to their ability to sequester metal ions. Some fungi have been known for a long

time to produce an enzyme, tannase, which allows them to grow on hydrolizable tannins. Tannase catalyzes the hydrolysis of ester bonds between a phenolic acid and alcohol (Scalbert 1991).

3.4.3 CARBOHYDRATES

3.4.3.1 Inulin-type fructans

One of the most distinctive features in the biochemistry of the Asteraceae is the production of storage polysaccharides based on fructose instead of glucose. These unusual polysaccharides are known as fructans or inulins, the latter name being derived form *Inula helenium*, the roots of which are a particularly rich source. Fructans also occur in the Campanulaceae, but are otherwise rare in the angiosperms. Structurally different branched-chain fructans, called levans, do, however, occur in certain grasses. Inulins differ from starches in that they appear to be simple straight chain polymers with relatively low molecular weight (<10 000), are water soluble and are unable to stain with iodine (Heywood, Harborne & Turner 1977).

Inulins are principally root constituents, and are found in quantity in biannual or perennial species. The nutritive value of composite vegetables is based on the presence of large amounts of inulin. As a carbohydrate source for humans, fructans are just as useful as glucans. The best known inulin-containing vegetable is the Jerusalem artichoke. Inulins have a special medicinal value in diabetic diets, since diabetic sufferers can tolerate fructose much better than glucose (Heywood, Harborne & Turner 1977).

3.4.4 Chromenes and benzofurans

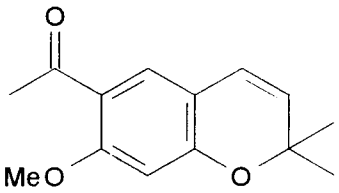
Chromenes (benzopyrans) and benzofurans are characteristic natural products of certain tribes of the Asteraceae. 167 chromenes and benzofurans have been isolated from 170 taxa of the Asteraceae up to 1983. They are biogenetically formed by combining one isoprene unit with a phenolic system. They are found in all the plant organs with the highest quantity in leaves, stem and capitula, comprising *ca* 5% of the dry weight. (Proksch & Rodriguez 1983)

The benzofuran nucleus, in which a benzene ring and a furan ring are fused together, is present in many plant products. The best known source of benzofurans is the family Asteraceae. A biological property many benzofurans share is antifungal activity. This includes both constitutive natural products and phytoalexins. Others are toxic to insects, fish, cattle and humans. For example, trematone, ingested by cattle from plants such as *Eupatorium rugosum* causes "trembling" symptoms which may lead to death. Furthermore it passes to cows milk, which, when consumed by humans, results in milk sickness (Harborne & Baxter 1993).

Several chromenes and benzofurans, such as ageratochromene (= precocene II) are volatile and can be extracted from plant material by steam distillation. However, a more effective and milder procedure is the solvent extraction of fresh or dried plants with organic solvents such as methylene chloride or methanol. Some of the compounds are bacteriostatic, for example, toxol inhibits the growth of *Bacillus cereus*. Toxol was reported to exhibit weak antitumor activity against P-388

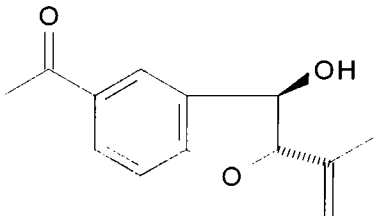
lymphocytic leukemia tumors. Trematone proved toxic to goldfish. Two chromenes, encecalin and 7-hydroxyencecalin and a benzofuran, 6-methoxyeuparin were phototoxic against several fungi and bacteria. They were active at a concentration of 100µg of each compound per assay after irradiation in long-wave UV light. They did not exhibit any antibiotic properties with dark controls, suggesting that the compounds are a new class of naturally occurring photosensitizers. Experiments on the mode of action of these bioactive chemicals suggest that an interaction with nucleic acids or intracellular molecules in light. Prococenes I and II, chromenes of a rarer structural type, lacking the methyl ketone group have been shown to act as anti-juvenile hormone in insects. Encecalin proved to be lethal, when applied to first instar nymphs of *Oncopeltus fasciatus* at a concentration of 1mg per 25-30 nymphs treated in one assay. When applied to artificial diets at concentrations present in natural populations of *Encelia farinosa*, it acts as a strong feeding deterrent to the insect *Heliothis zea*.

Chromene



Encecalin

Benzofuran



Toxol

(Proksch & Rodriguez 1983)

3.4.5 Phloroglucinol derivatives

Several phloroglucinol derivatives have been isolated from the genus *Helichrysum*, however, very few have been tested for biological activity. Several phloroglucinol derivatives from other genera display significant activity.

Phloroglucinol derivatives isolated from the pericarps of *Mallotus japonicus* (Euphorbiaceae) displayed anti-tumor-promoter-activity against several tumor cell lines (Arisawa *et al.* 1991). They were also tested for their ability to inhibit the activity of human immunodeficiency virus (HIV)-reverse transcriptase. Two had strong anti-reverse transcriptase activity (Nakane *et al.* 1991).

Phloroglucinol derivatives isolated from *Hypericum* (Guttiferae) have antibacterial, antiviral activity and showed marked antagonistic activity against thromboxane A_2 and leukotriene D_4. Antagonists of these chemical mediators are expected to be possible anti-allergic compounds (Tada *et al.* 1991).

3.4.6 Polymers

With the exception of enzymes and starches, polymers from higher plants have received little attention by chemists, biochemists or pharmacists. This is astonishing in the view of the wide use of water extracts of drug plants in ancient times. Proteins, lectins and polysaccharides are all classified under this heading. Bioactive polysaccharides display a general immuno-induced, anti-infectious, anti-tumoural and antiphlogistic activity. They can be classified into three groups: activators of the

reticulo-endothelial system (RES) in general, antitumour polysaccharides and those that have a pronounced influence on the complement system. The latter might be partially or totally responsible for the antiphlogistic activity of some polysaccharides.

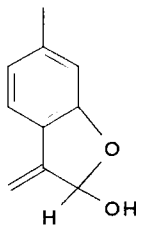
The arabinogalactans of *Echinacea purpurea* stimulate phagocytosis by the monocytes and at the same time induce them to produce various monokines, e.g. tumour necrosis factor (TNF-α), interleukin-1, or interferon-β_2, without activating B-lymphocytes. These mechanisms might be responsible for the excellent protection of mice against the consequences of otherwise lethal infections with *Listeria monocytogenes*, *Candida albicans*, and *Leishmania enviothi*.

Although many of these polysaccharides have not been carefully investigated in all immunologically available test models, it is likely that all polysaccharides with a high amount of glucuronic acid in their backbones have an influence on the complement pathway. From *in vitro* and *in vivo* experiments, performed so far, it can be concluded that these glucans exert their immuno-induced anti-tumour activities primarily by stimulating lymphocytes to liberate lymphokines (IL-2, MAF), thus activating NK cells and macrophages. Since many aqueous extracts of plants often contain mixtures of glycoproteins and polysaccharides, it cannot be excluded that the activity of these extracts is due to a synergism between the two classes of compound. (Wagner *et al.* 1995)

3.4.7 Essential oils

Volatile or essential oils are complex mixtures of steam-volatile plant constituents. Botanists connect the term essential oils with excretion. Essential oils are the volatile products deposited in dead cells (oil idioblasts), in oil cavities and ducts or in subcuticular spaces of glandular hairs. Members of the Asteraceae, with the exception of the Cichorieae, have secreting glandular hairs and schizogenous ducts. Many of them are aromatic plants and yield appreciable amounts of essential oil. Volatile constituents include monoterpenoids and sesquiterpenoids, acetylenes, phenylpropanoids and chromenes (Hegnauer 1977).

The phenolic monoterpenoid thymol and a large number of thymol derivatives, both free and esterified, are common constituents of certain taxa. Compound A, a thymol derived dihydrobenzofuranoid of species of *Helenium* has strong nematocidal properties (Hegnauer 1977).



A (Hegnauer 1977)

3.4.8 Phenylpropanoids

Phenylpropanoids are naturally occurring phenolic compounds which have an aromatic ring to which a three-carbon side chain is attached. They are derived biosynthetically from the aromatic protein amino acid phenylalanine. The most widespread are the hydrocycinammic acids caffeic acid, ferulic,

sinaptic and p-coumaric acids. These acids usually occur in plants in combined form as esters. Esters with quinic acid are particularly common, and the quinic acid of caffeic acid, chlorogenic acid, is almost universal in its distribution. Two other groups of phenylpropanoid include coumarins and the lignans. Phenylpropenes are normally isolated from plant tissues in the essential oil fraction, together with terpenes, and are lipid soluble (Harborne & Baxter 1993).

3.4.9 Lignans

Lignans are dimers of the same phenylpropanoid units that are involved in the biosynthesis of lignins of the plant cell wall. Lignans occur widely in the wood of gymnosperm (e.g., pine trees), and have also been recorded in some 50 angiosperm families. Lignans have antitumor and antiviral activity. (Podophyllotoxin is used externally for destroying warts.) Certain other lignans have allergenic, cathartic and cardiovascular effects (Harborne & Baxter 1977).

3.4.10 Cyanogenic glycosides

Cyanogenic glycosides are erratically distributed among vascular plants. Most are biosynthetically derived from one or other of the protein amino acids. Cyanogenic plants are known from six tribes of the Asteraceae. Most composites which are strongly cyanogenic belong to the Calenduleae, a predominantly southern African tribe. Some members of the Anthemideae and Cardueae contain prunasin-type glycosides (Hegnauer 1977).

CHAPTER 4: CHEMOTAXONOMY

Although probably every member of the family contains flavonoids and most contain volatile oils and triterpenes, it is the presence of unique structural types of two classes of natural products which characterize the family: namely, sesquiterpene lactones and a variety of different types of acetylenes. The family is further characterized by the lack of non-protein amino acids, iridoids and tannins; and with the exception of pyrrolizidine alkaloids in the Senecioneae (and to a minor extent, Eupatorieae), no major classes of alkaloids (e.g. indole, quinoline, isoquinoline) have been reported for the family.

A list is given below of the genera of the Asteraceae mentioned in this thesis with the tribes as recognized by Bentham (1873). All the tribes except Chicorieae belong to the subfamily Tubuliflorae. Chicorieae belongs to the subfamily Liguliflorae.

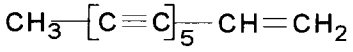
Table 2: List of genera.

Tribes	Subtribe	Genera
Vernonieae	Vernoninae	*Vernonia, Ethulia, Erlangea*
Eupatorieae	Ageratinae	*Eupatorium, Ageratum, Mikania*
Astereae	Asterinae	*Aster, Erigeron, Felicia*
	Conyzinae	*Microglossa, Nidorella, Conyza*
	Solidagininae	*Pteronia*
	Granginae	*Grangea, Dichrocephala*
Inuleae	Tarchonanthinae	*Tarchonanthus*
	Plucheinae	*Blumea, Pluchea*
	Gnaphalinae	*Achyrocline, Gnaphalium, Helipterum, Helichrysum*
	Relhaninae	*Metalasia, Relhania*
	Athrixinae	*Heterolepis*
	Inulinae	*Inula, Pulicaria*
		Sphaeranthus, Geigera,
Heliantheae	Melampodiinae	*Sigesbeckia, Acanthospermum*
	Ecliptinae	*Aspilia, Wedelia, Eclipta*
	Helianthinae	*Helianthus, Tithonia*
	Gaillardiinae	*Helenium*
	Coreopsidinae	*Bidens, Coreopsis*
	Bahiinae	*Schkuhria*
	Madiinae	*Madia*
	Galinsoginae	*Galinsoga, Spilanthes*
	Ambrosiinae	*Ambrosia, Parthenium, Xanthium*
Helenieae		*Callilepis, Ursinia*
Anthemideae		*Anthemis, Achillea, Artemisia, Asaemia, Athanasia, Chrysanthemum, Cotula, Eumorphia, Pentzia, Schistostephium, Lasiospermum, Leucanthemum, Matricaria, Tanacetum, Anacyclus, Eriocephalus, Ursinia*
Senecioceae		*Senecio, Arnica, Kleinia, Euryops*
Calenduleae		*Calendula, Dimorphotheca, Castalis, Osteospermum, Chrysanthemoides, Garuleum, Dipterocome*
Arctotideae	Arctotinae	*Arctotis, Arctotheca,*
	Gorteriinae	*Berkheya, Cullumia, Didelta, Cuspidata, Gorteria, Heterolepis, Hirpicium*
Cynareae		*Centaurea, Cnicus, Cirsium, Silybum.*
Mutisieae		*Dicoma, Gerbera*
Chichorieae		*Chichorium, Lactuca, Taraxacum, Hieracium, Picris.*

4.1 VERNONIEAE

The Vernonieae, although not well investigated chemically, probably are related to the Eupatorieae. (Mabry & Bohlmann 1977)

Acetylenes have been found in a small amounts in the roots of some species. The most widespread is the pentaynene (Harborne & Williams 1977).



pentaynene (Bohlmann 1988)

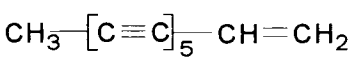
In the genus *Vernonia*, the *sesquiterpene lactones* are mostly of the simple germacranolide type. Three elemanolides and a guaianolide have also been found in Old World species. The sesquiterpene lactones vernolepin (from *Vernonia hymenolepis*) and elephantin (from *Elephantopus*) show significant activity *in vitro* against cells derived from human carcinoma of the nasopharynx and *in vivo* against rat carcinomas. Eremanthine, the sesquiterpene lactone of *Eremanthus elaeagnus* inhibits the penetration of the trematode *Schistosoma mansonii*. The old world species contain a small number of the simpler *flavonoid* patterns (Harborne & Williams 1977).

Vernonia seed oils contain oxygenated acids (8-90%); mainly (+)-12,13-epoxyoleic acid and vernolic acid. This epoxy acid was first identified in *Vernonia anthelmintica* Willd. and has also been found in *V. colorata* Drake, *V. amygdalina* Delile and *V. cinerea* Less. *V. anthelminthica* has potential as an industrial oil-seed crop, with yields up to 1t/ha. The achenes contain vernolic acid, which is mainly present in the oil as the triglyceride, trivernolin. Epoxidized *Vernonia* oil and trivernolin have potential as plasticizers with improved heat and light stability for polyvinyl chloride (Harborne & Williams 1977).

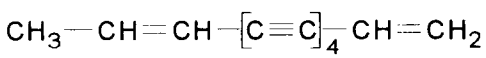
4.2 EUPATORIEAE

The Eupatorieae are not very distinct chemically. This tribe may be related to the Senecioneae by their pyrrolizidine *alkaloids*, albeit of a somewhat different type (Mabry & Bohlmann 1977). Pyrrolizidine ester alkaloids have been isolated from *Eupatorium* species (Domínguez 1977).

The *acetylenes* found in Eupatorieae are only pentaynene-type compounds (Mabry & Bohlmann 1977). The Eupatorieae contain the following acetylenes:



pentaynene



Tridecadiene-(1,11)-tetrayne-(3,5,7,9) (Bohlmann 1988)

A high percentage of *Eupatorium*, *Liatris* and *Mikania* species are the sources of germacranolide and guaianolide-like *sesquiterpene lactones*. Antileukemic germacranolides have been isolated from

Eupatorium cuneifolium, *E. semiserratum* and *Liatris* spp. Several guaianolides have been obtained from *Eupatorium* and *Liatris*; some are cytotoxic (Domínguez 1977).

Diterpenes are rare. The only ones reported are a kaurene derivative from *Mikania*, two from *Stevia* and geranylnerol derivatives from *Liatris* (Domínguez 1977). A kaurene derivative, stevioside, is an extremely sweet-tasting glycoside of *Stevia rebaudiana* which is used as a sweetener (Hegnauer 1977).

Triterpenes occur frequently, but rarely in high concentration; most are found as esters, a few as glycosides or free. Most of the triterpenes are oleanene- and ursene-types and are constituents of *Eupatorium* and some *Mikania* species. In the latter genus, friedelene and dammarene types have also been found. (Domínguez 1977)

The Eupatorieae is rich in polymethoxylated *flavones and flavonols* and their glycosides, particularly apigenin and quercetin derivatives. Several flavonoids show cytotoxic activity. Several genera contain flavonoids polyoxygenated in the A-ring (Domínguez 1977).

Some members produce essential oils. Essential oils of some *Ageratum* and *Eupatorium* species contain benzofuran and coumarin derivatives (Domínguez 1977).

4.3 ASTEREAE

Polyacetylenes, polyenes and related substances and, in certain groups, coumarins are characteristic, mainly in the roots (Herz 1977). The variation in acetylenic structures is clearly larger, but most common are closely related C_{10}-compounds (Bohlmann, Burkhardt & Zdero 1973).

Furansosesquiterpenes, such as 12-acetoxy-10,11-dehydrongaione have been isolated from species of the South African genera *Asaemia*, *Athanasia*, *Eumorphia*, *Lasiospermum*, *Phymaspermum*, *Stilnophytum* and *Ursinia*, all classified in Astereae (Hegnauer 1977).

As essential oils of Astereae are of little commercial significance, little is known of their composition. The rarity or absence of sesquiterpene lactones and alkaloids appear to distinguish the Astereae from several other tribes of Asteraceae (Herz 1977).

Diterpenes are largely of the labdane and clerodane type (Herz 1977). Accumulation of diterpenoids seems to be frequent in this tribe. The strong tendency of some of the Astereae taxa to produce furanoid and lactonoid diterpenoids may cause misidentifications during plant screening for pharmacologically active constituents. Lactones of the butenolide type could be confused with cardenolides; this has possibly happened with those species of *Vernonia* which were reported as containing cardenolides (Hegnauer 1977).

4.4 INULEAE

This large tribus with species distributed all over the world is botanically related to the tribus Astereae as well as to the Helianthieae (Bohlmann, Burkhardt & Zdero 1973).

Simple *polyacetylenes* are widespread. The simple pentayene and two related structures are universally distributed. Monothiophene acetylenes occur in three groups; Tarchonanthinae, Plucheinae and Agianthinae. Dithiophene acetylenics are found only in the Buphthalminae. Acetylenics with pyran and furan attachments, some with epoxy and/or chlorine substitution, occur characteristically in the Gnaphalinae (Harborne 1977).

Sesquiterpene lactones have been identified variously in these plants; the pattern is similar to those of the Heliantheae and Anthemideae in that all four major types of lactone are present. The only missing type, the eremophilanolide skeleton, is restricted to the Senecioneae (Harborne 1977).

Flavonoid pigments have been isolated, especially from species of *Gnaphalium* and *Helichrysum*. The most characteristic feature of the Inuleae flavonoids is the presence of flavonols lacking B-ring hydroxylation. 6- and/or 8-hydroxyflavonols and their methyl ethers occur regularly in the tribe. By contrast, anthochlor pigments occur only in *Gnaphalium* and *Helichrysum* (Harborne 1977).

Alkaloids appear to be uncommon and only one has been fully characterized, an aconitine-type structure from *Inula royleana* (Harborne 1977).

The subtribe Tarchonanthae has been excluded from the tribe Inulae following detailed taxonomic studies. However, no clear decision was made where to place this group which include three genera, *Synchodendron*, *Tarchonanthus* and *Brachylaena* (Bohlmann & Zdero 1982).

4.5 HELIANTHEAE

The Heliantheae is the most chemically complex tribe (Mabry & Bohlmann 1977).

Sesquiterpene lactones have been reported in four of the 15 subtribes: Melampodiinae, Gaillardiinae, Bahiinae and Ambrosiinae. Two of the structural types of sesquiterpene lactones are restricted to the Helianthae: the xanthanolides and psilostachyianolides. Most other types except the elemanolides (restricted to Vernonieae and Eupatorieae) and bakkenolides are represented in the tribe, the most frequent being guaianolides, pseudoguaianolides (=ambrosanolides), germacranolides and their derivatives. The Gaillardiinae is characterized by helenanolides and vermeeranolides both having the C-10 methyl α-orientated, which are totally absent from other tribes. However, helenanolides also occur in the Inulae (*Geigeria* and *Inula*) and the Senecioneae (*Arnica*) (Swain & Williams 1977).

So far eudesmanolides have not been reported very often from the tribe Helianthae while they are widespread in parts of the Inuleae and Anthemideae. According to Bohlmann *et al.* (1981), ent-kaurene derivatives seem to be typical of the subtribe Ecliptinae, but more species have to be examined to decide whether they are chemotaxonomically important (Bohlmann *et al.* 1981).

Diterpenoids of this tribe seem to belong mainly to the (-)-kaurene series; they may be accompanied by pentacyclic trachylobane-type compounds or by (-)-pimarene derivatives (Hegnauer 1977). Only five subtribes have been surveyed for *flavonoid* contents, but complex patterns of highly methylated flavones and flavonols with extra hydroxylation at the 6- or in both 6- and 8- positions are common in those species examined. Chalcones and aurones have been found in the Coreopsidinae. It is interesting to note that chalcones and aurones only occur otherwise in the family in *Helichrysum* (Inulae) and *Lasthenia* (Helenieae)

Although a relatively large number of genera are reported to contain *alkaloids*, very few have been characterized and those that have are very simple pyridine types, e.g. nicotine in *Eclipta alba* Hassk. The Helianthae contain a wider variety of *acetylenic compounds* than most other tribes in the Asteraceae. All 15 subtribes have genera with the ubiquitous C_{13} pentaynene or variants of it. The majority of the subtribes contain genera which synthesize C_{13} acetylenes with a monothiophene side chain. Di- and tri-thiophenes are found in *Bidens*, *Rudbeckia*, *Wedelia* and *Eclipta*. (These are found elsewhere in *Berkheya* (Arctotaceae) and *Tagetes* (Tageteceae). *Eclipta* species also have C_{13} thiophenic acetylenes with a side chain containing chlorine. Chlorine occurs in combined form in a number of pyrano- and furano-acetylenes in species of Inulae. The most interesting sulphur-containing acetylenes in the tribe are the epoxysulphones found only in *Gaillardia* and *Helenium* and these have not been found to occur elsewhere in the plant kingdom. *Spilanthes* contain insecticidal C12 (or C11) acid isobutylamides.

Macromolecular constituents. The Helianthae is the only tribe in which cytochrome c amino acid sequences have been determined (Swain & Williams 1977). Amides are known to occur in the genus *Spilanthes* (Hegnauer 1977).

4.6 TAGETEAE

All are native to the New World. Only one genus, *Tagetes*, is found naturalized in southern Africa. *Flavonoids*, volatile monoterpenes and ketones, sterols and carotenoids have been found in the flowers and leaves and acetylenic thiophenes have been detected in the roots of several species (Mabry & Bohlmann 1977).

The Tageteae, if separated from the old tribe Helenieae, may be a link between the Heliantheae and *Berkheya* of the Arctoteae in that both contain typical thiophene *acetylenes*. The Tageteae contain no *sesquiterpene lactones* (Mabry & Bohlmann 1977).

4.7 ANTHEMIDEAE

In the Anthemideae there is a group of South African genera (*Lasiospermum*, *Ursinia*, *Athanasia*, *Eumorphia*, *Asaemia*, *Stilpnophytum* and *Phymaspermum*) which are not related chemically to other Anthemideae and therefore their position is uncertain. They lack acetylenes but contain a group of unique furansesquiterpenes.(Mabry & Bohlmann 1977)

The tribe Anthemideae contains many aromatic plants, some of which are used in herbal medicine, e.g. *Matricaria chamomilla* L., *Chamaemelum nobile* (L.) All. and various species of *Artemisia*, *Achillea* and *Tanacetum*. Insecticidal substances have been found in members of the tribe in *Anacyclus*, *Achillea*, *Argyranthemum* and *Tanacetum* and particularly in the pyrethrum plant, *Tanacetum cinerariifolium* (Trev.) Schultz Bip. (Greger 1977)

The Anthemideae contain essentially only C_{17}-*acetylenes*, while the more widespread pentaynenes and ene-tetraynenes are not present; the latter compounds are replaced by many other complex acetylenes whose biogenetic pathways are completely different from those of the other tribes except for some C_{10}-acetylenes found in the tribe Astereae. Some C_{10}-acetylenes of a different type are also found in the tribe Cichorieae (Mabry & Bohlmann 1977). In some genera, amides with characteristic olefinic and acetylenic groups have been isolated. They form a distinct group of natural products and frequently possess insecticidal activity (Greger 1977).

The widespread C_{17}-compound, dehydrofalcarinone (DF) is the main component of the southern African genera *Cotula* and *Eriocephalus*. Corresponding alcohols and related C_{15} compounds have been isolated from the South African genera *Lidbeckia*, *Thaminophyllum* and *Peyrousea*. In a further group of southern hemispheric genera including *Ursinia*, *Athanasia*, *Lasiospermum*, *Phymaspermum*, *Stilpnophytum*, *Eumorphia* and *Asaemia*, polyacetylenes are completely absent, and instead, a number of characteristic furansesquiterpenes are present. There is a wide distribution of C_{14}-derivatives in *Tanacetum*, *Artemisia*, *Pentzia* and in some *Anthemis* and *Achillea* and in some representatives of the other genera. C_{13} derivatives have been found in *Chrysanthemum*, *Leucanthemum*, *Santolina* and *Matricaria*. Amides and dehydromatricariaester (DME) are present in *Anacyclus*, *Anthemis* and *Achillea* (Greger 1977).

The strong aromatic odours of many species of the tribe Anthemideae are mainly based on high concentrations of *terpenes*. The monoterpenes thujane and camphene derivatives such as thujone, camphor and borneol as well as 1,8-cineole are the major and most widespread structural types. 1,8-cineole camphor and isothujone probably contribute to the allelopathic effects of some species. The insecticidal activity is attributed to the action of six constituents: pyrethrin I, cinerin I, jasmolin I, pyrethrin II, cinerin II, and jasmolin II. The "irregular" monoterpenes have a wide and practically exclusive distribution in the Anthemideae (Greger 1977).

The *sesquiterpenes* caryophyllene and cadinene together with several closely related derivatives are the most widespread sesquiterpenes in the Anthemideae. The occurrence of bisabolol and related oxidation products in *Matricaria chamomilla* L. have received pharmaceutical attention because of their antiphlogistic activity. Furthermore, acyclic sesquiterpenes have been reported in *Anthemis cotula* L. (Greger 1977).

The formation of furansesquiterpenes in seven South African genera is of taxonomic importance. These genera are additionally characterized by a complete absence of polyacetylenes which are otherwise ubiquitous in the tribe. These genera are; *Athanasia*, *Lasiospermum*, *Stilpnophytum*, *Eumorphia*, *Asaemia*, *Ursinia* and *Phymaspermum* (Greger 1977).

Sesquiterpene lactones have been isolated from 10 genera of the Anthemideae. Germacranolides and particularly guaianolides dominate the tribe, whilst santanolides have been reported only from *Artemisia*. However, in *Artemisia*, more species have been examined than in the other nine genera, mainly because of the early use of santonin as an important vermifuge. In addition, certain lactones, especially in *Matricaria*, *Achillea* and *Artemisia* easily form azulenes, which are of some pharmaceutical importance. Both achillin and desacetoxymatricarin occur together in *Oncosiphon suffruticosum* (L.) Källersjö (Greger 1977).

Dehydroleucodin are formed in *Lidbeckia* and *Peyrousia*. Globicin and arborescin have been isolated from *Oncosiphon piluliferum* (L.f.) Källersjö. Estafiatin has been reported for *Cotula coronipifolia* L. and the closely related isoepoxy-estafiatin from *Pentzia elegans* DC (Greger 1977).

Luteolin and apigenin are the most widespread compounds in the Anthemideae and the flavonols quercetin, isorhamnetin and kaempferol are common. Many monosides (glucosides, glucuronides) but few biosides (rutinosides) have been reported for the tribe. 3-Glucoside is apparently a basic type and is widely distributed in large genera such as *Tanacetum*, *Achillea*, *Artemisia*, *Anthemis* and *Pentzia* (Greger 1977).

7-Glucosides predominate in such genera as *Chrysanthemum*. 5-Glycosides are apparent in *Leucanthemum* and *Cotula*. Hydroxycoumarins are common in the *Artemisia* species. Typical compounds in this group are herniarin, scopoletin and scoparone. Isofraxidin (7-hydroxy-6,8-dimethoxycoumarin in *Artemisia afra* Jacq. have been isolated from the roots only, whereas the flowers contain scopoletin (Greger 1977).

Amides are known to occur in the following taxa; *Achillea*, *Chrysanthemum* and *Anthemis* (Hegnauer 1977).

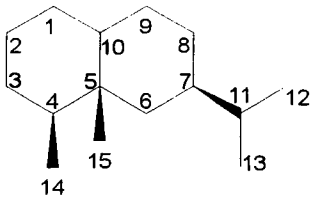
4.8 SENECIONEAE

The Senecioneae is chemically distinct from the other tribes and is characterized by several unusual chemical patterns:

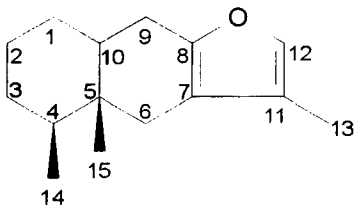
1. More than 150 species contain pyrrolizidine alkaloids. Pyrrolizidine alkaloids have also been reported from five species of *Eupatorium*, but the alkaloids in the latter resemble structural types found in the Boraginaceae rather than Senecioneae reported from five species of *Eupatorium*, but the alkaloids in the latter resemble structural types found in the Boraginaceae rather than Senecioneae.
2. It contains many unique and unusual eremophilane-sesquiterpene lactones and other derivatives.
3. The Senecioneae is distinguished by the absence of most acetylenes typical of other Asteraceae taxa (Mabry & Bohlmann 1977).

Chemically, *Arnica* do not belong to the Senecioneae, but rather share compounds suggestive of a position in or near the Heliantheae of Helenieae, since they produce thymol derivatives, polyacetylenes and pseudoguaianolides, while lacking pyrrolizidine alkaloids, eremophilane-type sesquiterpene lactones and other eremophilane derivatives. However, since there are senecoid genera which lack the typical Senecioneae chemistry and still clearly belong to this tribe, the chemical data alone cannot determine placement in or removal from the tribe (Mabry & Bohlmann 1977).

Many genera of the Senecioneae are characterized by the presence of sesquiterpenes with an eremophilane or furanoeremophilane skeleton but representatives of *Kleinia* do not contain furanosesquiterpenes (Robins 1977).



Eremophilane skeleton



Furanoeremophilane skeleton

Flavonoids were surveyed in leaves of 44 clones from 25 Senecio species, mainly those belonging to the succulent *S. radicans* complex. The common flavonoids identified were the 3-glucosides and 3-rutinosides of kaempferol and quercetin and apigenin 7-glucoside. The flavonoid chemistry, although variable in the group, was not obviously correlated with cytological or morphological patterns. However, there were significant correlations with plant geography. In particular, taxa from Madagascar, the Canary islands and Kenya were markedly different in their flavonoid complement from the South African and Namibian plants. The three plants from Madagascar, Kenya and the Canary islands contained only quercetin 3-glucoside, while the remainder from South Africa and Namibia contain quercetin 3-rutinoside (rutin) and either kaempferol 3-glucoside or

kaempferol 3-rutinoside or both. The exception is *S. angulatus* which lacks flavonols, having only two apigenin derivatives (Glennie *et al.* 1971).

Both flavonol glycosides and glycoylflavones are widespread in *Senecio* and the group is characterized by glycosylflavone in which the carbon linked sugar is rhamnose instead of glucose.

4.9 CALENDULEAE

The tribe Calenduleae has its primary centre of diversification in South Africa. *Acetylenic fatty acids* are found in *Dimorphotheca*, *Castalis* and section Blaxium of *Osteospermum*.

Diterpenes are common in the Calenduleae. Sandaracopimarene derivatives predominate in the Calenduleae (Hegnauer 1977). From *Garuleum bipinnatum* Less., *G. pinnatifidum* (DC.) L'Hérit., *Osteospermum fructicosum* (L.) Norl., *O. junceum* Berg. and *O. oppositifolium* (Ait.) Norl., the diterpenes sandaracopimar-15-en-8β-ol and derivatives thereof were isolated. *Triterpene* glycosides have been identified in the roots of *Calendula officinales* L. and free triterpenes were found in *Chrysanthemoides monilifera* Norl. Sterols have been identified in *C. officinales* flowers. The *cyanogenic glycosides* linimarin and traces of lotaustralin have been identified in several *Osteospermum* species and in *Dimorphotheca cuneata*.

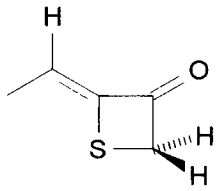
Dimorphecolic acid, a major *fatty acid* in the Calenduleae, has a potential for commercial use in protective coatings, urethane foams, chemical adducts as synthetic intermediates or components of plastics and resins. β-Dimorphecolic acid, 9-hydroxy-trans-10,trans-12-octadecacienoic acid, is restricted to the tribe Arctoteae whilst the conjugated triene, 8,10,12-octadecatrienoic acid is restricted to the tribe Calenduleae. The South African Calenduleae was surveyed with the hope that dimorphecolic acid might be commercially available at a competitive price. Five species of *Dimorphotheca* (out of the possible 7), the two species of *Castalis* and 5 species from the section Blaxium of *Osteospermum* contained dimorphecolic acid. The remaining sections of *Osteospermum* and other genera contained relatively high percentages of a conjugated trienoic acid instead of dimorphecolic acid. The fatty acids of 17 species of *Calendula* were examined and all contained calendic acid, trans-8,trans-10,cis-12-octadecatrienoic acid, as the major fatty acid in the seed oil. α -Dimorphecolic acid, 9-hydroxy-trans-10-cis-12-octadecanoic acid was identified in *C. officinales*. Another fatty acid has been identified in *Dimorphotheca sinuata* DC.; it is the cis,trans-isomer of linoleic acid which was also isolated from *Crepis rubra*. This fatty acid is unusual in that it contains trans-12-unsaturation as does β-dimorphecolic acid. *Dimorphotheca sinuata* DC. contains matricaria ester in common with a large number of Asteraceae (Guy Valadon 1977).

The tribe Calendulae can be divided in two groups: Sandarocopimarene derivatives (diterpenes) are typical of the genera *Osteospermum*, *Garuleum* and *Chrysanthemoides* but are absent in *Calendula* and *Castalis*. *Dimorphotheca* bridges the gap for it contains Sandarocopimarene- as well as Kaurene derivatives (Bohlmann & Grenz 1979).

4.10 ARCTOTIDEAE

The Arctoteae are not very uniform, chemically, although one group of genera has relatively complex thiophene-*acetylenes* while others have only pentaynenes of the type found in the Calenduleae, a tribe which is characterized by many diterpenes (Mabry & Bohlmann 1977). The genera *Berkheya*, *Didelta*, *Cullumia* and *Cuspidata* are characterized by thiophene acetylenes. No diterpenes have so far been isolated from the tribe Arctoteae. Epoxycarotenoids and xanthophylls are present in large amounts in some species examined that include *Arctotis arctotoides* (L.J.) Hoffm. and *Gazania rigens* R.Br. and *Dimorphotheca sinuata* DC.of the Calenduleae.

Some species contain the ubiquitous pentayne whilst some unusual thiophene acetylenes have been identified in the genera *Berkheya*, *Didelta*, *Cullumia* and *Cuspidata*. (Guy Valadon 1977) Thietanones have so far been found to be restricted to the tribe Arctotideae, subtribe Gorterinae. (Sørensen 1977)



Thietanone

No alkaloids have been found in the genus *Berkheya* . The sesquiterpene lactones from *Berkheya* and *Arctotheca* confirm that they are chemotaxonomically related.

4.11 CYNARACEAE

Volatile, and non-volatile terpenoids, acetylenes, phenolic compounds and especially hydroxycinnamic acid derivatives and flavonoids are characteristic of this tribe. Alkaloids and cyanogenic compounds are widespread, but their structures are mostly unknown. There is a high percentage of lipophilic compounds (lipids, terpenids, esterified and highly methoxylated constituents) (Wagner 1977). The Cynaraceae have some types of sesquiterpenes also found in the Heliantheae and also C_{17}-acetylenes which are present in both the Heliantheae and the Anthemideae. In the Cynaraceae widespread pentaynene- and enetetraynene-type compounds as well as thiophenes occur. These substances link the Cynaraceae the Arctoteae (Mabry & Bohlmann 1977).

Cnicin and monoterpenes have been isolated from *Cnicus benedictus* L. Sesquiterpene lactones of the elemanolide type have also been found in some *Centaurea* species.

The predominant *flavonoids* are flavones and flavonols. Flavanones and flavanonols are restricted to the genera *Carthamus*, *Centaurea* and *Silybum*. Highly methoxylated flavonols and flavones occur in remarkable profusion in *Centaurea* and *Cirsium*. *Silybum* are exceptional in that they contain

flavonolignans. Most of the flavonoids exist in glycosidic form. Normally they occur as 3-O-glycosides in the case of flavonols, and 7-O-glycosides in the case of flavanones. Besides the common fatty acids, the seed oil of some taxa of the Cynareae contain special epoxy and hydroxy-fatty acids with conjugated double bonds, found also in *Artemisia*, *Calendula*, *Cosmos*, *Helianthus*, *Tragopogon*, *Vernonia*, *Osteospermum* and *Dimorphotheca* species. The only species investigated (up to 1977) were *Xeranthemum annuum* and *Cynara cardunculus*. The hydroxy fatty acids isolated are α- and β-dimorphecolic acid and coriolic acid. The epoxy fatty acids found were coronaric and vernolic acid. Diterpenoids are lacking in this tribe (Hegnauer 1977).

4.12 MUTISIEAE

In species of the tribus Mutisieae already investigated, only small amounts of acetylenes have been isolated: The pentayn-ene, sometimes together with the ene-tetrayn-ene is typical. Only the genus *Dicoma* does not contain these hydrocarbons (Bohlmann, Burkhardt & Zdero 1973).

4.13 CHICHORIEAE

Members of the Cichorieae produce a characteristic triterpene-rich latex which is unique in the Asteraceae. However, latex canals are found in *Gazania* of the Arctotideae. Acetylenes are rare in the Cichorieae; nevertheless, those which are present may link the Cichorieae to the Astereae and Anthemideae (Hegnauer 1977). Acetylenes have been found only in the subtribus Crepidinae. However, only in the genus *Lactuca* could several compounds be found (Bohlmann, Burkhardt & Zdero 1973). Essential oils are not accumulated by members of the Cichorieae, which unlike the other Asteraceae, lack the secretory glandular hairs and schizogenous ducts (Mabry & Bohlmann 1977). Diterpenes are lacking in this tribe (Hegnauer 1977).

CHAPTER 5: DATABASE OF MEDICINAL USES OF THE ASTERACEAE

INTRODUCTION

The pharmaceutical company Noristan has developed a database of medicinal plants used in southern Africa. It contains entries on approximately 1200 plant species. The data was collected from traditional healers and others who use medicinal plants. The database also has references to papers in scientific journals on the chemistry and/or pharmacology of the medicinal plants. The database was recently handed over to the Traditional Medicines Programme (TRAMED) of the Medical School at the University of Cape Town.

Noristan had also done pharmacological research on several indigenous medicinal plants that include 27 species of the Asteraceae. The species are listed below. Extracts of the work done on each of them are included in chapter 5.

Ageratum conyzoides
Aspilia natalensis
Aster bakerianus
Athrixia phylicoides
Berkheya heterophylla
Brachylaena discolor
Chrysocoma ciliata
Conyza bonariensis
Conyza scabrida
Dicoma zeyheri
Elytropappus rhinocerotis
Euryops speciosissimus
Felicia muricata
Gazania krebsiana
Haplocarpha scaposa
Helichrysum nudifolium
Helicrysum panduratum
Helichrysum petiolare
Oncosiphon pulliliforum
Osmitopsis asteriscoides
Pentzia incana
Schistostephium heptalobum
Senecio babertonicus
Senecio cinerascens
Senecio tamoides
Vernonia natalensis
Vernonia oligocephala

The same method was used in each case: Air dried plant material was ground and extracted succesively with benzene, ethylacetate and methanol and the combined extracts were concentrated under reduced pressure. The extract was chromatographed in a silica gel column and eluted with a gradient of petrol-ether and increasing amounts of EtOAc (1:0, 9:1, 4:1, 1:1, 1:4, 1:9, 0:1), and then with a gradient of EtOAc and increasing amounts of MeOH (1:0, 9:1, 4:1, 1:1, 1:4, 1:9, 0:1). Similar fractions were combined to form 2 or 3 groups which were submitted for pharmacological tests. The pharmacological screen comprised the following tests:

The Irwin Dose-range study was used to determine the toxicity. Doses of 300, 100 and 30 mg/kg were administered intraperitoneally (i.p.) to rats. The LD_{50} (mg/kg) at 24 hours and at 7 days were

determined. Neurotoxicity was determined by recording the animals with paralysis and the ED_{50} (mg/kg) was determined.

The Writhing test was used to determine pain relieving effects. The extracts (usually 500 mg/kg) were administered orally. 45 Minutes later 1.0 ml of 1% acetic acid was administered intraperitoneally (i.p.). For a further 25 minutes the number of writhes was observed. The percentage of inhibition was calculated in each case.

The anti-inflammatory activity was determined with the carrageenan-induced oedema test. The test compound was administered *per os* (p.o.) to rats and followed by intraplantar injection of 0.1ml 1% carrageenan 45 minutes later. Another 3 hours later the mean change in foot volume was measured and the inhibition of the swelling at 3 hours post carrageenan was determined.

For antihypertensive activity, the blood pressure was measured before administering the test compound i.p. to mice. Two hours later the blood pressure was measured again. The percentage change in the mean blood pressure, from pre-dose value to post-dose was determined.

Screening for antimicrobial activity was normally done by testing against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Proteus mirabilis*, *Bacillus subtillis*, *Aspergillus niger* and *Candida albicans* at concentrations of 1, 10, 100 and 1000µg/ml. In all cases the zone of inhibition was measured.

Diuretic activity was determined by administering the test compound orally to rats and then measuring the urine volume at 2.5 and 5 hours post-dose. The mean urine volume as percentage of control and the mean electrolyte (mEq/volume) were determined.

Plant extracts were screened for anticonvulsant/narcotic analgesic activities by administering the test compound i.p. to four mice. Thirty minutes later a clip was placed on the tail and the mouse was observed for pain reaction. The number of mice not showing pain reaction was recorded. 50 mg/kg Metrazol was administered intravenously (i.v.) and the mouse was observed for a tonic extensor reflex. The number of mice not showing tonic extensor reflex was recorded. Diasepam and morphine sulphate were used as references. Test compounds were regarded as active when two of the four mice did not show any pain reaction.

In the ptosis reversal test, the test compound was administered i.p. to mice. 80 mg/kg tetrabenazine s.c. was administered 45 minutes later. After another 45 minutes ptosis reversal was observed as a percentage of the controls.

For the antiarrhythmia test, the test compound was administered i.p. to mice which were then exposed to a lethal concentration of chloroform vapour. The thorax was immediately opened to expose the heart on cessation of respiration. A score was given by visual inspection of the heart for arrhythmias. Score of 1 = no arrhythmia, ½ = almost no arrhythmia, but tachycardia, 0 = arrhythmia.

5.1 ACANTHOSPERMUM Schrank

Acanthospermum australe O. Kuntze and *A. hispidum* DC., two introduced weeds in South Africa, are strongly cyanogenic (Hegnauer 1977).

5.1.1 Acanthospermum australe (Loefl.) Kuntze

(=A. brasilum Schrank)

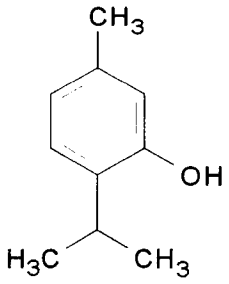
A. australe (Loefl.) O. Kuntze is used in the Amazon region for malaria-related symptoms, including liver disorders (Brandão *et al.* 1992) and in Paraguay for regulating fertility. *Acanthospermum australe* O.K. is an important crude drug which has traditionally been used in Paraguay for the treatment of blood stagnation, rheumatism and arthritis by internal administration and for swelling and bleeding by external application (Shimizu *et al.* 1987).

Flavonoids, phenols, steroids, alkaloids and tannins have been detected in the aerial parts and diterpene and sesquiterpene lactones (melampolides) have been reported (Debenedetti *et al.* 1987).

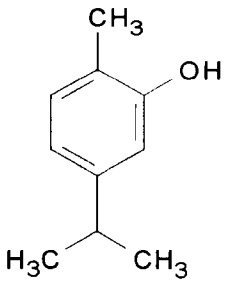
In screening tests for biological activities *A. australe* showed weak inhibitory effects on β-glucuronidase activity and on the growth of KB cells and high inhibitory activity towards rat lens aldose reductase. An EtOH extract of *A. australe*, was found to have a potent inhibitory activity toward rat lens aldose reductase (AR). From the active fraction of the extract, 5,7,4'-trihidroxy-3,6-dimethoxyflavone was isolated. It was found to have a higher activity ($IC_{50}=1x10^{-7}M$) than quercetin which is a known inhibitor of AR ($IC_{50}=1.8x10^{-6}M$). Other compounds isolated were caffeic acid and the flavonoids trifolin, hyperin, rutin and quercetin (Shimizu *et al.* 1987).

The roots of *Acanthospermum australe* (L.) Kuntze contain the widespread tridecapenta-3,5,7,9,11-in-1-en, thymol and isothymol, and its dihydroxyketone and Acanthospermal A and C and its 9-methoxy derivative. The aerial parts contain bicyclogermacrene, Germacrene A and C, α-humulene, spathulenol, phytol, a diterpene lactone and 15 melampolides (Bohlmann *et al.* 1984b). Thymol is antiseptic (20 times more active than phenol) and antifungal. It is used for destroying mould, for preserving botanical and biological specimens, and also in dentistry. It can irritate the gastric mucosa. Isothymol (carvacrol) is antiseptic (1.5 times the activity of phenol). It also shows antifungal and anthelmintic activities. It is used in mouth washes (Harborne & Baxter 1993). α-Humulene is used in perfumery. The acyclic diterpenoid, phytol, occurs in all chlorophyl containing plants as an ester of the propionic side chain of chlorophyll. It is used for the preparation of Vitamins E and K_1.

Two diterpene lactones with oxepane skeletal types, montanol and zoapatanol both have contragestational activity (Harborne & Baxter 1993).



Thymol



Isothymol

The air-dried aerial parts of *Acanthospermum australe* (Loefl.) Ktze contain germacrene D, the melampolide, 8β,9α-diangeloyloxy-14-oic-acanthospermolide, the germacranolide, 8β,9α-diangeloyloxy-15-hydroxy-14-oxo-4,5-cis-acanthospermolide, and diterpene lactones, the geranylgeraniol derivatives, Acanthoaustralide, acanthoaustralide-1-O-acetate and isoacanthoaustralide -1-O-acetate (Bohlmann *et al.* 1981).

Four 6-methoxy flavonoids have been isolated from the aerial parts. They are: 5,4'-dihydroxy-3,6,7-trimethoxy flavone (penduletin), 5,3',4'-trihydroxy-3,6,7-trimethoxy flavone (chrysosplenol D), 5,7,4'-trihydroxy-3,6-dimethoxy flavone and 5,7,3',4'-tetrahydroxy-3,6-dimethoxy flavone (axillarin) (Debenedetti *et al.* 1987). The flavonol axillarin has antiviral activity and inhibits lens aldose reductase (Harborne & Baxter 1993).

5.1.2 Acanthospermum glabratum (DC.) Wild

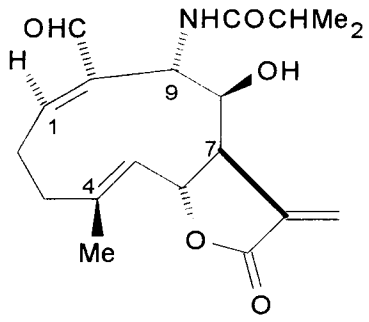
(=A. australe auct. non (Loefl.) Kuntze)

(=A. xanthoides (Kunth) DC. var. glabratum DC.)

Unlike *A. australe* O.K., chemical and pharmacological studies on *A. glabratum* have revealed no inhibitory activity towards rat lens aldose reductase (Shimizu *et al.* 1987).

The 50% aqueous athanol extract of the whole plant of *A. glabratum* (DC.) Wild demonstrated antitumor activity. This activity was found to be concentrated in the chloroform-soluble fraction after partition of a benzene extract of the plant. Chromatographic seperation of the complex chloroform fraction on silica gel afforded nine cytotoxic compounds, seven of which are new sesquiterpene lactones in the melampolide series. The new compounds isolated in addition to acantholide were acanthamolide, acanthospermolide, glabratolide, 9-hydroxyglabratolide, acanthoglabrolide, dihydroacanthospermal A and the known compounds acanthospermal A and 3,6-dimethoxy-4',5,7-trihydroxyflavone. Each of the isolates was examined in the Eagles carcinoma of the nasopharynx (KB) test system in culture. All the sesquiterpene lactones were cytotoxic as might reasonably be expected since each contains a α-methylene-butyrolactone moiety. The flavone derivative was inactive in this test system, although it did display marginal toxicity in the P-388 lymphocytic leukemia system *in vivo*. Dihydroacanthospermal A showed similar toxicity to acanthospermal A and consequently the cis-α,β-unsaturated aldehyde unit does not appear to enhance the cytotoxicity. Seven of the isolates were obtained in sufficient quantity adequate for *in vivo* testing; three of these, acanthospermolide, 9α-hydroxyglabratolide and dihydroxyacanthospermal A were active in the P-388

lymphocytic leukemia system in mice. The flavone derivative was previously shown to substantially reduce lactate production in Ascites cells, and in L-1210 cells alone and in the presence of sodium ion (Saleh *et al.* 1980). Marginal cytotoxic activity was observed with acanthamolide in the 9KB system in cell culture (ED_{50} 2.2μg/ml) (Saleh *et al.* 1977).



Acanthamolide (Saleh *et al.* 1977)

Isolation and identification of 3,6-dimethoxy-4',5,7-trihydroxyflavone: Whole plants of *A. glabratum* (DC.) Wild were collected in Tanzania, air-dried and milled to a coarse powder. This was extracted with benzene. The benzene extract was chromatographed on a column of silica gel PF-254 packed in benzene and eluted with mixtures of benzene and ethyl acetate of increasing polarities. Column fractions which were eluted with benzene-ethyl acetate (9:1), were combined and the residue chrystalized from methanol-chloroform to afford yellow needles. 3,6-Dimethoxy-4',5,7-trihydroxyflavone was inactive in the P-388 test system in mice at doses of 20, 10 and 5 mg/kg, and was inactive in the 9KB system in cell culture. In the P-388 leukemia test system in cell culture it showed ED_{50} 3,4μg/ml (Saleh *et al.* 1976).

5.1.3 Acanthospermum hispidum DC.

Acanthospermum hispidum DC. is an introduced weed. When stepping on a bur, where the skin is punctured, lesions might be caused which may take as long as six weeks to heal (Watt & Breyer-Brandwijk 1962). Seeds of *A. hispidum* DC. have toxic effects characterized by hemorrhaging, weakness and diarrhea. The plant contains sesquiterpenoids and phenolic compounds. Extracts of *Acanthospermum hispidum* and *Cajanus cajan* (L.) Millps. have been used by Brazilian people in an attempt to produce abortion. In order to evaluate the possible abortive and/or teratogenic effect of these plant extracts, female rats were treated with an infusion of *C. cajan* and *A. hispidum* (1:1.3). There was no significant change in the weight of the fetuses, and no change in the percentage of post implantation loss in the treated groups. However, there was an increase in the number of external malformations, and this was related to dose. The tendancy of the pregnancy to continue or terminate did not change with the treatment (Lemonica & Alvarenga 1994).

The roots of *A. hispidum* DC contain the widespread tridecapentaynene. The arial parts of *A. hispidum* collected in India yielded a diterpene galactoside named acanthospermol-β-galactosidopyranoside (Nair *et al.* 1975).

5.2 ACHILLEA L.

5.2.1 Achillea millefolium L. sens. lat.

(=A. millefolium L. subsp. lanulosa (Nutt.) Piper)

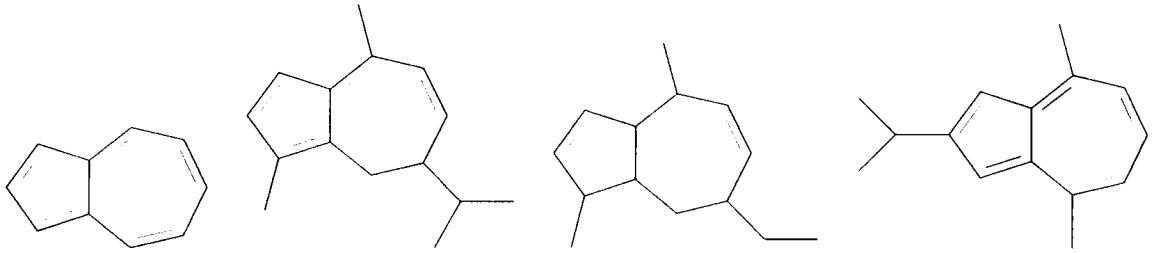
The *Achillea millefolium* complex is a group of scarcely separable species (regarded by some authorities as subspecies) of Asteraceae found primarily throughout the temperate and boreal zones of the northern hemisphere and, to a lesser extent, the southern hemisphere. Also confusing is the indiscriminate use of the common name, yarrow, in reference to several different species of *Achillea*. Much of the work reported under "*A. millefolium*" may refer to either *A. millefolium* sensu stricto or to any of a number of other species. *A. millefolium* sensu stricto is by far the most widespread, found abundantly in central and northern Europe and has been widely introduced in North America. *A. lanulosa* Nutt. is widely distributed across Canada and the northern United States (Chandler *et al.* 1982a).

Yarrow has been employed as a popular medicine since the Trojan War (ca. 1200 BC) when the Greek hero, Achilles, is said to have used the leaves of this plant to check the flow of blood from the wounds of his fellow soldiers - hence the generic name, Achillea. Yarrow was employed throughout North America by a number of Indian societies for a wide variety of purposes. The most common uses, involved treating bruises, sprains and swollen tissues; healing wounds; and providing relief from rashes and itching of various causes. The plant was also a popular febrifuge and enjoyed some use in treatment of the common cold. A number of its minor uses indicate that the plant is capable of imparting an analgesic (local anesthetic) and/or anti-inflammatory effect. Groups other than the North American Indians used it for its analgesic and anti-inflammatory effects. It was also a popular agent in treating fevers, diarrhea and dysentery (although it has been used as a laxative as well) and a number of ailments involving nerves and muscles (Chandler *et al.* 1982a). *Achillea millefolium* is used as a antipyretic and diaphoretic in cases of common cold and as an emmenagogue in Europe, USA and Asian countries. Use against cancer has also been reported (Tozyo *et al.* 1994). The yarrow is also used as a hair rinse to brighten, stimulate and strengthen blonde hair and as a shampoo to prevent baldness (Chandler *et al.* 1982a). Its use as an insect repellent, most likely refers to the various yellow-blooming species of *Achillea* and not to *A. millefolium* (Chandler *et al.* 1982a).

Over 120 compounds from this plant have been characterized. Many other compounds have been isolated but not completely identified and still others have been "detected" (Chandler *et al.* 1982a).

The plant yields a blue-coloured oil due to the presence of azulene and related compounds such as chamazulene. Pronounced anti-inflammatory activity is associated with the oil and azulene-like compounds and with water soluble glycoprotein extracted from the flower heads. It is generally agreed that *A. millefolium* L. is hexaploid and azululene free and that azulene is found in the closely related tetraploid plants, such as *A. lanulosa* Nutt. and *A collina* Becker. The constituents of the volatile oil and sesquiterpene lactones are listed by Chandler *et al.* (1982a).

It is well known that some plant essential oils are a characteristic blue colour which in most cases is due to components of azulene type. Among these oils the most famous are those from chamomile (Matricaria chamomila), yarrow or milfoil (various subspecies of *Achillea millefolium*) and wormwood (*Artemisia absinthium*). Various natural azulenes are known, for example, guajazulene, chamazulene and vetivazulene. Of them, chamazulene occurs most frequently (Verzár-Petri *et al.* 1979). Chamazulene has anti-inflammatory and antipyretic activities. Guaiazulene has anti-inflammatory activity (Harborne & Baxter 1993).



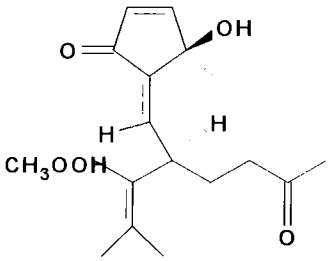
Azulene Guajazulene Chamazulene Vetivazulene

Achillicin, the major proazulene (prochamazulene) of *Achillea millefolium* L. ssp. *collina* Becker has been isolated and identified as 8-acetoxyartabsin. It is the first proazulene reported for the genus *Achillea* and has not been found previously in plants (Banh-Nhu *et al.* 1979).

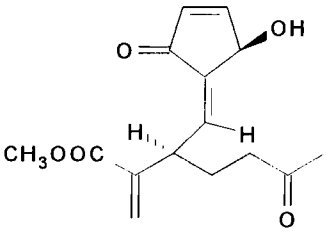
Tozyo *et. al.* (1994) isolated three new antitumor sesquiterpenoids, achimillic acids A, B and C as methyl esters from *Achillea millefolium* and determined their structures spectroscopically. The compounds were found to be active against mouse P-388 leukemia cells *in vivo* but they were inactive against L-1210 leukemia cells. Many antitumor sesquiterpenoids have been reported and their antitumor activity has been attributed to the α-methylene-γ-lactone structure. The achimillic acids obtained by Tozoyo *et al.* (1994) are antitumor sesquiterpenoids of unusual structure, lacking the α-methylene-γ-lactone moiety. Their activity is thought to be due to their α,β-unsaturated ketone or ester groups (Tozyo *et al.* 1994).

Extraction and isolation: Air dried flowers of *Achillea millefolium* were extracted twice with MeOH and the extract concentrated *in vacuo.* The residue was partitioned between *n*-butanol and water to give fractions soluble in *n*-BuOH and water. The *n*-BuOH fracton was triturated with benzene to yield benzene soluble and insoluble fractions. The benzene soluble fraction was chromatographed on silica gel and eluted with $CHCl_3$, $CHCl_3$:Me_2CO and $CHCl_3$:MeOH:H_2O. An active fraction was eluted with $CHCl_3$:MeOH:H_2O (30:10:1) and then MeOH. It was then dissolved in n-BuOH and extracted with 5%$NaHCO_3$. The aqueous phase was acidified with dilute HCl and extracted with n-BuOH. The n-BuOH phase was washed with water and evaporated to give fraction V. Fraction V was refluxed with methyl iodide and K_2CO_3 in dry acetone for 3h, with methyl iodide being asdded after 1 and 2h. After addition of water the reaction mixture was extracted with AcOEt and the organic phase was then washed with water and concentrated *in vacuo.* The residue was chromatographed on

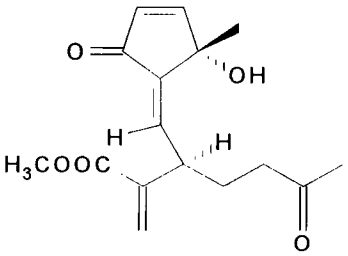
silica gel to give Achimillic acids A, B and C. The structures were determined using MS, ^{1}H-, and ^{13}C-NMR spectra. Mice were inoculated intraperitoneally with 106 P-388 cells in 0,1ml saline. Test compounds were suspended in vehicle and administered on the day following the tumor inoculation. Antitumor activity was evaluated by the increase in life span compared with controls (Tozyo *et al.* 1994).



Methyl Achimillate A



Methyl Achimillate B



Methyl Achimillate C

Observed spasmolytic activity of the yarrow has been attributed to the flavonoids. The flavonoids of *A. millefolium* include apigenin, apigenin glycosides, artemetin, casticin, 5-hydroxy-3,6,7,4'-tetramethoxyflavone, isorhamnetin, luteolin, luteolin glycosides, quercetin glycoside, rutin (quercetin rhamnoglucoside) and other undetermined flavonoids (Chandler *et al.* 1982a). The spasmolytic activity of *Achillea millefolium* has been attributed to the flavonoids apeginin 7-O-glucoside (cosmosiin) and luteolin 7-O-glucoside (cynaroside). The major compounds accumulated in the leaves are luteolin derivatives and apigenin derivatives in the flower head. *Achillea millefolium* is characterized by polymorphism and three subspecies are recognized. Only the pink flowering *A. millefolium* ssp. *alpestris* yields by hydrodistillation a blue coloured oil rich in chamazulene. Rutin, a flavonol 3-O-glucoside is found only in the alpestris subspecies leaves (Harborne & Baxter 1993). Apigenin (5,7,6'-trihydroxyflavone) has antibacterial, anti-inflammatory, diuretic and hypotensive activities. It inhibits many enzymes and promotes smooth muscle relaxation. The flavone luteolin (5,7,3',4' tetrahydroxyflavone) has anti-inflammatory and antibacterial activities. It inhibits iodothyronine deiodinase, protein kinase C, NADH-oxidase, succinoxidase, lens aldose reductase etc. Method: Air dried plant material, separated into leaves and flower heads, were ground and extracted with MeOH for 15min. The analysis were made by TLC and HPLC with a photodiode array detector in comparison with authentic markers (Guédon, Abbe & Lamaison 1993).

An alkaloid, achilleine, was first isolated from the yarrow and it was found to be an active hemostatic agent (Chandler *et al.*1982a). Achillein has anti-inflammatory activity (Harborne & Baxter 1993). Other alkaloids and bases of the yarrow include achiceine, achilletin, betain (glycine betaine, glycocollbetaine), betonicine (achilleine), choline, homostachydrine, moschatine (moscatine), stachydrine, trigonelline and other unidentified bases (Chandler *et al.* 1982a). Achillein has anti-inflammatory activity (Harborne & Baxter 1993).

Very little work has been done on sterols and triterpenes, but some papers and screening articles have reported their presence. The occurence of stigmasterol, β-sisterol, its acetate, a phytol and a diol were reported. Saponins have also been reported present (Chandler *et al.*1982a).

Falk *et al.* (1974) subjected the essential oil from the flowers of *Achillea millefolium* L. to gas chromatographic-mass spectrometic analysis. Plants were grown from seeds collected in the wild from Illinois. It was shown that only tetraploid plants produce azulene, whereas the hexaploid and octaploid plants do not. Of the 42 components selected for the study in the chromatograms, 24 components were identified by retention time data from two different columns and mass spectral fragmentation pattern. The compounds identified account for more than 95% of the oil. The components include; camphor (17,79%), sabinene (12,35%), 1,8-cineole (5,59%), α-pinene (9,41%), isoartemisia ketone (8.60%), β-pinene (7,13%), camphene (6,02%), terpinen-4-ol (4,31%), γ-terpinene (3,71%), p-cymene (3,69%), borneol (2,55%), bornyl acetate (2,10%), caryophyllene, limonene, α-terpinene, allo-ocimene, tricyclene, myrcene, terpinolene, copaene, an allo-ocimene isomer, humulene, Δ-cadinene and cuminic aldehyde (Falk *et al.* 1974).

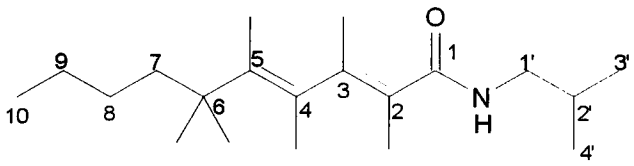
Camphor is an irritant; it affects the central nervous system and is toxic to humans. It is used commercially as a moth repellent and as a preservative in pharmaceuticals and cosmetics. Other uses are as a rubefacient and mild analgesic, and as topical antipruritic (Harborne & Baxter 1993). The presence of camphor may in part explain the use of *A. millefolium* as analgesic and for the relief of rashes and itching. 1,8-Cineole has anthelmintic, expectorant and antiseptic activities. It shows cockroach repellent activity and is used as a flavouring. Camphene is used for the reduction of the cholesterol saturation index in the treatment of gallstones (Harborne & Baxter 1993).

Chandler *et al.* (1982b) studied the sterols and triterpenes of *Achillea millefolium* L. Quantitavie TLC indicated that sterols and triterpenes represented ~ 6 and 54% of the nonsaponifiable materials in yarrow, respectively. β-sisterol was the major sterol present, representing ~75% of the sterols. Campesterol (19%), cholesterol (5%), stigmasterol (3%) and an unidentified sterol (6%)were also present. α-Amyrin was the major triterpene present, representing ~42% of this fraction, β-amyrin (33%) and taraxasterol (18%) were also present. Pseudotaraxasterol (4%) was also identified tentatively and the balance of three triterpenes was unidentified. Method: The aerial parts were dried in a forced air oven, milled to a coarse powder and then macerated in a chloroform-methanol (1:1, v:v) for 24h, repeated 3 times. The solvent was removed *in vacuo* the material was saponified and the non-saponifiable portions were extracted with ether and the solvent was again removed *in vacuo*. This was fractionated by preparative TLC and sterols and triterpenes were identified by nuclear magnetic resonance spectroscopy and combined gas chromatography - mass spectrometry (Chandler *et al.* 1982b). Sisterol has antihyperlipoproteinaemic acitivity (Harborne & Baxter 1993).

Various other compounds have also been obtained from the yarrow. They include the acids; ascorbic-, caffeic-, folic-, salicylic-, asconic- (achelleic-) and succinic acids and also carotenoids, coumarins, resins, tannins, polyacetylenes, polyamines and thiophene amides (Chandler *et al.*1982a). Caffeic acid has antibacterial, antifungal, antiviral and antioxidant acitivities. It is an analgesic and an anti-inflammatory agent, with hepatotoxic, anti-ulcerogenic and clastogenic activities also. It inhibits platelet aggregation *in vitro* and gonadotropin release, and affects both DNA binding and prostaglandin induction. Folic acid is a haematopoietic vitamin. Ascorbic acid (vitamin C) is

employed as antimicrobial and antioxidant in foodstuffs. Salicylic acid has been used as a food preservative and, in medicine, as a topical keratolytic. It can cause skin rashes in sensitive people. The acetyl derivative of salicylic acid is widely used as a mild pain killer (Harborne & Baxter 1993).

A methanol extract of *Achillea millefolium* L. tested at 1000ppm, resulted in 75% mortality of the mosquito larvae, *Aedes aegypti* in one day. Bioassy and TLC-monitored (developed with $CHCl_3$ or $CHCl_3$:acetone, 8:2) fractionation yielded a neutral fraction which was refined further by column chromatography to afford the antilarval N-(2-methylpropyl)-(E,E)-2,4-decadienamide which was identified by spectral methods and through comparison with a synthesized sample.



N-(2-methylpropyl)-(E,E)-2,4-decadienamide

Isolated and synthesized amides at 5ppm resulted in 98 and 100% mortality of 24h old *A. triseriatus* larvae. The N-(2-methylpropyl)-amides of decanoic and (E)-2-decenoic acids showed the same order of antilarval activity as N-(2-methylpropyl)-(E,E)-2,4-decadienamide, but N-(2-methylpropyl)sorbamide was inactive. The tribe Anthemidae of which *A. millefolium* as a member, is known for the production of highly unsaturated amides which are derived from C_{10}-C_{18} straight chain, polyunsaturated acids and isobutylamide, tyramine, piperidine, and dehydropiperidine. These amides were found to be insecticidal. N-(2-methylpropyl)-(E,E)-2,4-decadienamide is about a third as active as pyrethrins against the house fly, *Musca domestica* L., but inactive against the grain insect *Tenebrio molitor* L (Lalonde *et al.* 1980).

The plant has been used for centuries to check bleeding wounds and sores. The alkaloid, achilleine, is an active hemostatic agent which could account for its traditional use. The flavonoids have been shown to possess antispasmodic activity, and could therefore be responsible for some of the plants traditional uses. Also, a number of the plants compounds could be construed as contributing to its anti-inflammatory and antipruritic activities: azulene, chamazulene, the sesquiterpene lactones and some of the other constituents of the volatile oil (such as menthol and camphor), the tannins and possibly the sterols and triterpenes (Chandler *et al.* 1982a).

Some of these agents could account for the plants apparent effectiveness in treating some of the other skin afflictions. The alkaloid, achilleine, is an active hemostatic agent which could result from salicylic acid derivatives, eugenol, menthol of a number of other compounds present in the plant's volatile oils. The antipyretic activity could well be a consequence of the presence of salicylic acid derivatives, chamuzulene and/or other similar agents. Thujone is a known abortifacient and may, therefore be the active ingredient resoponsible for the use of these plants to treat a number of problems associated with the female reproductive system (Chandler *et al.* 1982a). Eugenol has anticonvulsant, antimitotic, antioxidant, hypothermic and spasmolytic activities. It also shows

antiyeast and central nervous system depressant activities. It inhibits prostoglandin synthesis by human colonic mucosa, the metabolism of arachidonic acid by human polymorphonuclear leukocytes, smooth muscle activity *in vitro* (humans and animals), and carrageenan-induced foot inflammation in rats. Also it inhibits induced platelet aggregation *in vitro*. It is used as antiseptic and anaesthetic in dentistry. Menthol has topical antipruritic, analgesic, and antiseptic activities. It is widely used to relieve symptoms of bronchial and nasal congestion, and internally as a carminative and gastric sedative. It can give rise to hypersensitive reactions, e.g., contact dermatitis. Uses include flavouring medicines, dentrifices and confectionary (Harborne & Baxter 1993).

Many of the plant's other uses can also be explained by the types of constituents present, such as the diuretic activity of the alditols and resins and the carminative action of the volatile oil. In addition, the expectorant, analgesic and diaphoretic properties of several of the constituents of the volatile oil may provide relief form some cold and influenza symptoms (Chandler *et al.* 1982a).

This type of argument, however, is not without its perils. For example, the plant exhibits hemostatic properties even though it contains coumarins. And, of course, the concentration of the constituent also determines whether or not the plant exhibits a given activity (Chandler *et al.* 1982a).

The occurance of several genotypes of *A. millefolium*, each with its unique chemical composition, might conceivably explain the fast number of medical attributes claimed for yarrow and why ethnic groups from different geographical areas used yarrow for considerably different reasons. It is important, then, to consider genotypes as well as the common variables of age of the plant, geographical location, seasons of harvest and plant parts when collecting plants for phytochemical investigations (Chandler *et al.* 1982a). *Achillea millefolium* L. is weakly to strongly cyanophoric (Hegnauer 1977).

5.3 ACHYROCLINE (Less.) DC

5.3.1 Achyrolcline stenoptera (DC.) Hilliard & B.L.Burtt

(=*Helichrysum gerrardii* Harv.)

(=*Helichrysum hochstetteri* (A.Rich.) Hook.f.)

(=*Helichrysum stenopterum* DC.)

It is used by Zulu women in making a lotion for washing themselves (Watt & Breyer-Brandwijk 1962).

5.4 AGERATINA Spach

5.4.1 Ageratina adenophora (Spreng.) R.M.King & H.Rob.

(=*Eupatorium adenophorum* Spreng.)

Eupatorium adenophorum L. (the author citation is probably a mistake) is aromatic and is used as an antiseptic and a blood coagulant. From the petroleum ether extract of the aerial parts, seven compounds were separated: isohexacosane, n-hexacosanic acid, β-amyrin, stigmasterol, lupeol, taraxasterol and salvigenin (5-hydroxy-4',6,7-trimethoxyflavone). Only epifriedelinol was separated

from the ethanolic extract. The acute toxicity determined in mice gave the LD50 of the ethanolic extract of *E. adenophorum* >1000 mg/kg given intraperitonealy (i.p.). No mortality in 24 hours was noted even after administration of extract of the dose level of 1000 mg/kg (i.p.). The extract showed increased spontaneous motor activity. It did not induce motor incoordination in mice. The effect of potentiation of pentobarbitone induced sleep was found to be insignificant (Ansari *et al.* 1983).

5.4.2 Ageratina altissima (L.) R.M.King & H.Rob.

(=Eupatorium rugosum Houtt.)

The anti-inflammatory activity of an ethanol extract of *Eupatorium rugosum* L. (which was treated to remove pigments with petroleum ether) was evaluated in rats using the carrageenin-induced pedal edema assay. A dose of 100 mg/kg x2 resulted in a 13% inhibition (Benoit *et al.* 1976).

Bohlmann, Mahanta *et al.* (1979) investigated the chemical composition of several populations of *Ageratina altissima* (L.) K. & R. It contained several chromenes.

5.5 AGERATUM L.

Plants of the genus *Ageratum* are known to contain chromenes, benzofurans, terpenoids and flavonoids (Vyas & Mulchandani 1986).

5.5.1 Ageratum conyzoides L.

Ageratum is used in folk medicine for the treatment of various diseases, especially for the treatment of wounds and burns. The fresh leaves are rubbed between both palms until well macerated, the juice is squeezed onto the wound and covered by a bruised but intact leaf. Dressing like this is usually done once a day and the process of healing is claimed to be enhanced (Duradola 1977). The processed extract is commonly employed to arrest bleeding from fresh cuts and for wound dressing. The coarsely beaten leaves are used to control epitaxis (Akah & Ekekwe 1995). It is used in many parts of Nigeria to promote wound healing. Preliminary experiments with rabbits showed that the crude plant extract was significantly superior to vaseline gauze as a wound dressing material (Adesogan & Okunade 1979). The coarsely beaten leaves are used to cover chronic leg ulcers. The juice from the bruised leaves is used to stop epitaxis (Akah 1988). It had been dispensed as an emetic, for treatment of fevers and externally in lotions for scabies. The root decoction or weak infusion of the whole herb is used by the Chagga as a general remedy for abdominal discomfort and pain (Iwu 1993). The raw root is chewed for digestive disturbances and in Tropical Africa the root is used for colic (Watt & Breyer-Brandwijk 1962). The Blacks of South Africa drink a decoction of the roots or of the whole plant for stomach ailments and stomach-ache. The raw roots are chewed for indigestion (Rood 1994). The leaves are also used as emetic (with water), purgative enema (with *Ocimum* and "bush pepper") and as purgative (Ayensu 1978). The plant is used in East Africa for the treatment of syphilitic sores (Iwu 1993). In Nigeria rubbing the leaves of the plant on the chest of the patient is a treatment for pneumonia (Duradola 1977) and an infusion of the leaf of the plant is used to treat colds and fever. The leaf decoction is said to be a good tonic and is taken internally for gastrointestinal pains and gonorrhoea. The leaf juice is dropped into the eyes to treat inflammation (Akah & Ekekwe 1995). In Sierra Leone, the plant is popularly known as the "Craw-craw" plant

because of its effectiveness (leaves) in treating craw-craw (Akah 1988). In Mexico and India the plant has been used as a tonic and stimulant and as a remedy for fever, colic, diarrhoea and rheumatism (Watt & Breyer-Brandwijk 1962). The leaf pulp is used in Liberia for children with pneumonia and the juice as an eye lotion. The juice of the root is used as an antilith (Ayensu 1978).

The plant yields essential oils (about 0,16%), of which ageratochromone is the principle constituent. The oil from the leaf also contains 6-dimethoxyageratochromone, phenols, phenolic esters, coumarin, and traces of eugenol (Iwu 1993). 6-Demethoxyageratochromene was identified by NMR and IR spectra as a component (20%) of the essential oil of *A. conyzoides* (Kasturi & Manithomas 1967). On oxidation the oil gives an intense vanillin odour due to the formation of ethyl vanillin (Watt & Breyer-Brandwijk 1962). Other constituents of the plant include the oxygenated chromone, conyzorigun, dotriaconthene, 7-methyoxy-2,2-dimethylchromene, 5,6,7,8,3',4',5'-heptamethoxyflavone (5-methoxynobiletin) (Iwu 1993), sisterol, stigmasterol (Adesogan & Okunade 1979) and the flavone, eupalestin (Vyas & Mulchandani 1984). Twelve polyoxygenated flavones have been isolated from *A. conyzoides*. They are ageconyflavones A (5,6,7-trimethoxy-3',4'-methylenedioxyflavone), B (5,6,7,3'-tetramethoxy-4'hydroxyflavone) and C (5,6,7,3',5'-pentamethoxy-4'-hydroxyflavone) and linderoflavone B, eupalestin, nobiletin, 5'-methoxynobiletin, 5,6,7,5'-tetramethoxy-3'4'-methylenedioxyflavone, sinensetin, 5,6,7,3',4',5'-hexamethoxyflavone, 5,6,7,8,3'-pentamethoxy-4'-hydroxyflavone and 5,6,7,8,3',5'-hexamethoxy-4'-hydroxyflavone (Vyas & Mulchandani 1986).

The plant has broad spectrum antimicrobial activity and the extract also showed *in vitro* anthelmintic activity (Iwu 1993).

A crude material isolated form the leaves of *Ageratum conyzoides* L. is shown to exhibit antibacterial activity against *Staphylococcus aureus in vitro.* Fresh leaves were macerated in a blender and extracted exhaustively with excess petroleum ether at room temperature. Condensation of the filtrate gave a yellow oil which dried at room temperature to a semi solid oily and gummy material. The gum was dissolved in a small volume of petroleum ether and chromatographed on a column of aluminium oxide and eluted with petroleum ether (10 fractions) and 10 fractions of petroleum ether-chloroform mixtures. Early fractions were yellowish oil, but later fractions became more solid and whitish-brown. Petroleum ether-chloroform (4/1) eluted a whitishbrown crystalline material which showed inhibitory activity against *Staphylococcus aureus* at a concentration of 1 mg/ml. The same fractions showed wound healing properties; burn-wounds of the rabbits treated with the compound healed in 7 days while that of the control (vaseline gauze) took 14 days to heal (Duradola 1977).

Akah (1988) studied the haemostatic effect of the aqueous extract of the leaves of *Ageratum conyzoides* so as to justify or deny its traditional use to arrest bleeding. The plants were collected in Nigeria and the air-dried leaves were ground to a powder which was macerated in water for 1 hour. The process was repeated three times and the combined extracts were concentrated to one half of their original volume. The extract, although preventing coagulation of whole blood, caused precipitation of some blood materials. Bleeding times also decreased. The extract contracted isolated arterial strips. The contractions were not affected by prazosin and phentolamine, but were

abolished in a "calcium free" solution and also in the presence of nifedipine. The contractions were abolished in a "calcium free" solution and by nifedipine but were not affected by prazosin and phentolamine suggesting that the extract may act directly on the blood vessels probably through calcium mobilization. Phytochemical analysis revealed the presence of tannins, saponins and flavonoids. The haemostatic effect of the leaf extract of *Ageratum conyzoides* probably results from vaso-constriction, and the formation of an "artificial clot" which tends to produce a mechanical plug to arrest bleeding from small blood vessels. Precipitation of blood constituents form a bung to plug the cut in the blood vessels. The ability of an extract to form an "artificial clot" and then arrest bleeding, may be attributed to its high tannin content (Akah 1988).

The chromatographic fractions of the petrol extract of the stem and leaves of *A. conyzoides* showed that the greatest wound healing activity contained more than 90% of the flavone 5'-methoxynobiletin. Air-dried stem and leaves of *A conyzoides* were extracted in petrol and the concentrate taken in 90% MeOH. after concentration of one third of the original volume, the remaining aqueous alcoholic solution was extracted with C_6H_6. The C_6H_6 extract was chromatographed on a Si gel column and eluted with EtO_2:petrol (1:1). 5'-Methoxymethoxynobiletin was identified by ^1H NMR and synthesis (Adesogan & Okunade 1979).

Noristan has done research on *Ageratum conyzoides* as described in the introduction to this chapter. Similar fractions were combined to form 9 groups. Groups 1-5 and groups 6-9 were combined and submitted for the pharmacological tests. In the anti-inflammatory tests the combined groups 1-5 showed 54.9% inhibition of carrageenan-induced foot oedema in mice at 500 mg/kg p.o. after three hours. The control phenylbutazone showed 69% inhibition at 75 mg/kg. In the secondary screening, the inhibition of group 4 was 43% at 300 mg/kg. In the antihypertensive tests there was a -17.47% change in mean blood pressure from pre-dose value at 2 hours with the admininstration of groups 1-5. The diuretic test revealed a 62% increase of Na^+ excretion 5 hours after administration at a dose of 500 mg/kg. and the combined groups 6-9 increased Na^+ excretion by 34%. The Irwin screen revealed the LD_{50}>300 and ED_{50} Neurotox.>300 mg/kg with signs of weak central nervous system depression observed at 300 mg/kg. Stigmasterol was isolated from group 4 and identified by NMR (Noristan not published).

5.5.2 Ageratum houstonianum Mill.

(=*A. mexicanum* Sims)

Benzofuran derivatives co-occur with chromenes in the roots of *Ageratum houstonianum*. It has been demonstrated that chromene derivatives exhibit contact toxicity to a number of herbivorous insects. A chronic feeding assay with neonate larvae of *Spodoptera littoralis* was performed with a diet spiked with a series of concentrations of a crude extract. The extract of the flowering heads of *A. houstonianum* caused complete mortalily of the larvae at 25% of the natural concentrations. Extracts of *A. houstonianum* leaves resulted in complete mortalily of the larvae at 50% of the natural concentrations or at the natural concentrations. Prococene II showed the highest feeding inhibition of the chromenes tested and also caused a dose dependant mortalilty of the larvae in the contact

toxicity bioassay (Srivastava & Proksch 1993). The essential oil from *Ageratum houstonianum* contain ageratochromene (Kasturi & Manithomas 1967).

The flavonoids, lucidin dimethyl ether, eupalestin and agecorynin C (Quijano *et al.* 1982) as well as the highly oxygenated flavones agehoustin A (5,6,7,8,2',3',4',5'-oktamethoxyflavone), agehoustin B (5,6,7,2',3',4',5'-heptamethoxyflavone), agehoustin C (3'-hydroxy-5,6,7,8,2',4',5'-heptamethoxy-flavone) and agehoustin (5,3'-dihydroxy-6,7,8,2',4',5'-hexamethoxyflavone) have been found in *A. haustonianum*.

A screening of 25 plant species showed that the leaves of *Ageratum houstonianum* exhibit absolute toxicity against *Microsporum gypseum* inhibiting the mycelial growth completely. *Mycosporum gypseum* cause ringworm, a prevalent disease of the tropics. The essential oil isolated from the leaves showed mycostatic property at minimum inhibitory concentration of 100 ppm and became mycocidal at 300ppm. The pure oil killed the mycelial disc (5mm dia.) of the test pathogen in one second. It showed broad mycotoxic spectrum inhibiting 30 out of 33 animal and human pathogenic fungi tested. Of the 33 pathogenic fungi tested, *Candida albicans*, *C. pseudotropicalis* and *Cryptococcus neoformans* were highly resistant to *Ageratum* oil, as they remained uninhibited even at 100ppm. However, *Trhichophyton* spp., *Blastomyces dermatitidis* and *Histoplasma capsulatum* were found to be very sensitive to the oil. The toxicity of the oil was not affected by temperature, autoclaving and storage. Further, the oil showed superiority over five prevalent antimycotic drugs viz. griseofulvin, jadit, multifungin, mycoderm and mycostatin. Essential oil (0.55%) was recovered from hydrodistillation of the fresh leaves through a Clevenger apparatus. The oil contained no phenolic compounds and was soluble in hexane, petroleum ether, benzene, chloroform, carbon tetrachloride, ether, n-butanol, propanol, methanol and ethanol. *Ageratum* oil may be used for topical therapy in medicine. Toxicity experiments on human skin showed no toxic effects (Pandey *et al.* 1983).

5.6 AMBROSIA L.

5.6.1 Ambrosia artemisiifolia L.

(=*A. maritima sensu* Wild)

The following compounds have been reported to occur in *Ambrosia artemisiifolia* L. of American origin: coronopilin, cumanin, dihydrocumanin, peruvin, artemisiifolin and isabelin as well as a guandine derivative, agmatin, a flavonoid-isorhamnetin, unidentified alkaloids, essential oil, fatty acids and higher aliphatic alcohols. In the same species growing in Australia a sesquiterpene dilactone, psiloctachyin A has been detected which is absent in the American plant. From a basic chloroform extract of *Ambrosia artemisiifolia* L. collected during the flowering period in a medicinal garden in Poland, the sesquiterpene dilactone, Psilostachyin B, belonging to the group of seco-ambrosanolides, was isolated (Raszeja & Gill 1977).

5.7 ANTHEMIS L.

5.7.1 Anthemis cotula L.

This is an introduced species. The unpleasant, acrid taste is obnoxious to domestic stock and is usually avoided (Watt & Breyer-Brandwijk 1962). It is sometimes called chamomile, but it is not the German chamomile, *Chamomilla recutita* L. (or previously called *Matricaria chamomilla* L.) *Chamomilla recutita* is a commonly used herb and a total extract of its bisabololtype, well known as Kamillosan®, is sold commercially. *Anthemis cotula* L. contains anthecotulid, a linear sesquiterpene lactone, that cause contact dermatitis in concentrations of up to 7.3% (Hausen *et al.* 1984).

5.8 ARCTOTHECA J.C. Wendl.

5.8.1 Arctotheca calendula (L.) Levyns

(=*A. calendulaceum* (L.) Lewin)

(=*Arctotis calendula* L.)

(=*Cryptostemma calendulaceum* (L.) R.Br.)

The juice of *Arcotheca calendula* Levyns is used as an antidote to strychnine. It has narcotic effects in rabbit (Watt 1976). *Arctotheca calendulaceum* (L.) Lewin has been reported to cause contact dermatitis (Rodriguez *et al.* 1976). In the Western Cape province a poultice of the herb of *Cryptostemma* sp., with that of *Arctotis* sp. and that of *Dimorphotheca* sp. is applied to sore breasts and as a douche for uterine cancer (Watt & Breyer-Brandwijk 1962).

5.9 ARCTOTIS L.

In the Western Cape province a poultice of the herb of *Arctotis* sp. with that of *Cryptostemma* sp. and of *Dimorphotheca* sp. is applied to sore breasts and as a douche for uterine cancer (Watt & Breyer-Brandwijk 1962).

The polyynes $MeCH{=}CH[C{\equiv}C]_4CH{=}CH_2$ and $H_3C[C{\equiv}C]_5CH{=}CH_2$ are common in the genus *Arctotis* (Bohlmann & Le Van 1977).

5.9.1 Arctotis arctotoides (L.f.) O.Hoffm.

(=*Osteospermum arctotoides* L.f.)

(=*Venidium arctotoides* (L.f.) Less.)

(=*Venidium decurrens* Less.)

The leaf juice of *Venidium arctotoides* Less. is a Xhosa remedy for epilepsy. It is said to produce nausea and tingling in the toes and fingers (Watt 1967). The Xhosa administer the leaf juice of *V. arctotoides* Less. in large doses for treatment of epilepsy, indigestion and cattarrh of the stomach. They also use the leaf juice or paste of the leaf as a local application to wounds. The application produces smarting (Watt & Breyer-Brandwijk 1962). The leaves of *V. arctotoides* are used externally for an itchy nose by the Xhosa (TRAMED database, index card 649). *V. decurrens* are used for the following by the Xhosa: Washing after giving birth; an itchy nose; the leaves are made into a paste

for tattoo wounds; the juice of the leaves is used for earache, and a decoction of the leaves is used as a gargle, emetic, purgative and enema (TRAMED database, index card 681).

The aerial parts of *A. arctotoides* afforded sesquiterpene lactones, the 11β,13-dihydroguaianolides as well as a chlorohydrine. Two 2Z-farnesol derivatives have also been isolated. An extract of the aerial parts of plants collected in Egypt have also yielded β-farnesene, lupeyl acetate, lupeol, stigmasterol, β-sisterol and abietic acid, guaianolides and a germacranolide. El Dahmy *et al.* (1986) suggested that 5α-hydroxy-guaianolides may be characteristic of the genus *Arctotis* (El Dahmy *et al.* 1986).

5.9.2 Arctotis auriculata Jacq.

(=*A. melanocycla* Willd. ex Harv.)

(=*A. namaquana* Schltr. ex Lewin)

Extracts of *Arctotis auriculata* exhibit antimycobacterial activity. The leaves, stems and roots are equally active against *Mycobacterium smegmatis*, with the active ingredient being mainly lipophylic in nature. (The MIC of the petroleum ether leaf extract was 8.5 mg/ml.) The lipophilic extracts of all three plant organs of *A. auriculata* inhibited the growth of *P. aeruginosa.* (The MIC of the petroleum ether leaf extract was 5 mg/ml) Infections caused by *Pseudomonas aeruginosa* are amongst the most difficult to treat with conventional antibiotics. *Staphylococcus aureus* proved sensitive to lipophilic extracts of the leaves as *A. auriculata.* The inhibition was however only slight. Extracts were inactive against *Candida albicans.* The plant contains tannins, distributed throughout, and flavonoids in the leaves and stems. Alkaloids and cyanogenic glucosides were detected in the leaves. Plants were cleaned with distilled water, seperated into leaves, stems and roots and air-dried in an oven at 40°C for 72h. The dried plant materials were milled to a fine powder and were successively extracted with petroleum ether, chloroform, ethanol and methanol. Aqueous extracts were prepared by adding the powdered plant material to warm water for 30 min, followed by a methanol extraction (Salie *et al.* 1996).

5.9.3 Arctotis stoechadifolia P.J.Bergius

(=*A. decumbens* Thunb.)

(=*A. grandis* Thunb.)

(=A. rosea Less., non Jacq.)

The plant has given positive antibiotic tests with *Staphylococcus aureus* (Watt & Breyer-Brandwijk 1962).

Halim & Zaghloul (1981) have isolated α-Amyrin, β-sisterol, isorhamnetin (quercetin 3'-methyl ether), quercetin, isorhamnetin-3-O-galactoside and quercetin-3-O-galactoside from the leaves of *A. grandis* Thunb. The air dried ground material was extracted with methanol, which was successively extracted with petroleum ether, chloroform and ethyl acetate using a liquid/liquid extractor. The petroleum ether extract was saponified by refluxing with 10% alc. KOH. The unsaponified material was extracted with ether and fractionated on an alumina column using benzene containing increasing amounts of ethyl acetate as eluent to afford α-amyrin and β-sisterol. The chloroform-soluble fraction

revealed the presence of the two flavonoid aglycones and the ethyl acetate-soluble fraction contained the flavonoid glycosides (Halim & Zaghloul 1981). The phytosterol, β-sisterol, has antihyperlipoproteinaenemic activity and is an essential component of plant cell membranes (Harborne & Baxter 1993). Quercetin is the commonest flavonoid in higher plants, usually present in glycosidic form. It inhibits many enzymes, e.g., protein kinase C, lipogenases, lens aldose reductase, 3',5'-cyclic adenosine monophosphate phosphodiesterases. It is a radical scavenger. Quercetin also inhibits smooth muscle contraction, and proliferation of rat lymphocytes. It is antigonadotropic, anti-inflammatory, antibacterial, antiviral and antihepatotoxic, and shows some mutagenic and allergenic properties (Harborne & Baxter 1993). The antibiotic activity of the plant extract could possibly be due to the flavonoid, quercetin.

The roots of *Arctotis grandis* Thunb. contain the widely distributed simple polyacetylenes, tridecapentaynene and tridecadiene-(1,11)-tetrayne-(3,5,7,9), and an unusual sesquiterpene acetate, 12-acetoxysesquisabinene (Bohlmann & Le Van 1978). Two guaianolides and a further sesquiterpene lactone have also been isolated from the plant (Halim *et al.* 1980). The aerial parts contain the sesquiterpene lactone, arctolide (Samek *et al.* 1977). Arctolide has cytotoxic and antitumour activities (Harborne & Baxter 1993).

5.10 ARTEMISIA L.

Members of the genus *Artemisia* produce a myriad of terpenoid compounds in their glandular trichomes. The surfaces of the leaves, flower parts, stems and other aerial parts of the shoots of virtually all species of *Artemisia* investigated are covered with capitate glands filled with resinous oils which contain most of the monoterpenes and virtually all of the sesquiterpene lactones of the leaf. As glands mature on the older leaves, the sacs rapture releasing the resinous oils over the leaf. Many of these compounds, especially the sesquiterpenoid lactones, are biologically active as fungicides, herbicides, antimicrobials, insecticides and insect antifeedants. Throughout history this genus has been the source of folk medicines, spices, flavourings and insect repellents. These properties of many of the terpenoids indicate that these compounds provide strong protection against pathogens, nematodes and herbivores (Duke *et* al. 1988).

Numerous terpenoids are strong phytotoxins. The sesquiterpenoid from the Asian species *Artemisia annua*, artemisinin, posess significant activity against multidrug-resistant malaria and was also found to be a potent phytotoxin. Two commercial herbicides are based on the chemistry of the monoterpenes from *Artemisia*: Chlorinated camphene was used as a herbicide in legume crops and cinmethylin is a close analog of 1,8-cineole. An endoperoxide seems to be a requirement for phytotoxicity of sesquiterpenoids (Duke *et* al. 1988).

Numerous terpenoids of *A. vulgaris* were found to be mosquito repellents. Several other monoterpenes found in *Artemisia* such as α-pinene have insect repellent properties towards other insect species. Sesquiterpenoids are known for their bitter tastes and thus might be expected to act

as antifeedants. For instance, the sesquiterpenoid, caryophyllene has aphid repellent activity. (Duke *et al*. 1988)

5.10.1 Artemisia afra Jacq. ex Willd.

Artemisia afra Jacq. known as African Wormwood or "wildeals", is one of the most widely used and popular medicines in South Africa. The usual preparation is an infusion or decoction, often made syrupy by the addition of sugar, especially when the medicine is for bronchial troubles. It is used for coughs and colds, chills, dyspepsia, loss of appetite, stomachache and other gastric dearrangements (indigestion?), colic, croup, whooping cough, gout and as a purgative (Watt & Breyer-Brandwijk. 1962) as an anthelmintic and as an anti-inflammatory agent (Iwu. 1993). The infusion or decoction is also used as a lotion to bathe haemorrhoids, as a hot bathe to bring out the rash in measles, and in the ear for earache. It is held in the mouth to ease the pain of gumboils and to hasten their bursting, and is taken in fevers and in "blood poisoning". The vapour from the boiling leaves is inhaled for respiratory infections, and the genitalia are steamed with the vapour for menstrual chill, and after childbirth. The vapour of a hot infusion is used to steam the throat in scarlet fever and the infusion used as a gargle. The plant is used for measles and other fevers, including malaria. The fresh tip of the plant is inserted into the nose for headaches and colds, and into a hollow tooth to relieve toothache. A poultice of the leaf is applied locally to relieve neuralgia, to the swelling in mumps and to the abdomen in infantile colic. In the last case the leaf is usually moistened with brandy (Watt & Breyer-Brandwijk. 1962). The leaf is inserted in the nostrils for headaches (by the Zulu) and for influenza or steam inhaled (by the Xhosa) (Hutchings & Van Staden 1994). A fermentation prepared with the heated herb is given to children with a sore throat (Iwu 1993). A brandy tincture is taken by the mouth for colic (Watt & Breyer-Brandwijk. 1962), while a weak infusion of the leaves is used in Tanzania (Iwu 1993). A tincture is used for relief of anthracosis ("miners phthisis") and was formerly used as an efficient vermifuge. An infusion has been used in the Western Cape as an eye lotion, and the leaf and stalk have been used as a discutient. The Zulu use an infusion as an emetic and a water or milk suspension of the ground plant as an enema for children and a decoction to be drunk as a blood purifier (Watt & Breyer-Brandwijk 1962).

The Southern Sotho take a decoction as as an enema for constipation, and make a lotion from the plant for washing the body. The Xhosa have used the plant, either alone, or together with the leaf of *Eucalyptus* sp., as an influenza remedy. The Manyika use a decoction of the leaf as a blood tonic to benefit "bad blood", stomach pains and pimples. In Eastern Africa the plant is used as an emetic, anthelminthic and febrifuge. An infusion of *A. afra* is said to be diaphoretic and bitter. The crude oil yields about 13.5% dextrorotatory camphor (Watt & Breyer-Brandwijk 1962), α- and β-thujone and 1,8-cineole as major constituents (Moody *et al.* 1994). The cold relieving effect of the aqueous extract of the plant has been ascribed to cineole. The oil is said to be toxic, producing haemorrhagic nephritis, non-fatty degeneration of the liver and pulmonary oedema and sometimes abortion in rabbit and guinea pig (Watt & Breyer-Brandwijk 1962). Thujone is used as a counterirritant and anthelmintic. Ingestion may cause convulsions. 1,8-Cineole has anthelmintic, expectorant and antiseptic activities. Also it shows cockroach repellent activity (Harborne & Baxter 1993).

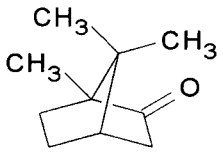
The oil was tested for antimicrobial and antioxidative properties. Twenty-five bacterial species and three filamentous fungi were used to assess the antimicrobial properties. Seeded plates had wells punched in the agar into which were placed 15µl of four concentrations of volatile oil dissolved in absolute alcohol. Fifteen test bacteria and one fungus showed a high degree of inhibition of growth caused by the volatile oil. The most susceptible organisms were *Acinetobacter calcoaceticus*, *Beneckea natriegens*, *Brevibacterium linens*, *Brochothrix thermosphacta*, *Citrobacter freundii*, *Klebsiella pneumoniae* and *Serratia marcescens*. It is interesting to note that one of the ethnopharmaceutical properties claimed for this oil is in the treatment of coughs and colds, conditions related to infection with *K. pneumoniae*. It is also noteworthy that this oil is strongly inhibitory to all three test fungi, and in particular to the mycotoxigenic strain *Aspergillus ochraceus*, where even in concentrations of 1µg/ml, an inhibition of over 60% was recorded. The oil exerted considerable antioxidant effect. Wells were punched into agar plates containing β-carotene and linoleic acid into which are placed 15µl of volatile oil. The intense orange coloration is lost during incubation and oxidation at 45°C for four hours. Plant volatile oils with anti-oxidative properties are noted by a zone of colour retention. The diameter of the zone of colour retention was 7.5mm, which compare favourably with many other culinary and medicinal plant volatile oils (Graven *et al.* 1992), β-Carotene has provitamin A activity. Linoleic acid (linolic acid) is a nutrient and an essential fatty adic component of vitamin E. It is regarded as a beneficial dietary component for men who may be prone to coronary heart disease (Harborne & Baxter 1993).

The aerial parts of *Artemisia afra* Jacq. ex Willd. were screened for prostaglandin-synthesis inhibitors. Prostaglandins are involved in the complex processes of inflammation and are responsible for the sensation of pain. A low activity of 65% and 19% inhibition of cyclooxygenase was obtained with the ethanol and aqueous extract respectively. Other *Artemisia* species have however been shown to possess anti-inflammatory activity (Jäger *et al.* 1996).

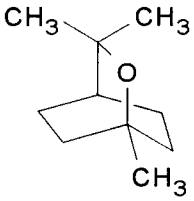
Graven *et al.* (1992) reported that the main constituants of the volatile oil (of plants collected in the full vegetative season in the wild) were α- and β-thujone (52%), 1,8-cineole (13%), camphor (15%) and α-pinene (2%), with other monoterpenes and sesquiterpenes under 2% (camphene, γ-terpinene, p-cymene and α-terpinolene. Volatile oil yield is between 0.3% and 1.4%. The analysis confirms the results of other authors. However, collection of plants from various parts of their natural habitat revealed considearable variation in levels of the individual constituents of the oil (for example α- and β-thujone 27-60%, camphor 4-23%, 1,8-cineole 1-14%) (Graven *et al.* 1992) In another quantative investigation by Moody *et al.* (1994) of the volatile oil of *A. afra*, only 3 of the 21 constituents were not identified, They found the main constituents were cis-2,7-dimethyl-4-octene-2,7-diol (19.03%), 1,8-cineole (17.55%), tricosane (13.92%) and 3,3,6-tyrimethyl-1,5-heptadien-4-one (11,67%). Campor (6.21%), linalyl propionate (4.96%) and α-styrene (4.03%) were also present. Moody *et al.* (1994) found only 1.66% α-thujone while others reported it as one of the major constituents of the oil. Other minor constituents include γ-elemene, which is probably an artefact formed during distillation, β-santalol and camphene (Moody *et al.* 1994). It is known that the composition of essential oil of *Artemisia* species varies considerably from one phytogeographical region to another

and also on the time of harvest (Ahmed & Misra. 1994). Earlier reports indicate the probable presence of ceryl cerotate, triacontane and quebrachitol (Iwu 1993).

Camphor is an irritant, it affects the central nervous system and is toxic to humans. It is used commercially as a moth repellent and as a preservative in pharmaceuticals and cosmetics. It is a mild analgesic and is also used as a topical antipruritic. 1,8-Cineole is the main constituent of oil of *Eucalyptus*. It has anthelmintic, expectorant and antiseptic activities and also shows cockroach repellent activity (Harborne & Baxter 1993). 1,8-Cineole enhances the penetration of hydrophilic compounds through the human epidermal membranes (Yamane *et al.* 1995).



(-) form
Camphor



1,8-cineole

(Harborne & Baxter 1993)

Bohlmann and Zdero (1972) extracted fresh, ground material of *A. afra* with Et_2O and the resulting extract separated by column chromatography and TLC. The flowerheads of *A. afra* are reported to contain the coumarin, scopoletin (Bohlmann & Zdero 1972). Scopelitin has hypotensive activity in animals and it also exhibits spasmolytic, antibacterial and antifungal properties (Harborne & Baxter 1993). The roots were found to contain, besides the isomeric coumarins (mainly 6) the known acetylenes (1-5), while the aerial parts contain thujone and umbelliferone-derivatives but no acetylenes as have been found in most other *Artemisia* species.

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2

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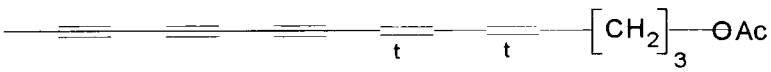

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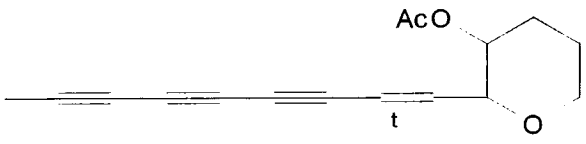

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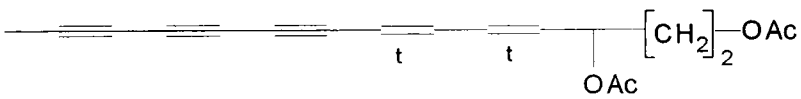

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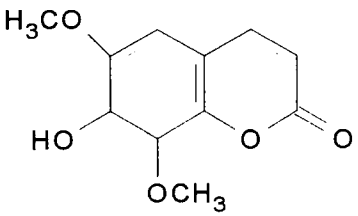
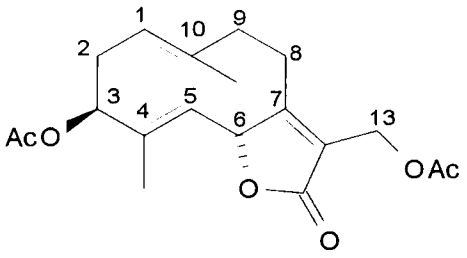


7 CH_3

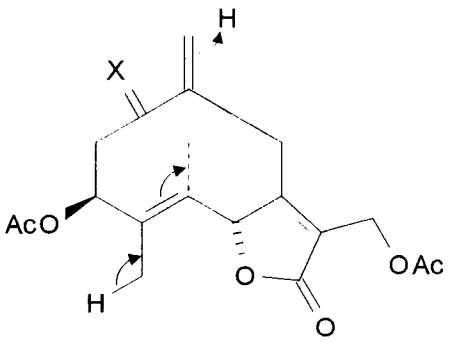
The polyacetylenes triyne-triene (7) and its derivative pontica epoxide (2) were also found in *A. afra* Jacq (Greger 1977).

Thujone is used as a counterirritant and anthelmintic and ingestion may cause convulsions. The coumarin, umbelliferone, has antifungal and antibacterial activities and is used in sunscreen lotions and creams (Harborne & Baxter 1993). Thujone is toxic with hallucinogenic and addictive properties. It is the toxic principle in *A. absinthium* L. and the liquor absinthe (Hutchings & Van Staden 1994).

Besides isofraxidin, which has been found in the aerial parts of *A. afra*, Jakupovic *et al.* (1988) isolated α- and β-thujone, camphor, ascaridol, spathulenol, several known guaianolides from the aerial parts and glaucolides, 6, 7a, 7b, 8 and 9. The roots afforded in addition to the acetylenes, -famesene, -humulene, squalene, iso-fraxidin and its -D-glucopyranoside as well as 12-hydroxy-α-cyperone. While the highly oxygenated guaianolides of types 1-5 are characteristic for *Artemisia* species, the isolation of glaucolides is very unusual. Glaucolides are only very common in the tribe Vernonieae, although some are reported from *Cotula* species (Jakupovic *et al.* 1988). The monoterpene, ascaridol has anthelmintic activity and is toxic to mammals. Squalene (the immediate precursor of all the cyclic triterpenoids) has bactericidal and antitumor activities and is also an immunostimulant. Umbelliferone has antifungal and antibacterial activities. It is used in sunscreen lotions and creams (Harborne & Baxter 1993).



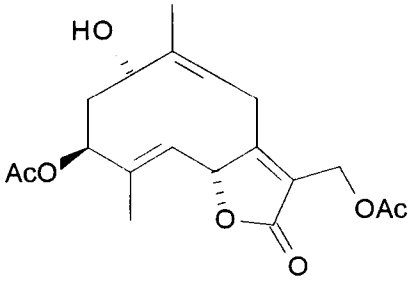
6 Artemisia glaucolide



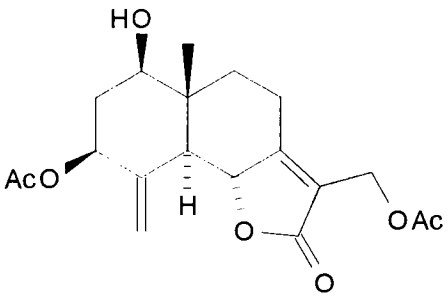
7a 7b

X αOH.H βOH.H

7) 1α- and 1β-Hydroxyafraglaucolide



8) 1α-Hydroxyisoafraglaucolide



9) Eudesmaafraglaucolide

The production of flavonoid aglycones in *A. afra* Jacq. is very low but Wollenweber and Mann (1989) identified six compounds by direct comparison with markers. They were found to be the flavones, luteolin, luteolin-7-methyl ether, apigenin-7-methyl ether (genkwanin), the 6 methyl and the 6,3'-dimethyl ethers of 6-hydroxyluteolin (nepetin and jaceosidin), and the flavonol quercetagetin-3,6-dimethyl ether (axillarin) and the coumarin scopoletin (Wollenweber & Mann 1989). Air dried leaf material was rinsed in acetone to dissolve the exudate (4% of d.w.). The resinous exudates were passed over a Sephadex column, eluted with MeOH to separate the flavonoids from the terpenoids. The yield of flavonoids was so small that they could only be identified by direct comparison with standards (Wollenweber & Mann 1989).

5.10.2 Artemisia vulgaris L.

In China *A. vulgaris* is used as a traditional herb medicine. Old leaves of this weed are dried and made into a moxa (soft wooly mass) which is used as a cautery (burning or searing) by being ignited on the skin. In Chinese cuisine, young leaves of this weed can be added to rice cakes or dumplings to impart a pleasant aroma. In rural areas of China bundles of the weed are slowly burned to produce smoke which is reportedly repellent to heamophagous insects. In a preliminary study, a benzene-methanol extract of *A. vulgaris*, when applied to human skin, showed repellancy against the yellow fever mosquito, *Aedes aegypti.*

Artemisia vulgaris L. contain insect repellents which can be released from the plant tissues by combustion. To isolate and identify the repellent compounds, the dried, pulverised whole plant were steam-distilled to give a repellent essential oil which was fractioned by column chromatography. Active fractions were analized by capillary GC and by combined GC-MS. A number of compounds, mainly monoterpenoids, were identified. When tested as repellents against the yellow fever mosquito *Aedes aegypti* L. (±)-linalool, (±)-camphor, (+)-camphor, (-)-camphor, isoborneol, (-)-borneol, terpinen-4-ol, and isobornyl acetate were active at 0.14 mg/cm^2 or higher. Nonanone-3, (α + β)-thujone, and bornyl acetate were active at 28 mg/cm^2 or higher. β-Pinene, myrcene, α-terpene, (+)-limonene, and cineole were active at 1.4 mg/cm^2. Of the repellent compounds identified, terpinen-4-ol was the most active and was as effective as dimethyl phthalate. The *Artemisia* essential oil showed 91% repellency (0.4 mg/cm2). Method: Air dried plants were pulverized and macerated in water overnight and steam distilled until no more volatile substance was obtained. The distillate was extracted three times with benzene, and the benzene extracts were combined and dried over Na_2SO_4. Evaporation of the solvent gave *Artemisia* essential oil. The oil was chromatographed on a Florisil column and eluted with hexane, hexane-benzene, benzene, benzene-acetone, acetone and then methanol. An olfactometer was devised for determining the repellency of the various fractions obtained during the isolation procedure and the various compounds identified during the GC and GC-MS analyses (Hwang et. al. 1985a).

On screening the major components of the essential oil of *Melaleuca alternifolia* for antimicrobial activity, it was found that terpinen-4-ol was active against all the test organisms while linalool

and α-terpineol were active against all the organisms tested with the exception of *Pseudomonas aeruginosa* (Carson & Riley 1995).

The root of *A. vulgaris* L. is antibiotic against *Candida albicans* (Towers *et al.* 1977).

In a capillary gas chromatogram, 24 peaks were seperated of which 13 were identified. Compounds identified were camphene β-pinene, myrcene, carvone, 1,8-cineole, α-thujone, linalool, β-thujone, camphor, isomenthone, borneol, terpinen-4-ol and estragole. The active fraction was composed of 26% camphor, 22% borneol, 8% terpinen-4-ol, 8% estragole, 6% camphene, 6% β-pinene, 5% isomethone and 19% minor compounds. These compounds were individually bioassayed for repellancy against *Aedes aegypti*. dl-Camphor, d-camphor and terpinen-4-ol exhibited more than 80% repelancy camparable to that of dimethyl phthalate. A mixture of α- and β-thujone and estragole posessed more than 80% repellency superior of that of deet. Linalool, (-)-camphor l-borneol, dl-isoborneol, l-methone and isomentoneshowed more than 70% repellency. β-pinene, myrcene, α-terpinene and 1,8-cineole showed some repellancy only at higher doses. Except for estragole which is a p-allylanisole, all compounds isolated and identified from *A. vulgaris* showing mosquito repellancy are monoterpenes (Hwang *et al.* 1985b).

Linalool has sedative and fungistatic activities and is antiseptic (five times stronger than phenol). Limonene is a skin irritant and has expectorant and sedative activities. Estragole stimulates liver regeneration. It shows hypothermic and DNA binding activities (Harborne & Baxter 1993).

The anti-inflammatory activity of an ethanol extract of *A. vulgaris* L. (which was treated to remove pigments with petroleum ether) was evaluated in rats using the carrageenin-induced pedal edema assay. A dose of 100 mg/kgx2 resulted in a 32% inhibition (Benoit *et al.* 1976).

5.11 ASPILIA Thouars

The genus *Aspilia* is important in the traditional medicine of African coutries such as Kenya, Tanzania, Ruanda, Burundi, Uganda, Mosambique and Nigeria. At least five species of African *Aspilia* including *A. mossambicensis* and *A. pluriseta* have widespread medical uses in East African countries. Leaves are used most commonly, although root preparations are important as well. Ailments treated are mainly skin infections, stomach problems, eye infections and venereal diseases. *Aspilia* species contain thiarubrines which are phototoxic (Towers & Champagne 1977).

Kaurene diterpenes are found widespread in the genus *Aspilia*. Kaurenoic acid has antibacterial and antihepatotoxic acitvity. Kaurenoic acid and grandiflorenic acid exhibit potent uterotonic activity (Page *et al.* 1992).

5.11.1 Aspilia eenii S.Moore

(=*A. attrivittata* Merxm.)

A. attrivittata is used in other parts of Africa for eye infections (Ayensu 1978).

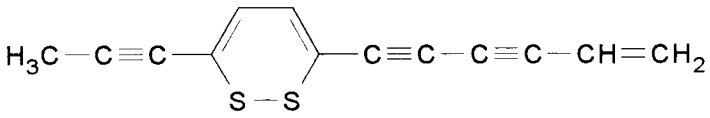
5.11.2 Aspilia mossambicensis (Oliv.) Wild

(=*Wedelia diversipapposa* S.Moore)

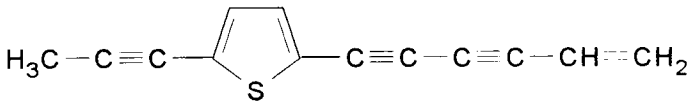
(=*Wedelia mossambicensis* Oliv.)

Two potent stimulators of uterine contraction, the diterpenes, kaurenoic acid and grandiflorenic acid were isolated from the leaves of *Aspilia mosambicensis*. This supports a hypothesis that wild chimpanzees consume *Aspilia* species for their pharmacological properties and may explain why female chimpanzees consume *Aspilia* leaves more frequently than do males. It is used in traditional medicine as a galactogogue and to alleviate menstrual cramps. *A. holstii* is administered as a galactogogue, as well as in the treatment of eclampsia, a complication in pregnancy (Page *et al.* 1992). The Shambala drink an extract of the root of *Aspilia holstii* O. Hoffm. for the relief of lumbago, sciatica and neuralgia (Watt & Breyer-Brandwijk 1962).

Thiarubrine A an antibiotic dithiane polyyne, is present in the roots but not in the leaves (Page *et al.* 1992). Polyines have been described from a number of higher plant families, but their thiophene and disulphide derivatives seem to be restricted to the Asteraceae. The thiophenes have been studied intensively since the discovery of their phototoxicity. Light independant antifungal and antibiotic effects of thiarubrine A have been described by Contabel and Towers (1989). It was shown to be toxic in the dark to *Candida albicans* and *Saccharomyces cerevisiae* as well as to a number of bacterial species at a concentration of 1ppm. Exposure to UV-A radiation enhances the toxicity of thiarubrine A. However, UV-A also rapidly converts thiarubrine A to thiophene A. This compound in turn is inactive in the dark, but inhibits *C. albicans* and other microorganisms at 0.1ppm in UV-A. The UV-phototoxicity of thiophene has made it very difficult to assess experiments in which thiarubrine A is exposed to UV-A, as one cannot readily seperate the activity of thiarubrine A from that of its thiophene conversion product. Thus, the observed inhibition of microorganisms by thiarubrine A in UV-A could be due to the compound itself prior to photoconversion, to the phototoxic thiophene A, or to a mechanism of toxicity involving the conversion process itself (Constabel & Towers 1989).



Thiarubrine A



Thiophene A

Constabel and Towers (1989) report that the disulphide ring is necessary for activity in the dark. The disulphide compounds showed greater inhibition zones in UV-A than in the dark. Furthermore, they were more toxic under these conditions than the corresponding thiophenes. This led to the hypothesis that the process of disulphide ring-thiophene conversion is important in the toxicity of the disulfide compounds in UV-A. Incandescent light, filtered through a layer of water, to eliminate

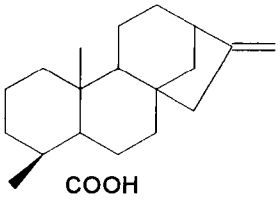
possible traces of UV light, caused rapid and complete conversion of thiarubrine A to thiophene A. Neither thiophene A nor α-terthienyl, included as a control was photosensitized. The visible light enhanced growth inhibition of thiarubrine A against *E. coli* and *S. cerevisiae* (Constabel & Towers 1989).

Two types of photosensitization occur in polyines. Type I, also called non-photodynamic, involves the formation of an activated species, probably a free radical, which then damages the cells. Straight-chain polyines are predominantly photosensitized by this process. Type II, or photodynamic photosensitizers, such as α-terthienyl transfer energy to molecular oxygen resulting in the formation of toxic singlet oxygen. In phenylheptatriyne (PHT), both types of photosensitization are in competition. Photosensitization of type I is more important afainst *E. coli* than type II and type II is more effective against yeast than type I. Thiophenes show a pattern of photosensitization similar to that of PHT (Constabel & Towers 1989).

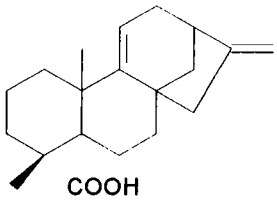
The target molecules of thiarubrine A in dark or light are not known, though it appears that different components are involved in each case. Viruses are unaffected by thiarubrine A unless irradiated with UV-A, and under these conditions membrane bound viruses are more susceptible than non-membrane bound viruses. Furthermore, the compound causes leakage of glucose or K^+ from monolamellar vescicles under UV-A, but not in the dark. Thus it appears that thiarubrine A or its thiophene product acts on membranes. In the dark a different target seems to be involved (Constabel & Towers 1989).

Kaurene diterpenes are found widespread in the genus *Aspilia*. Kaurenoic acid has antibacterial and antihepatotoxic acitvity. Kaurenoic acid and grandiflorenic acid exhibit potent uterotonic activity. *Ent*-kaur-16-en-15β-ol (kaurenol) stimulates progesterone production in rat and avian granulosa cell preparations alone but attenuates follicle stimulating hormone and luteinizing hormone-stimulated progesterone production (Page *et al.* 1992).

Method: Extraction: Ground dried leaves were repeatedly extracted in MeOH and combined extracts concentrated under reduced pressure. The crude green residue was treated with activated charcoal which resulted in a yellow oil which was chromatographed in a silica gel 60 column and eluted with a gradient of hexane and increasing amounts of EtOAc. 4α-kaur-16-en-18-oic acid (kaurenoic acid) and 4α-kaura-9(11),16-dien-18-oic acid (grandiflorenic acid) were identified by ^1H and ^{13}C NMR and EI-MS (Page *et al.* 1992). Kaurenoic acid and grandifloric acid were tested using an *in vitro* oestrogenised female guinea pig uterine assay. Aqueous suspensions of kaurenic acid and grandiflorenic acid showed uterostimulatory effect at 50 mg/ml concentration (Page *et al.* 1992).



Kaurenoic acid



Grandiflorenic acid

5.11.3 Aspilia natalensis (Sond.) Wild

(=*A. welwitschii* O.Hoffm.)

(=*Wedelia natalensis* Sond.)

The Zulu use an infusion of the leaf and stem of *Wedelia natalensis* Sond. as an emetic and as an enema in diseases of the chest and abdomen. They have also used an infusion of the root as an enema in diarrhoea and dysentery, and for fever an infusion of the root and leaf is used as an emetic, as an enema and as an internal remedy. The emetic action is also used for biliousness and for stomach and bowel disorders in general, but it is not prescribed to the child or to the pregnant woman. In the latter instance it is said to produce abortion. The bruised leaf, after steeping in water is used by the Zulu as a dressing for wounds. The leaf and root are used to kill vermin (Watt & Breyer-Brandwijk 1962). The leaves are also used for fevers and colds and infection of the respiratory system (TRAMED database, index card 1548).

Noristan has done pharmacological research on Aspilia natalensis. The method is described in the introduction to this chapter. The different fractions were combined to form three groups. The extracts were active in the writhing test, as a narcotic analgesic and a diuretic. Group 1 and 2 increased the Na^+ excretion by 108% and 138% respectively, $p<0.05$ at 500 mg/kg in both cases. Group 3 was the most active as analgesic with 3 of the 4 mice not showing any pain reaction with a dose of 90 mg/kg i.p. but with groups 1 and 2, at a dose of 300 mg/kg i.p., 3 and 2 of the 4 mice respectively did not show any pain reaction. (Three of the four mice did not show any pain reaction with the reference, morhpine sulphate at 3 mg/kg) In the writhing test, to determine pain relieving effects, group 1 caused a 37% inhibition, $p<0.05$ at a dose of 90 mg/kg p.o. but groups 1 and 2 were much less active. On secondary pharmacological investigation of the diuretic activity, it was found to be inactive, but a fraction of a methanol extract was highly active as an analgesic. Further separation of the fraction was however very difficult because of the high solubility in water and most of the plant material was left in the column (Noristan not published).

5.11.4 Aspilia pluriseta Schweinf. subsp. *pluriseta*

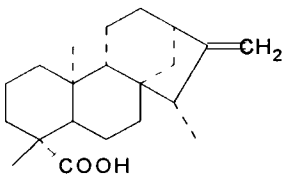
(=*A. brachyphylla* S.Moore)

(=*A. vulgaris* N.E.Br.)

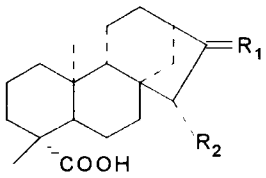
The leaves of *Aspilia pluriseta* are extensively used in folk medicine in Kenya by application on skin disease or onto fresh wounds. Lwande (1985) have isolated three kaurene diterpenoids from *A. pluriseta* that showed antibacterial activity against gram-positive and gram-negative bacteria. (-)Kaur-(16)en-(19)oic acid inhibits at 75μg/disc *Xanthomonas pelargonii*, a plant pathogenic

bacterium, and its activity abainst larvae of Lepidopters is known. 15β-angeloyloxy-ent-kaurenic acid and 15-β-tiglinoyloxy-ent-kaurenic acid inhibit *Escherichia coli, Bacillus mycoides, Macrococcus luteus, Bacillus subtilis* and *Staphylococcus aureus* at concentrations >100μg/disc (Lwande *et al.* 1985).

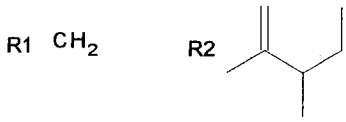
Method: Air dried plant material was extracted with MeOH in the cold and the extract evaporated. The crude oily residue was evaporated between $CHCl_3$ and water. The $CHCl_3$ evaporated to yield an oil which was further partitioned between hexane and MeOH:H_2O, 5:1. The hexane fraction was evaporated to yield an oil. A part was column chromatographed (Hexan-EtOAc, 9:1) yielding impure (-)kaur-(16)en-(19)oic acid and 15β-angeloyloxy-ent-kaurenic acid. Pure (-)kaur-(16)en-(19)oic acid and 15β-angeloyloxy-ent-kaurenic acid were obtained by preparative TLC ($CHCl_3$). The MeOH:H_2O was evaporated and the resulting aqueous mixture extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract yield an oil, column chromatography ($CHCl_3$:EtOAc, 8:2)of which afforded impure 15-β-tiglinoyloxy-ent-kaurenic acid which was purified further by preparative TLC (hexane:EtOAc, 6:4) yielding pure 15-β-tiglinoyloxy-ent-kaurenic acid. Antibacterial activity: The paper disc method was used. The antibiotic assay discs (Whatman no. 1,0.6 cm diameter) were loaded with a prescribed amount of compound (10-300μg/disc)in chloroform. The control disc was treated with 100μl chloroform and sufficient time allowed for the chloroform to evaporate. The discs were arranged in petri dishes containing Tryptone-soya agar which had been streaked with 0.1ml of the test bacterium ($3x10^8$ cells/ml by Mcfarland nephelometer barium sulphate standard). Plates were incubated at 37°C and diameters of inhibition zones measured after 24h. The experiment was repeated three times and the minimum inhibitary concentration recorded (Lwande *et al.* 1985).



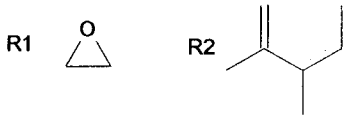
(-)kaur-(16)en-(19)oic acid



15b-angeloyloxy-ent-kaurenic acid



15-b-angeloyloxy-16, 17 epoxy-ent-kaurenic acid



The aerial parts of *Aspilia plureista* Schweinf. ssp. *plurista* contain the lactones, 1α-acetoxy-3β-isobutyryloxy-6-O-methacryloylsteiractinolid and 1α,3β-diacetoxy-6-O-methacryloylsteiractinolid-germacrene, and ent-kaurenic acid, 15α-tigloyloxy-ent-kaurenic acid, 15α-isovaleroyloxy-ent-kaurenic acid, 15α-isobutyryloxy-ent-kaurenic acid, germacrene D, α-humulene, phytol and lupeol. The roots contain ent-kaurenic acid, 15α-tigloyloxy-ent-kaurenic acid and ent-kauren-19-al, γ-humulene, germacrene D and traces of two thiophenes (Bohlmann, Jakupovic *et al.* 1983).

5.12 ASTER L.

Aster spp., as secondary selenium absorbers, may prove dangerous in hay to livestock. Many of them are used in folk-medicine as remedies for coughs, headaches, syphilis, stomach and intestinal complaints, internal parasites (as strong purgative) and as antidote for snakebites (Ross *et al.* 1984).

The genus *Aster* contain acetylenic compounds and umbelliferone derivatives (Tsankova & Bohlmann 1983).

5.12.1 Aster bakeranus Burtt Davy ex C.A.Sm.

(=*A. asper* J.M.Wood & M.S.Evans)
(=*A. bakeranus* Burtt Davy ex C.A.Sm. subsp. *angustifolius* Lippert)
(=*A. bakeranus* Burtt Davy ex C.A.Sm. subsp. *intermedius* Lippert)
(=*A. bakeranus* Burtt Davy ex C.A.Sm. subsp. *ovalis* Lippert)
(=*A. bakeranus* Burtt Davy ex C.A.Sm. subsp. *septentrionalis* Lippert)
(=*A. grauii* Lippert)
(=*A. hispidus* (Thunb.) Baker)
(=*Diplopappus asper* Less.)
(=*Diplopappus natalensis* Sch.Bip.)
(=*Felicia asper* Burtt Davy)

The "bulb" or root of *Aster hispidus* is used by the Xhosa as an enema for worms and a prolapsed rectum. Two tablespoons of the crushed root, mixed with warm water is used for the enema and also for weaning babies (Tramed database; index card 129). For the relief of colic the Southern Sotho inject an enema of a decoction of the root of *A. hispidus* Bak. made with *Helichrysum callicomum* and *Helichrysum rugulosum*. A very acrid resin (1.9%) has been isolated from the root and tuber. A decoction of the plant produces a strong emetic action, purgation and depression (Watt & Breyer-Brandwijk 1962).

The root is ground and snuffed by the Xhosa for headaches. This induces sneezing. They also use the pounded root to clean their nostrils. It is mixed with water and sniffed by the Zulu for headaches and they also use it for snakebite. It is reported to have been used in fatal human poisoning, but was not found in the victims stomach. Emesis and depressant effects were noted in animals, but no striking toxic effects of the roots and tubers were observed (Hutchings & Van Staden 1994).

Noristan has also done research on *Aster bakerianus* as described in the introduction to this chapter. Two groups of extracts were submitted for pharmacological evaluation. The Irwin screen for group 1 revealed LD_{50} >300 mg/kg while for group 2 the LD_{50}~55 and ED_{50} neurotoxic~55. Signs of CNS depression were observed, probably a neuroleptic, at all doses tested. All animals were dead 24 hours after administering 300 & 100 mg/kg of group 2. In the Writhing test group 1 showed a 50.88% inhibition of pain at a dose of 500 mg/kg (Aspirin had a 91.81% inhibition). Group 2 showed 26% inhibition at 50 mg/kg p.o. (Noristan not published).

The roots of *A. bakeranus* Burtt. Davy ex C.A. Smith. contain *ent*-kaurenic acid, *ent*-kauren-19-al, friedelin, euphone and further triterpenes, while the aerial parts contain squalene and the monoterpene, 6,7-dihydroxy-6,7-dihydro-*cis*-ocimene (Tsankova & Bohlmann 1983).

The strong purgative action may explain its use as vermifuge. The snuff is used for headaches and causes sneezing. The belief among many Africans that spirits (that are responsible for illness) are expelled by sneezing may account for its use in headaches.

5.13 ATHRIXIA Ker Gawl.

The mainly South African genus *Athrixia* (tribe Inulae) contains triterpenes, thymol derivatives and some diterpenes related to kaurene (Bohlmann, Wallmeyer & Jakupovic 1982).

5.13.1 Athrixia angustissima DC.

The Southern Sotho use the leaf and root of *Athrixia angustissima* DC. as a remedy for sore feet and as a tea (Watt & Breyer-Brandwijk 1962).

The aerial parts of *Athrixia angustissima* DC. contain the thymol derivatives 10-isobutyryloxyathrixolepoxide, 10-tiglinoyloxyathrixolepoxide, 7-acetoxy-10-isobutyryloxy-anthrixolepoxide, tiglinoyloxy-anthrixolepoxide and 7,10-diisobutyryloxyathrixolepoxide (Bohlmann & Zdero 1977c).

5.13.2 Athrixia elata Sond.

The leaf and root of *A. elata* Sond. is also a Southern Sotho remedy for sore feet and is used as a tea. The Tswana administer a decoction of the herb as a stimulant to a convalescent (Watt & Breyer-Brandwijk 1962). The roots of *A. elata* Sond. contain dammadienyl acetate, dammadienone, friedelin, thymol derivatives, ent-kaurenic acid and the 9,11-dehydro derivative and 4-formylathrixinone. The aerial parts contain squalene, germacrene D, caryophyllene, α-humulene, cinnamates, the triterpene, 2-β-hydroxyerythrodiol, and the seco-labdane derivative, seco athrixic acid (Bohlmann, Wallmeyer & Jakupovic 1982). The triterpene friedelin has a diuretic activity (Harborne & Baxter 1993).

5.13.3 Athrixia heterophylla (Thunb.) Less. subsp. *heterophylla*

(=*Aster heterophyllus* Thunb.)

A decoction of the root of *A. heterophylla* made with *Anemone caffra* E. & Z. ex. Harv. is a Xhosa remedy for mental disease. The dried root is also used as a part of the treatment (Watt & Breyer-Brandwijk 1962).

5.13.4 Athrixia phylicoides DC.

Commonly known as "kaffir tea". The Lobedu chew the leaf and swallow the juice as a cough remedy. The Zulu use a decoction of the roots as a cough remedy and purgative. An infusion of the plant is used as a blood purifier for sores and boils by the Zulu and Whites of South Africa. For the relief of sore feet, the Southern Sotho bathe them after scarification, with a decoction of the leaf of *Athrixia phylicoides* or with the root of *Athrixia elata* (Watt & Breyer-Brandwijk 1962) An infusion of

the root is reported for having aphrodisiac properties. An extract from the soaked roots and leaves is taken by the VhaVenda as an anthelmintic. The dried or fresh leaves are boiled and the extract is drunk with sugar as tea (Mabogo 1990).

Three groups of extracts of *Athrixia phylicoides* were submitted by Noristan for pharmacological evaluation. The method is described in the introduction to this chapter. The anti-inflammatory activity of group A was measured as 26% inhibition of carrageenan induced foot oedema. In the antihypertensive test there was a 22% reduction in mean blood pressure. For group B a mild to moderate CNS depression was observed at 30min. post dose and more severe at 90min. post dose at 300 mg/kg. It also had a narcotic analgesic effect at 300 mg/kg i.p. Two of the four mice did not show pain reaction when a clip was placed on the tail. (Three of four mice did not show pain with morphine sulphate at 3 mg/kg). Group C had a pronounced CNS stimulation at 30 & 90min. post dose (300 mg/kg). It had an antihypertensive effect with a 19% reduction in mean blood pressure (300 mg/kg i.p.). On further investigation, group 6 caused only a 3% decrease in mean blood pressure, but the actual change in heart rate was -87.5 (from 503 to 415). Group 3 caused a 19% decrease in mean blood pressure but only a drop of 25.6 in the actual heart rate. Weak transient CNS stimulation was observed only with groups 6 and 7 at 300 mg/kg and signs of CNS respiratory depression was observed with group 2 (Noristan not published).

The roots of *Athrixia phyllicoides* DC. contain dammaradienylacetate and a mixture of various norditerpenes; 4-formyl-athrixianone, 4-carbomethoxyathrixianione, 4-hydroxymethylathrixianione and 16,17-dihydro-16-17-epoxyathrixianione. The aerial parts contain germacrene D, linolenic acid and "p-hydroxyphenylpropan-3-ol-cumarat" (Bohlmann & Zdero 1977c).

5.14 BERKHEYA Ehrh.

The roots contain thiophene acetyl compounds which is quite active against fungi and nematodes.

5.14.1 Berkheya carduoides (Less.) Hutch.

(=*B. carduiformis* DC.)

(=*Stephanocoma carduoides* Less.)

The Xhosa drink a decoction of the root of *B. carduoides* (2 tablespoons three times a day (tds)) for the relief of pain. They also grind the leaves to a paste and apply it to pimples (TRAMED database, index card 134). The Xhosa drink the ground root in water for fits and for relief of rash or itching which occurs after visiting or crossing a river (TRAMED database, index card 135).

5.14.2 Berkheya carlinoides (Vahl) Willd.

(=*B. ecklonis* Harv.)

(=*B. pungens* (Thunb.) Willd.)

(=*Rohria carlinoides* Vahl)

A decoction of the root of *Berkheya carlinoides* Willd. is drunk by the Xhosa with the belief that it dissolves vesical calculi. It is said that a tincture of the root is diuretic and of great service in gravel (Watt & Breyer-Brandwijk 1962).

5.14.3 Berkheya carlinopsis Welw. ex O.Hoffm. subsp. *magalismontana* (Bolus) Roessler

(=*B. magalismontana* Bolus)

B. carlinopsis subsp. *magalismontana* afforded two guaianolides closely related to subluteolide (Bohlmann *et al.* 1984a).

5.14.4 Berkheya decurrens (Thunb.) Willd.

The Xhosa apply the pounded leaves externally to the skin when they get a rash or itching after visiting a river (T AMED database, index card 1254).

5.14.5 Berkheya discolor (DC.) O.Hoffm. & Muschl.

The Southern Sotho administer a decoction of *Berkheya discolor* O. Hoffman. & Muschl. to pacify a nervous patient during illness. In Basutoland the young leaf is cooked and eaten as a vegetable (Watt & Breyer-Brandwijk 1962).

5.14.6 Berkheya heterophylla (Thunb.) O.Hoffm. var. *heterophylla*

(=*Stobaea biloba* DC.)

(=*Stobaea heterophylla* Thunb.)

Berkheya heterophylla (Thunb.) O.Hoffm. var. *radiata* (DC.) Roessler

(=*Stobaea heterophylla* Thunb. var. *radiata* DC.)

Noristan has done research on B. heterophylla as described in the introduction to this chapter. Two groups (A & B) were submitted for pharmacological evaluation. In the Writhing test group A inhibited 29% of the number of writhes in rats caused by acetic acid i.p. It also caused a 6% reduction in mean blood pressure in the hypertensive test. It had some narcotic analgesic effect: Two of the four mice did not show any pain reaction when a clip was placed on the tail. Group 2 displayed weak CNS depression at 300 mg/kg. Its anti-inflammatory effect was demonstrated by 21,1% inhibition of carrageenan induced foot oedema in rats at a concentration of 500 mg/kg p.o. after 3 hours (Noristan not published).

5.14.7 *Berkheya montana* J.M.Wood & M.S.Evans

(=*B. arctiifolia* O.Hoffm.)

(=*B. bilabiata* N.E.Br.)

The Southern Sotho make a lotion for the treatment of bruises from the root of *B. montana* Wood & Evans (Watt & Breyer-Brandwijk 1962).

5.14.8 Berkheya pauciflora Roessler.

From the polar parts of the ether/petrolether extract of the air-dried, ground aerial parts of *B. pauciflora*, desacetyl laurenobiolide and a costic acid derivative were isolated (Bohlmann *et al.* 1984a).

5.14.9 Berkheya radula (Harv.) De Wild.

(=*B. adlami* Hook.f.)

(=*Stobaea radula* Harv.)

The Kwena and the Tswana (males only) drink a decoction of *Berkheya radula* De Willd. for pains in the back over the kidneys. In the Filabusi district of Zimbabwe, the powdered plant is rubbed into swollen testicles (Watt & Breyer-Brandwijk 1962).

Isocomene (berkheyaradulene), a sesquiterpene was initially isolated from *Berkheya radula* (Harv.) de Willd (Wenkert & Arrhenius 1983).

5.14.10 Berkheya rhapontica (DC.) Hutch. & Burtt Davy subsp. *aristosa* (DC.) Roessler var. *aristosa*

(=*Stobaea aristosa* DC.)

The Zulu take a decoction of the root of *B. rhapontica* Hutch. & Burtt Davy subsp. *aristosa* Roesch. var. *aristosa* and *Athrixia phylicoides* for a dry hacking cough (Watt & Breyer-Brandwijk 1962).

The roots of *B. rhapontica* (DC.) Hutch. et Burt Davy ssp. *aristosa* contain the unusual sesquiterpene hydrocarbons isocomene, modhephene and β-isocomene. There are also typical thiophene derivatives present (Bohlmann, Le Van *et al.* 1979).

5.14.11 Berkheya setifera DC.

(=*Crocodilodes setiferum* (DC.) Kuntze)

In Mpumalanga and the eastern parts of the Northern Province, Blacks drink a decoction of the roots for colds, coughs and other respiratory affections. It is one of the ingredients in a Southern Sotho remedy for sterility. A decoction of the root, made with the addition of *Dicoma anomala* is taken by them for biliousness and jaundice (Watt & Breyer-Brandwijk 1962). The leaves of *B. setifera* is used for rheumatism and indigestion and the root for ophthalmia and gonorrhea (TRAMED database, index card 1517). Pregnant Xhosa women (±6 months) drink the root in water to "make the stomach loose" (TRAMED database, index card 137). Pregnant Xhosa women (7-8 months) drink the root of a *Berkheya* sp. to enable the fetus to move (TRAMED database, index card 132). Extracts were tested by Noristan for antagonism of restraint induced gastric ulceration at 100 mg/kg p.o. but were found inactive.

The roots also contain isocomene, modhephene and β-isocomene and thiophene derivatives. The major compound was found to be α-terthienyl. The aerial parts contain triterpenes (Bohlmann, Le Van *et al.* 1979).

5.14.12 Berkheya speciosa (DC.) O.Hoffm. subsp. lanceolata Roessler

Berkheya speciosa (DC.) O.Hoffm. subsp. *ovata* Roessler

Berkheya speciosa (DC.) O.Hoffm. subsp. *speciosa*

(=*Stobaea speciosa* DC.)

The Zulu give an infusion of *Berkheya speciosa* DC., either as an enema or orally, for abdominal disorders especially pains after eating. An infusion of the root is thought to be efficacious in

schistosomiasis and is so used by the Zulu (Watt & Breyer-Brandwijk 1962). The leaves of *B. speciosa* is used for rheumatism and ophthalmia and the roots for gonorrhea. A *Berkheya* sp. used by the Xhosa for venereal diseases is poisonous (TRAMED database, index card 130).

The roots of *B. speciosa* (DC.) O. Hoffm. contain triterpenes and thiophene derivatives. The aerial parts also contain the triterpenes and one of the thiophene derivatives as well as a sesquiterpene lactone (Bohlmann, Le Van *et al.* 1979).

***5.14.13 Berkheya zeyheri* (Sond. & Harv.) Oliv. & Hiern** subsp. *rehmannii* (Thell.) Roessler var. *rehmannii*

(=*B. rehmannii* Thell.)

Berkheya zeyheri (Sond. & Harv.) Oliv. & Hiern subsp. *rehmannii* (Thell.) Roessler var. *rogersiana* (Thell.) Roessler

(=*B. rehmannii* Thell. var. *rogersiana* Thell.)

Berkheya zeyheri (Sond. & Harv.) Oliv. & Hiern subsp. *zeyheri*

(=*B. subteretifolia* Thell.)

(=*Stobaea zeyheri* Sond. & Harv.)

The Northern Sotho use the roots of *Berkheya zeyheri* for anorexia and restlessness. They boil the roots and give the decoction to the restless baby to drink (TRAMED database, index card 914). The roots of *Berkheya zeyheri* (Sond. et Harv.) Oliv. et Hiern. subsp. *zeyheri* contain lupeol and its Δ^{12} isomer, taraxasterol, 2-[thienyl(2)-ethinyl]-5-[prop-1-in-1-yl]-thiophene, the bithienyl derivatives and its dihydroderivative. The areal parts contain onopordopicrin (Bohlmann & Mohammadi 1983).

***5.14.14 Berkheya* spp.**

The presence of phototoxic thiophenes in the roots may explain the use of some species in the treatment of pimples and rashes/itches (which developed after visiting a river). The thiophenes may also account for the use of *Berkheya* spp. for gonorrhea and ophthalmia. The only species on which pharmacological testing was done was *B. heterophylla.* Assuming that the major components in the different species is the same and that they display the same pharmacological activities, interesting parallels could be drawn between the pharmacological activities displayed by *B. heterophylla* and the medicinal uses of *Berkheya* species. Several species are used for pain; *B. heterophylla* caused a 29% inhibition in the Writhing test (for pain) and it also had some narcotic analgesic effect. In addition, *B. heterophylla* display a mild anti-inflammatory effect. *B. heterophylla* also displayed weak CNS depression; two species are used for restlessness (*B. zeyheri* and *B. discolor*), but *B. setifera* is used to enable the fetus to move. *B. heterophylla* caused a 6% reduction in mean blood pressure; *B. carlinoides* is used as a diuretic and for gravel, and *B. radula* is used for pain associated with the kidneys. Some triterpenoids like lupeol acetate display antihypoglycaemic activity (Harborne & Baxter 1993).

5.15 BIDENS L.

5.15.1 Bidens pilosa L.

Bidens pilosa is a pantropical weed often listed in medical floras of the world. In Colombia it is used in the treatment of diabetes, in Mexico as an antiseptic, in Peru and the Hawain island for thrush and oral candidiasis, in the Canary islands, Cook island and Tonga as a vulnerary. In China it has been used in the treatment of wounds and ulcers (Towers & Champagne 1977).

The leaf sap or decoction is employed to treat colitis and diarrhoea. Whole fresh juice ot the plant is used for earache, conjunctivitis and as a heamostatic. It is also used in inflammatory reactions in Nigeria (Akah & Ekekwe 1995).

Bidens pilosa is an introduced plant from South America and is widely used in traditional medicine. An aqueous preparation of the plant is used in the treatment of wounds, against hyperemesis gravidarum as well as stomach ache, constipation as well as intestinal worms. The juice obtained by chewing or cooking of the roots is said to be effective against malaria and the Zulus chew young shoots as a remedy for rheumatism (Geissberger & Sequin 1991).

The juice of the plant is applied to burns or used to treat conjunctivitis and otitis and it serves as a styptic to stop bleeding from a wound. In Central and South America it is used against eye irritations, to treat ulcers, as a diuretic and choleretic and to lower the fever in the case of rubella and scarlatina (Geissberger & Sequin 1991). The warmed juice of the whole plant is used in Ghana for ear complaints and in West Africa for conjunctivitis and as styptic (Ayensu 1978). In China the crushed fresh plant or a decoction is used for wounds and chronic ulcers (Wat 1980). An infusion of the boiled leaves is drunk by the VhaVenda to stop long lasting menstruation (Mabogo 1990). The leaf juice, squeezed into the eyes is used in Ghana for eye complaints, as a styptic, and for ear complaints the leaves armed in water with peppers and juice is put into the ears. In the Ivory Coast and Upper Volta the leaf juice is squeezed in the eye in cases of jaundice (Ayensu 1978).

The Zulu administer the powdered leaf in water as an enema for abdominal troubles and in Tanzania an infusion of the plant, which is very bitter, is taken at hourly intervals in the treatment of dysentery (Watt & Breyer-Brandwijk 1962). The leaf juice is used for diarrhoea and colic in South Africa, Ivory Coast and Upper Volta. An infusion of the leaf and root is used for colic in the Ivory Coast and Upper Volta (Ayensu 1978). The flower is a Zulu diarrhoea remedy and they use an infusion of the leaf and root as a colic remedy (Watt & Breyer-Brandwijk 1962). The flower is also used in the Ivory Coast and Upper Volta for diarrhoea (Ayensu 1978). In Chinese traditional medicine it is used against enteritis, bacillary dysentery and pharyngitis (Geissberger & Sequin 1991). A decoction of the leaf with water is used in the Ivory Coast for coughs (Ayensu 1978).

Bidens pilosa L. var. *minor* scheff is a Shambala remedy for fits in children (Watt 1967). The Zulu rub the burnt seed into scarifications on the side of the trunk for the relief of pain. Among the Whites a

strong decoction of the leaf is taken in large doses at frequent intervals for the treatment of any inflammation (Watt & Breyer-Brandwijk 1962).

The young plant is relished by cattle, horse and mule and the hen and duck are also very fond ot the plant. It is said to have a high food value but is rich in volatile oil which has an objectionable odour and may taint mik. The young shoot, when an inch or two in height, is a favourite dish of the Pedi and the Venda as well as other Africans throughout South Africa and Swaziland. The young leaf is a West African pot-herb (Watt & Breyer-Brandwijk 1962). The leaves are cooked and eaten with porridge by the VhaVenda. It is alleged to be more delicious when cooked with some condiment such as marula seed kernals or peanuts. It is also included as a piquant in most other vegetables (Mabogo 1990). The crushed leaves or flower heads are used for thrush in the mouth by native Hawaiins (Towers *et al.* 1979).

"Ham-Hong-Chho" is a folk medicine in Taiwan, derived from the entire plants of *Bidens pilosa* L. var. *minor* (Blume) Sherff, *Bidens pilosa* L. and *Bidens chilensis* DC. It has been widely used in the treatement of acute and chronic appendicitis, nephritis, gastro-enteritis, diarrhea, influenza, pharyngitis, toothache, hepatitis and jaundice. The anti-inflammatory effects of the aquous extracts of the three plants against paw edema induced by carrageenan and chronic arthritis induced by complete Freund's adjuvant were determined in rats. Results indicated that paw edema induced by carrageenan was significantly decreased by treatment with aqueous extracts (150 or 300 mg/kg) of all three plants ($p<0.05$) and that the effects of *Bidens pilosa* var. *minor* was the most potent. *B. pilosa* var. *minor* at a dose of 150 mg/kg caused 37.8% inhibition after 3 hours and 57.7% inhibition after 5 hours and a dose of 300 mg/kg caused a 25,7% inhibition after 3 hours and a 46.1% inhibition after 5 hours. B. pilosa at a dose of 150 mg/kg caused inhibitions of 22.8% and 27% at 3 and 5 hours respectively, while 300 mg/kg caused 24.1% and 39.6% inhibition at 3 and 5 hours respectively. Indomethacin, an anti-inflammatory agent was tested for comparison. A dose of 10 mg/kg caused an inhibition of 68.6% and 49.6% at 3 and 5 hours respectively. However, only extracts of *B. pilosa* L. var. *minor* and *B. pilosa* L. significantly decreased the paw edema induced by complete Freund's adjuvant ($p<0.05$). Injection of complete Freund's adjuvant into the left hind paw produced inflamed "primary" lesion at the site of injection during the first three days. Thereafter, the swelling slowly subsided until the 9th day when the paw began to swell again ("secondary" lesion) and peaked in the third week. Anti-inflammatory activity of aqueous extracts (500 mg/kg i.p.) of *B. pilosa* L. var. *minor*. and *B. pilosa* L. were apparent as early as 2 days after injection of adjuvant and were maintained until the experiment was terminated on day 28. On day 16, aqueous extracts of *B. pilosa* var. *minor* and *B. pilosa* L. produced respectively 37.9% and 43.4% inhibition of edema of the injected paw (Chih *et al.* 1995).

The carrageenan-induced rat paw edema model is regarded as sensitive to most clinically effective anti-inflammatory agents. Carrageenan-induced edema is believed to be biphasic in nature, the first phase (±1 hour) being due to the release of histamine and serotonin and during the second phase, the release of dradykinin, protease, prostoglandin as well as lysosome occur. The administration of

B. pilosa is effective against the second phase of inflammation induced by carrageenan (Chih *et al.* 1995).

Mycobacterial adjuvant arthritis in rats has been used for detection and evaluation of compounds that may be of value in the treatment of rheumatoid arthritis in man. Adjuvant arthritis (AA) is a systemic disease. The syndrome of AA is swelling, pain and deformity in all four paws, which typically starts on day 10 or 11 after injection and peaks in the third week before going on to ankylosis and bony deformity at week five. In tests of short duration such as carrageenan induced edema in rats as well as in tests of longer duration, such as adjuvant-induced arthritis in rats, the aqueous extracts of *B. pilosa* L. var. *minor* and *B. pilosa* L. exhibited similar anti-inflammatory activity (Chih *et al.* 1995).

Aqueous and ethanolic extracts of *Bidens pilosa* L. were tested as part of a screen for prostoglandin-synthesis inhibitors of 39 plants used in traditional Zulu medicine to treat headache or inflammatory diseases. Prostaglandins are involved in the complex process of inflammation and are responsible for the sensation of pain. One of the highest activities was obtained by the ethanolic extract of *B. pilosa* L. with 90% inhibition. The aqueous extract caused only 22% inhibition. Dried leaves were ground and extracted with water or ethanol for 30 min in an ultrasound bath. The extraction mixtures were centrifuged, the supernatants decanted, or filtered when necessary, and then taken to dryness under vacuum. The residues were resuspended in water or ethanol, respectively, giving 2.5 mg residue/ml water and 20 mg residue/ml ethanol. Extracts were tested in an *in vitro* assay for cyclooxygenase inhibitors (Jäger *et al.* 1996). Cyclooxygenase is nessecary for prostaglandin-synthesis. (appendix 1)

A series of 15 Rwandese medicinal plants used by traditional healers to treat pulmonary diseases were screened for anti-*Mycobacterium tuberculosis* activity. Three plant extracts showed activity at 1000µg/ml. One of them was *Bidens pilosa* L. Plants were dried in an oven at 40°C and powdered mechanically. The plant material was extracted (five times) in a perculator with ethanol 95%. This ethanolic extract was evaporated under reduced pressure at 40°C. The residue was dissolved in 95% ethanol to obtain a concentration of 50 mg/ml. This was tested *in vitro* against 39 strains of Mycobacteria belonging to four different species. They are *M. tuberculosis*, *M. avium*, *M. simiae* and a new *M. simiae* like *Mycobacterium* species (SLM). It was active against *M. tuberculosis* at 500µg/ml against the two strains tested. It was tested againts another 19 strains of *M. tuberculosis* and was active against 13 strains at 100µg/ml. However, it showed no activity against *M. avium* and SLM at 1000µg/ml (Van Puyvelde *et al.* 1994). No mention was however made of phototoxicity.

Bidens pilosa L. contains a number of polyacetylenes which are phototoxic to bacteria, fungi, and human fibroblast cells in the presence of sunlight, artificial sources of long-wave ultraviolet light, or cool white fluorescent light. The principle photoactive compound in the leaf, phenylheptatriyne, is present in the cuticle as well as in the underlying cells (Wat *et al.* 1979b). The plant also contains monoterpenes, sesquiterpenes, a diterpene, flavones, flavonoids, glucosides and hydrocarbons. (Zulueta *et al.* 1995).

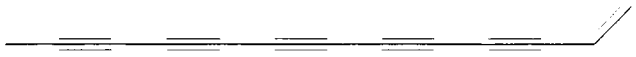
The non-polar fraction of the chloroform extract of the leaves of *Bidens pilosa* afforded stigmasterol, squalene, a mixture of aleidic acid and behenic acid and a novel diterpene, phytyl heptanoate (Zulueta *et al.* 1995).

Dried aerial parts of *Bidens pilosa* were ground and extracted successively with petrol ether, chloroform, methanol, and methanol/water. The antimicrobial activity of the crude extracts were determined. Only the petrol ether and methanol/water extracts showed an activity, mainly against Gram-positive bacteria which was rather modest compared with chloramphenicol. Several constituants were isolated from the crude extracts by repeated column chromatography on 150g of silica gel 60, eluted successively with 0.5%AcOEt in petrol ether, 1% AcOEt in petrol ether, 2-5-10-20-40-100% AcOEt in petrol ether, 10-20-50% MeOH in AcOEt. They were identified by chromatographic and spectroscopic comparison with authentic samples and with data from literature. The substances to be tested were applied to paper discs according to the method of Kirby and Bauer, or were deposited as solutions of petrol ether or H_2O in holes of 5mm diameter punched into the agar plates (Geissberger & Sequin 1991).

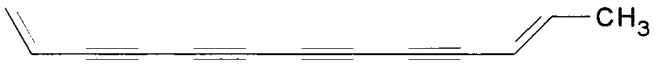
The antimicrobial activity ot the petrol ether extract is due to its content of phenylheptatriyne, linoleic acid and linolenic acid. The latter two are known bacteriostatics even at concentrations as low as 5-50ppm. This is in the range of solubility of these compounds in aquous media. It seems possible therefore, that the fresh juice of the plant or a concentrated aqueous extract may contain sufficient amounts of unsaturated fatty acids to be active against bacteria. Phenylheptatriyne (PHT), the main polyacetylene from the petrol ether extract of *B. pilosa* is active against Gram-positive bacteria but shows only weak activity against Gram-negative bacteria, dermatophytes, yeasts and molds. PHT is phototoxic because it is only active against microorganisms when irradiated with ultra-violet light with a wavelength of 360-370nm. Polyacetylenes 1 and 2 are also phototoxic but show bacteriostatic and fungistatic activity (even in the dark), which may explain why parts of *B. pilosa* are able to inhibit growth of *Candida albicans* in the dark. 1-Phenylhepta-1,3,5-triyne has anthelmintic and protozoocidal properties *in vitro* and in infected mice. Cercaries of schistosomal and echinostomal trematodes are paralized irreversably in the dark or under UV light within 5 to 15 min. at concentrations of 0.3ppm (Geissberger & Sequin 1991).

Phytosterols and n-alkanes that were isolated from the petrol ether extract are also said to have certain antibacterial activity. The pentacyclic triterpenes frielin and friedela-3β-ol have anti-inflammatory and anticonvulsant properties. The flavonoids luteolin 7-O-β-D-glucoside and quercetin 3-O-β-D-galactoside and luteolin, apigenin and apigenin 7-O-glucoside are known anti-inflammatory agents. However *B. pilosa* contains only small amounts of these compounds (Geissberger & Sequin 1991).

Phenylheptatriyne



Polyacetylene 1



Polyacetylene 2

(Geissberger & Sequin 1991)

Phenylheptatriyne (PHT) is a polyacetylene found in various species of Asteraceae with insect anti-feedant activity. When incorporated into the artificial diet of the dark-sided cutworm, *Euxoa messoria* larvae at concentrations of 10-300 ppm it interferes with their feeding activity. This level is within the range found in plants (McLachlan *et al.* 1982).

Phenylheptatriyne found in the leaves of *B. pilosa*, is a UV mediated antibiotic which is effective in low concentrations against *Candida albicans*, some other yeasts and pathogenic bacteria and fungi. In the light of the toxic photodermatitis caused by α-terthienyl and 8-methoxypsoralen (8-MOP) and other psoralens (8-methoxypsoralen and other psoralens are used in photochemotherapy in psoriasis), on human skin, Wat *et al.* (1979) tested a number of polyacetylenes on the skin of adults. The compounds (1% in ethanol) were applied in duplicate to the flexual forearm skin and covered with patches. The patches of one set were removed at 24hours and the sites were exposed to AV-A for up to 20 min. The patch-covered site served as control, being protected from the light. None of the polyacetylenes tested on human skin evoked erythema, blistering or hyperpigmentation with the exception of α-terthienyl. Many of the tested polyacetylenes were shown to be phototoxic or antibiotic against *Candida albicans*. The lack of apparent activity of photoactive polyacetylenes towards the human skin, coupled with their phototoxic effects on *Candida albicans* and other microorganisms, warrants further investigation into their use as UV-mediated antibiotics and in the topical treatment of dermatosis, and perhaps even psoriasis. 8-MOP and UV-A treatment of lymphocytes *in vitro* gives rise to chromosomal aberrations. Unlike psoralens, PHT does not form interstrand cross-likages with the calf thymus DNA (Wat *et al.* 1979).

Wat *et al.* (1980) have tested PHT against a variety of organisms. It is antibacterial, antifungal, and kills human skin fibroblast cells only in the presence of light at concentrations as low as 10ppm. Syrian hamster cells are killed by PHT at 1.6ppm on exposure to light, but it has no effect on these cells at concentrations up to 5ppm in the dark. Mosquito larvae (*Aedes aegypti*) were killed after 4.5min exposure to sunlight and at 2ppm PHT; in the dark 80% were dead after 48 hours. Thus PHT

is active in the dark as well as in the light, but a much higher dosage is required. PHT does not evoke phototoxic dermatitis in human epidermis, as do certain other phototoxic compounds like α -terthienyl. They found the achene, leaf and root extract from *Bidens pilosa* phototoxic and the flower phototoxic as well as antibiotic against *Candida albicans*. The phototoxic effects correlate with the presence of polyacetylenes and thiophenes (Wat *et al.* 1980).

Isolation of phenylheptatriyne from *Bidens pilosa*: Leaves of *Bidens pilosa* were ground in methanol with a Waring blender and the suspension filtered. The methanolic extract was diluted with an equal volume of water and extracted with petroleum ether. The petroleum ether extract, after reduction in volume, was passed through a column of activated alumina. Petroleum ether containg increasing amounts of ether was used as the developing solvent. The presence of phenylheptatriyne (PHT) in the eluate was monitored by UV spectroscopy. Fractions containing PHT were pooled and further purified by preparative TLC on alumina with petroleum ether as the solvent. Recrystallization from petroleum ether gave colourless prisms. PHT is present to the extent of 400-600μg/gm fresh weight (Wat *et al.* 1979b).

Known photosensitizers fall into two categories; those whose toxicity is enhanced by O_2 are called photodynamic sensitizers and include a very large group of naturally occuring compounds such as hypericin, chlorophyll, fagopyrin and synthetic compounds such as acridine orange, methylene blue and rose bengal and the second group of photosensitizers which do not require O_2 for their activity. These are most prominently represented by the furanocoumarins which occur naturally in the Apiaceae, Leguminoseae and other plant families. The furanocoumarins have generated considerable interest because of their use in the treatment of psoriasis. Their toxicity appears to be due to their photoaddition to pyramidines, leading to cross-likage of DNA (Arnason *et al.* 1980).

According to the current hypothesis, the furanocoumarin, 8-methoxypsoralen (8-MOP) and certain other linear furanocoumarins form covalent cross-linkages with thymine residues in native DNA in the presence of long-wave UV light. Oxygen is not required for this reaction. However, it was found that the mode of action of PHT is different from that of 8-MOP. There is a possibility that it acts with one strand of DNA as is the case with angular furanocoumarins, but this has yet to be determined (Wat *et al.* 1979b).

Arnason *et al.* (1980) studied the mechanism of action of PHT on *Escherichia coli* and *Saccharomyces cerevisiae* as test organisms. The survival curves for *E. coli* treated with PHT and ultraviolet (UV) radiation were obtained and have been interpreted quantitatively on the basis of a target theory model. The number of "targets" in the cell that must be destroyed before cell death occurs, was estimated at six, whereas the dose, D_0, that reduced the surviving fraction of the population to 1/e of its value was estimated to be 280J/m^2. The survival was enhanced in aerobic conditions as compared with anaerobic conditions, which is strong evidence that PHT does not behave as photodynamic sensitizer *in vivo*. This view was stronly confirmed by work with azide (a quencher of singlet oxygen), D_20 (which increases the lifetime of singlet oxygen), and superoxide

dismutase (which scavenges superoxide radicals). None of these treatments modified the survival curves significantly, indicating that activated species of O_2 are probably not involved in photosensitization with PHT *in vivo*. Cell respiration was found to be rapidly inhibited by mild treatments of PHT and UV radiation, suggesting that nuclear metabolism is not the primary target of photosensitization as is the case with another group of photosensitizers, the furanocoumarins. The available evidence indicates that PHT is another representative of a new class of phototoxic compounds. A mechanism of action involving production of free radicals is proposed by Amason *et al.* (1980).

Whole, air dried and finely ground plants of *Bidens pilosa* were extracted succesively with benzene, benzene:EtOAc 19:1, ethyl acetate and methanol. The benzene:EtOAc and ethyl acetate extracts were combined. The *Bidens pilosa* extracts exhibited a pain relieving effect in the writhing test. One fraction of the extracts (NH248) inhibited the number of writhes in rats by 50.7%; another (NH249) by 71.6% and a third (NH250) by 65.7% at concentrations of 500 mg/kg p.o. In the anti-inflammatory test two fraction (NH249 and NH259) inhibited the carrageenan induced foot oedema by 32.7% and 30.2% at 500 mg/kg respectively. Fraction NH250 at 300 mg/kg p.o. displayed narcotic analgesic activity (three of the four mice did not show any pain reaction). No interesting pharmacological effects were observed in the Irwing dose-range study. No antimicrobial activity was observed against any of the organisms tested, included *Candida albicans* at concentrations ranging from 1μg/ml to 1000μg/ml (Noristan not published).

Deposits of amorphous silica have been implicated as a possible cause of cancer. Parry *et al.* (1986) reported that *B. pilosa* bear sharply pointed salicified hairs on the leaves. The Transkei region of South Africa has a very high incidence of oesophageal cancer. The researchers obtained packages of vegetation from the food markets of Transkei known locally as "Umhlabangulo". It was found to consist largely of the leaves of *B. pilosa*. Electron micrographs of the leaves revealed multi-celled epidermial outgrowths or microhairs. The base of the trichomes were striated, it tapered to the point and was typically hollow. In contrast to the silification of the hairs in grasses, the deposists in the hair of *B. pilosa* was confined to the cell wall of the hair. *B. pilosa* has silicified hairs of similar dimensions to those of the glume hairs of *Phalaris canariensis* that have been associated with very high incidents of cancer of the oesophagus. Leaves of *Bidens* cause a significant increase in oesophagial cancer in rats (Parry *et al.* 1986). Feeding dried leaves of *Bidens pilosa* L. increased the multiplicity of esophageal papillomas in rats induced with methyl-n-amylnitrosamine (MNAN). The effects were significant but weak, in that the largest effect was a 2.2-fold increase in the number of papillomas/rat. No tumors were induced by the test carcinogens given without MNAN. Mirvish *et al.* (1985) concluded that an increased esophageal [3H]dThd-I indicates potential cocarcinogenicity and that *B. pilosa* was a weak esophageal cocarcinogen (Mirvish *et al.* 1985).

The allelopathic effects of root exudates of *Bidens pilosa* L. on seedling growth of *Lactuca sativa* L., *Phaseolus vulgaris* L., *Zea mays* L., and *Sorghum bicolor* (L.) were studied by Stevens *et. al.* (1985) and found that *Bidens pilosa* significantly inhibited seedling growth of all crops tested but *L. sativa*

was the most sensitive. Larger and older plants of *Bidens pilosa* caused greater inhibition of seedling growth of *L. sativa* and *P. vulgaris* than did smaller (younger) *B. pilosa* plants.

5.16 BLUMEA DC.

5.16.1 Blumea mollis (D.Don) Merr.

(=*B. lacera sensu* Harv.)

(=*Erigeron molle* D.Don)

Blumea mollis (D. Don) Merril is apparently not used medicinally in southern Africa.

A dark, brownish essential oil (0.034%) was obtained by steam distillation of fresh flowering plants of *Blumea mollis* DC, widely distributed in the Malwa region near Ujjain in India. 40% of the total oil was shown to be chrysanthenone (a chief constituent for perfume material). The remaining 60% constituents of this oil contain long chain aliphatic hydrocarbons: 2,3-dimethoxy-p-cymene 2,4,5-trimethoxy allylbenzene; caryophyllene-oxide; and 2-methyl-5-ester along with some unidentified residue (Geda & Bokadia 1982). *Blumea lacera* is used medicinally in the far East as antipyretic and for treatment of bronchitis and blood diseases. Campesterol has been isolated from a light petroleum and $CHCl_3$ extract of the aerial parts (Pal *et al.* 1972). The alkanes n-triacontane and n-hentriacontane, and the terpenoids 2,3-dimethoxy-p-cymene, chrysanthanone, 2,4,5-trimethoxyallylbenzene, methyl 5-isopropyl-2-methylcyclopenetenecarboxylate and caryophyllene oxide have been isolated from the essential oil of *Blumea mollis* DC by chromatographic methods (Geda *et al.* 1981). An investigation into the aerial parts of *B. mollis* (D. Don) Merril gave limonene, α- and β-farnesene and eugenol (Bohlmann, Wallmeyer *et al.* 1985).

5.17 BRACHYLAENA R.Br.

5.17.1 Brachylaena elliptica (Thunb.) DC.

(=*Tarchonanthus ellipticus* Thunb.)

The Zulu take an infusion of the decorticated root as an emetic, for pains in the side and whenever breathing is not normal (pneumonia?), and inject as an enema an infusion of the leaf for biliousness and backache. The Xhosa use a decoction of the leaf as a gargle for sore throats, ulcerations in the mouth and throat, and in quinsy and thrush. The leaf has a considerable reputation among the Whites of South Africa, (known as "bitterblaar") and the Africans as a remedy for diabetes. This was not supported by controlled observations. Subcutaneous and intravenous injections of an infusion in a large number of rabbits produced no effect upon the carbohydrate metabolism, but in some cases there was a slight fall in blood sugar percentage, which occurred haphazardly and in no way related to dosage. Treating six cases of glycosuria with this plant, resulted in glycosuria dissapearing temporarily only in two cases, but it could not be shown to be owing to the action of the plant. The decrease in glycosuria was accompanied by a rise in the blood-sugar level which indicates a rise in the renal threshold to sugar. The infusion is bitter, contains glucosides and is negative to tests for alkaloids. It produces a considerable amount of reaction when given subcutaneously. It was thought

that the benefit from its local use as a gargle, etc. arises from the demulcent and astringent affects of the mucilage and tannin respectively. Watt & Breyer-Brandwijk (1962) also report that the leaf is on the market as a commercial product under the name "Bitterine". An infusion made with five leaves and 250ml water was used for inflammation of the female genitals more than 50 years ago in a Cape Town hospital (Rood 1994).

In pharmacological testing by Noristan (not published), both extracts were only moderately active in the writhing test. The one afforded a 14.3% inhibition @ 300 mg/kg and the other 6.1% inhibition @ 100 mg/kg. The reference, aspirin inhibited pain by 86.9%.

5.17.2 Brachylaena discolor DC.

(=*B. discolor* DC. subsp. discolor var. *mossambicensis* Paiva)

(=*B. natalensis* Sch.Bip.)

An infusion of the leaf is used in diabetes and renal conditions by both the European and African. It is said to act as a tonic (Watt & Breyer-Brandwijk 1962). An infusion of the leaf is used by the VhaVenda for the treatment of roundworm infection (Mabogo 1990). The early Dutch settlers made an alkaline solution for soap-making from the ashes of the plant. The Zulu use the leaf as an ingredient in a remedy for intestinal parasites and it is also used as a roundworm remedy. The timber has been used in wagon building and is said to be excellent as boat timber, very durable as fencing posts and pick handles (Watt & Breyer-Brandwijk 1962). The Xhosa grind and boil the leaves and drink one tablespoon t.d.s. for coughing (TRAMED database, index card 141) and as a tonic (TRAMED database, index card 10726). The Xhosa use the root as an enema for heamorrhaging (TRAMED database, index card 10726).

Noristan has made two extracts of *Brachylaena disolor* DC. (desribed in the introduction to this chapter) which were submitted for pharmacological evaluation. The first was inactive and the second displayed antihypertensive (11% reduction in mean blood pressure and 8% reduction in mean heart rate) and diuretic (21% increase in Na^+ sectretion) activity.

5.17.3 *Brachylaena transvaalensis* E.Phillips & Schweick.

(=*B. discolor* DC. subsp. *transvaalensis* (E.Phillips & Schweick.) Paiva)

The aerial parts of *Brachylaena transvaalensis* Hutch. ex Phill. et Schweick, afforded linoleic (linolic) and linolenic acid, the acetylenic compounds, pentayene and tridecadiene-(1,11)-tetrayne-(3,5,7,9), germacrene D, lupeyl acetate, germacranolides, onopordopicrin, salonitolide, salonitenolide-8-O-2,3-epoxy isobutyrate and 11β,13-dihydrozaluzanin C. The roots afforded lupeyl acetate and its Δ^{12}-isomer, germacrene D, the acetylenic compounds, pentayene and tridecadiene-(1,11)-tetrayne-(3,5,7,9), 9-oxo-nerolidol and 12 lactones which included costunolide, dehydrocostuslactone, dehydrozaluzanin C, zaluzanin C, dihydrodehydrocostuslactone, 4β,15-dihydrodehydrozaluzanin C, a furanoheliangolide, tubiferin and three futher eudesmanolides (Bohlmann & Zdero 1982).

5.18 CALENDULA L.

5.18.1 Calendula arvensis L.

Calendula arvensis is a herbaceous plant used in Italian folk medicine as an anti-inflammatory, anticancer and antipyretic remedy. Extracts of the aerial parts have shown anti-inflammatory activity in carrageenan-induced oedema in rat paw. Two oleanolic acid glycosides were found to be active against vescicular stomatitis virus (VSV) infection but inactive against rhinovirus type B (HRV-1B) infection.

New sesquiterpene glycosides of the 4-epi-cubebol and alloaromadendrane type were isolated from the $CHCl_3$ extract. 4-O-β-D-fucopyranoside of the very rare 4-epi-cubebol was named arvoside A and was found to be toxic at concentrations >100μg/ml for HeLa and chicken embrio related (CER) cells while 4-O-(β-D-fucopyranosyl)-4-alloaromadendrol was found to be toxic at concentrations higher than 20μg/ml. The glycosides were tested against two RNA viruses: a minus strand virus (VSV) in HeLa cells and a plus strand virus (HRV, type 1B) in CER cells. In the experiments performed with HRV, type 1B in HeLa cells, arvoside A at 100μg/ml gave a reduction of more than 25% in cytopathic effect, while at 20μg/ml 4-O-(β-D-fucopyranosyl)-4-alloaromadendrol was inactive. In the VSV-infected CER cells all the glycosides tested showed some activity. 4-O-(β-D-fucopyranosyl)-4-alloaromadendrol was the most effective with a MIC_{50} of 14μg/ml. Arvoside A showed a MIC_{50} of 36μg/ml and completely inhibited virus plaque formation at 100μg/ml. The results indicate that this type of glycoside is generally more active against an enveloped-RNA virus (VSV) than towards a naked-RNA virus (HRV). The most active antiviral compounds seem to be those with the highest polarity. The polarity and the presence of the sugar portion seem essential for antiviral activity (Aquino *et al.* 1995).

5.18.2 Calendula officinales

Calendula officinales is not indigenous to Southern Africa but extracts of the plant are widely used. The whole plant, which was collected in India, was air-dried and ground and extracted with 50% ethanol. The extract was put through a biological screen of 61 tests. These include tests for antibacterial, antifungal, antiviral, anthelmintihic, antiprotozoal, anticancer, antifertility and hypoglyceamic activity. Antiprotozoal activity was observed against *Entamoeba histolytica* at concentrations of less than 125μg/kg *in vivo* and it had affect on contraction of the isolated guinea pig ileum. The LD_{50} value was 300 mg/kg (Dhar *et al.* 1968).

Calendula extracts are used cosmetically. A cream formulation containing 12% *Calendula* extract was tested on the skin of rabbits and gave a good vaso-protective activity. The saponin found in the whole plant, including bracts and involucre helps to give *Calendula officinales* sudorific and emmenagogue properties. Further, the saponin is based on oleanolic acid which is known to be a cholagogue. The drugs from *Calendula* are well known in central Europe where they are usually used as an infusion for treating urological, rheumatic, digestive and nervous troubles. The petals of *C. officinales* have protistocidal activity. Extracts of *C. officinales* seeds have phytohaemagglutin

activity and the extracts of the plant show estrogenic activity. *C. officinales* was shown to contain calendinn, ceryl alcohol and stigmasterol. Eighteen N-paraffins ranging from C_{18}-C_{35} were detected in fresh petals of *C. officinales* (Guy Valadon 1977).

The use of *Calendula officinales* preparations, for topical application, is widespread both in dermatology and in cosmetics, and one of the relevant pharmacological activities for this use is the anti-inflammatory one. Although the clinical effectiveness of the drug is well proved, the nature of the active principles is not clearly defined. Saponins and polysaccharides of *C. officinales* show some anti-inflammatory activity, but it has been demontrated that a lipophilic extract, obtained by supercritical CO_2 extraction and free from saponins and polysaccharides, accounts for the global activity of the drug. By means of bioassay-orientated fractionation of the CO_2 extract of *Calendula* flowers, the triterpenoids were shown as the most important anti-inflammatory principles of the drug. Among them, the faradiol monoester, appears to be the most relevant principle for the activity of the drug, due to its quantitative prevalence. The unesterified faradiol, not present in the extract, is the most active of the tested compounds and equals indomethacin in activity, whereas the monools ψ-taraxasterol, lupeol, taraxasterol, and β-amyrin are less active than the free diol. The anti-inflammatory activity of different CO_2 extracts is proportional to their content of faradiol monoester, which can be taken as a suitable parameter for the quality control of *Calendula* preparations (Della Loggia *et al.* 1994).

Three cellular subfractions of sterols were obtained from *Calendula officinalis* leaves and enzymatically characterized. The results revealed the predominance of free sterols in the microsomal fraction, of esters in the mitochondrial fraction and of steryl glucosides and acylated glucosides in the Golgi fraction (Janiszowska, Sobocinska & Kasprzyk 1979).

5.19 CALLILEPIS DC.

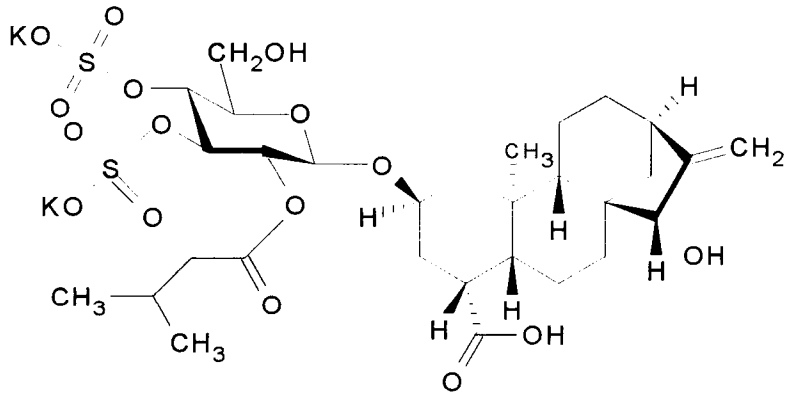
5.19.1 Callilepis laureola DC.

(=*C. glabra* DC.)

(=*C. hispida* DC.)

The Zulus and other African people regard "Impila", the rootstock of *Callilepis laureola* as a powerful medicine. Infusions of the tuber, admininstered orally or rectally, are reputed to ward off evil spirits. This tuber is however highly toxic inducing both liver and renal necrosis, with often fatal results (Bye *et al.* 1990). This plant is responsible for the deaths of many Zulu people in Natal that use it as a herbal medicine. They take a decoction of the root as a vermifuge and an infusion as a purgative and also use an infusion of the leaf as a purgative enema. The root is used for tapeworm and the Zulu apply a paste of the root to kill maggots in cattle. The root is gathered in winter as a cough remedy and for the treatment of whooping cough. The Swazi use the macerated leaf as an external disinfectant (Watt & Breyer-Brandwijk 1962).

Brookes *et al.* (1983) isolated atractyloside from the methanol extracts of the root-stock of *Callilepis laureola* while searching for the toxins responsible for the deaths of many people. The filtered extract, obtained by soaking the fresh shredded root-stock in methanol, was concentrated to a syrup. From this an extract was made using hexane and then ether. The extract was then diluted with methanol while stirring, to yield a precipitate consisting essentially of polysaccharides. The supernatant liquid was decanted and concentrated at 45°C under vacuum to a viscous syrup which contained large quantities atractyloside compounds. A solution of this syrup in water was saturated with potassium chloride, resulting in precipitation of the four crude atractylosides. Repeated crystallization of the mixture from hot water, provided atractyloside as a microcrystalline powder. The structure was confirmed by ^{1}H and ^{13}C n.m.r. spectroscopic and molecular rotation evidence (Brookes *et al.* 1983).



Atractyloside

The occurrence of atractyloside in *Callilepis laureola* and the hypoglycemic activity and renal necrotising activity of atractyloside were already reported in 1977 (Candy *et al.* 1977).

While most African mothers attending hospital would have made prior use of some form of home remedy, about 30% of black women in the Durban area use oral or rectal infusions of *Callilepis laureola*. Under certain conditions these measures produce recognisable acute hepato-renal disease. The essential components of this syndrome are hypoglyceamia, centrilobular liver necrosis and acute tubular necrosis. The most frequent symptoms are altered conciousness (coma, stupor, confusion), convulsions, diarrhoea and vomiting, tachypnoea, hypotonia, hyporeflexia. Significant findings on investigation were acidosis, hyperkalemia, azotemia and hyponatraemia (Bhoola, Coovadia & Watson 1983).

The hepatotoxin is unknown, but atractyloside has been identified as the nephrotoxin (Bye *et al.* 1990). Atractyloside is highly toxic to mammals (LD_{50} intramuscularly in rats 431 mg/kg), with strychnine-like activity (Harborne & Baxter 1993). Injection of atractyloside into rats produce dose dependent acute tubular necrosis (ATN) and hypoglycaemia, but does not cause centrular liver necrosis. ATN is produced only in a narrow dose range (47 mg/kg - 54 mg/kg) of the methanol extracts of the roots of the plant. Larger doses produce rapid death without ATN. Hypoglyceamia is

believed to be due to inhibition of glycogenolysis by atractyloside. The component of the roots causing liver necrosis has not yet been identified (Bhoola, Coovadia & Watson 1983).

Atractyloside, a diterpene glycoside competitively inhibits the transport of ADP across the inner mitochondrial membrane, so terminating the oxidative phosphorilation (Bye *et al.* 1990). Atractyloside is used experimentally because it is a specific inhibitor of ADP transport at the mitochondrial membrane (Harborne & Baxter 1993). Bye *et al.* (1990) developed an enzyme immunoassay specifically for atractyloside. The specificity of this assay makes it suitable for diagnostic purposes and may assist in confirming atractyloside mediated deaths.

Other compounds isolated from the rootstock of *Callilepis laureola* DC. include atractyloside 6'-O-isovalerate, carboxyatractyloxide, carboxyatractyloside 6'-isovalerate (Brookes *et al.* 1983), 7-oxo-10-isovalery-8,9-dehydro-8,9-epoxythymol isovalerate and two related thymol derivatives, identified as 7-hydroxy-10-isovaleroxy-8,9-dehydro-8,9-epoxythymol isovalerate and 7,9,10-trihydroxy-8-isovaleroxythymol isovalerate. A new ketol, 2-hydroxy-192-hydroxy-4-hydroxymethylphenyl)-ethanone was obtained as a degradation product of the latter two compounds (Brookes *et al.* 1985). Bohlmann & Zdero (1982b) reported the presence of germacrene D, bicyclogermacrene, α-humulene, 4-hydroxygermacra-1(10),5-diene, sisterol, lupeol, cadinol T and phellandrene-3,6-endoperoxide (Bohlmann & Zdero 1982b). The widespread pentaynene ($Me[C{\equiv}C]_5CH{=}CH_2$) and a thymol derivative, 7-oxo-10-isovaleroxy-8,9-dihydro-8,9-epoxy-thymolisovalerate were also reported from the roots of *Callilepis laureola* DC (Bohlmann & Zdero 1977b).

5.19.2 Callilepis leptophylla Harv.

Callilepis leptophylla is reported by Watt & Breyer-Brandwijk (1962) to be used by the Manyika as a remedy for cough, fever, "bad blood" and as a tonic. It was tested for its antihypertensive and analgesic activity by Noristan (not published). It did not show any significant anti-hypertensive activity and as an analgesic it was 9.5% effective in the writhing test at a concentration of 10 mg/kg.

5.19.3 Callilepis salicifolia Oliv.

C. salicifolia is apparently not used medicinally. The roots afforded traces of tridecapentayene, isocomene, stigmasterol, lupeol and as the main compound an aldehyde. Thymol derivatives, sesquiterpenes, sulfone and pinoresinol diisovalerate were also present. The aerial parts gave the same aldehyde as the roots as main component and also sesquiterpenes (derivatives of isocomene), and traces of germacrene D, α- and γ-humulene, α- and β-selinene (Bohlmann & Zdero 1982).

5.20 CARTHAMUS

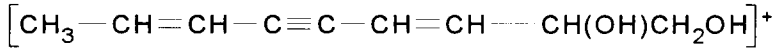
All *Carthamus* species have been introduced to southern Africa.

5.20.1 Carthamus lanatus L.

C. lanatus L. has been used as a diaphoretic, an emmenagogue, a resolvent, an antiseptic and a remedy for gangrene (Watt & Breyer-Brandwijk 1962).

5.20.2 Carthamus tinctorius L.

Safflower plants (*C. tinctorius* L) were wound inoculated with *Phytopthora drechsleri* Tucker, a fungus which incites a rot and stem rot disease of cultivated safflower. Extracts of diseased hypocotyls were highly toxic to the linear growth of the pathogen. The major toxic compound was isolated from the extracts and identified with the aid of UV, IR and mass spectroscopy as *trans-trans*-3,11-tridecadiene-5,7,9-triyne-1,2-diol (Safynol). The concentration of safynol increased 20 fold in infected safflower hypocotyls. It inhibited the linear growth of *P. drechsleri* to 50% at 12 µg/ml and 100% at 30µg/ml (Allen & Thomas 1971). No mention was made of phototoxicity.



trans-trans-3,11-tridecadiene-5,7,9-triyne-1,2-diol (Allen & Thomas 1971)

5.21 CENTAUREA

The genus are mostly Mediterranean but many species are distributed nearly over the whole world as aggressively invading weeds (Jakupovic, Jia *et al.* 1986). On account of their spininess all species of *Centaurea* are liable to be troublesome to both man and animal (Watt & Breyer-Brandwijk 1962). The Xhosa grind the leaves of a *Centaurea* sp. and drink it in water for an upset stomach (TRAMED database, index card 143). Many sesquiterpene lactones (highly oxygenated guaianolides and germacranolides) have been isolated from the large genus *Centaurea*. Closely related guaianolides are typical (Jakupovic, Jia *et al.* 1986).

5.21.1 Centaurea calcitrapa L.

Watt & Breyer-Brandwijk (1962) reported that extracts of *C. calcitrapa* L. have given positive results in antimalarial tests, which is interesting in the view of the old opinion that the plant is antifebrile. However, no reports were found to confirm that. The root and fruit have both been used as an antifebrile and the juice has been used in intermittent fever and in maladies of the eye (Watt & Breyer-Brandwijk 1962).

The plant is an irritant and yields the bitter principle calcitrapin which closely resembles or may be identical with cnicin which is emetic. Calcitrapin has apparently been referred to as calcitrapic acid (Watt & Breyer-Brandwijk 1962). Jakupovic, Jia *et al.* (1986) have isolated the sesquiterpene lactone, cnicin from *Centaurea calcitrapa*. Cnicin has antimicrobial and antibiotic activity (Wagner 1977a). *C. calcitrapa* contain 7-methylapigenin galacturonide and the phenolic compound aesculetin-7-glucoside (cichoriin). *C. calcitrapa* from Argentina also yielded two closely related lactones as well as aplotaxene, squalene, phytol, taraxasterol, 5,7-dihydroxy-6,3',4'-trimethoxyflavone and minute amounts of isomeric bisabolone derivatives (Jakupovic, Jia *et al.* 1986). All parts of the plant except the leaf contain a rennet-like enzyme. The plant is said to contain centaurin, an antifebrile, and the flower contains pectins, a blue dye, possibly inulin and cichorium-glucoside or cichorigenin (Watt & Breyer-Brandwijk 1962).

5.21.2 Centaurea cyanus L.

Centaurea cyanus is an introduced weed to South Africa. In Italy a decoction is used as a mild astringent and as a diuretic. The flower is not only used as a diuretic but has been used for scorpion sting and as an eye-wash. The plant has given negative tests for haemolysis and for the presence of flavonoids, alkaloids and tannins, but strongly positive tests for the presence of sterols (Watt & Breyer-Brandwijk 1962). Flavonoids have, however, been identified. *C. cyanus* contain the flavonoids 5,4'-diOH-7-Me-flavone-6-C-glucoside (swertisin), 5,4'-diOH-7-OMe-flavone-8-C-glucoside (isoswerisin), apigenin 4'-O-glucoside-7-O-glucuronide (Wagner 1977a). The plant contains polyenes and it is reported to contain cyanin. The plant has given negative antibiotic tests and the flower negative anti-malarial tests. The flower contains the pigment fragasin and dyanin chloride (Watt & Breyer-Brandwijk 1962).

5.21.3 Centaurea solstitiales L.

The yellow starthistle (*Centaurea solstitialis L.*) is a weed causing major problems in many parts of the world. It is suspected to be allelopathic. It causes equine nigropallidal encephalomalacia (ENE) in horses, commonly called "chewing disease" (Merril & Stevens 1985). In southern Europe the root has been used as a stomachic and the flower as a febrifuge. *C. solstitialis* L. has a considerable degree of antibiotic action against *Staphylococcus aureus* but none against *Escherichia coli.* It is active against 12 bacteria (Watt & Breyer-Brandwijk 1962).

C. solstitialis contain alkaloids, triterpenes, sesquiterpene lactones (Merril & Stevens 1985) and cyanogenic glucoside (Watt & Breyer-Brandwijk 1962). *C. solstitialis* contain several closely related guaianolides. A collection from Argentina gave nearly the same lactones as the sample from California (Jakupovic, Jia *et al.* 1986). The major sesquiterpene lactone (0.05%) of *C. solstitialis* is solstitialin A (Wagner 1977a; Merril & Stevens 1985). Other sesquiterpene lactones are solstitialin A-13-acetate, centaurepensin, scabiolide and stizolicin, repin, subluteolide, acroptilin, janerin and cynaropicrin, solstitiolide and episolstitiolide. Cynaropicrin has been reported to be cytotoxic (LD50 5μg/ml) to He La cells and centaurepensin toxic to 9KB (human nasopharynx carcinoma, ED50 1.7μg/ml), but the low levels found in the plant make it unlikely that they are the sole cause of ENE. The presence of a number of quite oxygenated guaianolides in yellow starthistle, *viz.* epoxides and epichlorohydrins, may be significant in the toxicity of this weed toward horses (Merril & Stevens 1985). It was shown that the sequiterpene lactones, acroptilin, repin, solstitiolide and centaurepensin neither inhibit germination nor retard the growth of the hypocotyl in lettuce seedlings after 48 hours. However, the growth of the root was markedly increased at 10 ppm (Stevens & Merril 1985).

5.22 CHROMOLAENA DC.

5.22.1 Chromolaena odorata (L.) R.M.King & H.Rob.

(=*Eupatorium odoratum* L.)

Chromolaena odorata is native to tropical America from where it has spread to other parts of the world (Irobi 1992). In Nigeria the leaf decoction of *Eupatorium odorata* L. is used to manage flu, fever and cold. The leaf extract is also very popular as a haemostatic agent, arresting bleeding from

cuts. The leaf juice is a good antiseptic and is used in wound dressing and skin infections. The whole plant extract is used as an anti-ulcer agent (Akah & Ekekwe 1995). It can also be used in pulmonary hemorrhage (Akah 1990). It is used as a fish poison in India (Talapatra *et al.* 1977). It is also used as a fish poison in the Himalayas and is known as a "fever" plant in Puerto Rico and for its toxicity to arthropods and higher animals in Nigeria (Arene *et al.* 1978).

It is used in traditional medicine for the treatment of skin infections. An ethanolic extract of *C. odorata* posesses some antibacterial activity against *Pseudomonas aeruginosa* (Gram negative) and *Streptococcus faecalis* (Gram positive) although the minimum inhibitory concentration is large. Concentrations of 30 mg/ml were needed to give an inhibitory action comparable with ciprofloxacin. The air dried powdered leaves of the plant were exhaustively extracted with 500ml of ethanol (95%) using a soxhlet apparatus for a period of 8 hours. The extract was then passed through membrane filters and concentrated *in vacuo* at 40°C (Irobi 1992).

The pressed extracts of the leaves of *Eupatorium odoratum* L. is popularly employed traditionally to arrest bleeding from cuts and for wound dressing. Plants were collected in Nigeria. Fresh leaves were air-dried and ground to a powder. It was soaked in distilled water for 24 hours and then filtrated and the filtrate lyophilized to obtain the extract as a solid material. Preliminary isvestigations showed that the leaf extract of *E. odoratum* significantly reduced bleeding time in guinea pigs and rabbits. The effects was traced to its vasoconstrictor activity similar to that of adrenaline. *In vitro* studies showed that the extract concentration-dependantly contracted both the rat and guinea pig vasa differentia and rabbit arterial strips while having no effects on isolated guinea pig ileum and rat stomach strip preparations. The extract-induced contractions were blocked by low concentrations of prazosin but not by atropine, propranolol, mepyramine or pimoxide. The ability of the alpha adrenoceptor antagonist (prazosin) to abolish the extract-induced contraction of the *vas deferens* and arterial strips at low concentrations suggest that the effect of the extract *E. odoratum* may be mediated directly or indirectly via alpha adrenoceptors. It may as well be inferred that the potent heamostatic activity of may be accounted for by the alpha adrenoceptor mediated vasoconstriction - a property well established for adrenaline. The active substances have not yet been isolated and identified (Akah 1990).

The Nigerian variety of *E. odoratum* was investigated for cytotoxic and antineoplastic constituents. The aerial portion of the plants (including the flowers) was extracted with chloroform. The extract was evaporated and redissolved in 9:1 methanol-water which was extracted with ligroin. The aqueous phase was diluted with water to 80% methanol and extracted with carbon tetrachloride. Finally the aqueous phase was diluted to 60% with methanol and extracted with chloroform. By evaluation of these fractions against the National Cancer Institute's KB cell line, cyctotoxicity (marginal) was found localized in the carbon tetrachloride fraction. Careful chromatographic separation of this material on a column of silica gel gave, principally isosakuranetin monomethyl ether, odoratin and 4',5-dihydroxy-3',7-dimethoxyflavone. The substances were characterized on the basis of physical measurements (principally infrared, proton magnetic resonance, and mass spectral determinations) and elemental

composition. Biological evaluation of the three constituents in KB and P388 cell lines did not reveal significant cytotoxicity (Arene *et al.* 1978).

It contains sesquiterpenes (d-,l-eupatene), sisterol, triterpenes (β-amyrin and lupeol), chalcone (odoratin), flavan (isosakuranetin) and the flavone salvigenin (Arene *et al.* 1978). A triterpene epoxide, epoxylupeol, has been isolated from *Eupatorium odoratum* Linn. along with salvigenin, lupeol and β-amyrin (Talapatra *et al.* 1977).

5.23 CHRYSANTHEMOIDES Tourn. ex Medik.

5.23.1 Chrysanthemoides monilifera (L.) Norl.

The Xhosa use a decoction of the leaves as an enema for fevers and colds (TRAMED database, index card 10727). The berry-like fruit of *Chrysanthemoides monolifera* (L.) Norl. subsp. *pisifera* (L.) Norl. is sweet and palatable and is eaten by Africans (Watt & Breyer-Brandwijk 1962).

The aerial parts of *Chrysanthemoides monolifera* ssp. *canescens* collected in Natal contain traces of pentaynene as well as two triterpenes. The roots contain pentaynene and diterpenes of the sandarocopimarene type (Bohlmann & Grenz 1979).

5.24 CHRYSANTHELLUM Rich.

5.24.1 Chrysanthellum indicum DC.

In Nigeria the whole plant is used to make a poultice for new boils. It is employed to treat fever in infants and to manage gonorrhoea and hepatitis. It is described as a good antibiotic agent (Akah & Ekekwe 1995).

5.25 CHRYSANTHEMUM L.

Chrysanthemum species contain sesquiterpene lactones, acetylenes, coumarins and flavonoids (El-Masry *et al.* 1984).

5.25.1 Chrysanthemum cinerariifolium (Trevir.) Vis.

The dried and powdered leaves of *Chrysanthemum cinerariaefolium* Vis. have been used for a long time as fly powder. The insecticidal activity is due to the presence of the following six constituents: pyrethrin I and II, cinerin I and II and jasmolin I and II. Pyrethrins are esters of pyrethrolone. The cinerins and jasmolins are analogous esters of cinerolone and jasmolone. Of these compounds, pyrethrin I and II show the strongest activity against *Musca domestica* L. and *Phaedon cochleariae* Fab., whereas both cinerins and both jasmolins have about the same activity, which is markedly less than that of pyrethrin. It is essential that the acid moiety contains a cyclopopane ring with gem-dimethyl-groups. Hydrogenation of the double bond decreases the toxicity. On their own, pyrethrolone and chrysanthemum-monocarboxylic acid are inactive. These studies have stimulated many chemical syntheses, in which the chrysanthemum acid is esterified with a non-naturally

occuring alcohol, and in which the natural alcohol components are esrterified with a modified acid (Wagner 1977b).

Pyrethroids have the advantage that they are practically non-toxic to warm-blooded animals, and the development of resistance against them is far less than for the synthetic insecticides. Pyrethroids rapidly lose activity by oxidative degradation. Antioxidants such as hydroquinone or tannins, so-called activators such as ethylene glycol ether and pinene, or synergistic agents are therefore added. Suitable synergistic agents are piperonyl butoxide, piperonyl cyclones or sesamin. The extracts are used as aerosols or dusting preparations (Wagner 1977b).

The sesquiterpene lactones tatridin A, tatridin B, dihydro-β-cyclopyrethrosin and three of the germacranolide-type [(11R)-11,13-dihydrotatridin-A, (11R)-11,13-dyhydrotatridin-B and (11R)-6-O-β-D-glucosyl-11,13-dihydrotatridin-B] were isolated from the flower heads of *C. cinerariaefolium* Vis. It also contained the flavonoids; jaceidin, apigenin, luteolin, apigenin-7-galacturonic acid methyl ester and apigenin-7-glucuronic acid. The sesquiterpene lactones as well as the flavonoids inhibited root growth of Chinese cabbage seedlings (Sashida *et al.* 1983).

5.25.2 Chrysanthemum segetum L.

Chrysanthemum leucantemum L., the corn marigold, is not used medicinally in South Africa. The root has been used as a pellitory and the flower as an insecticide (Watt & Breyer-Brandwijk 1962). The leaf has a marked antibiotic effect against *Mycobacterium tuberculosis.* The petal yields four flanonoid constituents gossypitrin (6% of dry material), quercimeritrin, chlorogenic acid and isochlorogenic acid. The herb contains coumarin and is rich in yellow dyestuff (Watt & Breyer-Brandwijk 1962).

Electrophoresis in different buffer systems was used to determine the coumarins in extracts of the roots and aerial parts from the plant *Chrysanthemum segetum* L. It was found that the coumarins are distributed differently, both quantitatively and qualitatively in the roots and aerial parts of the plants. The extracts of the roots show abundant herniarin (40%), duhydrocoumarin (30%) and umbelliferone (5%). Herniarin (26%) is also the major component if the extracts from the aerial parts of the plant, but the second highest is umbelliferone (18%) and then esculetin (12%), dihydrocoumarin (11%) and coumarinind acid (4%) (Ochocka *et al.* 1995).

5.26 CHRYSOCOMA L.

5.26.1 Chrysocoma ciliata L.

(=*Aster discoideus* Sond.)

(=*C. microcephala* DC.)

(=*C. tenuifolia* P.J.Bergius)

In the Western Cape province, this is an old remedy for gout, rheumatism and syphilis is made from this plant (also known as "bitterkaroo") as well as a lotion of the root for wounds especially for varicose ulcers. An extract is used for leucorrhoea and a decoction of the plant with *Peucedanum galbanum* for oedema. The plant alone is also taken for appendicitis, biliousness and

jaundice, constipation, erysipelas (an acute contagious disease caused by *Streptococcus pyogenes*, marked by a circumscribed red eruption on the skin, chills and fever) and typhoid fever (Watt & Breyer-Brandwijk 1962). The plant, mixed with *Arctopus echinatus* and *Pharnaceum linear* L.F. is used (eaten) in the treatment of tuberculosis and lung diseases (TRAMED database, index card 1262). The Xhosa use a decoction of the boiled leaves as a wash for rheumatism (TRAMED database, index card 145). It causes "kaalsiekte", an alopecia affecting kids and lambs. Fed without supplement to adult sheep and goats, it is poisonous. Post-mortem examination reveals acute gastro-enteritis (Watt & Breyer-Brandwijk 1962).

C. tenuifolia P.J.Bergius was collected for screening by Noristan because of the effect it has on sheep and goats and the possible diuretic and anti-inflammatory effects. The method used is described in the introduction to this chapter. Similar fractions of the extracts were combined to form 3 groups. Group 1 had a hypoglyceamic effect at a concentration of 200mg/kg p.o. and was antiviral (100mg/kg), and interferon ind. (200mg/kg p.o.), but is was toxic at 600mg/kg p.o. and at 200mg/kg i.p. Group 2 was inactive. Group 3 also displayed antiviral activity and interferon ind. It also displayed some antihypertensive activity (Noristan not published).

The aerial parts contain a C_{16}-acetylenic ester, the enynediene, methyl hexadeca-6,8,12-trien-10-ynoate and two other polyacetylenes (Bohlmann & Ahmed 1982).

5.27 CICHORIUM

This genus does not occur naturally in southern Africa. Most of the isolated sesquiterpene lactones isolated from *Cichorium* are guaianolides, but eudesmanolides and germacranolides have also been isolated (González 1977).

5.27.1 Cichorium intybus Linn.

Chicory (*Cichorium intybus* L.) is a commercial crop in the coffee industry and has become naturalized in South Africa (Watt & Breyer-Brandwijk 1962). In Europe, the basal leaves are used as a pot herb or as greens. For the latter purpose the leaf needs to be boiled in two changes of water in order to remove the bitter principle, intybin. In India the seed is reputed to be a tonic, demulcent and cooling and is used as a remedy for various biliousness and vomiting and as a menstrual stimulant. The root is used in Europe as a household remedy for chronic catarrh of the stomach, liver trouble and haemorrhoids (Watt & Breyer-Brandwijk 1962). Chicory has been used for local application in the treatment of acne, ophthalmia and inflammation of the throat. The root is believed to purify and enrich blood, reduce inflammation of soft tissues and prevents pain in the joints (Patel and Venkatakrishna-Bhatt 1983). A tea is used as choleretic. An intravenous injection doubled the amount of bile excreted after one hour (Rood 1994). The root contains inulin and chicorin, a bitter glucoside and is used as to increase apetite and aid digestion (Chicorin is probably identical with intybin) (Watt & Breyer-Brandwijk 1962).

Patel and Venkatakrishna-Bhatt (1983) investigated the efficacy of the root extracts of chicory in some dental ailments, with referece to its application as a gum massage, as an antimicrobial adjuvant

with dentrifice, against gingival inflammation and as an anti-plaque agent. Alcoholic and aqueous extracts were obtained by extracting the crude powder of dried and roasted roots with absolute alcohol and distilled water respectively by Soxhlet extractor. A dark brown viscous residue was obtained upon evaporation. Yield obtained from alcoholic and aqueous extracts was 46% and 18% w/w respectively. An elution was made with distilled water by keeping the ratio of 1 mg of crude drug equivalent to 1ml of final extract. Extracts were found to be free of sodium, potassium and calcium ions and their salts. Forty two patients with gingival inflammation and bleeding gums were randomly selected. They were advised to massage the inflammed/bleeding gums with chicory liquid extract twice a day before dental examination and continuously for a three week period. Gingival health status was recorded using gingival inflammation index (1 mild, 2 moderate, 3 severe) before the start of the use of the herbal preparation and at the end of each week for a three week period. The mean GI score before the treatment and at the end of every week for three weeks respectively were 1.9, 1.7, 1.5 and 1.3. The results were found statistically significant ($p<0.001$) at the end of the third week. No side effects were observed. Besides bleeding, pus and halitosis had either completely stopped or to a great extent reduced, concluding that an alcoholic extract is an effective medication as a gingival massage (Patel & Venkatakrishna-Bhatt 1983).

Patel & Venkatakrishna-Bhatt (1983) also assessed the effect of the chicory root extract on the efficacy of four commonly available dentrifices by performing antimicrobial tests, abrasion tests and measuring the pH of each dentrifice alone and in combination with chicory extract. The antimicrobial activity was assessed by employing an antibiotic sensitivity test by disc diffusion method. The bacterial plaque material was obtained by scraping the tooth with a sterile probe and inoculated in nutrient broth for 24h and then streaked on nutrient agar plates. Filter paper discs were autoclaved and covered on both sides with the tooth pastes. The zone of inhibition of the various dentrifices alone ranged from a maximum of 2.4 to a minimum of 1.3cm. The zone of inhibition of the various dentrifices in combination with chicory extract was significantly increased ($p<0.01$) ranging from maximum of 3.4 to a minimum of 2.4cm respectively. The dentrifices, having different active ingredients (detergent, formaldehyde, hexachlorophene and chlorophyll) with chicory extract produced a large zone of inhibition compared to the dentrifices used alone. The abrasiveness of the dentifices were significantly reduced when used in combination with the chicory extract. (From maximum abrasion of 40% and minimum of 26% for the dentrifices alone to a maximum of 23% and a minimum of 18%.) Dentrifices should not contain any ingredients that are too abrasive which would cause abrasion of the enamel. Furthermore, dentrifices should not contain any ingredients which are acidic enough to attact the teeth nor alkaline enough to irritate the inflamed gingival tissues. The pH of the four dentrifices tested alone ranged from a maximum of 7.5 to a minimum of 6.0. With the chicory extract the pH values ranged from a maximum of 7.0 to a minimum of 6.5 (Patel & Venkatakrishna-Bhatt 1983).

The antimicrobial activity was assessed by a disc diffusion antibiotic test using cultured gingival smear. The micro organisms are highly sensitive to chloramphenicol and streptomycin. The chicory extract occupied an intermediate position of susceptibility. The micro-organisms of inflammatory gingiva are resistant to penicillin and tetracycline, bur not resistant at all in cases of chicory extract.

The chicory extract was found to be a fairly good therapeutic agent in cases of periodontitis, particularly when applied for longer periods (Patel & Venkatakrishna-Bhatt 1983).

The latex of the plant contains caoutchouc, lactucin (Watt & Breyer-Brandwijk 1962), α- and β-lactucerol and other unidentified triterpenes. The flavonoids and phelolica have been studied intensively. From the fresh leaves of *C. intybus* L., chicoric acid (dicaffeyltartaric acid), caffeic, chlorogenic and neochlorogenic acids were isolated together with 3-ferulyl- and 3-*p*-caumaryl-quinic acids. An alcoholic extract of the leaves contained apigenin, its 7-O-L-aribinose, luteolin 7-glucoside, quercitrin and hyperin. From the latex of *C. intybus* L. small amounts of the carotenoid hexitols, mannitol and inositol were obtained (González 1977). The major anthocyanin of red leaves of *C. intybus* has been identified as cyanidin 3-O-β-(6-O-malonyl)-D-glucopyranoside (Bridle *et al.* 1984). From the stems, umbelliferone, 6,7-dihydroxycaumarin, scopoletin, cichoriin and aesculetin were obtained and in the flower heads two enzymes with transglucosidase activity were present and transformed cichoriin (aesculetin-7-glucoside) into aesculetin via the intermediate aesculetin (González 1977). Extraction of the crushed seed with benzene yields 4.72% of a fixed oil consisting of 21.7% of saturated acids, mainly stearic and palmitic and 78.3% of unsaturated acids, mainly oleic and linoleic. The unsaponifiable fraction gives phytosterol. The above ground parts have given negative tests for haemolysis and for the presence of flavonoids, alkaloids and tannins, but give positive tests for the presence of sterols (Watt & Breyer-Brandwijk 1962). 8--Deoxylactucin, lactucin and lactupicrin were isolated from *C. intybus* (St. Pyrek 1985).

From the methanolic extract of *C. intybus* L. the eudesmane type sesquiterpene lactone, cichoriolide A, and the glycosides, cichoriosides B and C have been isolated together with guaiane-type sesquiterpene lactones, 8-deoxylactucin and crepidiaside B, a germacrane-type sesquiterpene glycoside, sonchuside A, and a eudesmane-type sesquiterpene glycoside, sonchuside C. The cytotoxic activities of related glycosides and the aglycones were compared in the L-5178Y culstured system. The data suggest that the glycosides of the sesquiterpene lactones have a low toxicity towards L-5178Y cells as compared with the aglycones (Seto *et al.* 1988).

The plant shows little or no inhibition of bacterial growth, and has given negative results against the egg-cultivated mouse mammary tumour (Watt & Breyer-Brandwijk 1962). The anti-inflammatory activity of an ethanol extract of *Cichorium intybus* L. (which was treated to remove pigments with petroleum ether) was evaluated in rats using the carrageenin-induced pedal edema assay. A dose of 100 mg/kg x2 resulted in a 50% inhibition (Benoit *et al.* 1976).

5.28 CINERARIA L.

The unusual C_{11}-acetylenes with different degrees of unsaturation and rearranged eremophilanes may be characteristic for the genus (Bohlmann, Singh & Jakupovic 1982).

5.28.1 Cineraria aspera Thunb.

The leaves of *C. aspera* Thunb. are smoked for asthma and tuberculosis by the Sotho. It is reputed to be as intoxicating as *Cannabis sativa* (Hutchings & Van Staden 1994; Watt & Breyer-Brandwijk 1962).

5.28.2 Cineraria lyrata DC.

The Sotho inhale the smoke of the burning plant for colds (Hutchings & Van Staden 1994) and drink a decoction of the root to relieve colic. The ash of the plant is rubbed into incisions on the feet to relieve soreness (Watt & Breyer-Brandwijk 1962).

5.29 CIRSIUM

The genus *Cirsium* is not indigenous to southern Africa.

5.29.1 Cirsium arvense (L.) Scop.

Cirsium arvense Scop. (Canada thistle) is an introduced weed in South Africa. In the United States of America, the leaf and the root are used as an antiphlogistic, a tonic and a diuretic (Watt & Breyer-Brandwijk 1962).

The anti-inflammatory activity of an ethanol extract of *Cirsium arvense* L. (which was treated to remove pigments with petroleum ether) was evaluated in rats using the carrageenin-induced pedal edema assay. A dose of 100 mg/kg x2 resulted in a 37% inhibition (Benoit *et al.* 1976). An infusion of the powdered leaf gave acceleration of blood coagulation *in vitro*, *in vivo* moderate rise in blood pressure in rabbit followed by transitory fall and quick return to normal. The plant has given positive antibiotic tests with *Staphylococcus aureus*, *Escherichia coli*, *Micrococcus aureus* and *Bacillus subtilis*, although many negative antibiotic findings were reported (Watt & Breyer-Brandwijk 1962).

Triterpenes and taraxasterol were found in *Cirsium arvense* (L.) Scop. as wel as the flavonoids apigenin, luteolin, apigenin 7-O-glucoside and apigenin 7-O-rhamnoglucoside, 3-O-methylkaempferol, cirsimaritin, pectlarigenin, tricin 5-O-glucoside, quercetin 3-O-rhamnoglucoside, quercetin 3-O-digalactoside (Wagner 1977a).

The phototoxic fraction from *Cirsium arvensis* roots showed a single phototoxic, UV-absorbing compound when the chromatograms were tested on *Candida* plates. It seems unlikely that the sole acetylene listed from *Cirsium arvense*, $H_2C[C{\equiv}C]_5\text{-}CH{=}CH_2$ is the active compound since it has also been found in in the inactive *Doronicum austriacum* (Camm *et al.* 1975).

5.29.2 Cirsium vulgare Airy-Shaw

A brandy tincture is taken by the Whites of South Africa to improve appetite and is applied as a lotion to erysipelas and ringworm. In the Western Cape province a tincture of the plant is used as a diarrhoea remedy (Watt & Breyer-Brandwijk 1962). The root of *C. vulgare* is also used for muscular inflammation (TRAMED database, index card 4498).

5.30 CNICUS

5.30.1 Cnicus benedictus L.

Cnicus benedictus L. was introduced to Southern Africa. The Whites in South Africa take an infusion of *C. benedictus* L. for internal cancers, and a brandy tincture or an infusion for abdominal troubles. In Zimbabwe, it is an indigenous emetic. The plant has been used in Europe as a bitter tonic and in larger doses as an emetic. In Italy it is used as a bitter tonic, diuretic, sudorific and vermifuge. In the United States of America the leaf and top, collected when in flower, is used as a remedy for fevers and for dyspepsia and as a bitter tonic and also as a uterine sedative and haemostatic. An infusion is taken by the Quinalt Indian as a contraceptive, the preparation being regarded as capable of interfering with implantation or gestation. In Germany, large amounts are used as an emetic and a decoction is used as a local application to sores and frostbite (Watt & Breyer-Brandwijk 1962). *C. benedictus* contains a volatile oil, and a bitter principle, cnicin, which aids digestion. The dried flowering herb is used as a tonic, an emetic and a diaphoretic (TRAMED database, index card 7510).

The plant displayed a considerable degree of antibiotic action against *Staphylococcus aureus* and *Escherichia coli* but only restricted antibiotic activity against *Mycobacterium tuberculosis.* A 35% water extract of the whole plant is toxic to mosquito larvae, but extracts have proved ineffective against malaria (Watt & Breyer-Brandwijk 1962).

The herb has a feeble, unpleasant odour and an intensly bitter taste. It is rich in mucilage and contains tannin and 0.3% of volatile oil, as well as the bitter principle cnicin (guaianolide-type lactone) (Watt & Breyer-Brandwijk 1962). *C. benedictus* contain the flavonoids kaempferol 3-O-glucoside, luteolin, apigenin 7-glucoside and luteolin diglucoside. *Cirsium* species contain also chlorogenic acid, caffeic acid and 1,3-dicaffeylquinic acid and nicotinic acid.

Lactonic lignans were isolated from *Cnicus benedictus* collected in Belgium. The dried powdered herb was extracted with $CHCl_3$. Oils, waxes and chlorophyls were removed by eluting the extract on cellulose with H_2O:MeOH (4:1). After evaporation under reduced pressure, the H_2O:MeOH was purified by multiple dry-column chromatography on Si gel with $CHCl_3$:Me_2CO (4:3), to give two fractions; I, crude cnicin; and II, a mixture of five spots on analytical TLC that was identified as arctigenin, trachelogenin, nortracheloside, 2-acetonortracheloside and salonitenolide (Vanhaelen & Vanhaelen-Fatré 1975).

5.31 CONYZA Less.

5.31.1 Conyza aegyptiaca (L.) Aiton

(=*C. stricta* auct. non Willd., Dinter)

(=*C. transvaalensis* Bremek.)

(=*Erigeron aegyptiacus* L.)

It is reported that *C. aegyptiaca* has been used earlier in folk medicine (Metwally & Dawidar 1984) but it is apparently not being used in southern Africa. The plant contains β-amyrin, its acetate,

stigmasterol, campesterol, cholesterol, quercetin and its 7-arabinoside (Metwally & Dawidar 1984). Quercetin 3-rutinoside is the major flavonoid in *C. aegyptica* (L.) Ait (El-Karemy *et al.* 1987).

The powdered aerial parts of the plants which were collected in Egypt were extracted with Et_2O:petrol:MeOH (1:3:1). The extract of the aerial parts was first treated with MeOH to remove the long chain hydrocarbons and then partially seperated by CC with petrol and increasing amounts of Et_2O and finally Et_2O:MeOH (10:1) into four fractions. The four fractions were; sesquiterpene hydrocarbons, oxygenated sesquiterpenes and acetylenic esters and sterols. The first fraction was divided into the sesquiterpenes, α-curcumene, germacrene and β-farnesene on a silica gel column. The second fraction was divided into caryophyllenepoxide and lachnophyllum ester and matricaria ester and the third fraction was found to be stigmasterol. Similarly, the essential oils from the roots were seperated by CC into four fractions; sesquiterpene hydrocarbons, squalene and two acetylenic compounds (Metwally & Dawidar 1984).

5.31.2 Conyza bonariensis (L.) Cronquist

(=*Erigeron bonariensis* L.)

(=*Erigeron crispus* Pourr.)

(=*Erigeron linifolius* Willd.)

The ethanol extract of the aerial parts of *C. bonariensis* Linn. produced an increase in force of contraction of isolated rabbit heart, inhibited the acetylcholine-induced contractions of the isolated skeletal muscle and significantly decreased the serum sodium content in treated rats (Tariq *et al.* 1987).

Extracts of this plant were made by Noristan as described in the introduction to this chapter. Similar fractions were combined to form two groups. Group 1 was active in most of the screening tests. 500 mg/kg p.o. inhibited 35% of the number of writhes in the writhing test ($p<0.1$), and inhibited inflammation by 32% ($p<0.0001$). It also caused a reduction of 28% in the mean blood pressure ($p<0.02$) and a reduction of 17% in the mean heart rate ($p< 0.001$) @ 300 mg/kg i.p. It had an inhibitory effect on the growth of *Aspergillus niger* at a concentration of 1000µg/ml but not a readable zone. In the ptosis reversal test, the score was 64% of the control (DMI).

Group 2 inhibited inflammation by 36% ($p<0.001$) at a dose of 500 mg/kg p.o. The blood pressure was reduced by 5% ($p<0.02$) and the heart rate by 18% ($p<0.001$) with a dose of 300 mg/kg i.p. In the anti-ulcer test there was a 54% inhibition with a dose of 100 mg/kg x 2 p.o. (The reference, carbenolalone inhibited the ulcers by 50%). In the secondary pharmacological tests the inhibition of three fractions in the anti-inflammatory tests were greater than 46% at a dose of 300 mg/kg. Secondary anti-ulcer tests were also performed, but the best result obtained was only a 33% inhibition (Noristan not published).

The phytoconstituents present in the aerial parts are cardiac glycosides, flavonoids, tannins, volatile oils, sterols/triterpenes, anthraquiniones and coumarins (Tariq *et al.* 1987). *Conyza bonariensis* (L.)

Cronq. contain scutellarein 7-glucuronide as its major flavonoid, smaller amounts of hispidulin 7-diglucoside, quercetin 3-glucoside, 3'-glucoside and 3,3'-diglucoside and traces of luteolin 7-glucoside and quercetin 3-rutinoside (El-Karemy *et al.* 1987).

5.31.3 Conyza canadensis (L.) Cronquist

(=*Erigeron canadensis* L.)

Erigeron canadense L., an introduced weed in South Africa, was at one time used in orthodox medicine. The Southern Sotho drink a decoction of the leaf for sore throat and wash a sick child with a lotion made from it. They also treat ringworm with the plant alone and eczema with a preparation of the plant and *Sorghum dochna.* In the USA, the plant has been used for haemoptysis, cystitis, gonorrhoea and other genito-urinary diseases. It has also been used as a remedy for diarrhoea, dysenteries and as an application to wounds. An infusion of the leaf has been successfully used to counter the diarrhoea which develops in children allergic to milk, who are given soybean milk. The plant has a faint agreeable odour, a bitter taste and astringent properties. The sap and the powdered leaf are irritant to the skin. The plant, as a drug, produces smarting of the eyes, soreness of the throat and prostration. The plant has some antibacterial activity. The leaf and flower have given positive antibacterial tests against *Mycobacterium tuberculosis.* It is reported however, to have no effect on *Staphylococcus aureus* and *Escherichia coli.* The powdered seed is sharply aromatic and has a slight value as a flea repellent (Watt & Breyer-Brandwijk 1962).

The fresh leaf contains 0.2% to 0.66% of a volatile oil and the dry leaf yields 0.19 to 1.73%. The leaf also contains gallic acid and tannic acid. Oil of erigeron has been used as a diuretic, diaphoretic and styptic. It has an acrid taste and causes smarting of the eyes and soreness of the throat. It is a valuable remedy in all forms of haemorrhage, in diarrhoea and dysentery and in internal haemorrhaging and internal fever. The oil is composed of mainly limonene, but also contains enzyme derivatives of methyl caprate, matricaria ester and dihydromatricaria ester (Watt & Breyer-Brandwijk 1962).

5.31.4 Conyza obscura DC.

(=*Webbia kraussii* Sch.Bip.)

The Southern Sotho regard *C. obscura* DC. as a valuable fumigant in cases of illness. A decoction of the root is administered to a feverish patient (Watt & Breyer-Brandwijk 1962). The aerial parts of *C. obscura* contain scopoletin derivatives (coumarins) (Bohlmann & Jakupovic 1979). Scopoletin has hypotensive activity in animals. It also exhibits spasmolytic, antibacterial and antifungal activities (Harborne & Baxter 1993).

From the roots of *Conyza obscura* DC. collected in Natal, Bohlmann & Jakupovic (1979) could not identify any compounds, but from the aerial parts known scopoletin derivatives and similar coumarine derivatives were isolated. They include scopoletin-[2'3'-epoxy-3'methylbutyl-(1')]-ether, scopoletin-[2',3'-dihydroxy-3'-methylbutyl-(1')]-ether, scopoletin-[3'-methyl-buta-1c.3-dien-1'-yl]-ether and scopoletin-[3'methyl-buta-1t.3-dien-1'-yl]-ether.

5.31.5 Conyza pinnata (L.f.) Kuntze

(=*C. pinnatilobata* DC.)

(=*Erigeron pinnatus* L.f.)

Conyza pinnata O. Ktze is burnt by the Southern Sotho with *Amphidoxa gnaphaloides* in the hut of a sick person to drive away the illness (Watt & Breyer-Brandwijk 1962).

The roots of *C. bipinnata* (L.f.) O.Kuntze contain C_{10}-acetylene compounds while the aerial parts contain squalene, β-farnesene and a C_{10}-acetylene (Bohlmann & Jakupovic 1979).

5.31.6 Conyza podocephala DC.

Conyza podocephala is a common weed in South Africa. The Zulu use an infusion of the leaf of *Conyza podocephala* DC. as a remedy for coughs and colds and as a lotion for chafing. The Southern Sotho regard the plant as a valuable fumigant in cases of illness. A decoction of the root is administered to a feverish patient (Watt & Breyer-Brandwijk 1962).

The aerial parts of *C. podocephala* contain germacrene D, bicyclogermacrene, phytol, resorcinol derivatives and diterpenes, conycephaloide, 7-hydroxy-17-oxo-7,8-dehydro-8,17dihydro-conycephaloide (clerodane derivatives) and conypododiol (a dihydroxyfarnesyl methylfuran). Conycephaloide is similar to hautriwaic acid lactone found in *C. scabrida*. The chemistry of *C. podocephala* differs considerably from *C. obscura* which can be confused morphologically with the former (Bohlmann & Wegner 1982). Resorcinol is keratolytic and antiseborrhoeic agent and, in veterinary practice, a topical antipruritic and antiseptic agent (Harborne & Baxter 1993).

5.31.7 Conyza scabrida DC.

(=*Baccharis ivaefolia* L.)

(=*C. ivifolia* (L.) Less.)

The Xhosa grind the leaves of *C. ivaefolia* and use it as a snuff to relieve headaches (TRAMED database, index card 149; Hutchings & Van Staden 1994). The leaves are also used for cattarrh (TRAMED database, index card 1522). The Xhosa grind the leaves and smear it on a child who cries too much, and they drink the ground leaves in water when menstruation has stopped (TRAMED database, index card 149). Leaf infusions are taken by the Zulu for coughs and colds, and charred root powder is rubbed into cuts made on the chest for pleuritic pain. Decoctions are used for convulsions in children by various ethnic groups in South Africa (Hutchings & Van Staden 1994). An infusion of *C. ivaefolia* Less. is administered by the Whites of South Africa in fever and chest troubles and "to hasten the birth of the placenta" when delayed. The infusion is also taken by them for heart diseases and was much used as a remedy during the influenza epidemic of 1918. A poultice of the leaf is often applied to inflammations, especially inflammations within the abdomen. Watt & Breyer-Brandwijk (1962) believe the action of the poultice is physical, and not chemical. A decoction of the leaf is given to a child suffering from convulsions. The aromatic plant has been used in the Western Cape province as a vegetable. Among the Zulu a leaf infusion is taken orally, or as an enema for

colds and coughs, and the powdered, charred root is rubbed into incisions on the side of the chest in a child suffering from pleuretic pain. It is reported that the plant has been used for gall-sickness in stock and that it has a diaphoretic action. The names "oven bush" and "bakbos" arise from the use of the plant as a brush for sweeping out the oven (Watt & Breyer-Brandwijk 1962). The plant is aromatic and is reported to have diaphoretic action. The Bemba use the flowers of *C. spartiodes* O. Hoffm. as snuff for colds (Hutchings & Van Staden 1994).

Extracts of *Conyza scabrida* were made by Noristan according to the method described in the introduction to this chapter. Similar fractions were combined to form eight fractions which were then recombined to form three groups that were submitted for pharmacological screening. Group 1 caused a 41.6% inhibition of writhes in the writhing test at a dose of 500 mg/kg p.o. ($p<0.025$). On secondary pharmacological evaluation the inhibition of the 8 fractions varied from 85.4% to 30.2% inhibition at 300 mg/kg. Group 2 was inactive and group 3 displayed anti-inflammatory activity; 20.4% inhibition of carrageenan induced oedema at 500 mg/kg p.o. (Noristan not published).

The acetylene compound, dehydrofalcarinol and the diterpene, a derivative of hautriwaic acid is characteristic of the genus *Conyza*. In addition to quercetin, hautriwaic acid and hautriwaic acid lactone have been isolated from the aerial parts of *C. ivaefolia* Less (Bohlmann & Grenz 1972). The clerodane-derivative hautriwaic acid ("hautriwasäure") had been isolated previously from *C. ivifolia* L. (that was collected near Cape Town) and which is now known as *C. scabrida*. The aerial parts of *C. scabrida* DC. from the Transvaal gave in addition to dehydrofalcarinol, the main constituent hautriwaic acid, its acetate derivative and the widely distributed diol and two lactones and a mixture of diterpenic acids (12 clerodane derivatives and 9 diterpenes with unusual carbon skeletons) (Bohlmann, Grenz *et al.* 1983).

5.31.8 Conyza ulmifolia (Burm.f.) Kuntze

(=*Baccharis ulmifolia* Burm.f.)

(=*C. incisa* Aiton)

(=*Erigeron incisum* Thunb.)

The leaves are used for cattarrh (TRAMED database, index card 1522). A decoction of *C. ulmifolia* O. Ktze is a Zulu cough remedy (Watt & Breyer-Brandwijk 1962).

The roots contain the sesquiterpene ketone 8-oxo-α-selinene and the polyacetylene $Me[CH^{t}=^{t}CH]_2C{\equiv}CCH^{t}=CHCH_2OAng$ while the aerial parts contain germacrene D and a farnesene derivative (Bohlmann & Jakupovic 1979).

5.32 COTULA L.

The genus *Cotula* contain flavonoids, acetylene compounds, estafiatin, cinammic acid derivatives (Bohlman & Zdero 1979b), and polyacetylenes.

5.32.1 Cotula anthemoides L.

(=*C. microcephala* DC.)

The Xhosa insert the leaf into the nostrils as a remedy for headaches (Hutchings & Van Staden 1994). A decoction of *C. anthemoides* is a Xhosa remedy for head and chest colds and was much used during the influenza epidemic of 1918. In the treatment of a cold, the crushed leaf is sometimes stuffed into the nose. The Southern Sotho use a decoction of the leaf and root as a colic remedy. In Europe the plant has on occasion been used as a substitute for camilla (Watt & Breyer-Brandwijk 1962). *C. anthemoides* L. contain dehydrofalcarinone (Bohlman & Zdero 1979b).

5.32.2 Cotula heterocarpa DC.

The Xhosa grind the leaves of *C. heterocarpa*, mix it with water to a paste and apply it externally on a patient with measles (TRAMED database, index card 151).

5.32.3 Cotula hispida (DC.) Harv.

(=*Tanacetum hispidum* DC.)

The Southern Sotho drink a decoction of the root of *Cenia hispida* B. & H. for relief of nausea (TRAMED database, index card 4837). The roots of *C. hispida* (DC.) Harv. contain dehydrofalcarinone and *p*-hydroxycinnamic acid while the aerial parts contain dehydrofalcarinon, a sesquiterpenoid, lidbeckia lactone and another sesquiterpene lactone (Bohlmann & Zdero 1979b).

5.32.4 Cotula sericea L.f.

(=*Cenia sericea* (L.f.) DC.)

This plant is an excellent remedy for reducing high fever. During the 1918 flu epidemic, when doctors and medicine were unobtainable, many survived by boiling this plant and using it as a tea. In no time a restful sleep was promoted, and the very high fever broken (TRAMED databse, index card 1261).

5.32.5 Cotula villosa DC.

(=*C. multifida* DC.)

The Hottentots used *C. multifida* DC. in the treatment of rheumatism, of scalds and of skin diseases (Watt & Breyer-Brandwijk 1962).

5.33 CRASSOCEPHALUM Moench

5.33.1 Crassocephalum crepidioides (Benth.) S.Moore

(=*Gynura crepidioides* Benth.)

The Shambala snuff the powdered leaf of *Crassocephalum crepidioides* S. Moore in order to arrest nose bleeding. In West Africa, both the whole young plant and the semi-succulent leaves are mucilaginous and are used for soups and sauces. A decoction of the leaf is used as a mild stomachic (Watt & Breyer-Brandwijk 1962). The leaves, prepared as a lotion or a decoction, are employed by the Nigerians as an analgesic in headache. It is also employed in hepatitis (Akah & Ekekwe 1995).

5.33.2 Crassocephalum species not indigenous to southern Africa.

Crude methanol extracts of the leaves and stems of *C. multicorymbosum* of Rwanda, exhibited significant inhibition of carrageenin induced oedema at dose of 10.0g/kg (47.6% reduction after 3 hours, $p<0.001$; 52.2% reduction after 4 hours, $p<0,001$ and 58.8% reduction after 5 hours, $p<0.05$) (Chagnon *et al.* 1983).

5.34 CYNARA

5.34.1 Cynara scolymus L.

The volatile components of the globe artichoke were assesed by GC and GC/MS by MacLeod *et al.* (1982). Eight sesquiterpene hydrocarbons afforded the major group of components (over 42%), with β-selinene (*ca* 32%) as the main constituent. α-Cedrene was found to have globe artichoke aroma characteristics on odour evaluation of separated components at the exit of the GC column (MacLeod *et al.* 1982).

5.35 DICHROCEPHALA L'H,r. ex DC.

5.35.1 Dichrocephala integrifolia (L.f.) Kuntze subsp. *integrifolia*

(=*Cotula bicolor* Roth)
(=*D. capensis* (Less.) DC.)
(=*D. latifolia* (Lam.) DC.)
(=*Grangea latifolia* Lam.)
(=*Hippia integrifolia* L.f.)

In Central Africa, the fruit of *D. interifolia* are applied externally to wounds and a decoction of the leaves is drunk for hyperfunction of the lower gastro-intestinal tract (TRAMED database, index card 9373). A decoction of the leaves are also drunk for infection of the lower intestinal tract (TRAMED database, index card 4499).

5.35.2 Dichrocephala species not indigenous to southern Africa.

The leaves of *Dichrocephala bicolor* (Roth) Schltdl. are used as a folk medicine in Papua New Guinea for ulcers and swelling. Preliminary biological screening of the methanolic extract of *D. bicolor* showed antiviral activity in the reverse transcriptase test. Three isomers of dicaffeoyl quinic acid (3,4-, 3,5-, 4,5) and the flavonoids kaempferol 3-O-rutinoside and quercetin 3-O-rutinoside were isolated. This is the first reported chemical investigation of the genus *Dichrocephala* (Khan *et al.* 1993)

5.36 DICOMA

The genus *Dicoma* is not indigenous to southern Africa. The chemistry of the genus *Dicoma* showed that higly oxygenated germacranolides, especially those with O-functions at C-14 and C-15 may be typical, though *D. zeyheri* is an exception (Bohlmann, Singh & Jakupovic 1982b). The roots of

Dicoma argyrophylla Oliv. contain several polyacetylenes while the aerial parts only afford linoleic and linolenic acid together with their methyl esters (Bohlmann & Le Van 1978b).

5.36.1 Dicoma anomala Sond.

The root of *Dicoma anomala* is commonly used as dysentery remedy. A decoction is used by the Whites and Southern Sotho for intestinal worm infestation, for diahrroea and for gall-sickness in stock. The Southern Sotho sometimes simply chew the root and swallow the saliva for relief of dysenteries and diarrhoeas. They also use the decoction for venereal diseases and as a purgative, and apply the powdered plant to sores and wounds on horses (Watt & Breyer-Brandwijk 1962). The root is used for syphilis (TRAMED database, index card 1524). The Southern Sotho use a decoction of the root as a colic and toothache remedy while the Xhosa take the powdered root for the relief of colic. The Wemba snuff the powdered root bark for colds in the nose. It is said to cause lachrymation, sneezing and coughing. The Zulu administer a decoction of the root as an enema or orally, to children with "blood disorders", and use the charred root as paste for "scaby heads" in children. Blacks take a decoction of the plant for coughs and colds and sometimes apply it to ringworm. A decoction of the root with gin, is a remedy for haemorrhoids and the decoction mixed with "melkbos" for fevers by the Whites of South Africa. It is also used as an anthelmintic and antidysentery remedy in Tanzania. Small amounts of a volatile oil, a colourless crystalline glucoside $C_{39}H_{58}O_{11}$ and an amorphous alkaloid and a phytosterol $C_{28}H_{46}O$ have been isolated (Watt & Breyer-Brandwijk 1962).

Pharmacological screening was done by Noristan on *Dicoma anomala*. Fractions of extracts of *Dicoma anomala* were active in the writhing test with inhibition of 87% $p<0.0001$ and 60% $p<0.001$ at a dose of 500 mg/kg p.o. and a 36% inhibition in the anti-inflammatory test. Moderate hypocholesterolemic activity was confirmed in Triton-hypercholesterolemic mice at 400 mg/kg p.o., $p<0.01$. No evidence of estrogenic effect was determined in immature female mice at 200 mg/kg. A 400 mg/kg/day oral dose of the fraction resulted in a 14.4% reduction in serum cholesterol and 15.6% reduction in serum triglyceride. No other pharmacological or toxic effects were observed. Another fraction caused a 87% inhibition in the writhing test, $p<0.0001$ (Noristan not published).

An investigation of the roots of *Dicoma anomala* subsp. *cirsoides* (Harv.) Willd. collected in the Transvaal afforded stigmasterol, sisterol, lupenone, 11α, 13-dihydrotubiferin and two other eudesmanolides, 9α-hydroxy-dehydrozaluzalin and another guaianolide. The aerial parts gave germacrene D, lupeol, taraxasterol and four closely related germacran-8,12-olides. The aerial parts of *D. anomala* subsp. *anomala* afforded phytol, lupeol and its acetate, germacrene D and three germacran-8,12-olides; 14-acetoxyartemisiifolin-6-O-acetate, 14-acetoxyartemisiifolin-6-O-[2-methylbutyrate] and 14-acetoxyartemisiifolin-6-O-[2-methyl-3-hydroxybutyrate] while the roots gave no definite compounds (Bohlmann, Singh & Jakupovic 1982b). From *Dicoma anomala* Sond. caffeic acid has been reported. The roots of *D. anomala* Sond. ssp. cirsioides (Harv.) Willd. have afforded a triynediene (polyacetylene) while the aerial parts contain a polyacetylene, lupeol and some sesquiterpenes. The most polar is the lactone albicolide while the main constituent with molecular

formula $C_{19}H_{24}O_7$ must be a diacetate with an additional free hydroxyl group (Bohlmann & Le Van 1978b).

5.36.2 Dicoma capensis Less.

Both the Whites and Blacks take an infusion of the leaf of *D. capensis* Less. for febrile conditions. The preparation is said to be diaphoretic (Watt & Breyer-Brandwijk 1962).

5.36.3 Dicoma gerrardi Harv.

A hot decoction of the root of *D. gerrardi* Harv. is used by both Whites and Blacks as a remedy for diarrhoea and gripe in humans and in cattle (Watt & Breyer-Brandwijk 1962).

5.36.4 Dicoma speciosa DC.

A decoction of the root of *D. speciosa* DC. is a Zulu remedy for chest ailments (Watt & Breyer-Brandwijk 1962), especially as an expectorant (TRAMED database, index card 1524)

5.36.5 Dicoma tomentosa

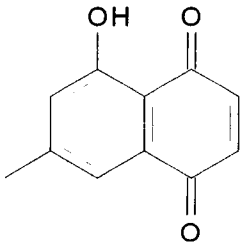
In other parts of Africa, *D. tomentosa* is used topically on infected wounds (TRAMED database, index card 1524). The Ovambo use it for malaria (TRAMED database, index card 3221) and for stomach ache (TRAMED database, index card 3225). The Ovambo make a tea from the whole plant which they give to children with stomach ache (Rodin 1985).

5.36.6 Dicoma zeyheri Sond.

The Blacks around Pilgrims Rest uses an infusion of the root of *D. zeyheri* for "umlundagazi" (a disease). The Xhosa and Mfengu take a decoction of the root for lumbago and other pains in the back. The Swazi take a decoction of the root in the treatment of anaemias (Watt & Breyer-Brandwijk 1962). The flowers and fruit are burnt and powdered for use against infection in VhaVenda woman by a disease known as "goni" which interferes with fertility and also causes infant deaths (Mabogo 1990). In Zimbabwe and in the Northern Province, a decoction of the root is drunk for stomach problems. They also drink the black ash in water and inhale the smoke (TRAMED database, index card 1304). A decoction of the root is used when children are teething (TRAMED database, index card 1303).

Dicoma zeyheri plants were extracted three times with dichloromethane-methanol 1:1. The extract was chromatographed in a silica gel column as described in the introduction to this chapter. Similar fractions were combined to form 6 groups. Groups 1-3 and groups 3-6 were combined in two groups (A & B) for pharmacological evaluation. Group A showed a 65% inhibition in the writhing test at 500 mg/kg $p<0.02$. It was active in the carrageenan induced anti-inflammatory test with 53% inhibition of swelling at 3 hours post carrageenan at 500 mg/kg $p<0.001$. (The reference, phenylbutazone inhibited swelling by 54%) It is antihypertensive with an 18% reduction in mean blood pressure and 6% reduction in mean heart rate, $p<0.05$ in both cases, at 300 mg/kg. It inhibits the growth of *Streptococcus pyogenes* at 1000µg/ml. In the anti-ulcer test a 30% inhibition resulted from a dose of 100 mg/kg, $p<0.1$ and a 37% inhibition with group B (Norsitan not published).

The roots of *D. zeyheri* collected in the Transvaal afforded β-farnesene, α-humulene, a pair af isomeric acetylenic compounds. The major components were 1 and 2 (Bohlmann, Singh & Jakupovic 1982b).



1

$Me(CH_2)_{10}CH=C=(CH_2)_3CO_2H$

2

(Bohlmann, Singh & Jakupovic 1982b)

Dicoma zeyheri afforded two acetylenic compounds also present in species from the tribe Centaureae and an allenic acid together with an ester (Bohlmann & Le Van 1978b).

5.37 DIMORPHOTHECA Vaill. ex Moench

Dimorphotheca species contain hydrocyanic acid or cyanogenic glucoside, which is one of the causes of "geilsiekte" in sheep. In the Western Cape province a poultice of the herb of *Dimorphotheca* sp., with that of *Arctotis* sp. and of *Cryptostemma* sp. is applied to sore breasts and used as a douche in uterine carcinoma (Watt & Breyer-Brandwijk 1962).

5.38 DITTRICHIA Greuter

5.38.1 Dittrichia graveolens (L.) Greuter

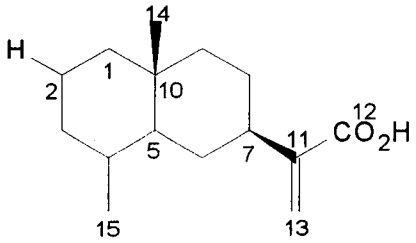
(=*Erigeron graveolens* L.)

(=*Inula graveolens* (L.) Desf.)

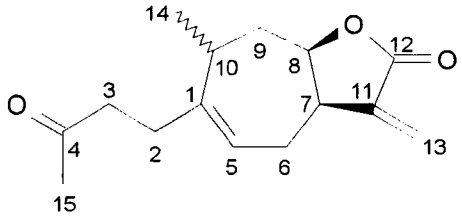
Inula graveolens Desf. is an introduced species which does not appear to be used in South Africa. In Europe it is a remedy for colic, dysuria and amenorrhoea, in the Mediterranean area of Europe for snake-bite and in Australia for asthma. In Australia the plant is reported to produce dermatitis venenata. The aromatic resinous oil of the plant is under suspicion of causing the condition. The plant is occasionally eaten by stock and as a result meat, milk and butter acquire an unpleasant flavour. The frequent administration of large doses of an extract of the plant produces paralysis, mainly in the hind limbs. A sticky and odorous substance with a bitter taste is secreted by the epidermal glands on the stem, leaf, sepal and flower peduncles (Watt & Breyer-Brandwijk 1962). It is used by the fishermen in the south of Italy to facilitate the capture of freshwater fish. The leaves are macerated in water and then steeped into the fishing place, causing a definitive sedative effect on the fish of the surrounding area (Lanzetta *et al.* 1991).

Several sesquiterpenes and flavonoids and some aromatic compounds and fatty acids have been isolated from *Inula graveolens* (Topcu *et al.* 1993). The ichthyotoxicity of *Dittrichia graveolens* was found to be due to the major sesquiterpenes 12-carboxyeudesma-3,11(13)-diene and tomentosin

(Lanzetta *et al.* 1991). 2α-Hydroxy-3,4-dehydro-4,15-dihydrocostic acid, 3α-hydroxycostic acid, ilicic acid related to 12-carboxyeudesma-3,11(13)-diene were also identified (Lanzetta *et al.* 1991).

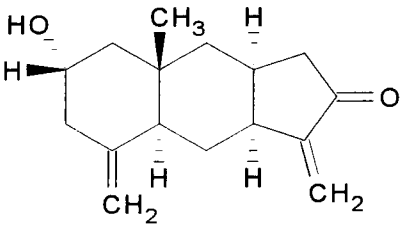


12-Carboxyeudesma-3,11(13)-diene



Tomentosin

Topcu *et al.* (1993) isolated a new eudesmanolide, 11,12-dihidroivalin and four known sesquiterpene lactones, ivalin, inuviscolide, 8-epi-inoviscolide and 8-epi-xanthatin-1B,5B-epoxide. The isolates were evaluated for their cyotoxic activity against cultured P-388 (murine lymphocytic leukemia), KB-3 (nasopharangeal carcinoma) and KB-V1 (vinblastine resistant cells). Ivalin showed activity with ED_{50} values of 0.14, 1.8 and 1.3μg/ml respectively. The other isolates were inactive. The isolates were tested against standard strains of *Bacillus subtilis*, *Staphylococcus aureus*, *S. epidermidis*, *Proteus mirabilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus*, *Streptococcus* and *Candida albicans*. None of the compounds are potent antimicrobial agents (Topcu *et al.* 1993). Ivalin is toxic to mammals (Harborne & Baxter 1993).

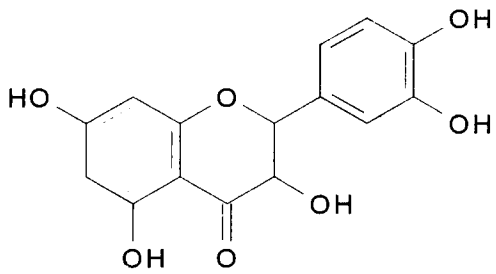


Ivalin

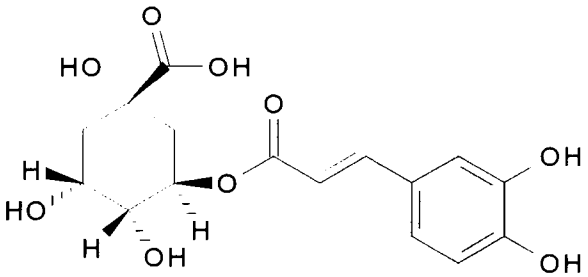
(Harborne & Baxter 1993)

Method: Air dried powdered plant material was extracted with petrol:Et_2O:MeOH (1:1:1). After filtration the extract was evaporated *in vacuo*, dissoved in a small amount of MeOH and kept in the refrigerator for one hour to remove the long chain of saturated hydrocarbons. The filtrate was concentrated and the residue was separated on silica gel with petrol containing increasing amounts of Et_2O and finally MeOH. The 9 fractions obtained were further separated on a Sephadex LH-20 column using the solvent system petrol-$CHCl_3$-MeOH (7:4:1). Sesquiterpenes obtained were further purified by prep. TLC as needed. The structure was established by spectral methods. Cytotoxic evaluation was done by treating cells with at least 5 concentrations of the various substances in triplicate. After the incubation period, the surviving cells were quantified by staining with a solution of sulphorhodamine B. ED_{50} values of ≤4μg/ml are regarded as active. The paper disc diffusion method was used for assesing the antibacterial activity (Topcu *et al.* 1993). Chiappine & Fardella (1980) have isolated a sesquiterpene lactone similar to cumanin.

Souleles and Philianos (1979) have isolated β-sisterol, quercetin, quercetin 3-O-methyl-ether, quercetin 3-O-glucoside, quercetin 3-O-galactoside, a glucoside of quercetin 3-O-methyl-ether and chloragenic acid from the aerial parts of *I. graveolens*. β-sisterol which has a widespread occurance in higher plants has antihyperlipoproteinaemic activity (Harborne & Baxter 1993). Quercetin is probably the commonest flavonoid in higher plants. It is known to inhibit many enzymes, e.g. protein kinase C, lipogenases, lens aldose reductase, 3',5'-cyclic adenosine monophosphate photodiesterases. It is a radical scavenger. Quercetin also inhibits smooth muscle contraction and proliferation of rat lymphocytes. It is antigonadotropic, anti-inflammatory, antibacterial, antiviral and antihepatotoxic, and shows some mutagenic and allergenic properties. Quercetin 3-methyl ether has antiviral activity. Quercetin 3-O-glucoside and quercetin 3-galactoside show antibacterial activity against *Pseudomonas maltophila*. Quercetin 3-galactoside is also a potent inhibitor of lens aldose reductase. Chlorogenic acid is antibacterial, antimutagenic, antitumor, antiviral activities as well as antioxidant and clastogenic activities (Harborne & Baxter 1993). Chlorogenic acid, together with caffeic acid and others are the main active components of *Artemisia scoparia*, a Chinese medicinal plant, used as choleretic and for the treatment of jaundice or cholecystitis. Chlorogenic acid, isochlorogenic acid and linalool from *Lonicera japonica*, another Chinese medicinal plant, is used for the treatment of virus infections (Xiao 1981).



Quercetin



Chlorogenic acid

Other *Inula* species:

Inula racemosa root containing iridine glycosides was given in doses of 500 mg per day for 15 days to rabbits in addition to the normal lab diet along with 0.5g cholesterol per day. Their blood was then investigated for free fatty acids, triglyserides, serum cholesterol and total serum lipids along with body weight. In all accounts there was a reduction. It is therfore hypolipdemic and is capable of reducing body weight (Ojha 1978).

5.39 ECLIPTA L.

5.39.1 Eclipta prostrata (L.) L.

(=*E. alba* (L.) Hassk.)

(=*E. erecta* L.)

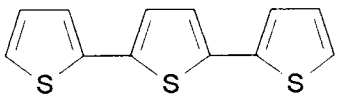
Eclipta prostata is used for "blackening" the hair in south east Asia and India, and for eye ailments in China (Towers & Champagne 1977). The leaf decoction is employed by the Nigerians as a mild laxative and as an emetic, while the infusion is used to control diarrhoea (Akah & Ekekwe 1995). Thiophenes occur in the leaves and other aerial parts of *Eclipta alba*. This species is well known in

Ayuverdic medicine of India and the juice of the leaves ("bhangra" in Hindi), mixed with sesame oil (coconut in Malaysia and Java) is considered an efficacious application in the treatment of vitiligo, athlete's foot, ringworm and some chronic skin diseases (Towers *et al.* 1979). The leaves are used in central Africa for ringworm and diarrhoea (TRAMED database, index card 1553). In Indian markets popular plant preparation for liver ailments include Liv.52 (Himalaya Drug Co.), Livomyn (Charak Pharm.) and Tefroli (TTK Pharma). *E. alba* L. Hassk happens to be present in all the three preparations. The plant is reported to contain wedelolactone, acetylene and thienyl derivatives. Handa *et al.* (1984) used carbon tetrachloride induced liver damage and measurement of sleep time after administration of pentabarbitone on the fith day of liver intoxication and drug administration as bioassay models. Reduction in sleep time in experimental animals under the test dose of the plant extract and fraction was the measure of anti-hepatotoxic activity. The petroleum ether extract did not exhibit any activity, whereas the ether extract containing wedelolactone and ethyl acetate fractions showed pronounced activity (Handa *et al.* 1984).

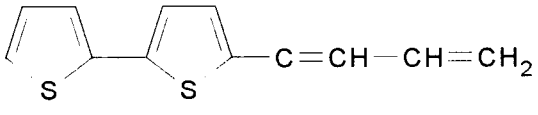
The light petroleum extract of the aerial parts of *Eclipta alba* (L.) Hassk. collected from flowering and fruiting plants in Egypt, yielded a phytosterol "A" $C_{29}H_{48}O$ (0.11%) and B-amyrin (0.06%), while the alcoholic extract afforded wedelolactone (0.02%), luteolin-7-glucoside (0.04%), a glucoside of phytosterol "A" (0.07%) and a glucoside of a triterpene acid (0.03%) (Sarg *et al.* 1981).

Ma-Ma *et al.* (1978) studied the protective effect of *E. alba* on the hepatic damage produced by carbon tetrachloride. Fresh leaves of *E. alba* were washed and mechanically ground, and the liquid extract thus obtained was filtered over six layers of gauze and stored at 4°C before use. 6.6ml/kg of this extract was given orally to guinea pigs 48, 24 an 4 hours before the admininstration of 2.0ml carbon tetrachloride / kg mixed with an equal volume of liquid paraffin through a stomach tube. Significant protection was evidenced by studying the mortality rate, serum aspartate aminotransferase, serum alanine aminotransferase and serum alkaline phosphatase activity in *E. alba*-protected and -unprotected groups of animals. The mortality rate at the end of 24 hours was 77.7% ($p<0.001$)in the unprotected group and 22.2% in the protected group. Serum enzyme activities were also significantly lower in the *E. alba*-protected group. The protective effect was also seen histologically, where centrilobular necrosis, hydropic degeneration and fatty change of the hepatic parenchymal cells were markedly reduced in the animals receiving *E. alba* treatment before carbon tetrachloride intoxication (Ma-Ma *et al.* 1978).

Eclipta prostrata posess a series of polyacetylenes and their thiophene derivatives. Two of the thiophenes ocurring in *E. prostrata*, α-Terthienyl and 5-(But-3-ene-1-ynyl)-2,2'-bithienyl have been tested and both of them are strongly phototoxic.



α-Terthienyl

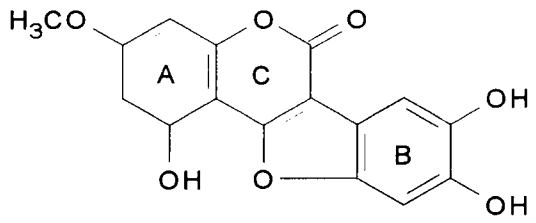


5-(But-3-ene-1-ynyl)-2,2'-bithienyl

The Chinese Chiang-su New Medical institute reports that fresh plant material of *E. prostrata* is effective in tests, in protecting the hands and feet of farmers from the inflammation and infections assosiated with working in paddy-fields (Wat 1980). α-Terthienyl is a nematocide, herbicide and an antimicrobial. It is phototoxic and induces photodermatitis in humans (Harborne & Watt 1993).

The whole plant of *E. alba* (Linn.) Hassk. was collected in India, air dried and ground and extracted with 50% ethanol. The extract was screened for antibacterial, antifungal, antiprotozoal, antianthelminthic, antiviral and hypoglyceamic activity and for effects on respiration, isolated tissues and central nervous system as well as anticancer activity. It was found to be antiviral against Ranikhet disease virus *in vitro* in concentrations of 0.064 haemagglutination (HA) unit/ml but it was not active against *Vaccinia* virus in concentrations of 50 pox-forming (PF) units/ml. It had an effect on the blood pressure but not on the rate or amplitude of respiration. It also had an effect on the contraction of the isolated guinea pig ileum. The maximum tolerated dose was 1000 mg/kg body weight administered intraperitoneally (Dhar *et al.* 1968).

The coumestan derivative wedelolactone isolated from *Eclipta alba* (L.) Hassk. has been found to be a potent and selective 5-lipoxygenase-inhibitor with an IC_{50} of 2.5μM in a porcine-leukocytes test system. As found by chemoluminescence, wedelolactone inhibits 5-lipoxygenase (5-LO) by an oxygen radical scavenger mechanism (Other 5-LO inhibitors are caffeic acid, nordihydroguaiaric acid and some flavonoids). The ethylacetate fraction of the methanol extract caused a 50% inhibition of 5-LO at a concentration of 2μg/ml (Wagner & Fessler 1986).



Wedelolactone (Wagner & Fessler 1986)

5.40 ELYTROPAPPUS Cass.

5.40.1 Elytropappus glandulosus Less.

(=*E. glandulosus* Less. var. *microphyllus* DC. p.p.)

E. glandulosus Less. var. *ambiguus* (DC.) Harv. = *E. gnaphaloides*

E. glandulosus Less. var. *longifolius* DC. = *E. longifolius*

E. glandulosus Less. var. *microphyllus* DC. p.p. = *E. glandulosus*

E. glandulosus Less. var. *microphyllus* DC. p.p. = *E. scaber*

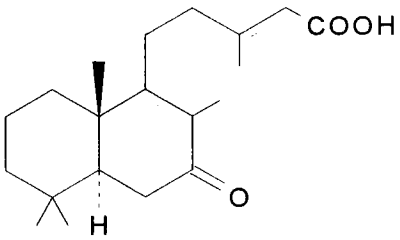
Elytropappus glandulosus Less. is recorded as being a good anthelminthic and is used for heart troubles in the Western Cape province (Watt & Breyer-Brandwijk 1962). *E. glandulosis* Less. ("Slangenbosch"), is mentioned by Thunberg (Trav. I., p. 268) as a good remedy for the expulsion of intestinal worms, when used in the form of a decoction (TRAMED database, index card 3176).

5.40.2 Elytropappus rhinocerotis (L.f.) Less.

(=*Stoebe rhinocerotis* L.f.)

An infusion of the tip of a twig of *Elytropappus rhinocerotis* Less. is taken by the Whites in South Africa as a tonic for lack of apppetite. A wine or brandy infusion was also taken as a stomachic bitter in indigestion and other conditions related to impaired digestion. The powdered top was also given to children with diarrhoea (Watt & Breyer-Brandwijk 1962; TRAMED database, index card 3175). The infusion and tincture is said to stimulate sweating. The plant was in vogue as a remedy during the 1918 influenza epidemic. It was also formerly used as a remedy for "krimpsiekte" in sheep. More recently the plant was used in the Western Cape province for diarrhoea, acidity and convulsions in children and for fevers including typhoid fever in children and adults. The plant is grazed in times when grazing is limited. The air-dried tip of the branch yields up to 10% of a wax-like material to organic solvents. The leaf is said to be strongly astringent (Watt & Breyer-Brandwijk 1962).

The air-dried and milled plant was succesively extracted with benzene, ethylacetate and methanol. Primary separation was achieved with benzene, ethylacetate and methanol. Separation was done on 30g of each extract and then divided into 4 groups according to the Rf. Group 1 was found to be inactive. Group 2 displayed analgesic (84% inhibition @ 500 mg/kg $p<0.001$), anti-inflammatory (68% inhibition @ 500 mg/kg $p<0.001$) and antimicrobial (against *Staphylococcus pyogenes* and *S. aureus*) activity. The activity of group 3 was very similar to that of group 2. Group 3 was analgesic (77% inhibition @ 500 mg/kg $p<0.001$), anti-inflammatory (45% inhibition @ 500 mg/kg $p<0.01$) and antimicrobial (against *Staphylococcus pyogenes* and *S. aureus*). Group 4 showed antimicrobial activity against *S. pyogenes*. The four groups were then separated further and then combined to form 9 fractions. These fractions were then again subjected to the writhing and anti-inflammatory tests. One fraction was 65% effective in the writhing test at a dose of 150 mg/kg ($p<0.01$) and another was 49% effective against inflammation at 150 mg/kg ($p<0.001$) (Noristan not published). Pharmacologically monitored seperation of the extracts led to the isolation of the labdane diterpene, rhinocerotinoic acid. Its absolute stereochemsitry was established by synthesis from sclareol. Rhinocerotinoic acid (LD50>300 mg/kg) causes 50% inhibition of the carrageenan-induced oedema in non-adrenalectomized rats as a dose of 150 mg/kg. A similar result was obtained when the test was done on adrenalectomized animals, indicating that the anti-inflammatory does not function *via* the adrenals. Rhinocerotinoic acid was also tested for anti-arthritic activity, which in practice is a favourable complement to anti-inflammatory activity; however, it failed to respond positively in this test.



Rhinocerotinoic acid (Dekker *et al.* 1988)

5.41 EMILIA Cass

Emilia is not indigenous to southern Africa

5.41.1 Emilia sagittata DC.

In Tanzania, *Emilia sagittata* DC. is put to several medicinal uses by the Swahili and Sukuma. A cold water compress of the bruised plant is applied to the eye in inflammations and the juice is applied in "pink-eye". The root is a colic remedy for sucklings. The plant is also used in the treatment of ulcerative processes. In Java and India, the plant is used as a remedy for asthma, for abdominal diseases, the juice for eye conditions and the leaf as a local application to contusions (Watt & Breyer-Brandwijk 1962).

5.41.2 Emilia sonchifolia DC.

In West Africa a leaf decoction of the plant is employed as a febrifuge. The juice from the fresh leaves is instilled in the eyes for the treatment of conjunctivitis. The leaf is used as an occasional vegetable for its laxative activity or eaten cooked in soup or fresh in salad as a health food. Infants are bathed with the leaf decoction for the prevention of high fever and convulsions (Iwu 1993). In Ghana the leaves of *Emilia sonchifolia* (Linn.) DC. are used with Guinea grains (seeds of *Afromomum melegueta* K. Schum belonging to the ginger family) and lime juice for sore throats (Ayensu 1978).

5.42 ERIGERON L.

Some *Erigeron* species have been found to show biological activity and the pyrone β-glycosides, erigeroside and 4-pyrone-3-β-D-glycopyranoside have been reported in their extracts (Mathela *et al.* 1984).

5.42.1 Erigeron karvinskianus DC.

Erigeron karwinskyanus De Candolle grows wild in various regions of Réunion Island where it is used in folk medicine. It is apparently not used in Southern Africa in folk medicine (Pieribattesti *et al.* 1988).

The essential oil obtained by steam distillation of the whole plant consists of sesquiterpene hydrocarbons (46%), polyacetylenic compounds (23%), monoterpene hydrocarbons (20%) and other oxygenated constituents (5%) Among the monoterpenes, (E)-β-Ocimene (15.7%) was the major component. Of the sesquiterpenoids, germacrene D and δ-guaiene are the main constituents (21%), followed by β-caryophyllene (6.8%), cadinene isomers and α-farnesene (8%) and β-curcumene (3.7%). The sum of the matricaria esters represented 62% of the total acetylenic fraction and was mainly composed by the (Z,Z)-isomer (Pieribattesti *et al.* 1988).

From the ethanolic extract of the aerial parts of *E. karwinskyanus* 3-hydroxy-4-pyrone 3-α-D-glycopyranoside was isolated (Mathela *et al.* 1984).

5.43 ERIOCEPHALUS L.

5.43.1 Eriocephalus africanus L.

(=*E. umbellulatus* DC.)

The plant has a distinctive fragrance and is known amongst the locals in the Western Cape as "Wild rosemary", "asmabossie" and "tontelbossie" (Salie *et al.* 1996). The leaf of *Eriocephalus africanus* L., when lightly rubbed, has a pleasant odour. Its herbaceous and balsamic odour is not unlike the herbal decoctions of tea, pine and dried herbs (Watt & Breyer-Brandwijk 1962). The plant has been used in the Cape as a diaphoretic and as a diuretic (Salie *et al.* 1996; Watt & Breyer-Brandwijk 1962). Infusions of this plant have also been used for treating coughs, colds, flatulence and colic (Salie *et al.* 1996). The Nama use a decoction of *E. umbellatus* DC. as a colic remedy. The early Cape settlers and Hottentots used it as a diuretic for dropsy. The Nama use of the plant is thus quite logical and it is possible that it produces the same degree of diuresis. It is used as a household medicine in the Western Province; a tincture for heart troubles and oedema; as a foot-bath, for delayed menstruation and for swelling and pain arising from a gynaecological conditions (Watt & Breyer-Brandwijk 1962).

The petroleum ether stem and methanol extracts only caused slight inhibition in the growth of *Staphylococcus aureus*. The MIC of the methanol root extract against *S. aureus* was 10 µg/ml. The lipophilic extracts of the leaves demonstrated some activity against *Candida albicans*. Plants were cleaned with distilled water, separated into leaves, stems and roots and air-dried in an oven at 40°C for 72h. The dried plant material was milled to a fine powder and was successively extracted with petroleum ether, chloroform, ethanol and methanol. Aqueous extracts were prepared by adding the powdered plant material to warm water for 30 min, followed by a methanol extraction (Salie *et al.* 1996).

Extraction of the whole plant with petroleum ether yields 0.3% of a green fairly dark attar, steam distillation *in vacuo* of which yields 10-15% of a fairly viscous yellowish volatile oil (Watt & Breyer-Brandwijk 1962).

5.43.2 Eriocephalus ericoides (L.f.) Druce

(=*E. glaber* Thunb.)

(=*Tarchonanthus ericoides* L.f.)

Eriocephalus ericoides Druce has been used in the Western Cape province as a diaphoretic and as a diuretic (Watt & Breyer-Brandwijk 1962).

5.43.3 Eriocephalus punctulatus DC.

Eriocephalus punctulatus DC. is used by the Southern Sotho with *Metalasia muricata* to fumigate the hut of a person suffering from a cold or from diarrhoea, and to fumigate a hut during illness or after death (Watt & Breyer-Brandwijk 1962).

From the leaf resin of *E. punctulatus* scutellarein-6,4'-dimethyl ether (pectolinarigerin) as well as 6,3'-dimethyl and the 6,3',4'-trimethyl derivatives of 6-hydroxyluteolin (jaceosidin and eupalitin) were obtained as crystalline products. Scutellarein-6,4'-dimethyl ether (pectolinorigenin) is

also one of the major flavones, while apigenin, luteolin and the rare luteolin-3',4'-dimethyl ether are minor flavones. In addition we found flavonols quercetin and quercetin-3'-methyl ether (isorhamnetin) as well as trace amounts of flavanones naringenin and eriodictyol (Wollenweber & Mann 1989). Air dried leaf material was rinsed in acetone to dissolve the exudate (13% of d.w.). The resinous exudates were passed over a Sephadex column, eluted with MeOH to seperate the flavonoids from the terpenoids. The flavonoid fractions were further fractioned by CC on polyamide and/or on silica, eluted with toluene and increasing amounts of MeCOEt and MeOH (Wollenweber & Mann 1989). Quercetin is known to inhibit platelet aggregation.

5.43.4 Eriocephalus racemosus L.

Eriocephalus racemosus L. has been used in the Western Cape province as a diaphoretic and as a diuretic (Watt & Breyer-Brandwijk 1962).

5.44 ERLANGEA Sch.Bip.

5.44.1 Erlangea misera (Oliv. & Hiern) S.Moore

(=*E. schinzii* O.Hoffm.)

(=*Vernonia merenskiana* Dinter ex Merxm. nom. nud.)

(=*Vernonia misera* Oliv. & Hiern)

The Ovambo use *Erlangea schinzii* for inflammation of the eyes (TRAMED database, index card 3219) and *E. misera* for fevers (malaria) in children (TRAMED database, index card 3221) and to relieve vomiting in children (TRAMED database, index card 3225; Rodin 1985).

5.44.2 Erlangea moramballae S. Moore

E. moramballae S. Moore is not indigenous to Southern Africa. In Tanzania, the Haya use the leaf of *Erlangea morramballae* S. Moore for abdominal troubles especially after childbirth. Among the Shambala the leaf is a remedy for meteorism and habitual abortion and the root is a remedy for fits in infants. The seed is said to cause inflammation of the eye (Watt & Breyer-Brandwijk 1962).

5.45 ETHULIA L.f.

5.45.1 Ethulia conyzoides L.

E. conyzoides L.f. subsp. *conyzoides*

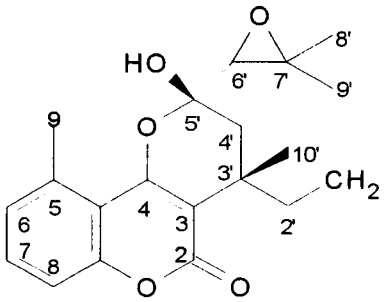
E. conyzoides L.f. subsp. *kraussii* (Walp.) M.G.Gilbert & C.Jeffrey

(=*E. kraussii* Walp.)

The Zulu use *E. conyzoides* L. as a remedy for intestinal parasites, for abdominal disorders and for colic. In Tropical Africa and Madagascar the plant is used as a counter-irritant, as a remedy for roundworm and for ophthalmia. *E. conyzoides* var. *gracilis* Asch. & Schweinf., growing wild in Egypt, is used in folklore medicine as an anthelminthic for roundworms and for abdominal disorders (Mahmoud *et al.* 1983). The seed contains saponin (Watt & Breyer-Brandwijk 1962).

Stems and leaves were collected in the flowering stage in Egypt, dried in the shade and coarsely powdered and extracted with light petroleum, ether and then ethyl acetate. The light petroleum extract contained two triterpenoids, α-amyrin and lupeol and a mixture of phytosterols, among which β-sisterol was present. The ether extract contained coumarins and two flavonoid aglycones recognized as apigenin and luteolin. The ethyl acetate extract contained the flavonoids luteolin, apigenin-7-O-glucosode and luteolin-7-O-glucoside (Balbaa *et al.* 1981). The 5-methyl coumarin compounds from the ether extract are known as ethuliacoumarin, cycoethuliacoumarin (Bohlmann & Zdero 1977) and isoethuliacoumarin A - C. The 5-methylcoumarin-4-glucoside have also been identified by Mahmoud *et al.* (1980). 5-Methylcoumarins are also present in other genera of the tribe Vernonieae and also in *Gerbera* belonging to the Mutisieae (Balbaa *et al.* 1980).

The alcoholic extract of the fresh aerial parts of *Ethulia conyzoides* var. *gracilis* Asch. & Schweinf. exhibits a significant anthelminthic activity when tested *in vitro* against *Ascaris lumbricoides* using santonin as a reference. Four coumarins were isolated and identified; ethuliacoumarin A was found to be responsible for the anthelmintc activity. Fractionation of the total alcoholic extract with different solvents and testing of each fraction showed that the activity occurred in the light petroleum fraction, while the aqueous fraction was inactive. Column chromatography of the active fraction resulted in the isolation and identification of lupeol, lupeol acetate, 7,24(28)-stigmastadiene-3-p-ol, 5-methyl-4-hydroxycoumarin and three other isomeric coumarins, ethuliacoumarin A, isoethuliacoumarin A and isoethuliacoumarin B. These compounds were identified by means of their IR, UV, MS and ^{1}H-NMR spectra, TLC and m.p. with reference substances. Only ethuliacoumarin A was found to have anthelmintic activity. 10μg/ml ethuliacoumarin A inhibited the myogenic contraction of the *Ascaris lumbricoides* for 4 min. A similar effect was obtained with 2μg/ml santonin. The yield of ethuliacoumarin A was 0.38% (Mahmoud *et al.* 1983).



Ethuliacoumarin A (Mahmoud *et al.* 1983)

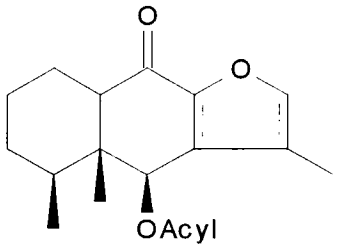
The roots of *Ethulia conyzoides* contain small amounts of the widespread pentaynene and "entetrainen" while the aerial parts contain two coumarins which are related to those of *Erlangea* and *Bothriocline*. They are Ethuliacoumarin and cycloethuliacoumarin (Bohlmann & Zdero 1977d).

5.46 EURYOPS Cass.

An *Euryops* sp. is used in the Western Cape province as snuff for headaches and taken for asthma and influenza. Many species were observed to be aromatic (Hutchings & Van Staden 1994). The Nama take a decoction of the resin from *Euryps* sp. in fevers. In the Western Cape province a *Euryops* sp., known as "Boesmanlandharpuis" is used as an internal remedy for influenza, asthma,

bronchitis and hoarseness, as a snuff for the relief of headache and as an ointment for carbuncles, boils and abscesses (Watt & Breyer-Brandwijk 1962). A hot alcohol extract of *Euryops floribundus* N.E.Br., contains 10% of resins and 2% of a waxy substance. It contains anisic acid, isobutyric acid, tiglic acid, angelic acid, lignoceryl alcohol, a ketol and several phenolic substances (Watt & Breyer-Brandwijk 1962).

More than 50 furanoeremophilanes have been isolated from representatives of several sections of the South African genus *Euryops* of the type illustrated below, together with more highly oxidized compounds (Robins 1977).



Furanoeremophilanes found in *Euryops* spp.

Several species are used for pain relief (including headaches). Extracts of *Euryops speciosissimus* DC. were found to be active in the writhing tests. It may be possible that some of the furanoeremophilanes are responsible for the pain relief. Helenalin, a sesquiterpene lactone, is also active in the writhing tests. (chapter 3)

5.46.1 Euryops evansii Schltr.

The Sotho burn and smoke the stems for headaches (Hutchings & Van Staden 1994). The roots and the aerial parts contain large amounts of furanoeremophilanes that include 1β,10β-Epoxy-6β-tiglinoyloxy furanoeremophilane and others. The aerial parts also contain quercetin (Bohlmann & Zdero 1978b).

5.46.2 Euryops spathaceus DC.

(=*Jacobaeastrum spathaceum* (DC.) Kuntze)

The Xhosa drink a decoction of *E. spathaceus* for pain relief (TRAMED database, index card 554). Both the roots and the aerial parts contain several furanoeremophilanes. The structures were determined by Bohlmann & Zdero (1978b).

5.46.3 Euryops speciosissimus DC.

(=*E. athanasiae* (L.f.) Harv.)

(=*E. megalanthus* Gand.)

Noristan made an extract of this plant, that was chromatographed as described in the introduction to this chapter. Similar fractions were combined to form two groups. At 500 mg/kg p.o. in the writhing test, group 1 inhibited 36% of the number of writhes, $p<0.1$, and group 2 inhibited 44% $p<0.05$. Group 2 also had a diuretic effect with a 206% increase in Na^+ excretion, $p<0.001$. Further writhing and diuretic tests were done on the 9 fractions but the results did not justify the isolation and identification of the active compounds for developing as medication (Noristan not published).

Both the roots and the aerial parts contain several furanoeremophilanes. The structures were determined by Bohlmann & Zdero (1978b).

5.47 FELICIA Cass.

5.47.1 *Felicia erigeroides* DC.

(=*Aster erigeroides* (DC.) Harv.)

(=*Aster erigeroides* (DC.) Harv. var. *schultesii* Harv.)

(=*Aster erigeroides* (DC.) Harv. var. *trinervius* (Turcz.) Harv.)

(=*F. natalensis* Sch.Bip. ex Walp.)

The Zulu inject an infusion of the leaf of *Aster erigeroides* Harv. as an enema. It is given for intestinal parasites, including "beetles", to relieve abdominal pain, especially if severe, as a strong purgative (Watt & Breyer-Brandwijk 1962) and also for the treatment of skeletal and genital infections (Salie *et al.* 1996). Leaves of *Felicia erigeroides* are used for severe abdominal pain (Hutchings & Van Staden 1994).

All the plant parts of *F. erigoides* exhibited activity against *Pseudomonas aeruginosa* and *Candida albicans*. The lipophilic extracts (chloroform and petroleum ether) inhibited the growth of *P. aeruginosa*, whereas the semipolar extracts (methanol and ethanol) were active against *C. albicans*. The ethanol extract of the root of this plant was very active against *C. albicans*, with an MIC of 2.5 mg/ml and an MFC of 5 mg/ml. Infections caused by *P. aeruginosa* are amongst the most difficult to treat with conventional antibiotics. Plants were cleaned with distilled water, separated into leaves, stems and roots and air-dried in an oven at 40°C for 72h. The dried plant materials were milled to a fine powder and were successively extracted with petroleum ether, chloroform, ethanol and methanol. Aqueous extracts were prepared by adding the powdered plant material to warm water for 30 min, following by a methanol extraction (Salie *et al.* 1996).

The aerial parts of *F. erigoides* DC. contain no acetylenic compounds. In addition to Germacrene D and neophytadiene a small amount of unidentified triterpenes was eevident. No compounds could be identified from the roots (Bohlmann & Fritz 1979). Germacrene D and neophyradiene have been isolated from *F. erigeroides* (Hutchings & Van Staden 1994).

5.47.2 *Felicia filifolia* (Vent.) Burtt Davy subsp. *filifolia*

(=*Aster filifolius* Vent.)

(=*Diplopappus filifolius* (Vent.) DC.)

(=*Diplopappus teretifolius* Less.)

(=*Diplostephium filifolium* (Vent.) Nees)

An infusion of *Aster filifolius* Vent. is taken with camphor as a tapeworm remedy by the Xhosa and the Kwena (Watt & Breyer-Brandwijk 1962). The Xhosa wash with a decoction of the leaves of *A. filifolius* for relief of rheumatism and spiderbite (TRAMED database; index card 127). The plant has been suspected of producing mortality in sheep and in tests it proved to be toxic to rabbits. The chief symptoms are weakness, acceleration of the pulse, tympanites, irregular respiratory rhythm and sometimes salivation. In the post mortems, cyanosis, subendocardial haemorrhages, congestion of various organs, fluid in the serous sacs and oedema of the lungs were found. Catarrhal gastro-

enteritis was also observed. Another author reported negative feeding tests and it is also reported that the plant is poisonous in some areas and regarded as useful fodder in others (Watt & Breyer-Brandwijk 1962).

The aerial parts of *Felicia filifolia* (Vent.) Burtt. Davy contain several polyacetylenes while the roots contain $AcOCH_2CH^t{=}CH[C{\equiv}C]_2CH{=}CHCH_2OAc$ and matricaria ester (Bohlmann & Fritz 1979).

5.47.3 Felicia hyssopifolia (P.J.Bergius) Nees

Felicia hyssopifolia (P.J.Bergius) Nees subsp. *glabra* (DC.) Grau

(=*Aster serrulatus* Harv. var. glaber (DC.) Harv.)

(=*Aster simulans* Harv.)

(=*F. lasiopoda* Hutch.)

Felicia hyssopifolia (P.J.Bergius) Nees subsp. *polyphylla* (Harv.) Grau

(=*Aster serrulatus* Harv. var. densus Harv.)

(=*Aster serrulatus* Harv. var. polyphyllus Harv.)

The Zulu drink a decoction of the root of *Aster serrulatus* Harv. for stomach troubles and as antidote in poisoning (unspecified). The decoction has a burning taste and is a purgative (Watt & Breyer-Brandwijk 1962).

5.47.4 Felicia muricata (Thunb.)

Felicia muricata (Thunb.) Nees subsp. *muricata*

(=*Aster muricatus* Thunb.)

(=*Aster muricatus* Thunb. var. *chrysocomoides* Sond.)

(=*Aster villosus* Thunb. p.p.)

(=*F. frutescens* R.E.Fr.)

F. muricata (Thunb.) Nees subsp. *strictifolia* Grau

F. muricata (Thunb.) Nees subsp. *cinerascens* Grau

(=*Detris dinteri* S.Moore)

The Southern Sotho crush and inhale *Aster muricatus* Less. to relieve headaches. They also believe that, if a portion of the plant is put into the food of an accused person, he readily confesses his guilt. It is a Southern Sotho medicine for a cow which has become ill after calving. The plant has been subjected to nutrition tests in sheep and is of fair value as fodder (Watt & Breyer-Brandwijk 1962). The Sotho inhale the vapours of the crushed plant for headaches (Hutchings & Van Staden 1994).

Noristan has done research on *F. muricata*. An extract was chromatographed in a silica gel column. The method is described in the introduction to this chapter. Similar fractions were combined to form 3 groups. Group 1 was slightly active in the antiviral test. It did not show any platelette aggregation of any significance and was inactive in inhibiting arachidonic acid induced pulmonary tromboembolism. Group 2 however, did show significant platelette aggregation. Group 3 was not toxic when 600 mg/kg was given p.o., but 48 hours after 200 mg/kg was given intraperitoneally (i.p.), all three mice died. No other significant pharmacological affects were observed (Noristan not published).

5.48 FLAVERIA Juss.

5.48.1 Flaveria bidentis (L.) Kuntze

(=*F. contrayerba* (Cav.) Pers.)

In Argentina it is used as digestive, emmenagogue, insecticide and tinctorial. The aerial parts of the plant (collected in Argentina) were macerated in ethanol for 24 hours and then heated to 50°C for 10 min. and then filtered. It was tested *in vitro* against *Herpes simplex* virus type-1. The result was a 99.4% inhibition. In addition it presented a virucidal activity reducing the viral infectivity at about 5% of the control value. The maximal non cytotoxic concentration was 6.25 mg/ml (Garcia *et al.* 1990).

5.49 GALINSOGA Ruiz & Pav.

5.49.1 Galinsoga parviflora Cav.

Galinsoga parviflora Cav. is an introduced weed. The Xhosa grind the leaves and take one tablespoon t.d.s. for snakebite (TRAMED database, index card 664).

Galinsoga parviflora Cav. has given negative antibacterial tests. A fluid extract has cardiovascular effects. In tests with frogs, a marked disturbance of the rhythm of both auricle and ventricle follows the application of a fluid extract to the isolated heart. An injection of 0.006ml/g body weight, into the ventral sac, apparently produces a partial A-V block and a marked slowing of the ventricle. The same dose subcutaneously in the guinea-pig kills in twenty-four hours. A 75% alcohol extract of the plant, in a dose of 0.000067ml raises the blood pressure of the dog, while 0.000134 ml of an 25% alcohol extract produces a fall in blood pressure. Both these extracts increase the rate of respiration (Watt & Breyer-Brandwijk 1962).

5.50 GARULEUM Cass.

5.50.1 Garuleum bipinnatum (Thunb.) Less.

(=*Dimorphotheca multifida* DC.)

(=*Osteospermum bipinnatum* Thunb.)

"Snake-root" aquired its vernacular name from its effects as an antidote against the bites of venomous snakes. The root has great similarity to the Radix Senegae of the Pharmacopoea. It is bitter and acrid, and contains a good deal of resinous substance, almost homogenous to that which we observe in the root of Polygala Senega. In the form of decoction or tincture, it is a great favourite in various diseases of the chest, asthma, and such affections where a free secretion of the mucus membrane of the lungs and bronchiae is desirable. It promotes perspiration, and acts as a diuretic in gout and dropsy (TRAMED database, index card 3165).

The root of *Garuleum bipinnatum* Less. was a much-prized snake-bite remedy among early settlers (Watt & Breyer-Brandwijk 1962). Farmers have also used a decoction or a tincture of it in various diseases of the chest. It is reported to be diaphoretic and diuretic. In the Transvaal a brandy extract of the root is one of the ingredients in a remedy for heamorrhoids used by the Whites. The root has

been used in the Western Cape in preparing a mouth-wash. Apparently the root has a digitalis type action (Watt & Breyer-Brandwijk 1962).

5.51 GAZANIA Gaertn.

A decoction of the whole plant of a *Gazania* sp., previously known as *Gazania pinnata* is drunk by the Xhosa to prevent miscarriage (TRAMED database, index card 699). Goats are fond of eating the leaves and flowers, which stimulate the production of a large amount of rich milk (Watt & Breyer-Brandwijk 1962). The subspecies of *G. pinnata* is now a different species.

5.51.1 Gazania krebsiana Less.

G. krebsiana Less. subsp. *arctotoides* (Less.) Roessler

G. krebsiana Less. subsp. *krebsiana*

G. krebsiana Less. subsp. *serrulata* (DC.) Roessler

(=*G. serrulata* DC.)

To relieve toothache, the Southern Sotho keep a hot decoction of the root of *Gazania serrulata* DC. in the mouth. They place the crushed plant, moistened with water, in the ear to relieve ear ache (Watt & Breyer-Brandwijk 1962).

Similar fractions of an extract of this plant made by Noristan, were combined to form 2 groups. The method is described in the introduction to this chapter. Signs of weak transient central nervous system depression were observed with group 1 at 300 mg/kg and 100 mg/kg. Two of the four mice administered with 300 mg/kg i.p., did not show any pain reaction (With morphine sulphate, three of the four mice did not show pain reaction). In the writhing test, 23.6% inhibition was observed with 500 mg/kg p.o. Group 2 showed signs of weak central nervous system depression at 300 mg/kg 90 minutes post dose (Noristan not published).

5.51.2 Gazania linearis (Thunb.) Druce var. *linearis*

(=*G. kraussii* Sch.Bip.)

(=*G. longiscapa* DC.)

(=*G. pinnata* (Thunb.) Less. var. *multijuga* (DC.) Harv.)

(=*G. subulata* R.Br.)

(=*Gorteria linearis* Thunb.)

Gazania linearis (Thunb.) Druce var. *ovalis* (Harv.) Roessler

(=*G. longiscapa* DC. var. ovalis Harv.)

(=*G. pottsii* L.Bolus)

A Southern Sotho purgative is made from the root of *Gazania longiscapa* DC. and the root of *Aloe* sp. (Watt & Breyer-Brandwijk 1962). A decoction of the root of *Gazania linearis* is given orally as a tonic to a child, who is thin and crying (TRAMED database, index card 663).

5.52 GEIGERIA Griess.

Vermeersiekte (vomiting disease) is a disease of stock resulting from the ingestion of various species of *Geigeria*. The Kwena and Kgatla rub the burnt and powdered herb of a *Geigeria* sp. into scarifications over the sternum to relief acute pains (Watt & Breyer-Brandwijk 1962).

5.52.1 Geigeria filifolia Mattf.

(=*G. africana* Griess. subsp. *filifolia* (Mattf.) Merxm.)

(=*G. passerinoides* Harv. p.p.)

The Sotho of Basutoland rub a preparation of *Geigeria africana* Gr. subsp. *filifolia* Merxm. into scarifications on the forehead, cheeks and neck of a child supposed to be suffering from parasites of the head (Watt & Breyer-Brandwijk 1962).

Two sesquiterpene lactones, griesenin and dihydrogriesenin have been isolated from *Geigeria africana* Gries and identified by NMR (De Kock *et al.* 1968).

5.52.2 Geigeria aspera Harv. var. *aspera*

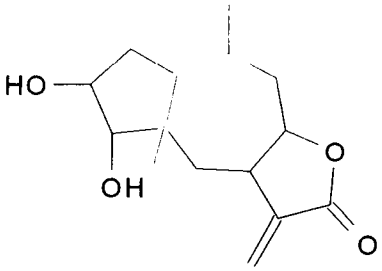
Geigeria aspera Harv. var. *rivularis* (J.M.Wood & M.S.Evans) Merxm.

(=*G. rivularis* J.M.Wood & M.S.Evans)

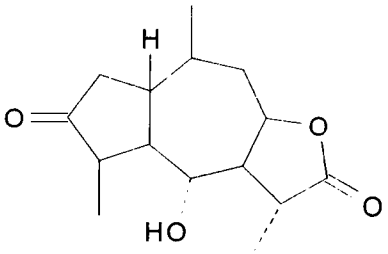
A decoction of the leaf and root of *Geigeria aspera* Harv. is a Swati remedy for giddiness (Watt & Breyer-Brandwijk 1962).

An ethanol extract of *Geigeria aspera* containing the sequiterpene lactones dihydrogriesenin, geigerinin and ivalin, produced typical vomiting disease symptoms in sheep. The ethanol extract or the individual purified compounds also produced strychnine-like nervous disorders in guinea-pigs and mice. The sesquiterpene lactones from *Geigeria* are inhibitors of mitochondrial respiration. The main targets of the sesquiterpene lactones appear to be electron transport complexes I and II as well as choline dehydrogenase complex of the respiratory chain (Gapar *et al.* 1986)(Van Aswegen *et al.* 1982). In general, sesquiterpene lactones are good alkylating agents and are therefore able to combine with sulphydryl groups in the key enzymes that control cell division and thus interfere with normal growth patterns (Gaspar *et al.* 1987).

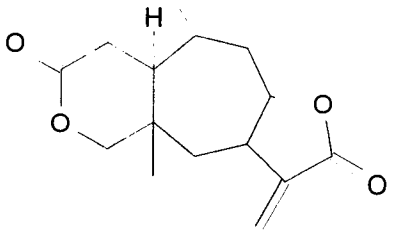
The sesquiterpene lactones, dihydrogriesin, geigerinin, ivalin and griesenin isolated from *G. aspera* and geigerin, vermeerin and gafrinin irreversibly inhibit the *in vitro* activity of three key glycolitic enzymes, namely phosphofructokinase, hexokinase and glyceraldehyde-3-phosphate dehydrogenase. Phosphofructokinase was inhibited irreversibly by all of the sesquiterpene lactones with ivalin giving the highest extent of inhibition. Values for the kinetic constants K_i (1.3mM) and k_p (2.2min-1) were established. Hexokinase and glyceraldehyde-3-phosphate dehydrogenase were also strongly inhibited at 1mM and 3mM concentrations of sesquiterpene lactones respectively. Phosphofructokinase and hexokinase were protected against inhibition by ivalin by their respective substrates, adenoside-5"-triphosphate (ATP) and glucose suggesting a common binding site for ivalin and ATP. It is known that the substrates ATP and fructose-6-phosphate protect phosphofructokinase from inhibition by the sesquiterpene lactones vernolepin, taxodiaone, taxodone, eupacunin and euparotin acetate (Gapar *et al.* 1986).



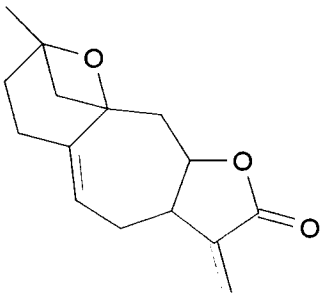
Geigerinin



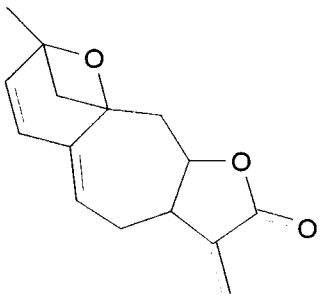
Geigerin



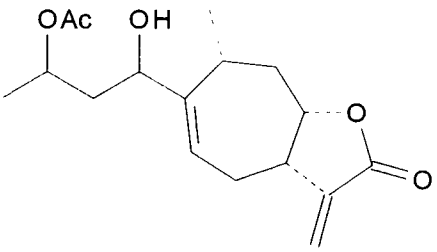
Vermeerin



Dihydrogriesenin



Griesenin



Gafrinin

(Gapar *et al.* 1986)

The observation of rapid alkylation of the sulphydryl group of L-cysteine by dihydrogriesin suggests that the *Geigeria* lactones may also act via alkylation of biologically important sulphydryl groups. Pre-incubation of ivalin with ditiothreitol decreased its inhibiting effect on phosphofructokinase, hexokinase and glyceraldehyde-3-phosphate dehydrogenase activities. In the light of the difference in the extent of inhibition of the different *Geigeria* inhibitiors at the same concentrations, it was concluded that although the α-methylene group may be the principle prerequisite for inhibition, the rest of the structure is aslo important (Gapar *et al.* 1986).

Gaspar *et al.* (1987) reported that the lactones from *Geigeria* inhibit the histamine release induced by Compound 48/80. Compound 48/80, a condensed product of N-methyl-p-methoxyphenethylamine with formaldehyde is a known histamine releaser and was used as a positive control. The sesquiterpene lactones from *Geigeria* were found to be incapable of inducing rat peritoneal mast cell degranulation at levels of 0.3-1.6mM. N-ethyl-maleimide (an alkylating agent of sulphydryl-catalized enzyme systems), too was unable to trigger mast cell secretion. Instead, it was observed that these compounds inhibited the release of histamine induced release induced by Compound 48/80. Pretreatment (alkylation) of the lactones and N-ethylmaleimide with the amino-acid, L-cysteine, reduced their inhibition ability of histamine release to a considerable extent, but not completely. Geigerin, which lacks an α-methylene group and the chemically prepared cysteine-adduct of dihydrogriesenin were also capable of inhibiting mast cell secretion by Compound 48/80, but to a lesser extent. Since the sesquiterpene lactones from *Geigeria* were unable to degranulate mast cells, it appears that direct histamine plays a minor or no role in vomiting disease (Gaspar *et al.* 1987).

However, contrary to these findings, it has been reported that helenalin, hymenovin, (which contains α-methylene-γ-lactone groups) thapsigargine and thapsigargicine (which contain no α,β-unsaturated-γ-lactone group) stimulated secretion of histamine from mast cells. Tenulin (which lacks an α-methylene group) was ineffective in causing mast cell secretion. Alkylation of helenalin and hymenovin with cysteine, also significantly reduced their ability to degranulate mast cells (Gaspar *et al.* 1987).

The roots of air-dried plant material of *Geigeria aspera* var. *aspera* afforded kessane, bicyclogermacrene, a thiophene and corresponding dithio compound, small amounts of sesquiterpene lactones and geigeranolide (major component, a acyclopropane derivative) and another thiophene, 2-prop-1-inyl-5(5,6-epoxyhex-3c-1-inyl)-thiophene. The arial parts gave carophyllen-1,10-epoxice, bicyclogermacrende, germacrene D, sesquiterpene lactones (major components), ivalin and several guaianolides and the acetate derivative of dihydrogriesenin. The aerial parts also contained nerolidol derivatives (Bohlmann, Zdero & Ahmed 1982). Air-dried plant material, collected in the Transvaal, were extracted with Et_2O:petrol (1:2) and the resulting extracts were seperated first by CC (Si gel) and further by repeated TLC (Si gel) using different solvent systems. Known compounds were identified by comparing the ^1H NMR spectra with those of authentic material (Bohlmann, Zdero & Ahmed 1982).

5.52.3 Geigeria burkeii Harv.

Geigeria burkeii is widespread in the Transvaal and does not seem to cause vermeersiekte. The toxicity of this species was tested at fourteen day intervals over a period of a year and it was found that the toxicity disappeared to such an extent after the first heavy summer rains that it was impossible to kill a sheep with the plant, whereas prior to these rains, 400 mg of the plant produced pronounced symptoms of vermeersiekte and 900 mg killed whithin 48 hours of administration (Watt & Breyer-Brandwijk 1962).

Chromatographic seperation of a ethanol extract of *Geigeria burkei* Harv. subsp. *burkei* resulted in the isolation and characterization of two known flavonoids, 5,7,3'.4'-tetrahydroxy-6-methoxyflavone (nepetin, eupafolin) and 5,7,4'-trihydroxy-6-methoxyflavone (dinatin, hispidulin). Both inhibit ADP-stimulated respiration with both sodium glutamate and sodium succinate as sustrates. 5,7,3'.4'-Tetrahydroxy-6-methoxyflavone gave 45% inhibition in sodium glutamate 10mM. (Oxygen consumption was measured in isolated guinea pig liver mitochondria.) It appears that the 3'-hydroxyl group is necessary for good inhibition of state 3. The fact that the ADP:oxygen ratio in the presence of the flavonoids was higher than in their absence, indicated that uncoupling of oxidative phosphorylation did occur. These two compounds were non-toxic at a dosage of 1g/kg to mice and guinea pigs, while the sesquiterpene lactone, ivalin, gave only a 32% inhibition of state 3 under identical conditions at 1mM and was toxic to mice and guinea pigs at 0.25g/kg subcutaneously. This could possibly be explained by the fact that flavonoids are excreted efficiently as their glucuronides. The observed inhibition of these two compounds could possibly play a role in their cytotoxicity observed against human carcinoma of the nasopharynx in cell culture (Coleman *et al.* 1984). Method: The air dried aerial parts of the plants were shaken twice with 96%EtOH for 24 hours. The

combined extracts were dissoved in H_2O:EtOH (2:1) and the aqueous solution was extracted first with hexane and then after removal of tar with $CHCl_3$, gave an oil. The oil was chromatographed on silica gel using C_6H_6, $CHCl_3$ and MeOH in different proportions. The two compounds were isolated from MeOH:$CHCl_3$ (1:9) fractions and characterized mainly on the basis of ^{13}C NMR (Coleman *et al.* 1984).

The roots of *G. burkei* Harv. *burkei* var. *burkei* afforded bisabolene (major component), γ-humulene, kessane, geigeranolide and 11β,13dihydrogeigeranolide and a lignane, the dimer of coniferyl alcohol isobutyrate. From the aerial parts α-humulene, germacrene D, bisabolene, caryophyllene, bicyclogermacrene, stigmasterol and a thiophene. The polar fractions contained a complex mixture of diterpenes from which geranyllinalol (main component) and eight derivatives were isolated. A remark was made that the amount of diterpenes must be higher, for difficult seperations caused considerable loss of material (Bohlmann, Zdero & Ahmed 1982).

The roots of *G. burkei* subsp. burkei var. *fruticulosa*, var. *zeyheri*, var. *elata* and var. *intermedia* all contained bisabolene as the major component. The main component of the aerial parts of *G. burkei* subsp. *diffusa* was thymol; 14,15-dihydro-14,15dihydrogeranyllinalol was the major component of the aerial parts of subsp. *fruticulosa* and 5-hydroxygeranyllinalol the major componenet in *G. burkei* subsp. *burkei* var. *elata*. Air-dried plant material, collected in the Transvaal, was extracted with Et_2O:petrol (1:2) and the resulting extracts were seperated first by CC (Si gel) and further by repeated TLC (Si gel) using different solvent systems. Known compounds were identified by comparing the ^1H NMR spectra with those of authentic material (Bohlmann, Zdero & Ahmed 1982).

5.52.4 Geigeria ornativa O.Hoffm.

(=*G. africana* Griess.)

(=*G. africana* Griess. subsp. *ornativa* (O.Hoffm.) Merxm.)

The Tswana crush the fresh leaves of *G. ornativa*, soak it in beer and drink this as a diuretic (TRAMED database, index card 1369).

5.52.5 Geigeria schinzii O.Hoffm. subsp. *karakowisae* Merxm.

G. schinzii O.Hoffm. subsp. *rhodesiana* (S.Moore) Merxm.

(=*G. rhodesiana* S.Moore)

G. schinzii O.Hoffm. subsp. schinzii

The Ovambos drink a decoction of the root of *G. schinzii* for tetanus and rabies as well as for cramps or spasms (TRAMED database, index cards 3227, 3223, 10714). The tea from the leaves given to babies with tetanus, is said to relax them (Rodin 1885).

5.53 GERBERA

The Southern Sotho take an infusion of a *Gerbera sp.* as a cough remedy (Watt & Breyer-Brandwijk 1962).

5.53.1 Gerbera ambigua (Cass.) Sch. Bip.

The leaves are cooked and eaten with porridge, preferably as a spice (Mabogo 1990). It is used for abdominal and heart pain in Zimbabwe (Hutchings & Van Staden 1994).

5.53.2 Gerbera burmannii Cass.

A Gerbera sp. closely related to *G. burmannii* Cass. is one of the ingredients in a Sotho remedy for sterility (Watt & Breyer-Brandwijk 1962).

5.53.3 Gerbera discolor

The Xhosa bandage circumcision wounds with the underside of the leaf (TRAMED database, index card 555).

5.53.4 Gerbera glandulosa

A decoction is given to teething children 3 times daily (TRAMED database, index card 1317).

5.53.5 Gerbera kraussii Sch. Bip.

The leaf of *G. kraussii* Sch. Bip. is taken by the Zulu as an anthelmintic and relief of stomach ache (Watt & Breyer-Brandwijk 1962).

5.53.6 Gerbera lanuginosa Benth.

Extracts of *G. lanuginosa* Benth. have shown antispasmodic activity (Hutchings & Van Staden 1994).

5.53.7 Gerbera piloselloides (L.) Cass.

The dried, powdered leaves are used as a snuff for headaches (TRAMED database, index card 1259). Roots of this plant are used for ear ache (Hutchings & Van Staden 1994). The Zulu apply an infusion of the root made with human urine, to the ear for ear ache. The Southern Sotho use a decoction of the root as a tonic and as eardrops in ear ache and a milk decoction or infusion for chest complaints. They also use the plant to fumigate the hut of a person suffering from a head cold (Watt & Breyer-Brandwijk 1962). The Xhosa also use it for pains in the chest and the leaf for wounds on the genitalia (circumcision wounds) (TRAMED database, index card 235).

5.53.8 Gerbera viridifolia (DC.) Harv.

The Sotho inhale the smoke of the plant for headaches (Hutchings & Van Staden 1994). For head colds, the Southern Sotho inhale the smoke from burning *G. viridifolia* Sch. Bip.

5.54 GRANGEA Adans.

5.54.1 Grangea maderaspatana (L.) Poir.

(=*Artemisia maderaspatana* L.)

A mixture of flavonoids extracted from *Grangea maderaspatana* showed oestrogenicity and anti-implantational activities in mice. The air dried aerial parts were extracted with Et_2O:petrol:MeOH

(1:1:1) at room temperature for 24h. The solvent was evaporated, the extract was then dissolved in MeOH, filtered and the filtrate, chromatographed over silica gel. The elution was done with solvents in order of increasing polarity. A fraction collected by eluting C_6H_6:CH_2Cl_2:Et_2O (1:1:1) yielded a yellow mass which contained a mixture of highly oxygenated flavonoids. This mixture was subjected to oestrogenicity and antifertility tests.

In the 3 day uterotophic bioassay, administration of the drug at a dose of 20 mg/kg body weight per day, intramuscularly to ovariectomized females, resulted in a highly significant ($p<0.001$) increase in wet uterine and vaginal weights. However, in comparison with conjugated oestrogen, the extract proved to be mildly oestrogenic. Administration of flavonoids causes a marked stimulatory change in the atrophic uterus and vagina of the ovariectomized mouse. Simultaneous administration of flavonoids and the conjugated oestrogen resulted in a decline in the uterine weight compared with the organ weight of the females treated with conjugated oestrogen alone. This can be explained on the basis of competitive inhibition between a weak and strong oestrogen at the level of receptor sites of oestrogen in the uterus. Flavonoids (flavones), if administered orally at the same dose level effectively interfere with all stages of pregnancy. Maximum interceptory efficacy was recorded when the drug was administered from days 4-6 *post coitum* (80%). However there was a reduction in the antinidational activity only if the drug was administered from days 1-3 (60%) and 7-9 *post coitum* (40%). The post-coital anti-fertility effect of flavonoids during different stages of pregnancy appeared to be due to its inherent oestrogenic nature. Flavonoids are similar to oestrogen in their basic structure, i.e. presence of benzopyrone ring (Jain *et al.* 1993)

Strictic acid, a novel diterpene with a ten-membered ring has been isolated from the petroleum ether extract of *Grangea maderaspatana* Poir. The compound has been identified by conventional spectral analysis and direct comparison (m.p., UV and IR) (Iyer *et al.* 1962). Conyzic acid, strictic acid and seconicoresedic acid are identical. Extraction of the above ground parts of *Grangea maderaspatana* Poir collected in India gave (-)-hardwickiic acid, *ent*-15,16-epoxy-1,3,13(16),14-cleroda-tetraen-18-oic acid and 3-hydroxy-8-acetoxypentadeca-1,9,14-trien-4,6-diyne (Pandey *et al.* 1984). *Grangea maderaspatana* (L.) Poir. contain quercetin 3-gentiobioside and 3-gentiobioside-7-glucoside (El-Karemy *et al.* 1987). The steroids chondrillasterol and chondrillasterone have been isolated from *Grangea maderaspatana* (Iyer & Iyer 1978).

5.55 HAPLOCARPHA Less.

5.55.1 Haplocarpha scaposa Harv.

(=*H. thunbergii* DC.)

The leaf of *Haplocarpha scaposa* is a Xhosa dressing for sores and wounds. The Southern Sotho take a decoction of the root and that of *Tephrosia semiglabra* for colds in the chest (Watt & Breyer-Brandwijk 1962). The Xhosa also drink a decoction of the root for infections in the respiratory system (TRAMED database, index card 702). A decoction of the root is a Southern Sotho remedy for

venereal diseases and for menstrual troubles e.g. excessive menstrual bleeding. It is used by the Whites of Dewetsdorp area as a cancer cure (Watt & Breyer-Brandwijk 1962).

Noristan made an extract of this plant, which was chromatographed in a silica gel column. The method is described in the introduction to this chapter. Similar fractions were combined to form 3 groups which were submitted for phamacological testing. All three groups were active in the writhing test. The inhibition was 57% ($p<0.01$), 41% ($p<0.05$) and 36% ($p<0.1$) respectively for the three groups. The six fractions were then also submitted for the writhing test. The best result obtained was a 53.2% inhibition ($p<0.001$) with one fraction administered at 100 mg/kg p.o. Groups 2 and 3 were weak central nervous system stimulants (Noristan not published).

The roots of *Haplocarpha scaposa* Harv. afforded mainly sesquisabinene and also derivatives of sesquisabinene, acetates (13-acetoxysesquisabinene) and aldehyde (sesquisabinen-12-al) as well as the acetylene, $Me(C{\equiv}C)_5CH{=}CH_2$ and β-farnesene. The aerial parts gave no characteristic compounds. The air-dried plant material, collected in the Transvaal was extracted with Et_2O:petrol (1:1) and the resulting extracts separated by CC (Si gel) and further by TLC (Si gel). Known compounds were identified by comparing the ^1H NMR with those of authentic material (Bohlmann & Wallmeyer 1982).

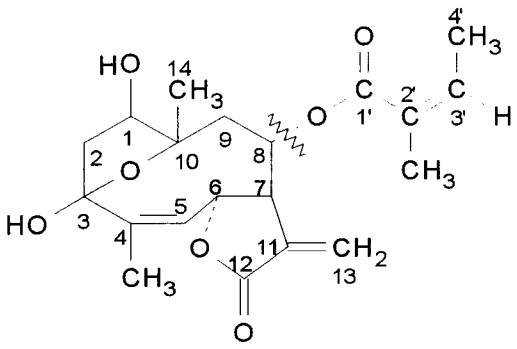
5.56 HELIANTHUS L.

5.56.1 Helianthus annuus L.

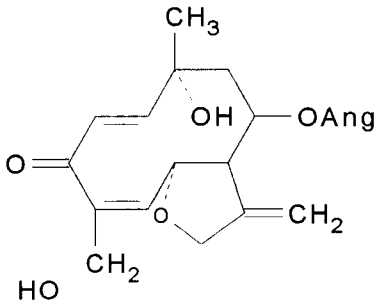
The sunflower, *H. annuus*, is a commercial crop. The seed oil is used for cooking oil and in the manufacture of margarine. The plant is apparently not used in southern Africa for medicinal purposes. In the Caucasus the leaf is used as a malaria remedy. A tincture of the leaf and flower with balsamics has been recommended in the treatment of bronchiectasis. A 10% tincture of the flower, made with 70% alcohol has been recommended as a febrifuge and is used in Poland, but tests have shown that it has no antipyretic affect. In Italy the aerial parts are used as diuretic a febrifuge and a stimulant. An infusion or decoction of the flower is used at van Rhynsdorp as a fly poison. An aqueous extract of the ligulate flower is toxic, 0.004g killing 50% of a group of mice by subcutaneous injection, but the extract is non-toxic to the rabbit by both subcutaneous and intramuscular injection but perfusion of the isolated rabbit ear with 1:1000 dilution results in dilation of the blood vessels. Subcutaneous injection in the cat temporarily lowers the blood pressure. Intravenous injection in the rabbit results in stimulation of respiration, a fall in blood pressure and finally cessation of heart beat and respiration. The extract has such a marked effect in stimulating intestinal contraction, that the use of it in intestinal atony has been recommended. The green aerial parts gave positive antibiotic tests with *Staphylococcus aureus* and negative with *Escherichia coli*. The root has given positive antibacterial tests against *Micrococcus tuberculosis* and negative results with several other pathogens (Watt & Breyer-Brandwijk 1962).

H. annuus contain germacranolides and heliangolides, C_3-C_{10} furanes and angelate side chains (Spring *et al.* 1986). Sesquiterpene lactones, the helangolides 15-hydroxy-3-dehydrodesoxyfruticin

and niveucin C, niveusin B and 3-ethoxy-niveucin-B were isolated by ethanol extraction from 4-week old sunflower seedlings cultivated in a greenhouse. The antibiotic effects were assessed with the agar diffusion test and a dilution test. These compounds were found to have an antibiotic effect on gram-negative and gram-positive bacteria as well as on some fungi. The minimal inhibition concentration (MIC) of 15-hydroxy-3-dehydrodesoxyfruticin is 15µg/ml for *Bacillus brevis* and 95µg/ml for the fungus *Eremothecium ashbyi*. *Eremothecium ashbyi* was particularly influenced by 3-ethoxy-niveusin-B. 15-hydroxy-3-dehydrodesoxyfruticin proved to be the most active substance in nearly all the test assays. At a MIC of 50µg/ml the effects on *Bacillus subtilis* are 50% stronger than other comparable substances such as helenalin. In addition, cytotoxic effects on mouse myeloma cells (NS-1) were also shown. 15-Hydroxy-3-dehydrodesoxyfruticin caused a 50% inhibition of cell proliferation (ED_{50}) at a concentration of 170nM and niveucin C at 330nM. The LD_{50}-values were 0.15µg 15-hydroxy-3-dehydrodesoxyfruticin/ml and 1.24µg niveucin C / ml. Both 15-hydroxy-3-dehydrodesoxyfruticin and niveucin C display their effects very quickly at concentrations above 0.1µ M. Especially in the case of 15-hydroxy-3-dehydrodesoxyfruticin, the ED_{50} and LD_{50} values do not differ greatly. By measuring ^{14}C-labelled thymidine, uridine and leucine incorporation into murine cells of the ascitic form of Ehrlich carcinoma (EAC) it could be shown that 15-hydroxy-3-dehydrodesoxyfruticin and niveucin C inhibit DNA and RNA synthesis, but do not affect the translation processes involved in protein synthesis. It was shown that the exocyclic methylene group in both molecules play an important part in triggering the described inhibitory effects. The two sesquiterpene lactones are also capable of inhibiting auxin-induced elongation growth of coleoptyl and hypocotyl segments (Spring *et al.* 1982).



Niveusin C

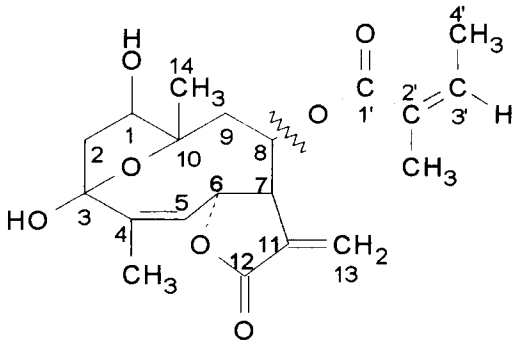


15-Hydroxy-3-dehydro-desoxyfruticin

The anti-inflammatory activity of an ethanol extract of *Helianthus annuus* L. (which was treated to remove pigments with petroleum ether) was evaluated in rats using the carrageenin-induced pedal edema assay. A dose of 100 mg/kg x2 resulted in a 26% inhibition (Benoit *et al.* 1976).

Annuithrin, a germacranolide was isolated from *H. annuus*. Leaves and stems of three week old plants were extracted in boiling EtOH, homogenized and filtered. The filtrate was evaporated *in vacuo* and the residue extracted by EtO_2. The crude extract was chromatographed by SC and further purified by HPLC. The structure of annuithrin was determined by IR, ^1H NMR, ^{13}C NMR and MS measurements. Growth assays on *Avena* and Helianthus with inductive displacement transducer showed that annuithrin inhibited the IAA-induced straight growth of stem segments from the

H. annuus analogue to that of *Avena* coleoptile sections. Annuithrin also have antibacterial qualities. However, fungi and yeast were either less inhibited or not inhibited (MIC 45µg/ml on *Bacillus brevis*; MIC 90µg/ml on *Proteus vulgaris*; MIC 90µg/ml on *Eremothecium ashbyi*.) *In vivo* DNA and RNA synthesis in cells of the ascitic form of Ehrlich carcinoma was drastically reduced by annuithrin (at an annuithrin soncentration of 20µg/ml about 50% inhibition of DNA synthesis and about 75% inhibition of RNA synthesis (Spring *et al.* 1981).



Annuithrin

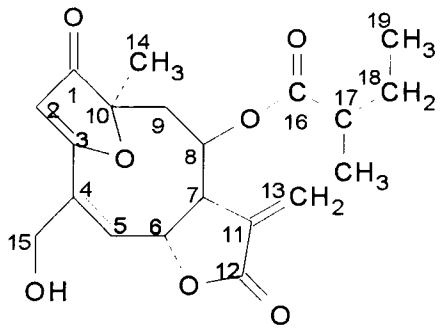
5.56.2 Helianthus argophyllus Torr. & A.Gray

H. argophyllus contain germacranolides, C_7-C_8 lactones and angelate side chains (Spring *et al.* 1986). The sesquiterpene lactone, argophyllone-B has been isolated from *H. argophyllus*. (Stiptanovic *et al.* 1985) Three germacranolide sesquiterpene lactones (argophyllin-A and -B and eupatolide), three diterpenoids (ciliaric acid, (-)-16-α-hydroxy-kaur-11-en-19-oic acid and (-)-16-α-hydroxykaurane) and one flavonoid (nevadensin) were isolated and characterized from a chloroform extract of *Helianthus argophyllus*. Their structures were deduced by ^{1}H NMR and ^{13}C NMR. Argophyllin-A and -B were found to show anti-auxin effects while eupatolide exhibited weak insecticidal activity. It showed weak activity against tobacco cutworm larvae (*Spodoptera litura*, 63% kill ater 48hr, 2000ppm in an artificial diet) and mosquito larvae (*Culex pipens*, 60% kill after 24hr in 10ppm solution) (Watanabe *et al.* 1982).

5.56.3 Helianthus debilis Nutt. subsp. cucumerifolius (Torr. & A.Gray) Heiser

(=*H. cucumerifolius* Torr. & A.Gray)

Acetone extracts from fresh leaves of *H. debilis* subsp. *cucumerifolius* (grown in a greenhouse in Germany) were chromatographed on TLC and screened for antibiotic activity on agar diffusion tests with *Bacillus brevis*. An active compound was identified and was further purified on HPLC. The furanoheliangolide, 17,18-dihydrobudlein A was identified by spectroscopical measurements (MS; ^{1}H and ^{13}C NMR) and spin decoupling experiments. The content in primary leaves of 3 to 4 week old plants was ±120µg/g fresh weight. 120µg 17,18-dihydrobudlein A per gram fresh weight showed complete protection against insect predation in choice experiments with larvae of *Locusta migratoria*. 17,18-Dihydrobudlein A shows strong antimicrobial activity (MIC: 16µg/ml on *Bacillus brevis* and is able to inhibit auxin-induced plant growth at a concentration of 10µM and more. It was found that in *H. annuus* increasing amounts 17,18-dihydrobudlein A could be extracted from leaf to leaf towards the apex. (Spring *et al.* 1986)



17,18-Dihydrobudlein (Spring *et al.* 1986)

The above ground parts of *H. debilis* Nutt. subsp. *cucumerifolius* (T & G)Heiser collected in Texas gave relatively large amounts of *ent*-kaur-16-en-19-oic acid and angelylgrandifloric acid. The following compounds were obtained in smaller quantities: grandifloric acid and its methyl ester, a methyl ester derived from another naturally occuring kauranoic acid. *Ent*-kaur-16-en-19-oic acid found in florets of *Helianthus annuus* inhibit larval development of the sunflower moth (*Homeosoma electellum* L.) and of several Lepidoptera species and have been implicated in imparting resistance to insect pests of several cultivated varieties of sunflower (Herz *et al.* 1983).

5.56.4 Helianthus tuberosus L.

Samples of the aroma volatiles of the Jerusalem artichoke were obtained by well established methods and were analyzed by GC and GC/MS. It contained one major component (β-bisabolene, ca 51%) and a range of saturated long-chain hydrocarbons (ca 22%). The sesquiterpene presumably contributes appreciably to the characteristic flavour of Jerusalem artichoke (MacLeod *et al.* 1982).

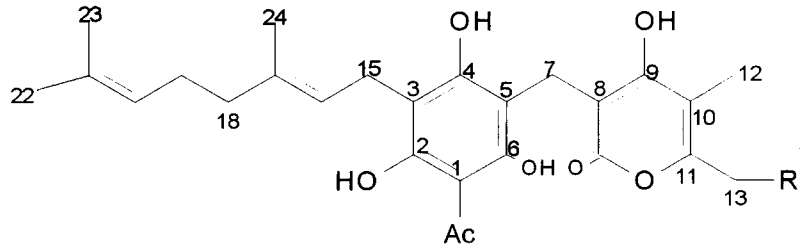
5.57 HELICHRYSUM Mill.

The genus *Helichrysum* contain flavones, chalcones, phthalide, aurones, phloroglucinol- and α-pyrone derivatives, acetylene components in particular chlorenolether, various triterpenes, diterpenes and monoterpene derivatives (Bohlmann, Mahanta & Zdero 1978). Some ethylenic compounds have also been isolated. Phloroglucinol derived compounds like ketones, as well as chalcones, flavanones and flavones with no functions at C-2' - C-6' seem to be characteristic. *H. zeyheri* is related to the group of *H. callicinum* where the typical phloroglucinols are replaced by the simple α -pyrone. Only α-Pyrone substituted phloroglucinols were present in *H. mixtum* and *H. cephaloideum* which are placed in the same group as *H. auriceps* which also contains these compounds. However these compounds have been isolated from the more remote *H. odoratissimum* and from species which are placed in the genus *Achyrocline*. Acyclic and monocyclic diterpenes have been reported from several species which most likely are not closely related. The same is true for the chalcones and flavones which are also common but not restricted to specific groups of *Helichrysum* species (Jakupovic 1986). Sesquiterpenoids have to date not been found in the genus *Helichrysum*, although guaianolides are known to occur in other genera in the tribe Inuleae (Bohlmann & Suwita 1979).

5.57.1 Helichrysum species not indigenous to Southern Africa

Helichrysum arenarium (L.) Moench has long been known as a medicinal plant. It yields inflorescentia helichrysi which has diuretic properties and have been used in diseases of the kidneys and the urinary bladder. It also has cholagogue and choleretic activity and stimulates the secretion of gastric juice. An extract from inflorescentia helichrysi is a component of such preparations as Cholesol®, Cholegran® and Gastrochol® (Poland). A group of flavonoids isolated from inflorescentia helichrysi are used in cases of cholecystopathy. Choleretic and diuretic properties of extracts from this material have been confirmed by pharmacological investigations. The medicinal properties are attributed mainly to the presence of flavonoids and coumarins, but they may also be influenced by other chemical components such as phenolic acids. Eleven phenolic acids were detected using GC. Caffeic and *p*-coumaric acids have antibacterial properties and salicylic acid has anti-inflammatory activity. Caffeic acid is a choleretic agent and the enhancement of gastric juice secretion may be associated with the presence of protocatechuic acid, which stimulates the secretory activity of the alimentary tract (Dombrowicz *et al.* 1992).

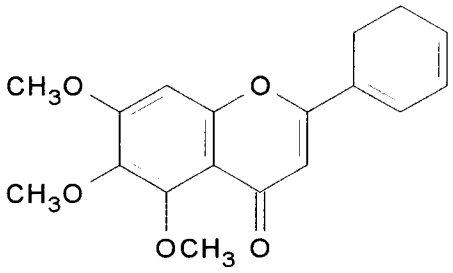
Three antifungal phloroglucinol derivatives have been identified from *Helichrysum decumbens* from Spain. The phloroglucinols prevented the growth of *Cladosporium herbarum* in a bioassay and are externally deposited on the plant surfaces together with other secondary metabolites (Tomás-Lorente *et al.* 1989).



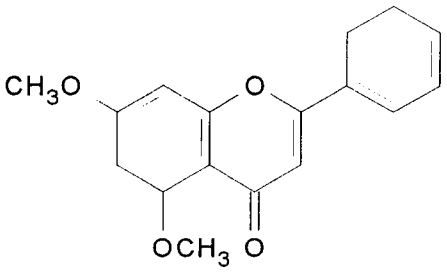
R	
1	H
2	Me
3	Et

Phloroglucinol derivatives (Tomás-Lorente *et al.* 1989)

Six flavones that are externally deposited on the leaf and stem surfaces of *H. nitens* from Malawi showed antifungal activity against *Cladosporium cucumerinum*. 1μg of dimethylchrysin and trimethylgalangin, 2μg of 5,6,7,8-tetramethyoxyflavone and 5μg of baicalein trimethyl ether, 3,5,6,7,-tetramethoxyflavone and 3,5,6,7,8-pentamethoxyflavone were sufficient to prevent the growth of the fungus. 50μg of alnetin and 5-hydroxy-6,7-dimethylflavone were inactive. The fully methylated flavones isolated from *H. nitens* show an antifungal activity similar to that of tangeritin. The antifungal activity decreases dramatically when the methyl group at position 5 is removed. 5,7-Dimethoxyflavone and 5,6,7,8-tetramethoxyflavone have been previously found in *Helichrysum herbaceum* (Tomás-Berberán *et al.* 1988).



Baicalein 5,6,7-trimethyl ether
(Antifungal activity)
(Harborne & Baxter 1993)



Chrysin 5,7-dimethyl ether
(Strong antifungal activity)

5.57.2 Helichrysum adenocarpum DC.

H. adenocarpum DC. subsp. *adenocarpum*

H. adenocarpum DC. subsp. *ammophilum* Hilliard

The Southern Sotho administer a decoction of the root of *Helichrysum adenocarpum* DC. to a child suffering from diarrhoea and vomiting (Watt & Breyer-Brandwijk 1962).

The roots contain mostly a mixture of triterpenes and a little trideca-1-ene-3,5,7-pentayne and an acetate derivative (Bohlmann, Zdero *et al.* 1980).

5.57.3 Helichrysum albirosulatum Killick

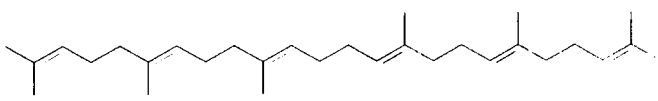
The aerial parts contain mainly 3β-hydroxy-isomanool and a aromadendrene derivative. The roots contain isomanool and a mixture of triterpenes (Bohlmann *et al.* 1978).

5.57.4 Helichrysum appendiculatum (L.f.) Less.

(=*Gnaphalium appendiculatum* L.f.)

The leaves are ground and rubbed on areas which cramps or on wounds. The ground and burnt roots are smeared on the body to relax the body and for swelling of the body (TRAMED database, index card 236). The root is also applied externally on wounds and the leaves are used for infection of the respiratory tract (TRAMED database, index card 1530). The leaf is a Xhosa remedy for chest troubles, sometimes, being eaten raw for this purpose. The plant is used as a remedy for smallpox and is said to be anthelmintic. The root is used in East Africa for colds and the leaf as a wound dressing (Watt & Breyer-Brandwijk 1962).

The roots and the aerial parts contain squalene (Bohlmann, Zdero *et al* 1980) The triterpene, squalene is bactericidal, antitumor and an immunostimulant.



Squalene (Harborne & Baxter 1993)

5.57.5 Helichrysum athrixiifolium (Kuntze) Moeser

(=*Gnaphalium athrixiifolium* O.Hoffm. ex Kuntze)

The Southern Sotho smoke the leaf for chest complaints (Watt & Breyer-Brandwijk 1962).

5.57.6 Helichrysum aureonitens Sch.Bip.

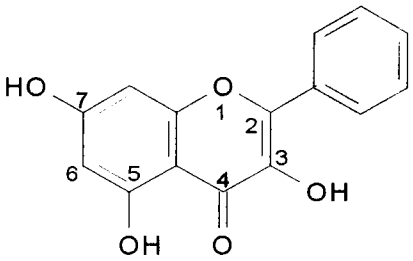
(=*H. helodes* Hiern)

The Zulu people have been using extracts from this plant topically for many generations against skin infections. Ethnomedical information from Kwazulu-Natal revealed that exudate from *H. aureonitens* has been used topically against herpes zoster (Meyer *et al.* 1996).

The antibacterial activity of extracts from *Helichrysum aureonitens* was investigated. The dichloromethane extract was active against all five gram positive bacteria tested, including *Bacillus subtilis* and *Staphylococcus aureus* but the methanol extract was only active against *Bacillus cereus*, *B. pumilus* and *Micrococcus kristinae*, while the water extract had no activity against any of the organisms. None of the extracts inhibited the growth of the five gram negative bacteria tested. Method: Air dried shoots (without flowers) were shaken separately for 5 min in CH_2Cl_2, MeOH and H_2O. The extracts were filtered and concentrated to dryness under reduced pressure. After the nutrient agar was prepared by autoclaving, 10 mg of the extract was dissolved in 0.2ml of MeOH and added to 9.8ml of nutrient medium to test at 1 mg/ml. The test organisms were streaked on the agar plates and incubated at 37°C and examined after 24h and 48h. Complete suppression of growth was required for the extract to be declared active (Meyer & Afolayan 1995).

The antimicrobial activity-guided fractionation of the acetone extract from the air-dried aerial parts led to the isolation of 3,5,7-trihydroxyflavone (galangin). Evaluation of the antibacterial activity of the compound against ten randomly selected bacteria indicated significant activity against all the Gram-positive bacteria tested with the minimum inhibitory concentration (MIC) ranging from 0.1 mg/ml (*Bacillus cereus*, *Micrococcus kristinae*) to 0.5 mg/ml. (*Bacillus pumilus*, *B. subtilits* and *Staphylococcus aureus*) The compound was not active on Gram-negative bacteria except for *Enterobacter cloacae* which was significantly inhibited at an MIC of 0.1 mg/ml. Galangin indicated considerable activity against the fungi tested with the exception of *Cladosporium herbarum*. *Penicillium digitatum* and *P. italicum* appeared to be particularly susceptible at a concentration of 0.01 mg/ml. The antimicrobial activity of galangin and the fact that it is the major constituent of the epicuticular extract from *H. aureonitens*, probably explains the use of this plant against a number of infections. Method: The air-dried aerial parts were shaken in acetone for 5 min. The resultant extract was concentrated to dryness. This was dissolved in acetone and subjected to column chromatography and eluted with absolute ethanol. The different fractions obtained were tested for antimicrobial activity by direct bioautography on thin layer chromatography (TLC) plates using *Bacillus subtilis*. The main active fraction was further purified by preparative TLC on silica gel with acetone:chloroform (2:25) and high performance liquid chromatography (HPLC). After the nutrient agar (for bacteria) and potato dextrose agar (for fungi) were prepared, galangin was added. To test at 0.5 mg/ml, 5 mg of galangin was dissolved in 0.1ml of acetone and added to 9.9ml of a molten

nutrient medium. The test bacteria were streaked on the agar plates, incubated at 30°C and examined after 24 and 48 h. Complete suppression of growth was required for it to be declared active. Prepared plates were innoculated with plugs obtained from the actively growing margin of fungi plates and incubated at 25°C for 3 days. Diameter of fungal growth was measured and expressed as means of percentage growth inhibition of three replicas (Afolayan & Meyer *in press*).



Galangin

The crude aqueous extract from shoots of *Helichrysum aureonitens* Sch. Bip. showed significant antiviral activity on herpes simplex type 1 (HSV-1) in human lung fibroblasts (HF) at a concentration of 1.35 mg/ml (w/v). Shoots (without flowers) were collected in Kwazulu-Natal. Non-homogenized plant material was boiled in distilled water for 30 min under reflux. The extract was filtered and concentrated to dryness at reduced pressure. The dry extract was later dissolved in water to a final concentration of 270 mg/ml. Dilutions of the plant extract were tested for antiviral activity at various concentrations. After one week, even at the high concentration of 8.44 mg/ml, HF cells treated with aqueous extract of *H. aureonitens* alone did not exhibit altered morphology or growth characteristics indicative of cytotoxic effects. In the assay to assess the possible antiviral properties of the extract, the virus control showed extensive CPE 36 h after infection, whereas the HSV-1 infected cells treated with the extract showed no CPE after one week. The plant extract exhibited significant antiviral activity at a concentration of 1.35 mg/ml (w/v). Although the minimum inhibitory concentration (MIC) of extract from *H. aureonitens* on HSV-1 is higher than the 7.2μg/ml of pure aloe emodin from *Aloe barbadensis* leaves, further purification of the extract will permit the isolation of the active compound and decrease the level of its actual effective dose (Meyer *et al.* 1996).

Bohlmann & Ziesche (1979) investigated the constituents of *H. aureonitens* Sch. Bip. The roots contained squalene and aureonitol. The aerial parts gave carryophyllene epoxide and a mixture of triterpenes (Bohlmann & Ziesche 1979). Squalene has bactericidal and antitumour activities; it is also an immunostimulant. Its main use is as an intermediate in the manufacture of pharmaceuticals, aromatics, surface active agents and rubber chemicals.

***5.57.7 Helichrysum aureum* (Houtt.) Merr.** var. *monocephalum* (DC.) Hilliard

(=*H. fulgidum* (L.f.) Willd. var. *monocephalum* DC.)

(=*H. fulgidum* (L.f.) Willd. var. *nanum* DC.)

The main constituents of the aerial parts and the roots of *H. aureum* var. *monocephalum* are kaurenic acids. The aerial parts also contain two acetoxykaurenic acids, 11β-acetoxykaurenic acid and 3α-acetoxykaurenic acid (Bohlmann *et al.* 1978).

5.57.8 Helichrysum auriceps Hilliard

(=*H. araneosum* Klatt)

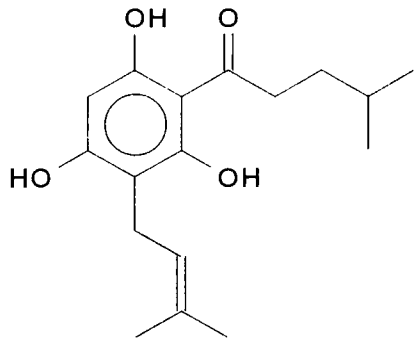
The roots contain two phloroglucin derivatives, auricepyron and 23-methylauricepyron, but nothing could be characterized from the aerial parts (Bohlmann & Zdero 1980b).

5.57.9 Helichrysum caespititium (DC.) Harv.

(=*H. lineare* DC. var. *caespititium* DC.)

Helichrysum caespititium and other *Helichrysum* species are widely used for their pain relieving, anti-infective and anti-inflammatory properties in the folk medicinal context. Acylated phloroglucinols and related compounds are common in the genus (Dekker *et al.* 1983). The plant is crushed, burned and inhaled by the Sotho for headaches (Hutchings & Van Staden 1994). A decoction of *H. caespititum* Sond. is drunk by the Kwena and the Kgatla in the treatment of gonorrhoea. The Southern Sotho, in addition to inhaling the smoke from a burning plant, for the relief of head and chest colds, take a decoction of the root as a remedy for nausea (Watt & Breyer-Brandwijk 1962).

Caespitin, a phloroglucinol derivative, 2-(4-methylpentanoyl)-4-(3-methylbuten-2-yl)-phloroglucinol was extracted from *Helichrysum caespititium*. This is the first phloroglucinol-related compound containing the isocaprophenone moiety in the genus *Helichrysum*. Caespitin show antimicrobial activity with significant inhibition against *Staphylococcus aureus, Streptococcus pyogenes, Cryptococcus neoformans, Trichophyton rubrum, T. mentagrophytes and Microsporum canis* (Dekker *et al.* 1983). Method: Air dried plant material was milled and extracted with ethyl acetate at room temperature for 48 hours. Caespitin was isolated by means of open column chromatography and preparative HPLC using benzene-ethyl acetate (9:1) as the mobile phase and was rechrystalized from benzene to yield straw-coloured crystals. The structure was determined by X-ray structure analysis (Dekker *et al.* 1983).



Caespitin

(Dekker *et al.* 1983)

Other findings from the work done by Noristan (not published) were anti-inflammatory action and possible inhibition of platelette aggregation. One fraction, given at 450 mg/kg i.p. caused 78.9% inhibition of swelling at 3 hours post carrageenan and 28.4% inhibition of platelet aggregation at 5 hours. Another fraction inhibited swelling by 82.4% at 360 mg/kg i.p.

5.57.10 Helichrysum callicomum Harv.

The Southern Sotho use it as an ingredient in an enema for colic (Watt & Breyer-Brandwijk 1962). The aerial parts of *H. calliconum* Harv. contain squalene, humulene, pinocembrin as main constituent the diterpene acid, 14,15-dihydrohelicallen-16-acid. It also contains hellicallen-16-al and hellicallen-16-ol. The roots contain small amounts of trideca-1-ene-3,5,7-pentayne, farnesene and the triterpene β-amyrin (Bohlmann & Abraham 1979a).

5.57.11 Helichrysum calocephalum Klatt

The Xhosa use the root of the plant for hyperfunction of the lower gastro-intestinal tract (TRAMED database, index card 1245). The Southern Sotho administer a decoction of the root to a child suffering from diarrhoea (Watt & Breyer-Brandwijk 1962).

5.57.12 Helichrysum cephaloideum DC.

(=*H. adscendens* (Thunb.) Less. var. *cephaloideum* (DC.) Moeser)

(=*H. adscendens* sensu Moeser)

(=*H. campaneum* S.Moore)

(=*H. infuscum* Burtt Davy)

(=*H. polyphyllum* Conrath)

The plant contains the same two phoroglucinol derivatives (pyrones) as *A. auriceps*; auricepyron and 23-methylauricepyron. The roots contain more than the aerial parts (Bohlmann & Zdero 1980b).

5.57.13 Helichrysum chionosphaerum DC.

(=*H. pondoense* Schltr.)

(=*H. randii* S.Moore)

The aerial parts of *H. chionospermum* afforded a humulene alcohol, an abietane derivative, atisirenic acid and two representatives of a new class of diterpenes. The structure of the basic acid, helifulvanic acid, was elucidated by NMR studies and by X-ray analysis (Bohlmann, Abraham & Sheldrick 1980).

5.57.14 Helichrysum cochleariforme DC.

(=*H. imbricatum* (L.) Less.)

(=*H. stellatum* (L.) Less. var. globiferum Harv.)

A decoction of the whole plant is drunk for infection of the respiratory tract (TRAMED database, index card 3173). *H. imbricatum* Less. has been used as a tea and an infusion as a demulcent in coughs and in pulmonary affections. In the Western Cape area the plant is used as a remedy for whooping cough, for other coughs and for bronchial catarrh and bronchitis (Watt & Breyer-Brandwijk 1962).

5.57.15 Helichrysum cooperi Harv.

The leaf of *H. cooperi* is a Zulu love philtre. The dry leaf is made into an ointment which is applied all over the body after a bath. As a result the desired lady finds the man irresistable (Watt & Breyer-Brandwijk 1962). The roots contain kaurenic acid and apigenin and the aerial parts contain, in addition, two acetoxy kaurenic acids (Bohlmann *et al.* 1978). The acetone extract of the flowers of a

species identified as being close to *H. cooperi* contain luteolin-7-glucoside, (-)-2-O-methylchiroinositol and a chalcone glucoside, helichrysin (Wright 1976).

5.57.16 Helichrysum crispum (L.) D.Don

(=*Gnaphalium crispum* L.)

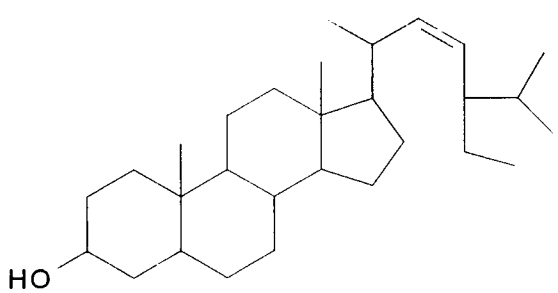
(=*H. crassifolium* auct. non (L.) D.Don)

(=*H. rotundifolium* sensu Moeser)

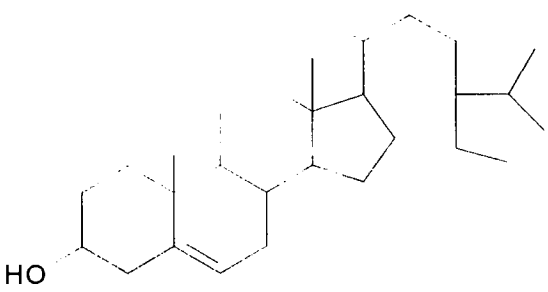
A tea made of the leaf of *Helichrysum crispum* is taken in the Western Cape province for heart trouble, kidney ailments, backache and as a calmative (Salie *et al.* 1996). The Whites of South Africa also use it as a remedy for "heart weakness" in man and animal. The medicine is said to quieten the heart's action. An infusion has been held in high repute in the treatment of hyperpiesia, coronary trombosis, and of bladder conditions (Watt & Breyer-Brandwijk 1962). Infusions of the plant are reported to be effective in the treatment of coughs, bronchitis, coronary trombosis, hypertension, urinary tract infections and tuberculosis (Salie *et al.* 1996).

Different extracts of *H. crispum* were screened for antimicrobial activity. It proved inactive against *Staphylococcus aureus* but was very active against *Pseudomonas aeruginosa*. In fact the whole plant inhibited the growth of *P. aeruginosa*, with the lipophylic extracts exhibiting the greatest activity. The petroleum ether leaf extract had an MIC of 10 mg/ml against *P. aeruginosa*. This extract and the aqueous stem extract also caused slight inhibitions in the growth of *Mycobacterium smegmatis*. Only the chloroform stem extract showed significant activity against *Candida albicans* with an MIC of 10 mg/ml. Plants were cleaned with distilled water, seperated into leaves, stems and roots and air-dried in an oven at 40°C for 72h. The dried plant materials were milled to a fine powder and were successively extracted with petroleum ether, chloroform, ethanol and methanol. Aqueous extracts were prepared by adding the powdered plant material to warm water for 30 min, followed by the methanol extraction. Salie *et al.* (1996) are currently involved in isolating the compounds which inhibited *M. smegmatis*, for testing against the pathogen *M. tuberculosis* (Salie *et al.* 1996).

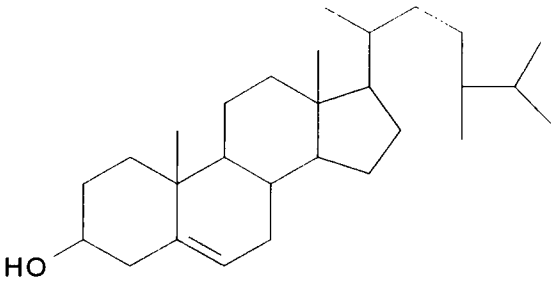
Method: The plant was homogenised with light petroleum and then continuously extracted (soxhlet) with chloroform and then methanol. The chloroform extract was clearly active in the analgesic test, but inactive in the blood sugar test. Chromatography of the chloroform extract, led to nine combinations. Two of the less polar combinations and two of the very polar combinations were active in the analgesic test. The three least polar combinations were active in the blood sugar test. The analgesic compound was identified as a three component mixture of stigmasterol, β-sisterol and campesterol (Noristan not published).



Stigmasterol



β-sisterol



Campesterol

The aerial parts of *H. crispum* Less. contain phloroglucinol derivatives (Bohlmann & Suwita 1979b)

5.57.17 Helichrysum dregeanum Sond. & Harv.

The Southern Sotho smoke the leaf of *H. dregeanum* for a head cold. An infusion is drunk by the Whites of South Africa for hiccups (Watt & Breyer-Brandwijk 1962).

5.57.18 Helichrysum foetidum (L.) Moench

(=*Gnaphalium foetidum* L.)

In the Eastern Cape province, the leaves are applied as a dressing for a festering sore on the skin, to relieve menstrual pain (TRAMED database, index card 1255) and it is used for inflammation of the eyes (TRAMED database, 1250). The leaf of *H. foetidum* Cass. is said to make an excellent dressing for a festering sore. The involucre leaf contains helichrysin. The plant has been used in the Western Cape Province as an aromatic and astringent (Watt & Breyer-Brandwijk 1962).

5.57.19 Helichrysum gerberifolium Sch.Bip. ex A.Rich.

(=*H. brunneum* Burtt Davy)

(=*H. davyi* S.Moore)

The root is externally applied to wounds and the leaves are used for infection of the respiratory tract (TRAMED databse, index card 1530). The root is used in East Africa for coughs and colds and the leaf as a wound dressing. Both the root and the leaf are said to contain helichrysin (Watt & Breyer-Brandwijk 1962).

5.57.20 Helichrysum kraussii Sch.Bip.

(=*H. steetzii* (Vatke) O.Hoffm.)

The Karanga smoke the dried flower and seed in a pipe for the relief of coughing and as a remedy for tuberculosis. The Lenge in Mozambique, use the ground, toasted plant, mixed with salt and other remedies, as a local application to the child's side. A decoction of the leaf is used as a wash for keloid scars (Watt & Breyer-Brandwijk 1962). The Venda drink a decoction of the root for problems of the genitalia (TRAMED database, index card 6759).

5.57.21 Helichrysum litorale Bolus

(=*Leontonyx angustifolius* DC.)

(=*Leontonyx spathulatus* Less.)

The whole of this little plant, *Leontonys angustifolius* DC., called "Beetbosjes" by the Boers, has an aromatic smell, and when pounded and mixed with lard or fat, is applied to ulcers (TRAMED

database, index card 3174). In the Western Cape province an ointment for boils, carbuncles and abscesses is made from this plant, *Cyanella lutea* and "tiendaegeneesbossie" (Watt & Breyer-Brandwijk 1962).

5.57.22 Helichrysum miconiifolium DC.

The Xhosa grind and boil the leaves and use it as a wash for pain after circumcision (TRAMED database, index card 545). The powdered root is used for intestinal parasites and for ticks on poultry (TRAMED database, index card 429).

The roots contain kaurenic acid and its derivatives (Bohlmann, Zdero *et al.* 1980)

5.57.23 Helichrysum mundtii Harv.

A decoction of *H. mundtii* is taken by the Southern Sotho as an ingredient in a colic remedy (Watt & Breyer-Brandwijk 1962).

Bohlman, Zdero *et al.* (1980) identified several compounds from the roots and aerial parts. The roots and the aerial parts of *H. mundii* Harv. contain the flavones helilandin-A-flavone and helilandin-B-flavone-5(O)-methylether, the chalcone derivatives 7,8H-7-hydroxyhelilandin and β-hydroxy-helilandin. The roots contain more than the aerial parts. The roots also contain oleanol acid (Bohlmann, Mahanta & Zdero 1978).

5.57.24 Helichrysum nudifolium (L.) Less.

(=*Gnaphalium nudifolium* L.)
(=*H. asperifolium* Moeser)
(=*H. leiopodium* DC.)
(=*H. leiopodium* DC. var. *denudatum* Harv.)
(=*H. nudifolium* (L.) Less. var. *leiopodium* (DC.) Moeser)
(=*H. nudifolium* (L.) Less. var. *obovatum* Harv.)
(=*H. nudifolium* (L.) Less. var. *quinquenerve* (Thunb.) Moeser)
(=*H. quinquenerve* (Thunb.) Less.)

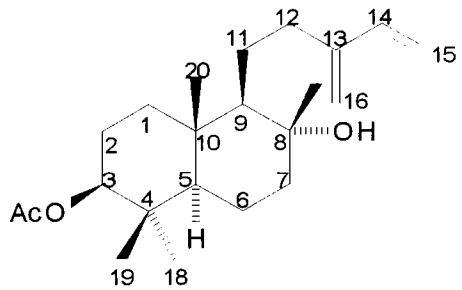
Helichrysum nudifolium Less. is a Hottentot remedy for colds. The Xhosa also use the leaf as a remedy for colds, sometimes eating it for this purpose. In the past the plant has been regarded as demulcent, and an infusion used in catarrh, phthisis and other pulmonary affections. The plant has also been used as a tea. The root is a remedy for coughs and colds and the leaf is used as a wound dressing (Watt & Breyer-Brandwijk 1962). The root is externally applied to wounds and the leaves are used for infection of the respiratory tract (TRAMED database, index card 1530). In Venda the root is boiled and the decoction is given to a child to encourage weaning (Mabogo 1990). The Xhosa apply the leaves to sores on the genitalia (TRAMED databse, index card 432). A decoction of the whole plant is drunk for infection of the respiratory tract. The Zulu drink a decoction of the root for chest troubles and as an emetic in similar conditions. The Tswana and Kwena drink a decoction of the root for "internal sores" and rub an ointment of the charred plant into scarifications over bruises. The Southern Sotho make a steam bath by pouring an infusion on hot stones for patients suffering from

fever or bad dreams. They use the plant as a poultice for swellings and administer a decoction as enema for a child suffering from colic (Watt & Breyer-Brandwijk 1962). Smoke from the plant is inhaled by the Zulu for relief of headaches (Hutchings & Van Staden 1994).

The extract of *Helichrysum nudifolium* was fractionated and combined to form 3 groups. The method is described in the introduction to this chapter. The principal action of the three groups was anti-inflammatory. At a concentration of 500 mg/kg, group 1 inhibited carrageenan induced oedema by 30.8% ($p<0.02$), group 2 by 24.2% ($p<0.1$) and group 3 by 28.5% ($p<0.2$) after 3 hours. In the writhing test, group 3 inhibited the number of writhes induced by acetic acid i.p. in rats by 24.7% ($p\sim0.02$). The plant was recollected and 10 fractions were tested for anti-inflammatory action. Fractions 2, 5 and 10 showed the best results with 37%, 31% and 31% inhibition respectively at 300 mg/kg. Some chemical work was done (Noristan not published).

Aqueous and ethanolic extracts of *Helichrysum nudifolium* (L.) Less. were tested as part of a screen for prostoglandin-synthesis inhibitors of 39 plants used in traditional Zulu medicine to treat headache or inflammatory diseases. Prostaglandins are involved in the complex process of inflammation and are responsible for the sensation of pain. One of the highest activities was obtained by the ethanolic extract of *Helichrysum nudifolium* (L.) Less. with 96% inhibition. The aqueous extract caused only 34% inhibition. Dried leaves were ground and extracted with water or ethanol for 30 min in an ultrasound bath. The extraction mixtures were centrifuged, the supernatants decanted, or filtered when necessary, and then taken to dryness under vacuum. The residues were resuspended in water or ethanol, respectively, giving 2.5 mg residue/ml water and 20 mg residue/ml ethanol. Extracts were tested in an *in vitro* assay for cyclooxygenase inhibitors (Jäger *et al.* 1996).

Isoabienol was the main constituent of the roots of *H. nudifolium* var. *nudifolium*. Isocomene, a sesquiterpene, an isoabienol derivative (depicted below), δ-cadinene, β-isocomene, silphinene, modhephene and isocomene-5,6-epoxide were found in the root of *H. nudifolium* var. *nudifolium* from the eastern parts of the Northern Province. The aerial parts gave in addition to squalene, isocomene, β-isocomene, modhephene, cadinene, caryophyllene and isoabienol, 5 phloroglucinol derivatives as wel as 2 diterpenes (Jakupovic *et al.* 1986). The triterpene, squalene, is bactericidal, antitumor and an immunostimulant (Harbourne & Baxter 1993).



Isoabienol derivative (Jakupovic *et al.* 1986)

The roots of *H. nudifolium* (L.) Less. contain the aromadendrene derivatives 8α-acetoxy-α-gurjunene and α-gurjunene. The aerial parts contain a diterpene-carbohydrate, squalene and α-curcumene (Bohlmann *et al.* 1978).

5.57.25 Helichrysum odoratissimum (L.) Sweet

(=*Gnaphalium odoratissimum* L.)

The Southern Sotho use *H. odoratissimum* Less. to fumigate huts, and their women make a pleasant perfumed ointment from the plant. The Chagga drink a decoction of the leaf to relieve abdominal pains and take the juice of the fresh leaf for heartburn. In East Africa the root is used for coughs and colds and the leaf as a wound dressing. Both are said to contain helichrysin. The aerial parts with flowers collected in Kenya yield 0.2% of a clear very pale yellow limpid volatile oil with a slight camphoraceous odour (Watt & Breyer-Brandwijk 1962). The Xhosa inhale the smoke of the plant for relief of headaches. *H. odoratissimum* (L.) Less. is also used for dysmenorrhoea in Rwanda and abdominal pains and colds in other parts of Africa (Hutchings & Van Staden 1994). *Helichrysum odoratissimum* (L.)Less, formerly known as *Helichrysum hochstetteri* (Sch.-Bip. ex A. Rich) Hook.f., is a widespread herb throughout Southern Africa where it is used to relieve abdominal pains, heartburn, coughs, colds and wounds. In the native medicine of Rwanda, *H. odoratissimum* is used to treat female sterility, menstrual pain, and eczema (Van Puyvelde, L *et. al.* 1989). The Xhosa also use the plant for spiritual purposes; as a fumigant when a baby is born (TRAMED database, index card 546), and for cosmetic purposes; they boil the plant, add it to fat and apply it to the skin (TRAMED database, index card 549).

Antimicrobial activity was found in the MeOH extract of the flowers of *H. odoratissimum.* Fractionation led to the isolation of two flavonoids, namely 3,5-dihydroxy-6,7,8-trimethoxyflavone and 3-*O*-methylquercetin and one chalcone, helichrysetin. Of the three products isolated, only 3-*O*-methylquercetin showed antimicrobial activity. The minimum inhibitory concentration (MIC) for *Staphylococcus aureus* (Gram-positive) was 6.25μg/ml and for *Candida albicans* 12.5μg/ml. It showed limited activity against Gram-negative bacteria. 3-*O*-Methylquercetin has also been found in *Vernonia amygdalina* and *Vernonia cinerea.* Method: The air-dried and powdered flowers were successively extracted in a perculator with petroleum ether, $CHCl_3$, H_2O and MeOH. The methanol extract was redisolved in MeOH-H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was chromatographed on a Si gel column in C_6H_6 and eluted with a C_6H_6/$CHCl_3$/EtOAc/MeOH gradient. 3-*O*-Methylquercetin was isolated form the $CHCl_3$-EtOAc fraction and was recrystallized from $CHCl_3$ (Van Puyvelde, L *et. al.* 1989).

5.57.26 Helichrysum pilosellum (L.f.) Less.

(=*Gnaphalium pilosellum* L.f.)

(=*H. latifolium* (Thunb.) Less.)

(=*H. pedunculare* (L.) DC. var. pilosellum (L.f.) Harv.)

The Southern Sotho use *H. latifolium* Less. as an ingredient in a colic remedy (Watt & Breyer-Brandwijk 1962).

5.57.27 Helichrysum pandurifolium Schrank

(=*H. auriculatum* Less.)

H. auriculatum Less. is demulcent and an infusion has been used in respiratory conditions. The plant was used in the early days as a tea. The plant is used in the Western Cape area as a remedy for heart trouble, backache and kidney disease (Watt & Breyer-Brandwijk 1962).

5.57.28 Helichrysum panduratum O.Hoffm.

H. panduratum O.Hoffm. var. *panduratum*

(=*H. auriculatum* Less. var. *panduratum* Harv.)

(=*H. auriculatum sensu* Oliv. & Hiern)

H. panduratum O.Hoffm. var. *transvaalense* Moeser

Air dried plant material of *Helichrysum panduratum* O.Hoffm. was ground and extracted three times with methanol and dichloromethane. The extracts were combined and concentrated under reduced pressure. The extract was chromatographed in the way described in the introduction to this chapter. Similar fractions were combined to form three groups. Group 1 had anti-inflammatory activity with a 29% inhibition of oedema at a dose of 500 mg/kg p.o. ($p<0.01$). Group 2 displayed a 78.6% inhibition in the writhing test for pain at 500 mg/kg p.o. ($p<0.001$). In the anti-inflammatory test it inhibited oedema by 51.2% at 500 mg/kg p.o. ($p<0.001$). It was anti-hypertensive with a 6% reduction in mean blood pressure after 2 hours at a dose of 300 mg/kg i.p. (sistolic $p<0.05$). It had a weak antimicrobial effect against *Stapylococcus aureus* at 1000μg/ml. A mild CNS stimulation was observed with group 3 and only 20% inhibition in the writhing test and 12% inhibition in the anti-inflammatory test was observed (Noristan not published).

The roots of *H. panduratum* O. Hoffm. contain the thiophene compound helipandurin and the sesquiterpene, β-farnesene while the aerial parts contain only squalene and germacrene D (Bohlmann & Abraham 1979b).

5.57.29 Helichrysum pedunculatum Hilliard & B.L.Burtt

(=*H. pedunculare* auct. non (L.) DC.)

The root of *H. pedunculare* is externally applied to wounds and the leaves are used for infection of the respiratory tract (TRAMED database, index card 1530). The inside of the leaf is applied to the circumcision wound (TRAMED database, index card 430).

Antibacterial assays of *Helichrysum pedunculatum* showed that dichloromethane extracts are active against all the gram positive bacteria tested (*Bacillus cereus*, *B. pumilus*, *B. subtilis*, *Micrococcus kristinae* and *Staphylococcus aureus*), as well as two gram negative bacteria, *Enterobacter cloacae* ad *Serratia marcescens*. *Klebsiella pneumoniae* and *Escherichia coli* showed resistance to all the extracts tested. A water extract was effective against *Staphylococcus aureus* and *Micrococcus kristinae*, while a methanol extract showed no activity against any of the tested organisms. The antibacterial activity of dichloromethane extract was also investigated by direct bioassy on TLC plates against *S. aureus* (Meyer & Dilika 1996).

5.57.30 Helichrysum petiolare Hilliard & B.L.Burtt

(=*H. petiolatum* auct. non (L.) DC.)

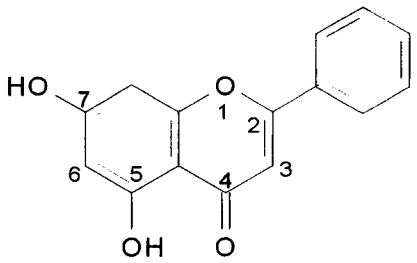
Air dried plant material of *Helichrysum petiolare* was ground and extracted three times with methanol and dichloromethane. The extracts were combined and concentrated under reduced pressure. The extract was chromatographed by Noristan. The method is described in the introduction to this chapter. Similar fractions were combined to form 10 fractions. Fractions 1-6 were combined to form group 1 and, and fractions 7-10 were combined to form group 2. Both groups were submitted for pharmacological evaluation. Group 1 displayed anti-hypertensive activity; causing a reduction of 21% in mean blood pressure and a 6% reduction in the heart rate at 300 mg/kg i.p., $p<0.1$ and $p<0.1$ respectively. Group 2 was inactive (Noristan not published).

5.57.31 Helichrysum platypterum DC.

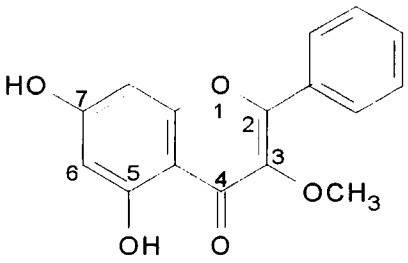
(=*Cassinia alba* O.Hoffm.)

(=*Gnaphalium amplum* Kuntze)

A decoction of the root of *H. platypterum* DC. is drunk by the Southern Sotho male to renew virility (Watt & Breyer-Brandwijk 1962). The aerial parts of *H. platypterum* DC. from Cathedral peak in Natal gave two phloroglucinol derivatives, but material from a location in the Transvaal gave 11 chromane derivatives (Jakupovic *et al.* 1986). Chromenes have insecticidal activity (Harbourne & Baxter 1993). Another location in the Transvaal gave 5 prenyl phloroglucinols and chrysin, galangin-3-O-methyl ether and pinobanksin (Jakupovic *et al.* 1986). The flavone chrysin has anti-inflammatory activities. It inhibits iodothyronine deiodinase, lens aldose reductase and histamine release from rat peritoneal mast cells. It also induces oestrogen and synthetase and haemoglobin. Galangin has antibacterial activity and is a potent inhibitor of bull seminal cyclo-oxygenase activity (Harborne & Baxter 1993). Chrysin is metabolized to apigenin (4',5,7-trihydroxyflavone) in the rat (Hackett 1986).



Chrysin



Galangin-3-O-methyl ether

(Harbourne & Baxter 1993)

The roots of *H. platypterum* DC. contain two kaurenic acids and small amounts of polyacetylenes. The aerial parts contain two phloroglucinol derivatives (Bohlmann, Zdero *et al.* 1980).

5.57.32 Helichrysum psilolepis Harv.

A decoction of the root of *H. psilolepis* Harv. is a Southern Sotho remedy for painful menstruation (Watt & Breyer-Brandwijk 1962).

5.57.33 Helichrysum rugulosum Less

H. rugulosum is used by the Southern Sotho to fumigate a hut when a child has a cold and they also use the plant as an ingredient in an enema for colic (Watt & Breyer-Brandwijk 1962).

Both the aerial parts and the roots of *Helichrysum rugulosum* afforded a complex mixture of prenylated flavanones and chalcones. The air-dried plant material was cut into small pieces and extracted with ether:petroleum (1:2) ether for 12h. The extract was separated by combined column chromatography (SiO_2), thin layer and high pressure liquid chromatography. Finally the known chalcones 2',6'-dihydroxy-4'-(3,3-dimethylallyloxy)-chalcone and a 2',4',6'-trihydroxychalcone derivatives and the methoxy derivative, 4',6'-dihydroxy-2-methoxychalcone-4'-O-[3,3'-dimethylallyl ether] and two flavones together with 6,8-bis-(3,3'-dimethylallyl)-5,7-dihydroxyflavanone and 7-O-8-bis-(3,3'-dimethylallyl)-5,7-dihydroxyflavanone which have two dimethyl allyl groups and the methoxy derivative, 7-hydroxy-5-methoxyflavanone-7-O-[3,3'-dimethylallyl ether] were obtained (Bohlmann & Misra 1984).

5.57.34 Helichrysum setosum Harv.

It is used by the Southern Sotho to fumigate a hut (Watt & Breyer-Brandwijk 1962).

5.57.35 Helichrysum splendidum (Thunb.) Less.

(=*Gnaphalium splendidum* Thunb.)

(=*H. strictum* (Lam.) Druce)

The leaves are boiled and the steam is inhaled to induce sweating. It is used together with *Senecio* species for pimples (TRAMED database, index card 547).

The roots of *H. splendidum* DC. contain germacrene D, terthienyl, nerolidol and a thiophene derivative. The aerial parts contain germacrene D, bicyclogermacrene, squalene, a dihydrochalkone, spathulenol and a flavonol (5,3',4' trihydroxy-3,7,8-trimethoxyflavone). Two sesquiterpene lactones; helisplendiolid and 2-desacetoxy-11β,13-dihydroxyxanthinin have also been found in the aerial parts. Sesquiterpenoids have to date not been found in the genus *Helichrysum*, although guaianolides are known to occur in other genera in the tribe Inuleae (Bohlmann & Suwita 1979a).

5.57.36 Helichrysum sutherlandii Harv.

(=*H. pulvinatum* O.Hoffm. ex Kuntze)

(=*H. sutherlandii* Harv. var. *semiglabrum* N.E.Br.)

The Southern Sotho rub the powdered ash into scarifications on the body of the sick (Watt & Breyer-Brandwijk 1962).

The roots contain a labdane derivative and a small amount of trideca-1-ene-3,5,7-pentayne. The aerial parts contain the chalcone derivatives and phloroglucinol derivatives (Bohlmann, Zdero *et al.* 1980). The roots of *H. sutherlandii* Harv. contain only the widely distributed trideca-1-ene-3,5,7-

pentayne. The aerial parts contain the chalcone derivatives helilandin A, helilandin B and 7,8-H-helilandin A (Bohlmann, Mahanta & Zdero 1978).

5.57.37 Helichrysum uninervium Burtt Davy

The Swazi use the plant as a purgative or an emetic. They add one teaspoon of the plant to a soft porridge which is then eaten by the patient (TRAMED database, index card 1230).

5.58 HIRPICIUM Cass.

5.58.1 H. gorterioides (Oliv. & Hiern) Roessler subsp. *schinzii* (O.Hoffm.) Roessler

(=*Berkheyopsis schinzii* O.Hoffm.)

The leaves are ground and boiled by the Ovambo to make a tea for upset stomach (Rodin 1985).

5.59 INULA L.

5.59.1 Inula glomerata Oliv. & Hiern

The introduced weed, *Inula glomerata* Oliv. & Hiern is used medicinally by the Lobedu. A decoction of the leaf alone, or of the leaf and root, is bitter and is taken to improve swallowing, when there is difficulty in doing so from the presence of "pimples" on the tongue (Watt & Breyer-Brandwijk 1962).

5.60 KLEINIA Mill.

5.60.1 Kleinia longiflora DC.

(=*Senecio longiflorus* (DC.) Sch.Bip.)

It is taken as a purgative or emetic (TRAMED database, index card 1347) and in the Mokeetsi district of Transvaal it is used as a snuff plant (Watt & Breyer-Brandwijk 1962). The Ovambo also use it as purgative or emetic (TRAMED database, index card 10710). Stems are boiled and the infusion drunk to cause vomiting, or crushed in cold water with the same effect in cases of poisoning (Rodin 1985). The VhaVenda chew the green and fresh branches and swallow the juice as emetic, especially when poison has been taken accidentally. It is believed that when a man chews a soft branch, love is induced in any woman he may meet (Magobo 1990).

5.61 LACTUCA

The Ovambo drink a tea made of the leaves of a *Lactuca* sp. for stomach ache and the pregnant women use it to "keep cool" during pregnancy. TRAMED database, index cards (10712; 3223) It is also used as a female douche when finely grated and mixed with water (Rodin 1985).

5.61.1 Lactuca sativa L.

The garden lettuce, *Lactuca sativa* L., has been credited with narcotic properties and has been used in pulmonary tuberculosis. In Italy a decoction of the aerial parts has been used as an emollient and stimulant. The plant in various forms is extensively used in Mauritius as a medicine. The seed is said to be slightly aromatic and to have a bitter taste, and an infusion of it has been used in fevers

particularly typhoid. A decoction of the seed has been used as a demulcent and a preparation of the seed for bronchitis, particularly cronic bronchitis. A suitable dilution of an infusion of the plant increases the work and amplitude of the heart. Perfusion of blood vessels results in dilation. Administration of suitable doses to cats result in a fall of blood pressure. Extracts are ineffective as antibiotics against *Staphylococcus aureus* and *Escherichia coli* (Watt & Breyer-Brandwijk 1962).

The latex contains the triterpenes α- and β-lactucerol and of the phenolics, the main caffeic acid derivative is dicaffeyltartaric acid. Rutin was also obtained. Flowering specimens were reported to contain the alkaloid hyoscyamine, but it was not identified unequivocally (González 1977). The α- and β-amyrins, germanicol and taraxasterol are triterpenes to be found in the organs of many species belonging to the Asteraceae. Only α- and β-amyrins and germanicol were present in the lettuce tap root. Taraxasterol could not be found in this organ. The acylated form of germanicol is predominant, as with the amyrins. The amyrins and germanicol compounds are localized mainly in the cortex. The latex expecially is the richest in amyrins and germanicol compounds. Amyrin compounds have been found previously in different plant membranes (Doireau *et al.* 1983).

In addition to tridecapentayene and the corresponding thiophenes, mainly monoterpenes, some flavones and coniferyl diangelate have been isolated from the *Pluchea* group of the Inuleae (Bohlmann, Wallmeyer *et al.* 1985).

5.62 LAGGERA Sch.Bip. ex W.D.J.Koch

5.62.1 Laggera decurrens (Vahl) Hepper & J.R.I.Wood

(=*Blumea gariepina* DC.)

(=*L. gariepina* (DC.) Randeria)

The root of *Blumea gariepina*, mixed with roots of other plants and pig fat, is used for swollen feet (TRAMED database, index card 1286). The Ovambo drink a decoction of the root for colds (TRAMED database, index card 3216 and 10709). Herbage is heated and applied by the Ovambo as facial poultice to relieve colds (Rodin 1985) Watt & Breyer-Brandwijk (1962) mention that *Blumea gariepina* DC. is used medicinally by the Swazi, but no detail is available. The leaf yields to steam distillation 0.5% of a volatile oil which consists of 66% of cineol, 10% of d-fenchone and ±6% of citral (Watt & Breyer-Brandwijk 1962).

Blumea gariepina DC. afforded carryophyllene, isocomene, β-isocomene, silphinene, modhephene, thymol, its acetate, large amounts of thymoquinone, its corresponding acetoxy derivative as well as phenolic compounds, 5-acetoxy-2-hydroxythymol, 2-acetoxy-5-hydroxythymol and 5-acetoxy-2-hydroxythymol acetate and the diol, 7β,12-dihydroxyhimachal-2-ene (Bohlmann, Wallmeyer *et al.* 1985).

5.62.2 Laggera crispata (Vahl) Hepper & J.R.I.Wood

(=*Blumea alata* (D.Don) DC.)

(=*Blumea crispata* (Vahl) Merxm.)

(=*Blumea pterodonta* DC.)

(=*Erigeron alatum* D.Don)

(=*L. alata* (D.Don) Sch.Bip. ex Oliv.)

(=*L. pterodonta* (D.Don) Sch.Bip. ex Oliv.)

The leaf of *Laggera alata* Sch.Bip. is narcotic and is smoked by Bapunu and Bavungu (Watt 1967). The Xhosa grind the leaves of *Blumea alata*, mix it with cold water and use this as a gargle for sore throats (TRAMED database, index card 140). The Ovambo use an infusion as an enema (Rodin 1985). It is used as a tea for asthma and a hot decoction is taken for fever (Rood 1994).

An investigation of the aerial parts of *Blumea alata* (D. Don.) DC. afforded in addition to α-humulene, caryophyllene and squalene, minute amounts of cuauthemone derivatives (sesquiterpenoids). The roots yielded α-humulene, trideca-3,5,7,9pentayn-1-ene and thymohydroquinone dimethyl ether (Bohlmann, Wallmeyer *et al.* 1985).

5.63 LASIOSPERMUM Lag.

5.63.1 Lasiospermum bipinnatum (Thunb.) Druce

(=*Lidbeckia bipinnata* Thunb.)

The Black people in the Middelburg district of the Eastern Cape province use an infusion of *Lasiospermum bipinnatum* Druce for chest affections. The plant is pleasantly scented and the Southern Sotho make an ointment with it. They also use it to fumigate the sickroom. The plant has been suspected of producing poisoning in stock (Watt & Breyer-Brandwijk 1962). The Xhosa give a decoction of the leaves to babies as a laxative. It is antiscorbutic and antirheumatic. The decoction has a very sweet taste (TRAMED database, index card 552).

5.64 LEUCANTHEMUM Mill.

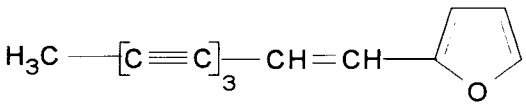
5.64.1 Leucanthemum vulgare Lam.

(=*Chrysanthemum leucanthemum* L.)

More than 700 polyines and related compounds have been isolated from species of Asteraceae, some of them have been shown to be phototoxic in long wavelength ultraviolet light (UVA 320-400nm) towards bacteria, fungi, membrane-containing viruses, nematodes and insects (Hudson 1991). Wat *et al.* (1980) found that the disc flower, pistil and stamen, leaf and root of *C. leucanthemum* are phototoxic to *Candida albicans*. Hudson (1991) evaluated polyines containing various furanyl and thiophene groups for antibiotic, antiviral and cytotoxic activities in the presence and absence of UVA. One compound, a furanopolyine, which had been previously isolated in very small amounts from the roots of *Chrysanthemum leucanthemum*, was synthesized as a mixture of 24% cis and 76% trans. It had impressive activity against a range of microorganisms, and membrane containing viruses as well as cytotoxic activity. It was tested on a yeast, *Candida albicans*, three

gram-positive bacteria (*Staphylococcus albus, Streptococcus fecalis and Bacillus subtilis*) and three gram-negative bacteria (*Escherichia coli, Salmonella typhimurium, Pseudomonas aeruginosa*). *P. aeruginosa* was completely resistant to all compounds tested but the other compounds were very sensitive to the furanopolyine in UVA. No effects were obtained in the dark. It was substantially more effective than α-terthienyl. Two membrane containing viruses, the DNA-virus MCMV (murine cytomegalovirus, a herpes virus) and the RNA virus SV (Sindbis, a Togavirus) were used for the tests. The furanopolyine was very active against SV, almost as potent as α-terthienyl and was also active against MCMV. It had significant cytotoxic activities in UVA. It is bevieved that the principal targets for polyines and thiopenes are membrane components, which are damaged by singlet oxydation or possibly radicals.

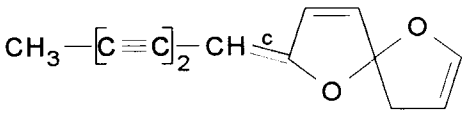
Antibiotic tests: The agar diffusion test was used in the preliminary screening for activity. Compounds were dissolved in 95% ethanol to a concentration of 1 mg/ml. Ten microlitres of each sample were spotted on sterile discs of Whatman filter paper. The air dried discs were placed on agar plates which had been spread with one of the microorganisms. Sabouraud's Dextrose Agar was used for the yeast and Nutrient Agar as culture medium for the bacteria. Tests were carried out in duplicate, one series to be irradiated and the second being maintained in the dark. All plates were incubated in the dark for 30min. at 37°C and the series to be irradiated was placed under a bank of four Blacklight Blue lamps for 2 hours. This series was transferred to the dark at 37°C and all the plates were screened after 24h of incubation. The zone of inhibition was measured.



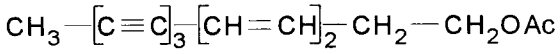
Furanopolyine

(Hudson *et al.* 1991)

The roots of *Chrysanthemum leucanthemum* contain at least 15 polyacetylenes in low concentration except for compound 1 which is present to the extent of 0.13 μg/mg. This is sufficient to give a positive phototoxicity test against the fungi *Candida albicans* and *Microsporum canis* and photoxic and antibiotic activity against *Microsporum gypseum*, phototoxic against the gram positive bacteria *Bacillus subtilis* and *Staphylococcus albus*, but not against the Gram negative bacteria. The flower parts contain compound 2 in a relatively large amount (0.7 μg/mg). Compound 2 is phototoxic toward *Candida albicans*, and displays phototoxic and antibiotic activity against *Microsporum canis Microsporum gypseum* and *Trhichophyton mentagrophytes*. It is also phototoxic against the Gram positive bacteria, *Bacillus subtilis* and *Streptococcus faecalis* and against the gram negative bacteria, *Proteus vulgaris* . It is both phototoxic and antibiotic against the Gram positive *Staphylococcus albus*.



Compound 1



Compound 2 (Towers *et al.* 1977)

Disc florets of *Chrysanthemum leucanthemum* (the activity is localized in the immature achene) were frozen with solid CO_2, and ground to a powder with a mortar and pestle. The powder was allowed to thaw at 4°C in EtOH. The material was filtered and the solids re-ground in EtOH and then in Et_2O. The filtrates were combined, filtered and evaporated to a tar. Tar was triturated in 2 5ml aliquots of petrol. Part of the extract was separated on a column of neutral alumina plus 10% celite developed with 3% Me_2CO in petrol. A band with strong UV absorpsion (366nm) showed phototoxic activity. Several other fractions showed antibiotic activity. The UV absorbing band was concentrated and applied to Eastman Chromagram sheets (Si gel without fluorescent indicator). The strips were developed in three solvent systems; C_6H_6:Me_2CO, 9:1 ; toluene:petrol 1:1 ; petrol:Me_2CO, 9:1. The UV absorbing areas were marked with pencil, and each series of separated compounds was cut from the sheet and cut longitudinally. One half of each strip was placed face down on a *Candida* plate under UV, and the other strip was placed on a plate incubated in the dark. The area of growth inhibition correlated with two UV-absorbing spots. The UV spectrum suggested that it was a polyacetylene. The UV-spectrum was very similar to that of $H_3C[C{\equiv}C]_3$-$[CH{=}CH]_2$-$(CH_2)_3$-OAc (Camm *et al.* 1975).

The flower heads and roots of *Chrysanthemum leucanthemum* L., collected in Denmark, were washed and air-dried, ground and extracted, first with light petrol and then with Et_2O. The solvents were removed and the extracts were subjected to column chromatography [Si gel], using light petrol (bp<50) and light petrol containing increasing percentages of Et_2O as eluting solvents. For further separation repeated preparative TLC was applied. Hydrocarbon fractions were further separated by means of columns of 10% caffeine in Si gel or 5% for TLC. Amounts of the isolated acetylenes were usually determined by UV. Amounts of compounds with triyne chromophores were, however determined from the NMR-integrals as relative amounts of mixtures with dienetriyne chromophores before separation. Relative amounts of C_{16} and C_{17} hydrocarbons were determined by means of GLC after separation of triyne and dienetriyne compounds on caffeine-Si gel. MS was with direct inlet and GLC-MS was used for some of the studies. The major compounds isolated from the flower heads of *Chrysanthemum leucanthemum* include β-farnesene, $Me(C{\equiv}C)_3CH_2CH^{c}{=}CH(CH_2)_4CH{=}CH_2$, $Me(C{\equiv}C)_3(CH^{t}{=}^{t}CH)_2(CH_2)_3CH{=}CH_2$, $Me(C{\equiv}C)_3(CH^{t}{=}^{t}CH)_2CH_2CH_2OAc$, and $Me(C{\equiv}C)_3CH_2CH^{t}{=}CH\text{-}CH_2CH_2CH_2OAc$. From the roots β-farnesene was the major component and compund 1 (Wrang & Lam 1975).

The whole plant, which was collected in India, was air-dried and ground and extracted with 50% ethanol. The extract was put through a biological screen of 61 tests. These include tests for antibacterial, antifungal, antiprotozoal, antiviral, hypoglyceamic, effects on respiration, effects on isolated tissues, effects on the central nervous system and anticancer activity. It was active in the isolated guinea pig ileum contraction test and had effects on the central nervous system, the amphetamine induced hyperactivity test and caused hypothermia (Dhar *et al.* 1968).

5.65 LEYSERA L.

5.65.1 Leysera gnaphalodes (L.) L.

(=*Asteropterus dinteri* Rothm.)

(=*Asteropterus gnaphalodes* (L.) Rothm.)

(=*Asteropterus gracilis* Rothm.)

(=*Asteropterus incanus* (Thunb.) Rothm.)

(=*Callisia gnaphalodes* L.)

(=*L. incana* Thunb.)

(=*L. tenuifolia* Salisb.)

Leysera gnaphalioides L. has an agreeable odour and the infusion has a pleasant sweetish taste. This is emollient and has therefore been much used in catarrh, coughs and pulmonary tuberculosis. An infusion of the leaf and flower is taken as a tonic in loss of appetite. In the Cedarberg the plant is used as a tea, the infusion being pleasant and aromatic in flavour and stimulating in action (Watt & Breyer-Brandwijk 1962). "Very few of our indigenous plants are so much in domestic use as this one, known as 'Geele-bloemetjes-thee'. When crushed or rubbed between the fingers it gives an agreeable scent, and the infusion has a pleasant, sweetish taste. It is emollient and for that reason is highly recommended in catarrh, cough and even consumption. Some of our apothecaries have added this plant to the *species pectorales*" (TRAMED database, index card 3177).

5.66 LITOGYNE Harv.

5.66.1 Litogyne gariepina (DC.) Anderb.

(=*Epaltes alata* (Sond.) Steetz)

(=*Epaltes gariepina* (DC.) Steetz)

(=*Ethulia alata* Sond.)

(=*Ethulia gariepina* DC.)

(=*L. glabra* Harv.)

(=*L. scabra* Harv.)

The Tswana use *Epaltes gariepina*. The plant is tied to the head and "draws out" severe headache. The Tswana name means "small fire", probably due to the intense pain sensation caused (TRAMED database, index card 1203). The leaves are crushed and applied to inflamed eyes (TRAMED database, index card 1372). An *Epaltes* sp. is used by the Ovambo for the treatment of siphilis (TRAMED database, index card 3228). The roasted leaves are powdered and mixed with butter (presumably unsalted) and smeared on open syphilitic wounds. The treatment is said to be painful (Rodin 1985). *Epaltes alata* Steetz., in the late flowering and seeding stage, is toxic to stock (Watt & Breyer-Brandwijk 1962).

5.67 MATRICARIA L.

5.67.1 Matricaria chamomilla L.

The ordinary European wild chamomile *Matricaria chamomilla* L., has become well-established as a household medicine in the Western Province and is used with the following objectives: convulsions in

children; diarrhoea; colic and acidity; hysteria and sleeplessness; the steam from the tea for sore throat; hot compresses for croup and diphtheria; rheumatism, sciatica, gout and lumbago; as a cold or warm compress for inflammation of the eye; with buchu for pains in the bladder region and for colic (Watt & Breyer-Brandwijk 1962).

5.67.2 Matricaria nigellifolia DC. var. *nigellifolia*

(=*Sphaeroclinium nigellifolium* (DC.) Sch.Bip.)

Matricaria nigellifolia DC. var. *tenuior* DC.

The Xhosa and Mfengu use *Matricaria nigellifolia* DC. as an anthrax and skin remedy. The Mfengu treat skin infection by inhaling the vapour from the boiling leaf in water and applying a paste of the leaf to the skin. The plant is bitter and contains volatile oil. It is the cause of bovine staggers disease or "stootsiekte" in stock. The active principles are the bitter substance and the volatile oil. Both *M. nigellaefolia* and its variety *tenuior* is toxic and the toxin is apparently cumulative (Watt & Breyer-Brandwijk 1962). It is a remedy for rash ("bite of the river"). Ground into a paste, it is used to heal wounds. The sap is taken orally against a wheezy chest (TRAMED database, index card 1248).

5.68 MELANTHERA Rohr

5.68.1 Melanthera biflora (L.) Wild

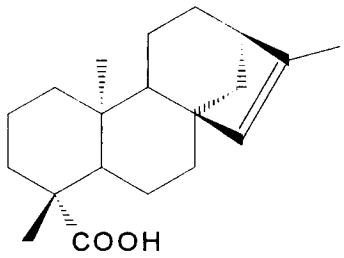
(=*Verbesina biflora* L.)

(=*Wedelia biflora* (L.) Wight)

The plant is used in Thai folk medicine for headaches and fevers, and a decoction of the leaves is vulnerary and antiscabious, the leaves are used for dressing ulcers and the juice of the leaves is given internally with cow's milk as a tonic after childbirth. (Miles *et al.* 1993) In the Philippines, a decoction of the fresh roots is administered as an emmenagogue and a diuretic (Miles *et al.* 1990).

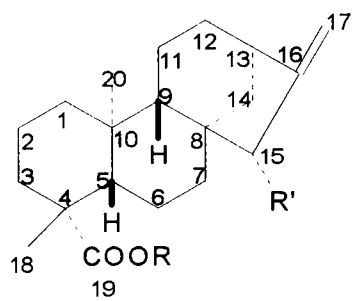
16-ene-kaur-19-oic acid, 24-ethylcoprostanone, stigma-7-en-3-ol, stigmasterol, grandiflorenic acid and ent-kauradienoic acid have been isolated from extracts of stems of *W. biflora*. The methylene chloride extract of the leaves posessed antifeedant properties against the cotton weevil (*Anthonomus grandis* Boh.), and antifungal activity against *Pythium* altimum and *Rhizoctonia solani*. Utilization of the antifungal bioassay led to the isolation of veratrylidenehydrazide, 3,3'-di-*O*-methylquercetin, 2,7-dihydroxy-3(3'-methoxy-4'-hydroxy)-5-methoxyisoflavone and 3',7-di-*O*-methylquercetin were isolated from the methylenechloride extract of dried leaves of *Wedelia biflora*. Dried powdered leaves were extracted with CH_2Cl_2 in an extractor for seven days at room temperature. The CH_2Cl_2 solution was removed and evaporated *in vacuo*. The resulting crude extract was dissolved in $CHCl_3$ and added to silica gel. The $CHCl_3$ solvent was removed *in vacuo* to yield a dry sample which was chromatographed on an open column of silica gel. The column was eluted with a hexane-CH_2Cl_2-MeOH system. The structures were elucidated from spectroscopic evidence. 3,3'-di-*O*-methylquercetin showed antifeedant activity against the boll weevil of 50%, 2,7-dihydroxy-3(3'-methoxy-4'-hydroxy)-5-methoxyisoflavone showed activity against the fungus *R. solani* (78%) and 3',7-di-*O*-methylquercetin exhibited 100% inhibition agaist the fungus, *R. solani*

and 71% inhibition against the feeding of cotton boll weevils (Miles *et al.* 1993). Five compounds with antifeedant and/or antifungal activity were isolated from extracts of the stems of *Wedelia biflora*. They include 16-methylkaur-15-en-19-oic acid, 24-ethylcoprostanone, stigmast-7-en-3-ol, stigmasterol, grandifloric acid and *ent*-kauradienoic acid (Miles *et al.* 1990). Method: The air-dried and milled stems of *Wedelia biflora* were defatted by continuous extraction with methyl chloride for 7 days at room temperature and repeated four times. The solvent from the combined extracts were removed *in vacuo*. Column chromatography was performed on silica gel and eluted with an increasing hexane in methylene chloride solvent system. The fractionation procedure yielded fractions containing six compounds. The antifungal bioassay was performed using the paper disc method. Papers that were soaked in test solution were placed on growth media which were inoculated with various fungi. The zone of growth inhibition surrounding the disc were measured. *Pythium ultimum* and *Rhizoctonia solani* were used. The antifungal activity was shown as a % T/C value, where % T/C = inhibition zone radius (mm) caused by sample / inhibition zone radius (mm) caused by control x 100. 16-methylkaur-15-en-oic acid showed 100% inhibition of feeding of boll weevils at a dose of 2.9 mg and extremely high activity against the fungi *P. ultimum* (240%) and *R. solani* (280%). 24-Ethylcoprostanone showed excellent boll weevil antifeedant activity (90%), but was only moderately active against fungi. Grandifloric acid (1.0 mg) showed activity against the fungi *P. ultimum* (70%) and *R. solani* (78%). *Ent*-kauradienoic acid showed antifeedant activity against boll weevils (83%) (Miles *et al.* 1990).



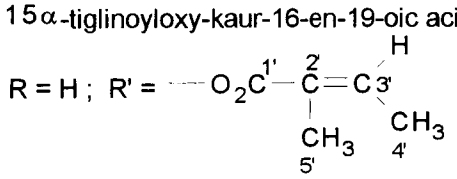
16-Methylkaur-15-en-19-oic acid (Miles *et al.* 1990)

Kaur-16-en-19-oic acid is moluscicidal (against *Biomphalaria glabrata*) and 15α-tiglinoyloxy-kaur-16-en-19-oic acid is miracidicidal (against *Schistosoma mansoni*). Both were isolated from *W. scaberrima* Benth. from Brazil (Tomassini & Matos 1979).



Kaur-16-en-19-oic acid
R = R' = H

15α-tiglinoyloxy-kaur-16-en-19-oic acid



7

(Tomassini & Matos 1979)

***5.68.2 Melanthera scandens* (Schumach. & Thonn.) Roberty** subsp. *dregei* (DC.) Wild

(=*Lipotriche brownii* auct. non DC., Harv.)

(=*Psathurochaeta dregei* DC.)

(=*Trigonotheca natalensis* Sch.Bip.)

Melanthera scandens (Schumach. & Thonn.) Roberty subsp. *madagascariensis* (Baker) Wild

(=*M. madagascariensis* Baker)

In Nigeria the decoction and paste of the leaf of *M. scandens* (Schum. et Thonn.) Brenan is used to arrest bleeding from cuts and wounds. It is also used to relieve inflammation and promote wound healing. The leaf paste is applied after circumcision to achieve rapid healing (Akah & Ekekwe 1995). An infusion of the root of *Melanthera scandens* Brenan is used by the Zulu as an emetic and an infusion of the leaf and stem as an emetic for children. In West Africa the leaf and the flower, both fresh, are widely used as a haemostatic and to cleanse the surface of a sore by absorbing any exudate. A decoction has even been admininstered for pulmonary haemorrhage. In Ghana, the juice of the leaf, mixed with salt and lime juice, is used as eye drops. An infusion of the leaf is drunk by a woman in childbirth, as cough medicine for a child and mixed with white clay, as a medicine for stomach troubles. In southern Nigeria a decoction of the leaf is used as a lotion for the face and eyes to relieve a febrile headache and the plant is said to be used for washing horses. The plant might be non-toxic for in West Africa it is a favourite food of the hare (Watt & Breyer-Brandwijk 1962).

5.69 METALASIA R.Br.

***5.69.1 Metalasia muricata* (L.) D.Don**

(=*Gnaphalium muricatum* L.)

(=*M. ericoides Sieber* ex DC.)

(=*M. umbellata* Cass.)

The Southern Sotho use *Metalasia muricata* Less., along with *Eriocephalus punctulatus*, to fumigate the hut of a person suffering from a cold or from diarrhoea, and a hut during illness or after death. The plant is readily eaten for short periods by sheep and apparently acts as a tonic (Watt & Breyer-Brandwijk 1962).

5.70 MICROGLOSSA DC.

***5.70.1 Microglossa mespilifolia* (Less.) B.L.Rob.**

(=*Aster mespilifolius* Less.)

(=*Erigeron natalensis* Sch.Bip.)

(=*Nidorella mespilifolia* (Less.) DC.)

The Zulu administer a strong infusion of the leaf and stem of *Microglossa mespilifolia* Robinson for feverishness in man and as a tonic to domestic stock. The Zulu also administer a strong infusion of the bruised and crushed herb by the mouth in the treatment of "lumps in the female genital system". The powdered plant material is intensely irritant to the eyes and the respiratory tract (Watt & Breyer-

Brandwijk 1962). The Xhosa take a steam bath and inhale the steam from the boiled leaves for pimples (TRAMED database, index card 706).

5.70.2 Microglossa spp. not indigenous to southern Africa.

The leaf of *Microglossa oblongifolia* O. Hoffm. is a Shambala toothache remedy. In Tanzania a decoction of the leaf is taken as a fever remedy. The Masai use a maceration of the leaf as an ophthalmic application in cattle and on sores (Watt & Breyer-Brandwijk 1962).

In Tanzania a medicine for fractured limbs is made of the leaf of *Microglossa pyrifolia* O. Ktze. The Haya use the plant for the relief of stomach pains and apply the leaf to the inside of the nose of man and cattle for coryza. It is used in the Cameroons for severe cough. The Shambala use the plant as a remedy for chronic cough with fever. In Ghana an enema is made from the plant and is used for fever in an infant. A decoction of the plant has been regarded as a reliable remedy for yellow fever, black fever and for dropsy. The leaf is odorous and a tea-like infusion of it is taken for fever with headache, as a lotion or fumigation to cause perspiration and sometimes also as an inhalation. The powdered root is used as a snuff to relief colds. The Shambala also use the plant for pain in the head, chest and shoulders with chronic rhinitis, for heartburn, epilepsy and fits in children, hookworm, furunculosis and for impotence. In Liberia the plant is used as anthelminthic. The juice of the warmed leaf is used as eye-drops and as a ringworm application. The juice of the root is also used as eye drops, particularly in cataract. The application to the eye produces a burning sensation lasting for some 10 to 15 minutes. The crushed root from which the sap has been obtained is mixed with shea butter and applied to the eylids to reduce swelling. In Java it is a vegetable plant and it is often cultivated in the garden in West Africa (Watt & Breyer-Brandwijk 1962).

5.71 MIKANIA Willd.

5.71.1 Mikania capensis DC.

The Zulu apply a paste of the leaf of *M. capensis* DC. and other plants over the bladder (the skin being previously being annointed) for a "disease" of the urinary organs contracted from intercourse with a girl. They also use the paste as a local application to venereal sores. The plant has caustic effects (Watt & Breyer-Brandwijk 1962). The leaf of *Mikania capensis* DC. is smelled and used as poultice for headaches by the Zulu. It is also used for head colds as well as painful rectums in children (Hutchings & Van Staden 1994).

5.71.2 Mikania cordata (Burm. f.) B.L. Robinson

(*M. cordata* Hilliard non (Burm.f.) B.L.Rob. = *M. natalensis*)

The Tsonga use *Mikania cordata* Robinson as a remedy for snake bite and scorpion bite. These uses are also found in Brazil. In Nigeria a decoction is given for coughing and the leaf juice is a remedy for sore eyes. In West Africa the leaf is used as a soup vegetable and as cattle fodder. The sulphuric acid extract inhibits the growth of *Staphylococcus aureus* (Watt & Breyer-Brandwijk 1962). *Mikania cordata* is frequently used in Asian and African traditional medicine. In Nigeria the plant decoction is used for coughing, while the sap is used for sore eyes (Akah & Ekekwe 1995).

A flavone, mikanin (characterized as 3,5-dihydroxy-4',6,7-trimethoxyflavone), has been isolated together with epifriedelinol from the roots and fumaric acid from the leaves and stems of *Mikania cordata* (Burm. f.) B.L. from Malaysia. The root powder was continuously extracted with light petroleum and then with methanol. The light petroleum extract yielded in addition to mikanin and epifriedenol, friedelin and stigmasterol. The methanol extract , besides giving mikanin, showed the presence of glucose and fructose. The leaves and stems, dried and powdered were extracted with ether. The ether extract had furnished the sesquiterpene lactones, mikanolide and dihydromikanolide (Kiang *et al.* 1968).

Antihepatotoxic

The methanolic fraction of the root extract of *M. cordata* (Burm., B.L. Robinson) demonstrated a significant normalization of lipid peroxidation and related enzymatic makeup in tetrachloride (CCl_4)-induced hepatotoxicity in mice and protection of liver cells against CCl_4-intoxication. Acute single intraperitoneal administration of CCl_4 (1ml of 20% v/v in olive oil/kg body weight) in mice decreased albumin and increased globulin level and thereby reduced the albumin-globulin ratio. A lower blood urea level was also noticed after treatment of mice with CCl_4. A 1 hour pretreatment with the root extract tended to reverse the features which were found to be dose dependant, but the results were statistically significant in the dose range of 100-150 mg/kg. The *M. cordata* root extract (at 150 mg/kg) dramatically improved the level of hepatic microsomal RNA (42.2%; $P<0.001$) and cytochrome P-450 content (70.2%; $P<0.001$) that were altered in CCl_4-induced liver damage. Based on these observations, it is considered that *M. cordata* root extract may alleviate the deleterious effects of CCl_4, protect the liver cells and activate the hepatic reticuloendothelial system-mediated defence mechanism as well as the regeneration of protein synthesis (Mandal *et al.* 1993).

In India *M. cordata* (Burm., B.L. Robinson) is consumed as a vegetable and thought to be efficacious in the treatment of itch and as a poultice for wounds. Bishayee and Chatterjee (1994a) have reported potent antihepatotoxic activity of a methanolic extract of this plant root against carbon tetrachloride-induced acute liver damage in mice. This antihepatotoxic potency of this extract is presumed to be related to an increased repair of hepatic parenchyma through improved ribosomal capacity and protein turnover. They also reported on the possible anticarcinogenic response of *M. cordata* root extract as evidenced from its ability of inducing a marked increase of cytosolic glutathione s-transferase activity and reduced glutathione content in mouse liver and other extrahepatic tissues. In the view of the correlation between the inhibition of carcinogenesis and microsomal oxidation and cytosolic detoxification, they investigated whether *M. cordata* root extract could modulate the hepatic xenobiotic-detoxifying pathways and assosiated cellular defence mechanisms in rats. Although oral administration of the methanolic extract of this plant root (50, 100 or 150 mg/kg for 4, 8 or 12 weeks) has been found to have very little effect or no effect on hepatic microsomal cytochrome P-450 and cytochrome b_5 contents as well as NADPH cytochrome *c* reductase activity, it afforded a marked induction of uridine diphosphoglucuronyl transferase activities of liver microsomes. The extract also significantly increased the activities of microsomal uridine diphosphoglucose dehydrogenase, reduced

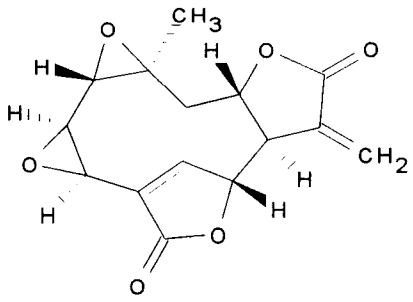
nicotinamide adenine dinucleotide (phosphate): quinine reductase and cytosolic glutathione *s*-transferases with the concomittant elevation in the contents of reduced glutathione. All these effects were found to be dose dependant and maintainded during 12 weeks of extract treatment. Results of the study clearly indicate that the intracellular contents of active intermediates of various xenobiotics including chemical carcinogens would be reduced by the specific enhancement of drug-detoxifying enzymes in the liver of rats with the plant extract (Bishayee & Chatterjee 1994a).

Anti-ulcer

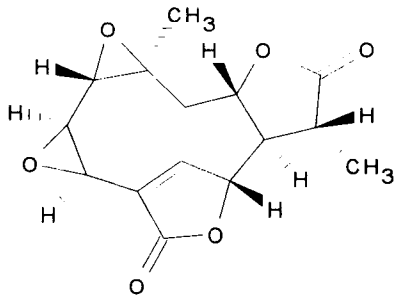
Oral administration of the methanolic fraction of *M. cordata* (Burm.) B.L. Robinson root extract (50, 100, or 150 mg/kg) significantly prevented the occurence of water -induced gastric ulcers in a dose dependant manner. The extract also dose-dependantly inhibited gastric ulcers induced by ethanol, aspirin and phenylbutazone. The ED_{50} values of the extract in the water-immersion-, ethanol-, aspirin- and phenylbutazone-induced gastric ulcers were found to be 95.1, 109.7, 125.5, and 136.2 mg/kg respectively. A dose of 150 mg/kg the inhibition of the ulcer index for aspirin-induced gastric ulceration was 65% ($p<0.001$), for phenylbutazone-induced gastric ulcer was 62% ($p<0.001$), and 73% of the control ($p<0.001$) for ethanol-induced lesions. The highest dose level of 150 mg/kg afforded significant reduction ($p<0.001$) in lesion index with 80% inhibition of lesions, induced by water immersion stress. The magnitude of response in this ulcer model was slightly less than that of cimetidine. *M. cordata* root extract thus appears to be most effective in the stress model and least effective in preventing damage induced by non-steroidal anti-inflammatory drugs (NSIAD) e.g. aspirin and phenylbutazone. In stress-induced ulceration, the neurotransmitter, γ-aminobutyric acid (GABA), levels in the glandular zone of the stomach were attenuated, while NSAID have no such action. Bishayee & Chatterjee (1994b) proposed that the effect of the root extract in the stress model could be attributed to the increase in GABA levels in the stomach. The volume, acidity, and peptic activity of the gastric juice in pylorous-ligated rats were not altered upon administration of the extract (100 or 150 mg/kg), but it significantly and dose-dependantly promoted gastric mucus secretion in normal as well as stress- and ethanol-induced ulcerated animals. The anti-ulcer activity of the *M. cordata* root extract may be due to the modulation of defensive factors through an improvement of gastric cytoprotection. It is established that the increased gastric mucus secretion appears to be an important mechanism of cytoprotection related to antiulcer effects of prostoglandins and cimetidine, a selective antagonist for the histamine H_2-receptor. The method of extraction was identical to that used by Bhattacharya *et al.* (1988) (Bishayee & Chatterjee 1994b).

Antimicrobial

Eight germacronolides were isolated from *Mikania cordata* (Burm. f.) B.L. Robinson by Aguinaldo *et al.* (1995). Four were identified as mikanolide, dihydromikanolide, deoxymikanolide and scandenolide. Mikanolide and dihydromikanolide have antibacterial and antifungal activities; they inhibit the growth in culture of a bacterium *Staphylococcus aureus* and also of the yeast *Candida albicans* (Rodriguez *et al.* 1976).



Mikanolide



Dihydromikanolide

Method: Ground air-dried leaves were extracted with $CHCl_3$. The extract was concentrated *in vacuo* to yield a crude extract. The crude extract was dissolved in hot MeOH, then mixed with 4%$Pb(OAc)_2$ solution. The mixture was shaken and allowed to stand for 2 days, then filtered over Celite. The entire filtrate was concentrated *in vacuo*, and then partitioned with $CHCl_3$, followed by *n*-BuOH. The $CHCl_3$ layer was dried with Na_2SO_4. Both extracts were separately concentrated *in vacuo*. The $CHCl_3$ and BuOH extracts were subjected to repeated column chromatography. It was characterized by ^1H NMR and ^{13}C NMR (Aguinaldo 1995).

Central nervous system depressant

Neuropharmalogical studies have been conducted with the methanolic fraction of the root extract of *Mikania cordata* (Burm) B. L. Robinson on experimental animals. It was found to produce alterations in the general behaviour pattern, reduction in spontaneous motility (58,6% inhibition at a dose of 100 mg/kg, ('p', versus control, by 't' test, < 0.02), hypothermia, potentiation of pentobarbitone sleeping time, analgesia (doses of 25 mg/kg showed significant analgesic activity against acetic acid-induces writhing test, but no analgesic action could be detected in the tail clip or caudal immersion tests), reduction in exploratory behaviour pattern and suppresion of aggresive behaviour. The extract also caused suppression of conditioned avoidance response and showed antagonism to amphetamine toxicity. The observations suggest that the root of *M. cordata* posesses a potent central nervous system (CNS) depressant action similar to the tranquilizer drugs. However, no anticonvulsant activity could be found to occur with the root extract against pentylenetetrazole-induced convulsion or strychnine-induced convulsion and lethality. The root extract in doses upto 1500 mg/kg (i.p.) did not produce any mortality in male albino mice upto 24 hours after administration. Method: The air-dried powdered root of *Mikania cordata* was extracted in a Soxhlet extractor with petroleum ether. The petroleum ether extract was discarded. The residue was subsequently extracted with chloroform and the chloroform extract was also discarded. Subsequently, the residue was extracted with methanol. On complete evaporation of the methanol by distillation of the extract, a blackish-brown substance was obtained which was kept at 4°C until use. Just before pharmacological testing the substance was dissolved in a mixture or popylene glycol and water (1:4) (Bhattacharya *et al.* 1988).

Anti-inflammatory

Air-dried powdered roots of *M. cordata* (burm) B.L. Robinson was extracted successively with petroleum ether, chloroform and methanol. Anti-inflammatory activity was investigated in male albino

rats. Carrageenan inflammation was induced by injecting 0.1ml of 1% carrageenan into the subplantar tissue of the right hind paw. The root extract significantly inhibited carrageenan-oedema in rats. "True" anti-inflammatory substances can be distinguished from the substances exerting their anti-inflammatory effects by virtue of anti-irritancy action, by locally administering them in the carrageenan test. The effects of *M. cordata* root extract was due to "true" anti-inflammatory activity, since the mixture of the root extract and carrageenan produced a reduction in paw oedema. The root extract had an inhibitory effect on the formation of granulation tissue when tested by the cotton pellet granuloma test, and also showed significant inhibition of formaldehyde-induced arthritis in rats. The root extract demonstrated significant analgesic activity when examined by acetic acid induced writhing response (Bhattacharya & Chaudhuri 1987).

The leaves of *Mikania cordata* (Burm.) B.L. Robinson, are used for medicinal purposes in the Phillipines. A sesquiterpene lactone, scandenolide, from *M. cordata* showed potent inhibition of luminol-dependant chemiluminescence of whole blood exposed to opsonized zymosan, a technique used to detect compounds with potential anti-inflammatory activity. Since a number of plants known to contain sesquiterpene lactones have historically been used as anti-inflammatory and anti-pyretic treatments, Ysreal and Croft (1990) decided to investigate the effect of scandenolide on lipid mediators released by inflammatory rat polymorphonuclear leukocytes. Prostaglandins and leukotrienes are known to be mediators of inflammation and more recently the ether linked phospholipid, platelet activating factor (PAF), has also been implicated as a potent inflammatory mediator. They found that scandenolide inhibits in a dose dependant manner the formation of the lipoxygenase products leukotriene B_4 (LTB_4) and 5-hydroxyeico-satetraenoic acid (5-HETE), with IC_{50} of 15μM and 30μM respectively, as well as PAF (with an IC_{50} of < 20μM and nearly complete inhibition at doses up to 100μM) in calcium ionophore stimulated rat peritoneal leukocytes. In contrast the formation of the cyclooxygenase product thromboxane B_2 (TXB_2) was not inhibited by scandenolide. The presence of a compound in *M. cordata* which inhibits some of the inflammatory mediators such as leukotrienes and PAF may at least explain in part some of its medicinal properties. Similar experiments conducted with the sesquiterpene lactone coronopilin isolated from *Ambrosia psilostachya*, at the same doses showed no inhibition of either LTB_4 or PAF production. Scandenolide was isolated form *M. cordata*, purified by recrystallisatioan and identified by spectroscopic methods (Ysreal & Croft 1990).

The roots of *Mikania cordata* (Burm. f.) B.L. Robinson collected in Natal, contain a number of diterpenic acids and kaurenic acid methyl ester and its derivatives. The aerial parts also contain the kaurenic acid methyl esters (Bohlmann, Natu & Mahanta 1978).

5.71.3 *Mikania natalensis* DC.

(=*M. cordata* Hilliard non (Burm.f.) B.L.Rob.)

The leaf is smelled and used as a poultice for headaches by the Zulu (Hutchings & Van Staden 1994).

5.72 NIDORELLA Cass.

All six of the 20 species investigated chemically by 1982 contain dehydrofalcarinone or its derivatives and only three afforded diterpenes (Bohlmann & Wegner 1982b).

5.72.1 Nidorella resedifolia DC. subsp. *resedifolia*

(=*N. densifolia* O.Hoffm.)

(=*N. hirta* DC.)

(=*N. krookii* O.Hoffm.)

(=*N. pinnatilobata* DC.)

(=*N. rapunculoides* DC.)

(=*N. resedifolia* DC. var. *subvillosa* Merxm.)

(=*N. solidaginea* DC.)

Nidorella hirta DC. is used by the Southern Sotho to fumigate a hut when a child is feverish (Watt & Breyer-Brandwijk 1962). *Nidorella residifolia* plants are boiled and used to wash feet to clear corns (TRAMED database, index card 4335).

5.73 NOLLETIA Cass.

5.73.1 *Nolletia ciliaris* (DC.) Steetz

(=*Leptothamnus ciliaris* DC.)

The Sotho smoke the leaf for relief of headaches (Hutchings & Van Staden 1994).

5.74 ONCOSIPHON Källersjö

5.74.1 Oncosiphon glabratum (Thunb.) Källersjö

(=*Matricaria glabrata* (Thunb.) DC.)

The wild chamomile, *Matricaria glabrata* is employed often, and with the same good effect as *Matricaria chamomilla*, or *Anthemis nobilis* (TRAMED database, index card 3164). *Matricaria glabrata* DC. contains "a superfluity of volatile oil" and is therefore an excellent antispasmodic especially in colic. It used to be recommended for dyspepsia and other gastric derangements on account of its aromatic bitter taste, and as an excellent external application to inflammations (Watt & Breyer-Brandwijk 1962).

5.74.2 Oncosiphon piluliferum (L.f.) Källersjö

(=*Cotula globifera* Thunb.)

(=*Cotula pilulifera* L.f.)

(=*Matricaria globifera* (Thunb.) Fenzl ex Harv.)

(=*Matricaria pilulifera* (L.f.) Druce)

(=*Pentzia globifera* (Thunb.) Hutch.)

(=*Pentzia pilulifera* (L.f.) Fourc.)

Pentzia globifera Hutch was a remedy for convulsions, of the Whites in the Western Cape province (Watt 1967). The Hottentot takes an infusion of the flower and leaf in typhoid and other fevers. A

decoction is an old-fashioned "Dutch" remedy to bring out the rash in measles and both Xhosa and Mfengu take it as an antifebrile. Extracts of the plant have given negative results in malaria. The plant is very bitter and has a "heavy smell" from the volatile oil it contains. The plant has been suspected of causing enzootic icterus in sheep but 300g produces no effects (Watt & Breyer-Brandwijk 1962). The flowers of *Matricaria globifera* are used for typhoid fever (TRAMED databse, index card 1558).

Extraction of the plant was done by Noristan in the way described in the introduction to this chapter. Group 1 was diuretic and increased the volume by 24%, p~0.02 at 500 mg/kg p.o. A weak central nervous system depression was also observed at 300 mg/kg. Group 2 was diuretic with a 9.9% increase of volume, p<0.01 at 500 mg/kg (Noristan not published).

5.74.3 Oncosiphon suffruticosum (L.) Källersjö

(=*Cotula tanacetifolia* L.)

(=*Pentzia suffruticosa* (L.) Hutch. ex Merxm.)

(=*Pentzia tanacetifolia* (L.) Hutch.)

(=*Tanacetum suffruticosum* L.)

Pentzia suffruticosa Hutch. contains much resin and a volatile oil with a strong, peculiar taste. It was used by the early settlers as a tonic, antispasmodic and anthelmintic. It was thus used in flatulency, gout, amenorrhoea and particularly for its anthelmintic properties. It was administered either as a powder or as an infusion, the latter being both diaphoretic and diuretic. A fomentation of the plant quickly resolves inflammations (Watt & Breyer-Brandwijk 1962).

5.75 OSMITOPSIS Cass. emend. K.Bremer

5.75.1 Osmitopsis asteriscoides (P.J.Bergius) Less.

(=*Leucanthemum asteriscoides* (L.) Kuntze)

(=*Osmites asteriscoides* P.J.Bergius)

(=*O. asteriscoides* (L.) Cass.)

(=*O. calva* Gand.)

Osmitopsis asteriscoides is taken by the Whites of South Africa to relieve body aches and pains. It produces sweating. They have also used it extensively with *Artemisia afra* and *Eucalyptus globulus* in the treatment of influenza. A tincture or an infusion is taken for rheumatism, and a poultice of the leaf is applied to cuts and swellings. The plant enjoys a great reputation as a remedy for stomach troubles. In the Western Cape area it is used in the treatment of erysipelas. In the past, external application of the plant was made to relieve inflammations and colic. It contains much volatile oil with a camphoraceous odour and taste. The yellowish-green volatile oil resembles oil of cajeput and contains camphor. Fresh plants from the Caledon district contains 0.69% of the volatile oil which contains 64% cineol (Watt & Brayer-Brandwijk 1962). The whole plant, called *Bellis*, is impregnated with a great deal of an aromatic volatile oil, which from its odour and taste, seems to contain camphor, hence its virtues as an antispasmodic, tonic and resolvent. In the form of infusion it is frequently and advantageously employed in cough, hoarseness and in diseases of the chest generally

and is said to be also very serviceable in flatulent colic. Infused in spirit, it acts as a powerful external remedy, and Thunberg relates, that he has succesfully cured paralysis with embrocations of the *Spiritus Bellidus* (TRAMED database, index card 3178).

Air dried plant material was extracted by Noristan as described in the introduction to this chapter. The extract was fractionated and the similar fractions were combined to form 3 groups. All three groups were active in the writhing test with inhibition of 43.8% ($p<0.05$), 47.5% ($p\sim0.01$) and 41.1% ($p<0.05$) respectively for the three groups at 500 mg/kg p.o. Group 2 had a narcoltic analgesic effect at 300 mg/kg i.p. (2 of the 4 mice did not show pain reaction). A possible weak transient central nervous system stimulation was observed in group 2 and with group 3 there was a 77% increase in Na^+ excretion (Noristan not published).

5.76 OSTEOSPERMUM L.

Several species of *Osteospermum* are toxic to stock, producing hydrocyanic poisoning (Watt & Breyer-Brandwijk 1962). An unspecified species, probably *O. junceum*, is used by the Xhosa. They grind the leaves and drink it in water for a prolapsed rectum and give it to children with diarrhoea (TRAMED database, index card 565). The root of an *Osteospermum* sp. is drunk by someone suffering from wind (TRAMED database, index card 569).

5.76.1 Osteospermum herbaceum L.f.

(=*O. zeyheri* Spreng. ex DC.)

The Xhosa drink 3 tablespoons t.d.s. for amenorrhoea (TRAMED database, index card 564).

5.76.2 Osteospermum imbricatum L. subsp. *nervatum* (DC.) Norl. var. nervatum

(=*O. glaberrimum* O.Hoffm.)

(=*O. nervatum* DC.)

The Zulu use *Osteospermum imbricatum* subsp. *nervatum* T. Norl. as an emetic in nausea accompanied by biliousness and as a remedy in uncomplicated biliousness (Watt & Breyer-Brandwijk 1962). *Osteospermum nervatum* is also used for indigestion (TRAMED database, index card 1559).

In addition to triterpenes, dimethoxycinnamaldehyde and trematone derivatives were isolated. On reinvestigation, the roots gave tridecapaentaynene, 3,4-dimethoxycinnamaldehyde and two trematone derivatives as well as three resacetophenone derivatives. The arial parts afforded the glucopyranosides, caffeic acid [4-hydroxyprenyl]-ester β-D-glucopyranoside and 4-O-[4-hydroxyprenyl]-caffeic acid 4'-O-β-glucopyranoside which could only be purified as their acetates (Jakupovic, Zdero *et al.* 1988).

5.77 OTHONNA L.

Twenty furanoeremophilanes have been identified from five sections of the genus *Othonna*. The genus is characterized by relatively strongly oxidized furanoeremophilanes, oxygen functions at C-2, C-3 and C-6, and is distinguished from the other genera by the occurence of compounds with an oxidized C-14 methyl group and the absence of furanoketones (Robins 1977).

5.77.1 Othonna furcata (Lindl.) Druce

(=*Ceradia furcata* Lindl.)

(=*Doria ceradia* Harv.)

(=*O. aeonioides* Dinter)

Othonna furcata is used as a wound dressing (TRAMED database, index card 1513).

O. furcata (Lindl.) Druce contains furanoeremophilanes (Jakupovic, Pathak *et al.* 1987).

5.77.2 Othonna graveolens O.Hoffm.

(=*Senecio cacteaeformis* Klatt)

The resinous excretion of *Othonna graveolens* O. Hoffm. is used by the African in the Namib as an incense (Watt & Breyer-Brandwijk 1962).

The arial parts of *O. cf. graveolens* O. Hoffm. gave no furoeremophilanes but two sesquiterpene senecioates, 13-senecioyloxy-caryophyllene and 12-senecioyloxy-bicyclogermacrene (Jakupovic, Pathak *et al.* 1987).

5.77.3 Othonna natalensis Sch.Bip.

(=*O. scapigera* Harv.)

The Southern Sotho use the root of *Othonna natalensis* Sch. Bip. as a vermifuge in the calf. The Zulu also use the plant as an anthelmintic, but for human patients only, and take an infusion of the root for relief of nausea (Watt & Breyer-Brandwijk 1962). According to the TRAMED database, the root is used for roundworms and for indigestion (index card 1538).

The chemical composition of *O. natalensis* L. Sch. Bip. was investigated by Bohlmann & Knoll (1978). The roots contain three furanoeremophilanes.

5.78 PARTHENIUM L.

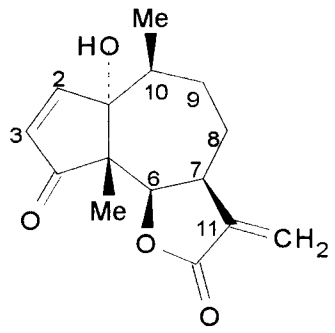
5.78.1 Parthenium hysterophorus L.

Parthenium hysterophorum L. is an aggressive weed of the Americas and has spread in the last hundred years to Australia, Africa and Asia. In some parts of India it is responsible for a high incidence of allergic contact dermatitis (Picman *et al.* 1980).

An alcoholic extract of *P. hysterophorus* was shown to suppress the growth of both axenic and polyxenic cultures of *Entamoeba histolytica*. Parthenin, an α-methylene-γ-lactone sesquiterpene lactone (of type ambrosanolide) was isolated from an alcoholic extract of *P. hysterophorus* plant material and characteized by physico-chemical and spectroscopic methods. It was shown to posess antiamoebic activity. The activity was tested *in vitro* against axenic and polyxenic cultures of *Entamoeba histolytica*. The minimum inhibitory concentration (MIC) values of parthenin obtained from the two sets of *in vitro* tests were found to be 10-12.5μg/ml. These values are comparable to that of the standard drug metronidazole. The *in vitro* effectivity of metronidazole was found to be lower

(10-12.5μg/ml) than observed by others (1-5μg/ml). Parthenin was however, less effective *in vivo* as compared to metronidazole. The LD_{50} and MLD of parthenin in mice were found to be 450 and 600 mg/kg respectively. The sesquiterpene lactone proved toxic within the therapeutic range (Sharma & Bhutani 1988).

Parthenin, a sesquiterpenoid lactone from *Parthenium hysterophorus*, has been reported to have anti-amoebic activity but Phillipson *et al.* (1995) found it was inactive against *E. histolytica in vitro* although it proved to be active against *Plasmodium falciparum* (K1) *in vitro* with an IC_{50} value of 1.29 μg/ml. Parthenin is said to be too toxic to warrant further investigation but doses of up to 100 mg/kg/day have been given to rats without toxic reactions. The biological activity of parthenin and other sesquiterpene lactones containing an exocyclic methylene γ-lactone moiety is ascribed to their high reactivity forming Micheal addition adducts with nucleophiles such as thiol groups which are present in a number of enzymes and proteins. Parthenin is considerably less active than artemisinin. For comparison, the IC_{50} of artemisinin is 0.001μg/ml (Phillipson *et al.* 1995). Parthenin was reported to inhibit sporangial germination and zoospore mobility in *Sclerospora graminicola* but such activity against the conidial development of *Aspergilus flavus* was lacking. The sesquiterpenes, helenalin and tenulin have also been found in *P. hysterophorus* (Rodriguez *et al.* 1976).



Parthenin (Phillipson *et al.* 1995)

Allergic contact dermatitis from *P. hysterophorus*, an extraordinary agressive weed which was introduced to India from the Americas in 1956, has become an important dermatological and health problem in certain cities in India. Parthenin was found to be the major allergen in *P. hysterophorus* (Rodriguez *et al.* 1976). Coronopilin was identified as the second major sesquiterpene lactone and tetraneurin-A as a minor sesquiterpene lactone in samples of the plant from both India and Central America (Picman *et al.* 1980).

5.79 PECHUEL-LOESCHEA O.Hoffm.

5.79.1 Pechuel-Loeschea leubnitziae (Kuntze) O.Hoffm.

(=*Pluchea leubnitziae* (Kuntze) N.E.Br.)

Pluchea leubnitziae N.E.Br. has been used as a remedy for bone diseases, for peptic ulcers and for venereal diseases. If cattle and sheep eat the plant, the meat is bitter and has a disagreeable smell,

as does the milk and butter. Experiments have shown that the plant produces gastritis in animals (Watt & Breyer-Brandwijk 1962). The Ovambo use *Pluchea leubnitziae* for colds. The root is inhaled (TRAMED database, index cards 3216; 10709). The plant is heated over a fire and the fumes are inhaled to relieve colds. The plant is also powdered and boiled and drunk as tea for a fever called *omuela* (Rodin 1985).

5.80 PENTZIA Thunb.

5.80.1 Pentzia globosa Less.

(=*P. globifera* Licht. ex Less.)

The Xhosa take an infusion of the leaf of *Pentzia globosa* O. Ktze. for stomach troubles. The plant is valued as a feed for sheep and goats. In the Western Cape province, the plant is used to make a wound salve, and together with *Tarchonanthus camphoratus* and possibly also *Pentzia virgata,* it is used as a poultice on the chest for bronchitis. For erysipelas and for pain after eating, the woody parts of this plant and of *Antizoma capensis* are chewed and the saliva swallowed (Watt & Breyer-Brandwijk 1962).

5.80.2 Pentzia incana (Thunb.) Kuntze

(=*Chrysanthemum incanum* Thunb.)

(=*P. virgata* Less.)

Near Middelburg C.P. an infusion of the leaf is commonly used by the blacks for relief of stomach trouble. Under the name *Pentzia virgata*, it has been used in the Western Cape with *Tarchonanthus camphoratus* and possibly also with *Pentzia globosa* as a poultice on the chest for the relief of bronchitis. For erysipelas and for pain after eating, the woody parts of *Pentzia incana* and of *Antizoma capensis* are chewed and the saliva swallowed. The plant has also been used in the Western Cape province as a bitter and as a tonic. It is valued as grazing for all types of domestic stock (Watt & Breyer-Brandwijk 1962).

This plant was extracted by Noristan in the same manner as described in the introduction to this chapter. The extract was fractionated and similar fractions were combined to form 10 fractions which were recombined to form two groups. A possible very weak effect on the central nervous system was observed 90 minutes post dose at 300 mg/kg of group 1. An inhibition in the writhing test was also noted at 500 mg/kg p.o. ($p<0.2$). Group 2 displayed antihypertensive activity with a 18.08% reduction in mean blood pressure and analgesic activity with 2/4 mice not showing any pain reaction in the tail clip experiment. Secondary pharmacological tests were done on the antihypertensive activity of the different fractions (Noristan not published).

5.81 PLECOSTACHYS Hilliard & B.L.Burtt

5.81.1 Plecostachys serpyllifolia (P.J.Bergius) Hilliard & B.L.Burtt

(=*Helichrysum serpyllifolium* (P.J.Bergius) Pers.)

A decoction of the whole plant is used for infection of the respiratory system (TRAMED database, index card 3127) *H. serpyllifolium* Less. is demulcent and an infusion has been used in respiratory

conditions. A tea made from the plant has apparently been much liked in the past. 10% of an acrid resin has been isolated from the root of a *Helichrysum* sp., thought to be identical to *H. serpyllifolium*, the resin producing vomiting and purgation when given to a dog (Watt & Breyer-Brandwijk 1962).

The roots contain the widely distributed pentaynene, trideca-1-ene-3,5,7-pentayne, the triterpene β-amyrinacetate, and the coumarins obliquin and two of its substituted derivatives. The examination of the aerial parts gave only very little trideca-1-ene-3,5,7-pentayne. Obliquin has to date been found only in the genus *Phaenocoma* (Bohlmann & Zdero 1980c).

Trideca-1-ene-3,5,7-pentayne occurs widely in roots of many species of Asteraceae (Harborne & Baxter 1993).

Trideca-1-ene-3,5,7-pentayne (Tridecapentaynene)

5.82 PLUCHEA Cass.

***5.82.1 Pluchea dioscoridis* (L.) DC.**

(=*Baccharis dioscoridis* L.)

A decoction of the root of *Pluchea dioscoridis* DC. is a Shangana remedy for colds. In Tanzania, some tribes boil the plant in water for several hours and evaporate the fluid to obtain "salt". In the Orient the leaf and root have been used as a stimulant, as a comforting medicine and as an aromatic (Watt & Breyer-Brandwijk 1962).

A sesquiterpene lactone, a thiopehene acetylene, flavonoids and sterols and triterpenes have been isolated from *P. dioscoridis* (L.) DC. A reinvestigation of the aerial parts collected in Alexandria (Egypt) afforded also the angelate, 1β-angeloyloxy-9α-hydroxy-α-cyclocostunolide (Omar *et al.* 1983). A reinvestigation of the aerial parts of *Pluchea dioscoridis* collected in Egypt afforded, in addition to the known compounds (a thiopheneacetylene and two eudesmanolides), five new eudesmanolides and a thiophene derivative. The eudesmanolides were identified as 9α-hydroxysantamarin, the corresponding 11β,13-dihydroderivative, 9α-angeloyloxy ludovicin A, the corresponding isovalerate and the 3-methylisovalerate (Bohlmann, Metwally & Jakupovic 1984).

5.83 PRINTZIA Cass.

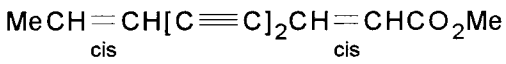
***5.83.1 Printzia aromatica* (L.) Less.**

(=*Inula aromatica* L.)

Printzia aromatica Less. is strongly aromatic. The leaf has been taken as a tea for the relief of chills (Watt & Breyer-Brandwijk 1962).

5.83.2 Printzia pyrifolia Less.

The Southern Sotho inject an enema made from *Printzia pyrifolia* Less. in the treatment of internal tumors (Watt & Breyer-Brandwijk 1962). The Xhosa boil the leaves for one hour and drink two tablespoons t.d.s. for whooping cough (TRAMED database, index card 624). The roots of *Printzia pyrifolia* contain matricaria ester while the aerial parts only yield methyl *p*-coumarate (Bohlmann & Zdero 1978).



Matricaria ester

5.84 PSEUDOCONYZA Cuatrec.

5.84.1 Pseudoconyza viscosa (Mill.) D'Arcy

(=*Blumea aurita* (L.f.) DC.)

(=*Blumea viscosa* (Mill.) V.M.Badillo)

(=*Conyza aurita* L.f.)

(=*Laggera aurita* (L.f.) Sch.Bip. ex C.B.Clarke)

(=*Laggera lyrata* (Humb., Bonpl. & Kunth) Leins)

Blumea aurita DC. is strongly aromatic and sticky and an infusion of it is used in Angola as a local application for the relief of rheumatic pains (Watt & Breyer-Brandwijk 1962).

The roots of *Blumea viscosa* (H.B.K.) Badillo, collected in Guatemala, gave α-humulene, thymohydroquinone dimethyl ether and coniferyl diangelate (Bohlmann, Wallmeyer *et al.* 1985).

5.85 PSEUDOGNAPHALIUM Kirp.

5.85.1 Pseudognaphalium luteo-album (L.) Hilliard & B.L.Burtt

(=*Gnaphalium luteo-album* L.)

The cooked leaf is a Zulu foodstuff. The Southern Sotho burn the plant in the hut of a feverish child. The Australian Aborigine used the plant as a general remedy for sickness. It has given positive spot tests for the presence of alkaloids (Watt & Breyer-Brandwijk 1962).

5.85.2 Pseudognaphalium undulatum (L.) Hilliard & B.L.Burtt

(=*Gnaphalium undulatum* L.)

(=*Helichrysum montosicolum* Gand.)

The Southern Sotho burn the plant in the hut of a feverish child (Watt & Breyer-Brandwijk 1962).

Two labdane derivatives, one with a new carbon skeleton and a flavol was isolated and an unknown diterpene lactone was present (Bohlmann & Ziesche 1980).

5.86 PTERONIA L.

Bohlmann, Grenz & Zdero (1975) have determined that this genus contain no acetylenic compounds.

5.86.1 Pteronia camphorata L. var. *camphorata*

(=*P. camphorata* L. var. *aspera* (Thunb.) Harv.)

(=*P. laricina* Houtt. ex DC.)

A plaster, made from *Pteronia camphorata* L., is used in the Western Cape province for drawing boils (Watt & Breyer-Brandwijk 1962).

5.86.2 Pteronia incana (Burm.) DC.

(=*Chrysocoma incana* Burm.)

(=*P. xantholepis* DC.)

Pteronia incana produces mainly 5,3',4'-trihydroxy-6,7,8-trimethoxyflavone (sideritiflavone), 5,4'-dihydroxy-6,7,8,3'-tetramethoxyflavone (3'-methyl sideritiflavone) and 5,7,3'-trihydroxy-6,8,4'-trimethoxyflavone (acerosin). These flavones were isolated by preparative TLC, while traces of 5,4'-dihydroxy-6,7,8-trimethoxyflavone (xanthomicrol), 6-hydroxyluteolin-6,7-dimethyl ether (cirsidiol) and kaempferol-3,7-dimethyl ether were identified by direct comparison with markers.

Air dried leaf material was rinsed in acetone to dissolve the exudate (5% of d.w.). The resinous exudates were passed over a Sephadex column, eluted with MeOH to seperate the flavonoids from the terpenoids. The flavonoid fractions were further fractioned by CC on polyamide and/or on silica, eluted with toluene and increasing amounts of MeCOEt and MeOH (Wollenweber & Mann 1989).

5.86.3 Pteronia onobromoides DC.

In Namaqualand *Pteronia onobromoides* DC. is much appreciated by the local Hottentot as a medicine and cosmetic. It is used by them as a "buchu". It has a powerful odour (Watt & Breyer-Brandwijk 1962). They mix it with grease and use it as a lotion for the skin (TRAMED database, index card 3006).

5.86.4 Pteronia stricta Aiton var. *stricta*

(=*P. camphorata* L. var. *stricta* (Aiton) Harv.)

An infusion of the leaf of *Pteronia stricta* Ait. is used in the George-Knysna area for intestinal disorders. The dried leaf contains 1.8% of volatile oil, with a deep yellow colour and a powerful "eucalyptus" odour. It contains 50% of cineol, 17% of phellandrene and 2% of sylvestrene (Watt & Breyer-Brandwijk 1962).

5.87 PULICARIA Gaertn.

The genus *Pulicaria* contains the widespread polyacetylenes, thymol derivatives and flavones (Bohlmann, Ahmed & Jakupovic 1982).

5.87.1 Pulicaria scabra (Thunb.) Druce

(=*Erigeron scabrum* Thunb.)

(=*Inula capensis* Spreng.)

(=*P. capensis* DC.)

In the Lydenburg area an infusion of *Pulicaria scabra* Druce is used by the Whites as a lotion for bathing haemorrhoids. The Zulu apply a paste of the powdered leaf to the vagina for the treatment of tumours and take the powdered leaf as a tonic for colds (Watt & Breyer-Brandwijk 1962).

The investigation of the aerial parts of *Pulicaria scabra* (Thunb.) Druce afforded a flavonoid sulphate, thymol derivative, carryophyllande derivative and seven other related compounds; three sesquiterpenes (14-hydtoxy-caryophyllen-7-one, 14-hydroxy-5,6-cis-caryophyllen-7-one and 14-acetoxy-5,6-cis-caryophyllen-7-one) and four ether linked caryophyllanes (puliscabrin, 5,6-cis-puliscabrin, 5,6-cis-5'-epi-puliscabrin and the ester, 4,14-di-2,15-dihydro puliscabrin). The roots gave tridecapentaynene, stigmasterol and a rare sesquiterpene alcohol which had previously been reported from *Pulicaria dysenterica*. The chemistry of this species is similar to that of *P. dysenterica* but differs from that of the other genera of the subtribe Inulinae. The air-dried plant material was collected in the Transvaal and was extracted with Et_2O:petrol (1:2) and the resulting extracts were separated by CC (Si gel) and repeated TLC (Si gel). Known compounds were identified by comparing the ^1H NMR spectra with those of authentic material (Bohlmann, Ahmed & Jakupovic 1982).

5.88 SCHISTOSTEPHIUM Less.

5.88.1 Schistostephium crataegifolium (DC.) Fenzl ex Harv.

(=*S. villosum* Hutch.)

(=*Tanacetum consanguineum* DC.)

(=*Tanacetum crataegifolium* DC.)

The leaf of *Schistostephium crataegifolium* Fenzl. is smoked by the Southern Sotho for chest complaints and an eye lotion is prepared from the root. The plant has been suspected of being toxic to stock, but 200g produces no effect in sheep (Watt & Breyer-Brandwijk 1962).

The aerial parts of *Schistostephium crataegifolium* (DC.) Fenzl. ex Harv., collected near Lydenburg, afforded germacrene D, bicyclogermacrene, lupeol, its acetate, bisabolene derivatives (7-hydroxy-11-peroxybisabol-2,9t-diene and 7-hydroxy-11-peroxybisabol-2,11-diene), a prostaglandin-like acid (4-[7-carboxyheptyl(1)]-5-pent-2-en-yl(1)-cyclopent-2-en-1-one), a flavone, several eudesmanolides (denatin A acetate, desacylchrysanin-6-O-methacrylate, desaculchrysanin-6-O-senecioate, desacyltanapsin-6-O-methacrylate, desacyltanapsin-6-O-senecioate and tanapsin) as well as germacranolides (1β,10α-epoxydesacetyl laurobiolide senecioate, 1α,10β-epoxydesacetyl laurenobiolide senecioate and angelate, 14-acetoxydesacetyl laurenobiolide, 14-acetoxy-4β,5α-epoxydesacetyl laurenobiolide, 1α-peroxy-1-desoxytatridin B-6-O-methacrylate, and 1βperoxy-1-desoxytatridin B-6-O-methacrylate) while the roots gave germacrene D, bicyclogermacrene and dehydrofalcarinone. The aerial parts of the same species collected near Zeerust afforded

germacrene D, bicyclogermacrene, α-pinene, borneol, bornyl acetate, two neridilol derivatives, the corresponding ketone and several germacranolides (3β-acetoxy-9β-hydroxycostunolide, 9β-hydroxy-3 β-isobutyryloxycostunolide, 9α-isobutyryloxydesacetyl laurenobiolide, 9α-isovaleroxy- and (2-methylbutyryloxy)-desacetyl laurenobiolide, 9α-isobutyryloxy-4β,5α-epoxydesacetyl laurenobiolide). The aerial parts of a third sample collected near Baberton afforded germacrene D, bicyclogermacrene, several nerolidol derivatives (6,11-dihydroxy-6,7,10,11-tetrahydro-7,14,9,19-bisdehydronerolidol, 4-[7-carboxyheptyl(1)]-5-pent-2-en-yl(1)-cyclopent-2-en-1-one), costic acid and its derivatives, himachalol, as well as several germacranolides, while the roots gave longifolene, β-santalene and the allohimachalene derivatives (Bohlmann, Jakupovic, Ahmed & Schuster 1983).

5.88.2 *Schistostephium flabelliforme* Less.

(=*S. argyreum* (DC.) Fenzl ex Harv.)

(=*Tanacetum argyreum* DC.)

Schistostephium flabelliforme Less. is aromatic and bitter and an infusion of it is used by the Xhosa for coughs (Watt & Breyer-Brandwijk 1962) and for colds (TRAMED database, index card 627).

5.88.3 Schistostephium heptalobum (DC.) Oliv. & Hiern

(=*S. saxicola* Hutch.)

(=*Tanacetum heptalobum* DC.)

An extract of this plant was fractionated by Noristan as described in the introduction to this chapter. Similar fractions were combined to form 7 fractions which were recombined to form two groups. Group 1 was found to be anti-hypertensive. The blood pressure was reduced by 13% and the heart rate by 1.8% at a dose of 300 i.p. Group 2 was diuretic with a 22% increase in Na^+ excretion with no increase in volume (Noristan not published).

The aerial parts of *Schistostephium heptalobum* (DC.) Oliv. et. Hiern., collected near Duiwelskloof, afforded germacrene D, bicyclogermacrene, squalene, chrysanthemone, caryophyllene epoxide, lupeol and its acetate, the eudesmanolides which include 1α,3α-dihydroxyarbusculetin B and douglanin acetate and geracranolides which include 9β-hydroxy-4α, 5β-epoxycostunolide and 1β,10α-epoxyhaageanolide acetate, while the roots gave germacrene D, caryophyllene, β-bisabolene, caryophyllen-1,10-epoxide, α-humulen-1,10-epoxide, lupeyl acetate, taraxasteryl acetate, stigmasterol, sisterol, nerol isovalerate, cadinol, dehydrofalcirinone, cycloartenone and a germacranolide. The aerial parts of a small collection near Lydenburg afforded germacrene D, 5-hydroxy-6,7,4'-trimethoxyflavone and several germacranolides, while the roots gave stigmasterol, sisterol and β-eudesmol (Bohlmann, Jakupovic, Ahmed & Schuster 1983).

5.88.4 Schistostephium hippiifolium (DC.) Hutch.

(=*Tanacetum hippiifolium* DC.)

Schistostephium hippaefolium is used by the Xhosa. They grind the leaves and drink it t.d.s. in water for coughing. They boil and drink the leaves for infectious fevers and grind it to a paste which they apply to the skin for measles (TRAMED database, index cards 621; 622).

5.88.5 Schistostephium umbellatum (L.f.) Bremer & Humphries

(=*Cotula umbellata* L.f.)

(=*Peyrousea argentea* Compton)

(=*Peyrousea calycina* DC.)

(=*Peyrousea oxylepis* DC.)

(=*Peyrousea umbellata* (L.f.) Fourc.)

In the Eastern Cape province, the leaves of *Peyrousea argentea* are applied externally for headaches (TRAMED database, index card 1257).

5.89 SCHKUHRIA Roth

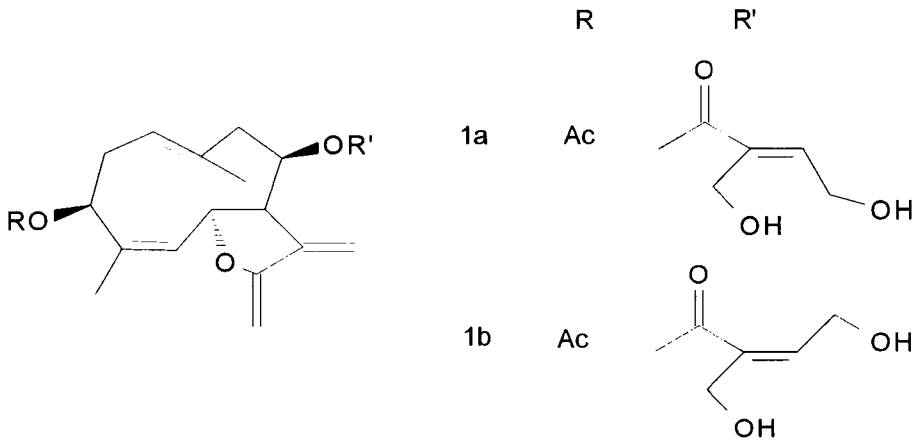
Schkuhria is an American genus recently moved from the tribe Helenieae to Heliantheae (Herz & Govindan 1980). The taxonomy of the Argentinian species was clarified by Cabrera who recognized two species, with three varieties each; *S. pinnata* (Lam.) Kuntze and *S. multiflora* H. et. A., Heiser (Pacciaroni *et al.* 1995). *S. pinnata* is the only species of this genus occuring in Southern Africa.

5.89.1 Schkuhria pinnata (Lam.) Cabrera

(=*S. bonariensis* Hook. & Arn.)

Schkuhria pinnata (Lam.) Kuntze and its varieties have some use in the popular medicine of Argentine as insect repellents or insecticides, particularly to kill flies (Pacciaroni *et al.* 1995). The powdered leaf of *Schkuhria pinnata* (Lam.) Kuntze is swallowed with water as a remedy for malaria, for influenza and for colds. The plant is readily eaten by cattle and is one of the most common causes of tainted milk in Zimbabwe (Watt & Breyer-Brandwijk 1962).

Pectolinarigenin, the known heliangolide eucannabinolide, schkuhrin II, chromolaenolide, santhemoidin A, a known heliangolide and four new heliangolides and schkuhripinnatolide were isolated from *S. pinnata* var. *abrotanoides* (Roth) CaBr. (Pacciaroni *et al.* 1995).



1a - Eucannabinol (Pacciaroni *et al.* 1995)

Eucannabinolide, which has been isolated from *S. virgata*, exhibits significant activity against lymphoxytic leukemia P388 in the mouse (Herz & Govindan 1980).

The fresh aerial parts were extracted with Et_2O:petrol, 1:2 and the resulting extract was separated first by CC (Si gel). The polar fractions (Et_2O:MeOH, 20:1) were further separated byTLC (Si gel, $CHCl_3$:C_6H_6:Et_2O, 1:1:1) affording several heliangolides and the unusual aromatic compound schkuhrianol (Bohlmann & Zdero 1981) The germacranolide 11,13-dehydroeriolin was found in *S. pinnata* collected in Mexico (Romo De Vivar *et al.* 1982). The roots contain pentaynene and two other acetylenic compounds (Bohlmann & Zdero 1977e).

5.90 SENECIO L.

The genus *Senecio* contains pyrrolizidine alkaloids which cause molteno disease in stock. Fatal senecio poisoning has been reported from the Riversdale district. On many occasions plants containing pyrrolizidine alkaloids grow among wheat and their seeds are harvested along with the cereal, and the alkaloids are incorporated into bread. This may cause poisoning known as bread poisoning.

Combinations of anticancer drugs belonging to different classes where the toxicity does not overlap are extensively used in clinics. For example, polyene antibiotics and probenecid were used in an attempt to increase cell membrane permeability for anticancer therapeutic agents. Both saponin and digitonin could make plasma membrane permeable to various substances without impairing the function of the intracellular organelles. Calcium channel blockers enhance *Vinca* alkaloids *in vitro* and *in vivo* in murine tumours as well as *in vitro* cytotoxicity in human leukaemic cell lines. The combined effects of cyclophosphamide and extracts of plants belonging to *Senecio* species were assessed on experimental transplantable S180 tumour. Combined administration of cyclophosphamide and methanolic extracts of *Senecio chrysanthemoides*, *S. densiflorus* and *S. jacquemontanus* led to prolonging the life span of S180 (ascitic) tumour bearing mice. The extracts alone had no effect on survival of tumour-bearing mice. The same extracts and the same combinations had no effect on S180 solid tumour (Indap & Gokhale 1986).

***5.90.1 Senecio albanensis* DC.** var. *albanensis*

(=*S. leiocarpus* DC.)

Senicio albanensis DC. var. *doroniciflorus* (DC.) Harv.

(=*S. doroniciflorus* DC.)

(=*S. fibrosus* O.Hoffm. ex Kuntze)

The root of *S. albanensis* DC. is a Southern Sotho colic remedy and has a negative feeding test in sheep (Watt & Breyer-Brandwijk 1962).

It contains furanoeremophilanes, but nothing could be positively identified from the roots of *S. albanensis* DC. var. *doronicoflorus* (DC.) (Bohlmann, Zdero, Berger *et al.* 1979).

***5.90.2 Senecio asperulus* DC.**

The Southern Sotho administer *S. aperulus* DC. to a horse suffering from a cold and apply a decoction as a lotion for their own feet and legs when aching. They also use the plant as a charm for bad dreams in children (Watt & Breyer-Brandwijk 1962).

5.90.3 Senecio barbertonicus Klatt.

Air dried plant material was milled and extracted three times with methanol-dichloromethane and the combined extracts were concentrated under reduced pressure. The extract was fractionated as described in the introduction to this chapter. Similar fractions were combined to form 9 fractions. Fractions 1-5 were combined to form group 1 and fractions 6-9 were combined to form group 2. Group 1 inhibited inflammation by 37%, $p<0.001$ and group 2 by 34% $p<0.001$ @ 500 mg/kg p.o. Group 1 reduced the mean blood pressure and heart rate by 11% and 5% respectively while the reduction in group 2 was 23% and 5% respectively at a dose of 300 mg/kg. Its antimicrobial action was confined to the inhibition of the growth of *Aspergillus niger* at 1000µg/ml. The zone of inhibition in group 2 was 1.6cm. In the anti-ulcer test, 100 mg/kg of group 1 given 2x p.o., resulted in 31% inhibition $p<0.01$ while the inhibition of for group 2 was 55% $p<0.02$ (Noristan not published).

S. barbertonicus contains acylpyrrole and triterpenes (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.4 Senecio brachypodus DC.

(=*S. natalensis* Sch.Bip.)

The Xhosa drink a decoction of the leaves for nervous fits (TRAMED database, index card 630). The root of *S. brachypodus* DC. is a Swazi and Shangaan remedy for syphilis and an infusion is a Southern Sotho medicine for colds and other respiratory troubles (Watt & Breyer-Brandwijk 1962). It has been found to produce a cicatrizing effect in skin diseases (Watt & Breyer-Brandwijk 1962).

S. brachypodus contains highly oxygenated germacrene and a triterpene. *S. brachypodus* Hilliard et Burtt. (author citation is probably a mistake) does not contain furanoeremophilanes (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.5 Senecio bupleuroides DC.

(=*S. bupleuroides* DC. var. *denticulatus* DC.)

(=*S. bupleuroides* DC. var. *falcatus* Sch.Bip.)

S. bupleuroides DC. is an ingredient in an Southern Sotho remedy for chest troubles. A feeding test in sheep has proved negative. Nonetheless retrorsine 0.16% and isatidine 0.7% have been isolated from the plant (Watt & Breyer-Brandwijk 1962)

S. bupleuroides contain pyrrolizidine alkaloids (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.6 Senecio burchellii DC.

(=*S. lichtensteinensis* Dinter)

The Xhosa make a decoction of the leaves which they drink for chest pains (TRAMED database, index card 650). *S. burchellii* DC. is one of the causes of human *Senecio* poisoning in the Riversdale district (Watt & Breyer-Brandwijk 1962).

5.90.7 Senecio cinerascens Aiton

(=*Cineraria seminuda* Klatt)

(=*S. namaquanus* Bolus)

(=*S. tomentosus* Salisb.)

An extract of the plant was fractionated by Noristan. The method is described in the introduction to this chapter. Similar fractions were combined to form 8 fractions. Fractions 1-4 were combined to form group 1 and fractions 5-8 were combined to form group 2. Group 1 inhibited oedema by 46% $p<0.1$ at 500 mg/kg p.o. in the anti-inflammatroy test. On further purification a fraction was found to inhibit 35% oedema, $p<0.1$ at a dose of 150 mg/kg p.o. A 54% inhibition in the writhing test, $p<0.05$ at 500 mg/kg and a 38% increase in Na^+ excretion @ 300 mg/kg with no increase in volume were noticed. In the antiarrhythmia test it scored 2.5/5. Group 2 displayed 45% inhibition in the anti-ulcer test, $p<0.1$ @ 100 mg/kg p.o. and anti-hypertensive activity with 11% and 12% reduction in the mean blood pressure and heart rate respectively at a dose of 300 mg/kg i.p. (Noristan not published)

5.90.8 Senecio coronatus (Thunb.) Harv.

(=*Cineraria coronata* Thunb.)

(=*S. lasiorhizoides* Sch.Bip.)

(=*S. lasiorhizus* DC.)

The Xhosa use the root as an enema for pain in the abdomen (TRAMED database, index card 652). They also drink a decoction of the root for swelling of the lower gastro-intestinal tract (TRAMED database, index card 652), as a purgative (Watt & Breyer-Brandwijk 1962) and infection in the respiratory organs (TRAMED database, index card 652). The Southern Sotho use the plant as an emetic and mix it with their tobacco. It has been suspected of causing poisoning in cattle in the Ventersdorp district (Watt & Breyer-Brandwijk 1962).

5.90.9 Senecio deltoideus Less.

(=*Cacalia scandens* Thunb.)

(=*Mikania auriculata* Willd.)

(=*S. durbanensis* Gand.)

(=*S. fimbrillifer* B.L.Rob.)

(=*S. mikaniae* DC.)

(=*S. mikaniaeformis* DC.)

In the Eastern Cape province a paste of the leaves are externally applied for inflammation of the eyes and on the skin for rashes or itching (TRAMED database, index card 653, 1263).

S. deltoideus contains C_{11}-acetylenes, C_{17}-acetylenes and chinolesters (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.10 Senecio dregeanus DC.

A decoction of the root is taken by the Southern Sotho as an emetic in chest colds and as a remedy for madness (Watt & Breyer-Brandwijk 1962).

***5.90.11 Senecio elegans* L.**

(=*S. elegans* Willd.)

(=*S. pseudo-elegans* Less.)

In the Transkei the stem scale is used for athsma (TRAMED database, index card 1249). *S. elegans* contain furanoeremophilanes and thymol derivatives (Bohlmann, Zdero, Berger *et al.* 1979).

***5.90.12 Senecio erubescens* Aiton** var. *erubescens*

A decoction of the root of *S. erubescens* is taken by the Southern Sotho for nausea and rheumatic fever. The leaf is sometimes also mixed with their tobacco (Watt & Breyer-Brandwijk 1962). *S. erubescens* contain highly oxygenated eremophilanes (Bohlmann, Zdero, Berger *et al.* 1979).

***5.90.13 Senecio ficoides* (L.) Sch.Bip.**

(=*Kleinia ficoides* (L.) Haw.)

S. ficoides Sch. Bip. contains inulin. Both the leaf and stem are edible (Watt & Breyer-Brandwijk 1962). *S. ficoides* contains triterpenes (Bohlmann, Zdero, Berger *et al.* 1979).

***5.90.14 Senecio glanduloso-pilosus* Volkens & Muschl.**

(=*S. serratus* (Thunb.) Sond.)

The Southern Sotho use a decoction of *S. serratus* Sond. to wash persons suffering from swollen limbs or internal tumours (Watt & Breyer-Brandwijk 1962)

***5.90.15 Senecio haworthii* (Sweet) Sch.Bip.**

(=*Kleinia haworthii* (Sweet) DC.)

S. haworthii Sch. Bip. contains inulin. The herb has been used for chest complaints (Watt & Breyer-Brandwijk 1962)

***5.90.16 Senecio ilicifolius* L.**

(=*S. quercifolius* Thunb.)

It is taken by the Xhosa as an aphrodisiac (TRAMED database, index card 639) but it causes human poisoning (Watt & Breyer-Brandwijk 1966).

***5.90.17 Senecio inaequidens* DC.**

(=*S. burchellii* DC. p.p.)

Two pyrrolizidine alkaloids, senecionine and retrorsine, have been isolated from *Senecio inaquidens* (Röder *et al.* 1981). Senecionine is hepatotoxic, pneumatotoxic and genotoxic. It is mutagenic to *Drosophila* chromosomes, but not in the Ames test. It is also anticholinergic in rats (Harborne & Baxter 1993). It shows antitumor activity against Walker 256 carsinosarcoma. The LD_{50} (i.v. in rats) is 41 mg/kg and causes lung lesions (Buckingham & Macdonald 1996). Retrorsine is hepatotoxic and pneumatotoxic. It is mutagenic to *Drosophila* chromosomes and in the Ames test (Harborne & Baxter 1993). Material of *Senecio inaequidens* DC collected from several places in Natal showed some differences in composition but most compounds were found in the different populations. The

benzofurans are typical. However, no acyl pyrroles reported before, were found (Bohlmann & Zdero 1978).

S. inaequidens contains aromatic furanoeremophilanes and acylpyrrole (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.18 Senecio inornatus DC.

(=*S. caulopterus* DC.)
(=*S. diversidentatus* Muschl.)
(=*S. fraudulentus* E.Phillips & C.A.Sm.)
(=*S. macroalatus* M.D.Hend.)
(=*S. ommanei* S.Moore)
(=*S. serra* Sond.)
(=*S. sneeuwbergensis* Bolus)

A decoction of the root of *S. fraudulentus* Phillips and Smith is a Zulu remedy for palpitations and for phthisis. It is also a Kwena and Tswana remedy for coughs and difficult breathing (Watt & Breyer-Brandwijk 1962).

The roots of *Senecio inornatus* DC afforded large quantities of benzofurans, with cacalol being the main component. The aerial parts also yielded several benzofurans (Bohlmann & Zdero 1978). *S. inornatus* contain aromatic furanoeremophilanes (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.19 Senecio latifolius DC.

(=*S. sceleratus* Schweick.)

The leaves of *S. latifolius* is applied externally as a wound dressing. Seneciofoline has been isolated from the plant (TRAMED database, index card 1543). The Xhosa apply the leaves to burns (TRAMED database, index card 567)(Watt & Breyer-Brandwijk 1962). The plant is of great ritual significance to the Mpondo (Watt & Breyer-Brandwijk 1962).

5.90.20 Senecio microglossus DC.

(=*S. cupulatus* Volkens & Muschl.)

In the Lydenburg district, the Lobedu uses *S. microglossus* DC. in making a lotion for bathing sores and sore places (Watt & Breyer-Brandwijk 1962)

5.90.21 Senecio oxyriifolius DC.

(=*S. orbicularis* Sond. ex Harv.)

In the Northern Province and Zimbabwe, *S. orbicularis* is cooked and then used as a compress for infection and the water in which it was cooked is drunk alone or mixed with *Eucalyptus* (TRAMED database, index card 1348, 1349). A decoction of the root of *S. orbicularis* Sond. is taken by the Zulu for shivering fits during fever. They also use the leaf to foment swellings in animals (Watt & Breyer-Brandwijk 1962). A Mpondo female herbalist uses the root of *S. oxyriaefolius* DC. as a remedy for

benzofurans are typical. However, no acyl pyrroles reported before, were found (Bohlmann & Zdero 1978).

S. inaequidens contains aromatic furanoeremophilanes and acylpyrrole (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.18 Senecio inornatus DC.

(=*S. caulopterus* DC.)
(=*S. diversidentatus* Muschl.)
(=*S. fraudulentus* E.Phillips & C.A.Sm.)
(=*S. macroalatus* M.D.Hend.)
(=*S. ommanei* S.Moore)
(=*S. serra* Sond.)
(=*S. sneeuwbergensis* Bolus)

A decoction of the root of *S. fraudulentus* Phillips and Smith is a Zulu remedy for palpitations and for phthisis. It is also a Kwena and Tswana remedy for coughs and difficult breathing (Watt & Breyer-Brandwijk 1962).

The roots of *Senecio inornatus* DC afforded large quantities of benzofurans, with cacalol being the main component. The aerial parts also yielded several benzofurans (Bohlmann & Zdero 1978). *S. inornatus* contain aromatic furanoeremophilanes (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.19 Senecio latifolius DC.

(=*S. sceleratus* Schweick.)

The leaves of *S. latifolius* is applied externally as a wound dressing. Seneciofoline has been isolated from the plant (TRAMED database, index card 1543). The Xhosa apply the leaves to burns (TRAMED database, index card 567)(Watt & Breyer-Brandwijk 1962). The plant is of great ritual significance to the Mpondo (Watt & Breyer-Brandwijk 1962).

5.90.20 Senecio microglossus DC.

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In the Lydenburg district, the Lobedu uses *S. microglossus* DC. in making a lotion for bathing sores and sore places (Watt & Breyer-Brandwijk 1962)

5.90.21 Senecio oxyriifolius DC.

(=*S. orbicularis* Sond. ex Harv.)

In the Northern Province and Zimbabwe, *S. orbicularis* is cooked and then used as a compress for infection and the water in which it was cooked is drunk alone or mixed with *Eucalyptus* (TRAMED database, index card 1348, 1349). A decoction of the root of *S. orbicularis* Sond. is taken by the Zulu for shivering fits during fever. They also use the leaf to foment swellings in animals (Watt & Breyer-Brandwijk 1962). A Mpondo female herbalist uses the root of *S. oxyriaefolius* DC. as a remedy for

unsteadyness on the legs and purgation (Watt & Breyer-Brandwijk 1962). It has been found to produce a cicatrizing effect on skin diseases (Watt & Breyer-Brandwijk 1962).

The aerial parts of *S. serratuloides* DC. var. *gracilis* Harv. contains linoleic acid (linolic acid) and a mixture of triterpenes. It does not contain furanoeremophilanes (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.27 Senecio speciosus Willd.

(=*S. concolor* DC.)

The Zulu take a decoction of the leaf and stalk of *S. speciosus* Willd. for pleurisy and other pains in the chest (Watt & Breyer-Brandwijk 1962). The ash of the plant is sometimes rubbed into incisions in the side. The leaf has been used as remedy for dropsy (Watt & Breyer-Brandwijk 1962) (TRAMED database, index card 1543). It has been found to produce a cicatrizing effect on skin diseases (Watt & Breyer-Brandwijk 1962). The Zulu also use the dried, ground leaves as snuff for headaches (Hutchings & Van Staden 1994).

S. speciosus contains highly oxygenated eremophilanes (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.28 Senecio subscandens

The plant is used for colic, fever and toothache and in Central Africa, the leaves are used for fevers and colds (TRAMED database, index card 1543)

5.90.29 Senecio tamoides DC.

Senecio tamoides DC. is one of the ingredients in a Zulu remedy for anthrax (Watt & Breyer-Brandwijk 1962).

Extraction was done by Noristan as described in the introduction to this chapter. Similar fractions were combined to form 10 fractions. Fractions 1-5 were combined to form group 1 and fractions 6-10 were combined to form group 2. Group 1 displayed significant anti-inflammatory activity. It inhibited swelling in carrageenan induced oedema by 72.8% at 500 mg/kg, $p<0.001$. It caused 69.6% inhibition in the writhing test, $p<0.001$ at 100mg/kg p.o. The anti-inflammatory action was reflected by a reduction of 51.7% in mean blood pressure and a reduction of 17.8% in the mean heart rate 2 hours after 300 mg/kg was administered i.p. It was highly antimicrobial against *Staphylococcus pyogenes*. The zone of inhibition was 1.82cm at 1000µg/ml. In the anti-ulcer test a 43.1% inhibition was recorded. Group 2 displayed only moderate antihypertensive activity. The ten fractions were then tested for anti-inflammatory, antiulcer and antimicrobial activity. One fraction inhibited inflammation by 84.2% at 300 mg/kg and inhibited *Staphylococcus aureus* and *Candida albicans* at 1000µg/ml. The best anti-ulcer activity was a 36.6% inhibition at 100mg/kg (Noristan not published). It has been found to produce a cicatrizing effect on skin diseases (Watt & Breyer-Brandwijk 1962).

S. tamoides contains pyrrolizidine alkaloids (Bohlmann, Zdero, Berger *et al.* 1979).

5.90.30 Senecio tanacetopsis Hilliard

(=*S. tanacetoides* Sond. ex Harv.)

The Southern Sotho smoke the leaf of *S. tanacetoides* Sond. to stop nosebleeding (Watt & Breyer-Brandwijk 1962).

5.90.31 Senecio vulgaris L.

S. vulgaris is an introduced species in South Africa which has become a common garden weed. In Europe it is used for dysmenorrhoea and amenorrhoea and is said to have a soothing effect on the female genital system. In the USA the plant is used as a diaphoretic, a diuretic, a tonic and an emmenagogue. The alkaloids senecionine and senecine have been found in the plant. It has been found to produce a cicatrizing effect on skin diseases (Watt & Breyer-Brandwijk 1962). *S. vulgaris* contains pyrrolizidine alkaloids and "chinolester" (Bohlmann, Zdero, Berger *et al.* 1979).

5.91 SIGESBECKIA L.

5.91.1 Sigesbeckia orientalis L.

S. orientalis is a local but dominant weed in Tanzania and Kenya (Watt & Breyer-Brandwijk 1962). The whole plant extract has antibacterial activity. It is used to treat skin lesions, leprosy, siphilis, venereal diseases and ring worm. It is also used for ulcers, as a purgative and anti-emetic (Akah & Ekekwe 1995). The plant has also been used as a stimulant and to promote sweating, and applied externally to wounds, carbuncles and ulcers. The herb is diaphoretic, alterative, stimulant and astringent and has been used to stimulate urine secretion. The fresh plant has been regarded as antiseptic, and has been applied to ulcers. The juice of the fresh herb, applied as a dressing to wounds, leaves a varnish-like coating as it dries. The plant has been used as a purgative and is thought to be emetic. In China it has been used as an anthelmintic. A substance, resembling salicylic acid has been isolated from the plant. A chrystalline bitter principle, darutine has also been isolated (Watt & Breyer-Brandwijk 1962).

The plant contains the sesquiterpene lactones orientalide and darutoside as well as two other melampolides. The more polar fractions of the extract also contain the diterpene darutigenol (Barua *et al.* 1980).

The whole plant of *S. orientalis* was collected in India, dried, ground and extracted with 50% ethanol. The extract was screened for antibacterial, antifungal, antiprotozoal, antianthelminthic, antiviral, hypoglyceamic activity and effects on respiration, contraction of isolated tissues, the central nervous system as well as anticancer activity, but the extract was only active in the isloated guinea pig ileum test. Preliminary fractionation involved extraction with benzene, followed by partitioning with chloroform-methanol-water. This confirmed the anti-acetylcholine activity of the extract (Dhar *et al.* 1968).

5.92 SILYBUM

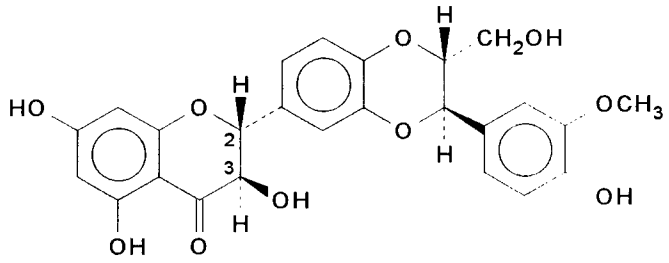
5.92.1 Silybum marianum Gaertn.

The milk thistle, *Silybum marianum* is an introduced weed in South Africa (Watt & Breyer-Brandwijk 1962). It was often used in traditional medicine as a remedy for hepatic diseases (Quercia *et al.* 1981). The seeds of this plant are used in controlling heamorrhaging. In homoeopathy, the drug is used for jaundice, cirrhosis of liver, dropsical conditions and pathological conditions related to liver and gall stone (Varma *et al.* 1980).

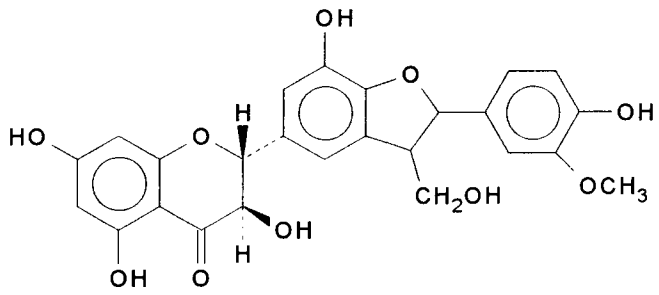
Silybin is a natural product obtained from *Silybum marianum*, together with the isomers, silydianin, and silychristin. These three constituents differ only in the linkage of the taxifolin moiety to coniferyl alcohol. The liver protective action of silybin and of silymarin [a mixture of silybin, silydianin and silychristin] has been established *in vivo* and in many *in vitro* liver damage models. In almost all models the protective effect was highly significant (Hikino *et. al.* 1984). Particularly impressive was the demonstration of antagonism against α-amanitin and phalloidin, the otherwise fatal toxins of the death cap fungus. Phalloidin binds chiefly to the liver microsomes and causes acute haemorrhagic liver distrophy. Interaction of phalloidin with intracellular microphilaments (actin) leads to the destruction of the hepatocyte membrane. Death in experimental animals occurs within a few hours. When administered prophylactically before phalloidin poisoning silymarin is 100% effective in preventing the toxicity of phalloidin. Even when administered up to 10 minutes after phalloidin, silymarin can completely counteract the toxic effects. Presumably silymarin blocks the binding of phalloidin to receptors on the cell membrane surface and hinders α-amanitin to penetrate through the membrane into the cell nucleus (Wagner 1981). Furthermore silybin has been found active on the polymerase A of hepatocytes, which corresponds with a stimulation of proteien synthesis in liver cells. Silybin also inhibits inhibitory action in carbo tetrachloride (CCl_4)- and D-galactosamine (GalN)-induced cytotoxicity in primary cultured rat hepatocytes *in vitro* (Hikino *et. al.* 1984). The action of silymarin is due to the protection of intact liver cells or cells not yet irreversibly damaged by acting on the cell membrane and stimulation of protein synthesis, and by this an increase in the production of new liver cells (Wagner 1981).

From the white flowering variety of *S. marianum* L., 3-Deoxyisosilybin (Silandrin) and 3-Deoxysilydianin (Silymonin) were isolated as well as three 3-deoxy-flavonolignans posessing 2R- and 2S-configurations (silyhermin (3-deoxysilychristin) and neosilyhermin A and B). Their flavonoid precursors, naringenin, eriodictyol, apigenin and chrysoeriol have also been isolated (Fiebig & Wagner 1984). Hikino *et. al.* (1984) evaluated flavonolignans and related compounds from the fruits of *Silybum marianum* for their antihepatotoxic effects. The substances were added in CCl_4 to 34hr-precultured hepatocytes, and the GPT values in the medium, 60 min therafter were examined. Prominent antihepatotoxic actions were found in silandrin, 3-deoxysilychristin, silybin and silymonin at a dose of 1.0 mg/ml. Silychristin, silydianin, 5,7-dihydroxychromone and naringenin also showed significant preventative effects. GPT levels in the culture medium were also measured 30h after treatment of 1.5h-preincubated hepatocytes with the substances and GalN. Silydianin and silymonin

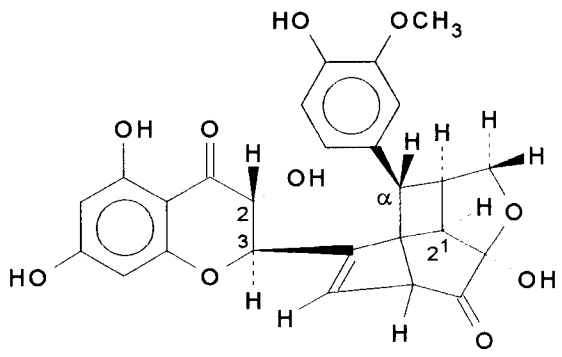
were effective in preventing galactosamine-produced cell lesions. Silybin and related compounds showed antihepatotoxic activity in a dose dependant manner, but in certain congeners, the strongest activity was observed at a dose of 0.1 mg/ml and weaker activity was found at higher dose (1.0 mg/ml). This may be explained by the fact that these substances displayed toxicity at the higher doses when the hepatocytes were treated for a long time in the assay method using GalN-induced cytotoxicity. In order to examine wether the inhibitory effects were given simply by inhibition of the enzyme activity or not, the actions of the constituents on GPT were determined. Most of them exhibited no, or only weak enzyme inhibiting activity and these were not comparable to the observed antihepatotoxic activity. Therefore, the reduction of the GPT level by these constituents is largely due to the inhibitory activity against cell lesions. The only exception was 3-deoxysilychristin, which produced a considerable inhibition. It is therefore presumed theat the 3-deoxy-compounds are more powerful antihepatotoxic agents than their 3-hydroxy-derivatives. The mode of linkage between the taxifolin and coniferyl alcohol moiety seems to have no great influence (Hikino *et al.* 1984).



Silybin



Silychristin



Silydianin

Silybin, silydianin and silychristin, the main components of silymarin, the active principle in the milk thistle (*Silybum marianum* (L.) Gaertn.), are tightly but reversably bound to human albumune and polyvinylpyrrolidone *in vitro*. The binding of medicines to plasmaprotein plays an important role in the pharmacological action in mammals. It impedes the passage of the active molecules from the vascular system to the tissues and slows down its excretion significantly. This can detrementally affect the onset and duration of the active molecule (Bachner-Jaschke & Koch 1979).

Betaine hydrochlorides and amino acids have been isolated from the seeds of *Silybum marianum*. Betaine hydrochlorides donates methyl groups in the synthesis of choline in the liver and could contribute to the antihepatotoxic principle of the drug (Varma *et al.* 1980). Quercia *et al.* (1981) reported an HPLC analytical method for the assay of the antihepatotoxic principles of *Silybum marianum*. The amines tyramine and histamine were also found in *S. marianum* L. (Wagner 1977a).

5.93 SOLANECIO (Sch.Bip.) Walp.

5.93.1 Solanecio angulatus (Vahl) C.Jeffrey

(=*Crassocephalum bojeri* (DC.) Robyns)

(=*Crassocephalum subscandens* (A.Rich.) S.Moore)

Crassocephalum subscandens S. Moore is used by the African in Tanzania for abdominal pains, convulsions, fever, toothache and cancer and also as antidote for the irritant poisoning of *Clematis* (Watt & Breyer-Brandwijk 1962). The leaf is an East African remedy for convulsions (Watt 1967).

5.94 SONCHUS

The genus *Sonchus* was introduced to southern Africa.

5.94.1 Sonchus asper

The Xhosa drink a tea made of the root for sharp stabbing pain. The root is also applied to a sore that will not heal (TRAMED database, index card 231).

5.94.2 Sonchus dregeanus

The Xhosa drink a decoction of the root for a sharp stabbing pain. It is also used by them for coughing. The Xhosa also mix the leaves with water and apply it to an itchy or sore skin. This causes the skin to peel in two layers (TRAMED database, index card 232). The Xhosa grind the root, mix it with water and drink one tablespoon t.d.s. for nervous fits (TRAMED database, index card 645).

5.94.3 Sonchus oleraceus L.

In Nigeria an infusion of the root is chiefly employed to treat liver troubles, jaundice and as blood purifier and also to treat ulcers (Akah & Ekekwe 1995). In Venda the leaf is eaten alone or used to add a piquant taste to cooked vegetables. It may also be dried and stored for future use. The inclusion of some condiment makes it all the more delicious (Magobo 1990). The early Cape settlers applied the juice of *Sonchus oleraceus* L. for cleansing and healing ulcers. They also make an

ointment from a decoction for wounds and ulcers. The herb has been used for liver troubles and as a blood purifier, and the juice as eye drops. The Pare of Tanzania use the root as vermicide eaten raw or boiled with banana. It is apparently used chiefly for roundworm. The United States Dispensary states that the brownish gum obtained by evaporating the plant juice to dryness is said to be a powerful cathartic and that it has also been used in the treatment of opium addiction. The youg leaf contains 4.1 mg/100g vitamin C. It yields 0.14-0.22% of caoutchouc. It gives negative antibacterial tests (Watt & Breyer-Brandwijk 1962).

The milky juice of *Sonchus oleraceus* when extracted in saline gave agglutination with red blood cells (Khanna & Sehajpal 1980). Lectins are carbohydrate-binding proteins or glycoproteins of non-immune origen which agglutinate cells or precipitate polysaccharides or glycoconjugates. It has been known for years that some lectins preferentially agglutinate malignant cells: these cells are agglutinated at a 3 to 100-fold lower lectin concentration than normal ones. The high affinity with which lectins bind to oligosaccharide (glycan) side chains linked to a peptide backbone of membrane glycoproteins and the fact that the envelope glycoprotein of HIV is highly glycosylated might lead one to expect HIV infectivity and virus-cell fusion to be inhibited by those lectins that are specific for glycans present in gp120 molecules. (GP120 is a glycoprotein in the capsule of the virus that binds with cells) Orchid lectins are active against HIV-1 and HIV-2 as well as against cytomegalovirus in about 3 orders of magnitude below the toxicity threshold (Wagner *et al.* 1995). The stem contains taraxasterol (González 1977).

5.94.4 Sonchus schweinfurthii Oliv. & Hiern.

The Haya use *S. schweinfurthii* as a remedy for sore eyes and the Shambala administer a decoction of the leaf in the treatment of habitual abortion, of fits in a child and of chicken-pox (Watt & Breyer-Brandwijk 1962).

5.95 SPHAERANTHUS L.

In Tanzania a *Sphaeranthus* sp. is used as an abortifacient by the Kikuyu and *Sphaeranthus* spp. are in general use in Tanzania as an anticonception medicine. An infusion of the plant is drunk by the woman immediately before coitus. It is said to cause headaches and even delirium (Watt & Breyer-Brandwijk 1962). The powdered leaves of a *Sphaeranthus* sp. are used by the Ovambo woman as under-arm deodorant (Rodin 1985).

5.95.1 Sphaeranthus indicus

The vapour of the oil of *Sphaeranthus indicus* induces sleep (TRAMED database, index card 1562).
An 50% methanol extract of *S. indicus* Linn. from India was found to be hypoglyceamic (Dhar *et al.* 1968).

5.96 SPILANTHES Jacq.

5.96.1 Spilanthes mauritiana (Pers.) DC.

(=*S. acmella* auct. non (L.) Murray)

(=*S. africana* DC.)

Spilanthus acmella Murr. (Ose-ani)

The Xhosa chew the flower of *Spilanthus mauritiana* DC. for the relief of toothache and in the treatment of pyorrhoea. This is done for about one minute, by which time the mouth is numb and tingling. These effects last for about 20 minutes, but the toothache does not recur. The Zulu apply the moistened powdered leaf to a hollow tooth to relieve pain and rub it on the lips and gums of a child suffering from a sore mouth. The application is said to be soothing and to stimulate the flow of saliva. The Chagga use the root as a toothache remedy and a decoction of it as a mouth-wash for inflammations of the buccal cavity and for sore throat. An infusion of the herb is used as febrifuge (Watt & Breyer-Brandwijk 1962). In Nigeria a decoction of the flowering tops and leaves is used as hemostatic and analgesic agent, for treatment of sore throat, dysentery, chest pain, various skin diseases, gonorrhoea and as a diuretic and blood purifier (Akah & Ekekwe 1995). It is used in Central Africa for fevers and colds (TRAMED database, index card 1544). In Camaroon the plant is used as a snake-bite remedy and in the treatment of articular rheumatism. The flower and the fruiting head is rubbed on the forehead for the relief of headache. In India the plant has been used as a remedy for kidney stone, bladder and kidney affections, leucorrhoea, scurvy, suppression of menses and paralysis of the tongue. The plant can be added to salads and is regarded as antiscorbutic, diuretic and a tonic to the digestive tract. In Java it is used as fodder for cattle and horses. Both the the herb and root are acrid. In West Africa the flower head is regarded as edible. The flower head is reported to produce stupefication of fish and to be used as fish poison (Watt & Breyer-Brandwijk 1962).

The plant yields 0.33% volatile oil which is highly toxic to fish. Spilanthol has been isolated from the flower. It has a hay-like odour and a strong local anaesthetic action. An ether extract of the fresh flowering top is toxic to the anopheline larva in dilutions as low as 1:100 000, the lethal agent aparently spilanthol (Watt & Breyer-Brandwijk 1962). The air-dried whole plant of *S. acmella* Linn. was extracted with light petrol followed by 90% EtOH. It contained a mixture of α-and β-amyrins identified as their acetates, lauric, myristic, palmitic (major component), linoleic and linolenic acid as their methyl esters as well as myricyl alcohol, stigmasterol and sisterol-O-β-D-glucoside (Krishnaswamy *et al.* 1975).

The whole plant of *S. acmella* Murr. was collected in India, dried, ground and extracted in 50% ethanol. The ethanol extract was screened for antibacterial, antifungal, antiprotozoal, antianthelmintic, antiviral, hypoglyceamic and anticancer activity and for effects on respiration, isolated tissues and the central nervous system. It affected only the blood pressure and the isolated guinea pig ileum. The maximum tolerated dose was 100 mg/ml (Dhar *et al.* 1968).

5.97 STOEBE L.

In the early days of the Cape colony, the settlers used a decoction of *Stoebe* sp. as an anthelmintic. *Stoebe* sp. smells like valerian and may be of some effect in epilepsy (Watt & Breyer-Brandwijk 1962).

5.97.1 *Stoebe cinerea* (L.) Thunb.

(=*Seriphium cinereum* L.)

In the Western Cape province area *Stoebe cinerea* Thunb. is used as a remedy for heart trouble. The plant yields a volatile oil, the yield varying from a trace to 0.7%. The oil contains 1.65 to 2.52% of citral (Watt & Breyer-Brandwijk 1962).

5.98 SYNCARPHA DC.

Several species of *Helipterum* (now known as *Syncarpha*) were used in the Western Cape province as remedies for jaundice and biliousness, for liver diseases and for croup and diphtheria (Watt & Breyer-Brandwijk 1962). They are listed below.

5.98.1 *Syncarpha eximia* (L.) B.Nord.

(=*Gnaphalium eximium* L.)

(=*Helipterum eximium* (L.) DC.)

5.98.2 *Syncarpha speciosissima* (L.) B.Nord.

S. speciosissima (L.) B.Nord.subsp. *angustifolia* (DC.) B.Nord.

(=*Helipterum speciosissimum* (L.) DC. var. *angustifolium* DC.)

S. speciosissima (L.) B.Nord. subsp. *speciosissima*

(=*Helipterum seminudum* Sch.Bip.)

(=*Helipterum speciosissimum* (L.) DC. var. *speciosissimum*)

(=*Xeranthemum speciosissimum* L.)

5.98.3 *Syncarpha variegata* (P.J.Bergius) B.Nord.

(=*Helichrysum variegatum* Thunb.)

(=*Helipterum variegatum* (P.J.Bergius) DC.)

5.98.4 *Syncarpha vestita* (L.) B.Nord.

(=*Helichrysum vestitum* (L.) Willd.)

The roots of *S. vestita* contain the coumarin obliquin and small amounts of polyacetylenes (Bohlmann & Zdero 1980c).

5.99 TAGETES L.

5.99.1 *Tagetes erecta* L.

α-Terthienyl and 5-(3-buten-1-ynyl)-2,2-bithienyl were isolated as the active insecticidal components from the root extracts of *T. erecta* L. The topical LD_{50} of partially purified *T. erecta* root extract was

8.1 mg/g for *Rhysopertha dominica* (F.) and 4.3 mg/g for *Tribolium castaneum* (Herbst) (Weaver *et al.* 1994).

The flavonols kaempferol, kaempferol-7-O-rhamnoside and kaempferitrin have been reported from the leaves and 6-hydroxy-kaempferol-7-glucoside, quercetagetin and quercetagetrin from the flower heads (El-Emary & Ali 1983).

5.99.2 Tagetes minuta L.

Tagetes minuta L. is an introduced weed known as "kakiebos". *T. minuta* is a strongly scented annual (Héthelyi *et al.* 1989). Steam distillation yields 0.5% of a strong smelling volatile oil (Watt & Breyer-Brandwijk 1962). The essential oil is known to have tranquilising, hypotensive, bronchodilatory, spasmolytic and anti-inflammatory effects and also have insecticidal activity as well as antimicrobial activity (Héthelyi *et al.* 1989). The oil is strongly repellent to the bowfly and is useful as a bowfly dressing (Watt & Breyer-Brandwijk 1962).

The VhaVenda inhale the vapours of the leaf for relief of headaches. They also drink (a decoction of) the leaves for infections in the respiratory system (TRAMED database, index cards 6759; 6760). In other parts of Africa the leaves are applied externally on swelling (TRAMED database, index card 3079). The Xhosa use the leaves for parasites (TRAMED database, index card 646). The Lobedu apply either the pounded and moistened leaf or powdered leaf to maggots in the ear of the donkey or elsewhere in its body. An infusion of decoction of the plant is used by the Whites of South Africa as a lotion for haemorrhoids. In Brazil it is used as an anthelmintic. The flower is used medicinally in the north-west part of Argentina as a stomachic, a purgative, a diuretic and a diaphoretic. It is also used in South America as a stimulant, an emmenagogue and hysteria remedy (Watt & Breyer-Brandwijk 1962). The leaves of *Tagetes minuta* L. are used in Kenya to repel mosquitoes and safari ants and have been found to kill larvae of the mosquito *Aedes aegypti* (Maradufu *et al.* 1978). When other food is scarce, the young plant is frequently eaten by cattle and imparts an objectionable taste to milk and butter (Watt & Breyer-Brandwijk 1962).

Marigolds, *Tagetes* spp. are a useful intercrop in acriculture. Populations of *Meloidogyne* spp. nematodes have been reduced by intercropping marigolds (Weaver *et al.* 1994).

Experiments were conducted to determine the speed of action and toxicities of extracts of *Tagetes minuta* L., a source of naturally occurring insecticidal compounds. LC_{50} values for male and female Mexican bean weavils, *Zabrotes subfasciatus* (Boheman), were determined for floral, foliar, and root extracts of *T. minuta*. The 24h LC_{50} values ranged from 138µg/cm^2 for males exposed to the root extract (most susceptible) to 803µg/cm^2 for females exposed to the folair extract (least susceptible). Increasing the duration of exposure to 48h decreased all LC_{50} values 20-30µg/cm^2. Males were more susceptible than females. The time to incapacitation for 50% of the test insects (IT_{50}) for floral and foliar extracts indicated fast-acting, volatile components, whereas the root extract data indicated slower-acting components, which is probably a result of the interaction of

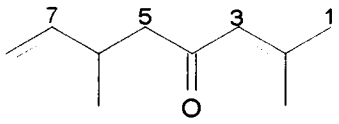
photophase with time-dependent efficacy. The pronounced enhancement in efficacy between 18 and 24 hours is the cumulative result of photoactivation of toxins from the root extract. Further, α-terthienyl is known to be photoactivated. This requirement for both prolonged exposure and light make the root extract the least practical material tested for insecticidal activity in stored products. It was therefore suggested that the root extract (which contains photoactivatable components) could be used for mosquito control rather than for control of storage pests. Floral and foliar extracts of *T. minuta* may be useful as insecticides for controlling stored-product pests. Root and foliage material was harvested over a 2 to 3 week period ≈2 months before maximum bloom. The root material was washed with tap water at harvest. All plant portions were placed in large plastic self-sealing bags, sealed and transported to the laboratory were the bags were opened, flushed with nitrogen and resealed. The material was stored in a 10°C refrigerator until extraction. The plant material was placed in a round bottom three neck flask and covered with distilled water. This flask was connected to a vapour arm of a Lickens & Nickerson distillation extractor. A round bottom boiling flask containing HPLC-grade methylene chloride was connected to the other vapour arm. The extractor was fitted with a Liebig condensor through which cool water was circulated to reduce loss of volatile components. This extraction was carried out for 5 hours. The root extract contained more thiophenes than the extracts for either aerial portion. Also, the floral extract contained more α-terthienyl than the foliar extract, in addition to having a higher number of terpenoids with low molecular weights. Extract yields also varied for the three tissues: the flower yield was 0.68% ± 0.01%, the foliar yield was 0.28% ± 0.05%, and the root yield was 0.12 ± 0.02% (Weaver *et al.* 1994).

Essential oils were extracted by means of Clevenger steam distillation of plant material that was grown in a botanical garden in Hungary. The following components and ratios of the essential oils were determined by GC/MS: β-ocimene (22%), dihydrotagetone (13%), tagetone (19%) and ocimenones (44.3%). The inhibitory effects of the essential oils on multiplication were examined for a total of 40 micro-organism strains. The agar diffusion system as well as "atmospheric" examinations in which the essential oils were adsorbed onto a paper disc which was attached to the lid of the petri dish, was used. In the last case only compounds which were volatile and microbiologically active displayed an effect. In the antibacterial study, it was found that in the agar diffusion system, the oil of *T. minuta* caused complete inhibition in 85% of Gram-positive strains and 100% of Gram-negative strains while the multiplication of fungi was 100% inhibited by *T. minuta* oil using both methods (Héthelyi *et al.* 1989).

The acyclic monoterpenes tagetone, linalool, ocimene, citral and myrcene and the monocyclic monoterpenes; limonene, α-phellandrene, p-cymene, carvone and α-terpeneol have been isolated as well as the bicyclic monoterpenes; α-pinene, β-pinene, camphene, sabinene and the sesquiterpenes eudesmol and aromadendrene (Rodríguez & Mabry 1977). Two flavonoids, quercetagitrin and patuletrin have been isolated from *T. minuta* L. and monomethyl esters of fumaric acid and syringic acid were found in whole flowering plants of *T. minuta* L. (Rodríguez & Mabry 1977). Weaver *et al.* (1994) isolated and identified by gas chromatography/mass spectroscopy the following components of the floral, foliar and root extracts of *T. minuta* : Para-cymene, limonene, cis-ocimene (31,9% in the

flower, 2,6% in the foliage), trans-ocimene, dihydrotagetone (13,5% in the flower, 47,5% in the foliage and 0.2% in the roots), linalool, alloocimene, a mixture of alloocimene and cis-epoxy-ocimene, cis-tagetone, trans-tagetone (19,1% in the flower, 6,0% in the foliage), terpinen-4-ol, alpha-gurjunene, alpha-humulene, germacrene-D, germacrene-B, 5-(but-3-ene-1-inyl)-2,2'-bithiophene (42.9% in the roots), palmitic acid (10.6% in the roots), alpha-terthienyl (2.1% in the flower, 0.4% in the foliage and 9,9% in the roots), 5-methyl-2,2',2''-terthiophene, 5-(4-Acetoxy-1-butenyl)-2,2'-bithiophene and an unknown thiophene (Weaver *et al.* 1994).

The leaves of *Tagetes minuta* L. are used in Kenya to repel mosquitoes and safari ants and have been found to kill larvae of the mosquito *Aedes aegypti*. Maradufu *et al.* (1978) have isolated (5E)-ocimenone, the factor responsible for the mosquito larvicidal activity. The fresh leaves and flowers of the plants were ground in a blender and the resulting mass was steam distilled. The distillate was extracted with *n*-hexane and dried over anhydrous sodium sulphate. More than 50 peaks were observed when the oil was submitted to high-pressure liquid chromatography (HPLC) on a
μ-porasil column. Fractions were assayed for larvicidal activity. Bioassay tests showed that a 40ppm concentration of (5E)-ocimenone affected 100% mortality of larvae of *Aedes aegypti* in 24 hours. Ocimenone in its isolated state, i.e. when it is not in the plant, is unstable in water (20-30°C). Approximately 75% of the compound is decomposed in 1 hour (Maradufu *et al.* 1978).



(5E)-Ocimenone (Maradufu *et al.* 1978)

Laboratory tests using polyacetylenes from the Asteraceae indicated that α-terthienyl, a phototoxic thiophene from *Tagetes* spp. had an LC_{50} of 19ppb for *A. aegypti* larvae when combined with near UV radiation (Weaver *et al.* 1994).

Thiophene-containing plants such as *Tagetes* spp. have been used traditionally as medicines applied externally for skin and eye infections and internally for intestinal parasites and also as insecticides (Marles *et al.* 1992). α-Terthienyl and other thiophene compounds are localised in the roots of some Asteraceae plants, *e.g. Tagetes* (Towers *et al.* 1979).

Tagetes species contain thiophenes, biological active secondary metabolites of many species of the Asteraceae. Thiophenes such as α-terthienyl has a high level of phototoxicity to herbivorous insects, phytopoathogenic fungi and their elicitation after fungal infection are observations consistent with the hypothesis that they play a significant role in chemical defence (Marles *et al.* 1992). The nematocidal and larvicidal activity of α-terthienyl is also dependent on UV-A (Towers *et al.* 1979). α-Terthienyl has also been shown to cause dose dependent phototoxicity to human skin, consisting of erythema, edema, crusting, erosion and inhibition of hair growth, when administered topically or intradermally (Marles *et al.* 1992). The phototoxic reactions with α-terthienyl were biphasic with burning pain and

spreading edema appearing within 10 minutes exposure of sunlight or UV irradiation followed by erythema and later by hyperpigmentation persisting for 10 months, localised to the test sites. Histopathological examination of acutely affected skin revealed "sunburn" cells in the epidermis (Towers *et al.* 1979). This toxicity is due primarily to a type II photooxidative process involving production of singlet oxygen, $O_2,(^1\Delta_g)$, with unsaturated membrane lipids and membrane associated proteins being the primary targets of photooxidative damage. αT has a half life in sunlight of approximately 4 hours (Marles *et al.* 1992). The principal target of this compound appears to be membrane fatty acids, particularly unsaturated ones, which are oxydised by the singlet oxygen that is produced by irradiating α-terhienyl with UVA. α-Terthienyl (in the presence of UVA) rapidly and efficiently inactivated viruses with membranes, but not bacteriophages. However the inactivated virus still retained its integrity, and it was able to penetrate susceptible cells, although it did not replicate (Hudson *et al.* 1993).

In the light of therapeutic potential of thiophenes for viral infections and cancer, Marles (1992) evaluated 15 synthetic analogues against murine cytomegalovirus (MCMV) and Sindbis virus (SV) and murine mastocytoma cells (P815). After irradiation with near UV light, α-terthienyl and most of its analogues had significant toxicity, with minimum inhibitory concentrations in the range of 0.02-40μM. In the absence of near UV radiation, only one analogue had antiviral activity and five were cytotoxic. The carboxylic acid and hydroxyl-substituted analogues were more potent than αT against MCMV. (The minimum concentration to completely inactivate 100pfu of virus for αT is 0,14μM). The Sinbis virus was significantly more sensitive to αT than MCMV (0.02μM). The MIC_{50} values against P815 cells for αT is 0.08μM. The hydroxyl and thiomethyl analogues were more cytotoxic than αT. General conclusions of the relation between chemical structure and their phototoxicity were that extensive conjugated unsaturation and absorpsion of light in the near UV-range with high extinction coefficient, quantum yield (Φ_Δ) of $O_2(^1\Delta_g)$. and hydrophobicity all play important roles in phototoxicity. Some specificity of thiophene analogues against particular organisms was observed (Marles *et al.* 1992).

The different effect of the thiophene analogues against the two viruses may reflect their lipid and protein compositions. There is evidence that the viral membrane lipids and proteins are not the only targets of thiophene phototoxicity. Infectivity of the bacteriophage T4, which does not have a membrane or any lipid content, can be reduced by αT plus near UV to the same degree as murine cytomegalovirus (MCMV - a DNA herpes virus which replicates in the nucleus of mouse cells) and Sinbis virus (SV - a RNA virus) but at much higher concentrations. This suggests that α-terthienyl can interact with viral proteins or DNA. Inactivity of MCMV retained its integrity (asssessed by electron microscopy) and was still capable of adsorbing to and penetrating cells. However the DNA and RNA replication and viral late proteins were not produced, suggesting a block of viral gene transcription. αT does not appear to significantly affect DNA structure or function in mammalian cells, since no sister chromatid exchanges or chromosome abberations were found in treated Syrian hamster cells (Marles *et al.* 1992).

Non-light-mediated ("dark") toxicity of thiophenes has also been reported against insects, crustaceans, nematodes and cultured mammalian cells, but not against vertebrates, bacteria and viruses except at very high concentrations. Mammalian toxicity of thiophenes appears to be several orders of magnitude less than their toxicity to viruses and cultured cells: rats can tolerate injections i.p. of αT at >5 mg/kg body weight in the absence of near-UV exposure (Marles *et al.* 1992).

α-Terthienyl was evaluated for activity against the human immunodeficiency virus (HIV-1). HIV-1 was also very susceptible to α-T, and the effect was almost totally dependent on UVA radiation. The antiviral activity specially required long wavelenth light (UVA, 320-400nm). The compound had no or little activity in visible light or in the dark. The anti-HIV effect was UVA-dose dependant and was proportional to the concentration of α-T, according to several parameters of virus infectivity and replication. (As little as 0.01μg/ml (about 0.03μM) caused partial inactivation of the virus (10^3 $TCID_{50}$) while 0.1 and 1.0μg/ml completely abolished virus infectivity; *i.e.*, there was no cytopathic effect (cpe) in the inoculated cultures and no p24 protein was produced.) The efficacy was decreased to some extent by the presence of bovine serum in the reactions, but under optimal conditions 0.1μg/ml. α-T ($3x10^{-7}$) could inactivate 10^4 - 10^5 infectious particles. In contrast poliovirus and Coxsackievirus infectivity were relatively resistant to α-T + UVA. The fact that the two non-membrane containing viruses were largely resistant to α-terthienyl + UVA, supports the concept of a membrane target. The possibility of alternative targets can however not be ruled out, and several studies have shown that α-T is capable of adversely affecting DNA at >5μg/ml and proteins. α-T + UVA did show interactions with p24 protein, the two enteroviruses and with one or more components of bovine serum. Unsaturated compounds in the serum can quench singlet oxygen and thereby reduce the effect of the antiviral agent. Some photodynamic dyes, such as porphyrins and cyanins can bind to serum proteins or lipoproteins and can facilitate the penetration of the agents into the cells. Several phytodynamic agents have been proposed for the use in decontamination of blood products, where a number of viruses constitute potential hazards. Furocoumarins, in particular 8-methoxypsoralen, have been advocated for this and similar applications and is in use as a treatment mode, called photopheresis, for some blood disorders and in AIDS patients. (Hudson *et al.* 1993)

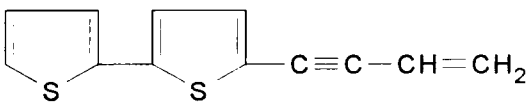
Numerous studies have evaluated the insecticidal properties of α-terthienyl and its analogues. The toxicogenetics of α-terthienyl were also examined for three species of Lepidoptera. The topical LD_{50} for *Manduca sexta* (L.)was 10μg/g, but for *Heliothis virescens* (F.) it was 470 μg/g and for *Ostrinia nubilalis* (Hübner) the LD_{50} was 700μg/g. This difference was likely caused by a rapid clearance of the toxin by the more tolerant species, which may have preadapted rapid elimination of this toxin via evolutionary associations with the Asteraceae. This elimination was fascilitated by higher levels of cytochrome P450 in those species (Weaver *et al.* 1994).

Oduor-Owino and Waudo (1994) compared the efficacy of nematicides and nematicidal plants, *Tagetes minuta* and *Datura stramonium* on root-knot nematodes. Ethylene dibromide (EBD) gave the

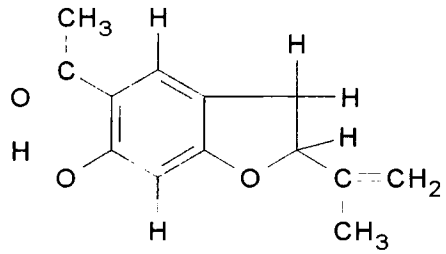
most effective reduction of galling, but supported poor plant growth due to its phytotoxic effects. Although Aldicarb and EBD were more effective in suppressing nematode development than intercropping with *Tagetes* or *Datura* plants, the plants increased shoot heights, dry weights and fruit yields significantly more than EBD. *Datura stramonium* was slightly more effective than *Tagetes minuta* in boosting fruit production. Aldicarb is toxic to mammals. Although the nematocidal plants may compete with economically important crops, this is outweighed by the destructive effects on nematodes and the stimulation of plant growth (Oduor-Owino & Waudo 1994).

Hausen & Helmke (1995) gives a short review of known cases of contact dermatitis in cultivars of marigold (*Tagetes* sp.): Skin lesions were reported among men working with *Tagetes minuta* L. and weed dermatitis was also reported among farmers in South Africa. It was also reported that two farmers aquired specific hypersensitivity to *Tagetes minuta*. Cases of eczema have also been caused by the marigold (Hausen & Helmke 1995).

Short ether extracts of ornamental cultivars of *Tagetes* sp., commonly known as marigold, and isolated compounds were used in sensitising experiments on guinea pigs. This revealed the presence of three constituents that must be considered as contact allergens. They were identified as 5-(3-buten-1-ynyl)-2,2'-bithiophene, α-terthienyl and hydroxytrematone. In sensitized animals, butenylthiophene showed moderate to strong sensitizing potency, while α-terthienyl was less strong and hydroxytrematone weak. These results demontrate that at least some of the thiophenes possess not only phototoxic activity but also sensitizing properties (Hausen & Helmke 1995).



Butenylbithiophene



Hydroxytremetone

(Hausen & Helmke 1995)

5.100 TARAXACUM

5.100.1 Taraxacum officinale Weber

Taraxacum officinale is almost a cosmopolitan weed. The Xhosa drink a decoction of the root for pain in the chest (TRAMED database, index card 648). In the USA the young leaf has been used as greens in salad and the root as a bitter tonic in disease of the liver and in dyspepsia. Large doses are said to be purgative and diuretic. The herb and the root is used for liver troubles and jaundice, and as blood purifier, as purgative and the juice as eye drops. The plant has given negative antibiotic tests and negative tests for haemolysis. Slightly positive antibiotic tests against *Mycobacterium tuberculosis* have been reported (Watt & Breyer-Brandwijk 1962).

The roots contain the triterpenes β-amyrenol, taraxasterol and taraxerol and the flowers contain unidentified triterpenes. The green leaves contain 6.0 mg% carotene. Taraxanthin, luteolin epoxide and mono- and dipalmate have been isolated from the flowers. Taraxanthin corresponds to cis-5,6-monoepoxy-luteolin and luteolin epoxide is in the form of its trans isomer. The petals yielded neoxanthin, a pigment having the properties of deepoxyneoxanthin and polar xanthophylls. It was found that the amount of carotenoid epoxides increased with altitude, while the amount of monooxygenated carotenoids decreased (González 1977).

The root contains a very small amount of enzyme capable of hydrolizing amygdalin; p-hydroxyphenylacetic acid; 4-dihydroxycinnamic acid; a small amount of choline; 1.8% of a solft oily resin which yields a monohydric alcohol taraxasterol; a monohydric alcohol homotaraxasterol; androsterol; homoandrosterol; cluytianol; palmitic-, cerotic-, mellisic- and oleic acids (Watt & Breyer-Brandwijk 1962).

5.101 TARCHONANTHUS L.

5.101.1 Tarchonanthus camphoratus L.

(=*T. abyssinicus* Sch.Bip.)

(=*T. camphoratus* L. var. *litakunensis* (DC.) Harv.)

(=*T. minor* Less.)

All parts of *Tarchonanthus camphoratus* L. have a camphoraceous odour and the leaf has been regarded as containing a fair amount of camphor. In the past the dried leaf has been smoked by the Hottentots and Bushmen and is said to produce a slight narcosis. The Southern Sotho inhale the smoke from the burning green branch for the relief of headache. They also use the plant in the treatment of venereal diseases. The Rolong do the same with the smoke from the burning fresh plant, as well as smoking rheumatic joints with the smouldering green twig and drinking an infusion of the fresh leaf for stomach troubles. It is reported that an infusion of the leaf is a diaphoretic and was used by the early settlers of the Western Cape for the relief of spasmodic asthma, as a tonic and as a "resolvent". The Muslim chewed the leaf and the Hottentot smoked it with the same medicinal objectives (Watt & Breyer-Brandwijk 1962). The leaves, in the form of an infusion are used by the Hottentot. It is said to be useful in spasmodic asthma. It promotes perspiration (TRAMED database, index card 3166). An infusion of the leaf is taken for abdominal pains, and the plant is used as a toothache remedy. In the Western Cape province the plant is used in a number of ways: a hot poultice of the leaf on the chest for the relief of asthma, bronchitis, hoarseness and inflammation and in plague, a tincture of the leaf internally for the same conditions, except plague, a tincture in a hot bath for paralysis and in the treatment of cerebral haemorrhage; as an ointment for the same purposes; an ointment is rubbed in hot for the relief of chilblains on hands and feet (Watt & Breyer-Brandwijk 1962). The Tswana boil the leaves and use it to wash sore eyes (TRAMED database, index card 4345). In Tanzania the leaf is used for massaging the body and is put into fat used for anointing the skin. The capitula is used for stuffing pillows. The leaf does not appear to be toxic, for the foliage is much browsed by cattle, sheep and goat. The plant is said to be repellent to insects. A wound from a splinter of its wood, produces a troublesome sore, difficult to heal. The wood, which is

strongly aromatic and camphoraceous in odour is said to be useful in the manufacture of musical instruments and of fancy joinery. The wood has been used for making assegai shafts and is excellent for firewood (Watt & Breyer-Brandwijk 1962).

The leaf has given negative antibiotic tests. No scientific confirmation of the leaf containing camphor could be found. The plant yields to steam distillation 0.107% volatile oil. Tarchonyl alcohol has been isolated fom the dried leaf (Watt & Breyer-Brandwijk 1962).

The plant was collected for Noristan for pharmacological testing of possible analgesic and anti-inflammatory effects. A fraction of the petroleum ether extract, caused a 39.3% inhibition in the writhes test at 300 mg/kg p.o., $p<0.2$ (Noristan not published).

5.102 TITHONIA Desf. ex Juss.

5.102.1 Tithonia diversifolia (Hemsl.) A.Gray

(=*Mirasolia diversifolia* Hemsl.)

A decoction of the leaves of *T. diversifolia* is used in Central Africa for pain in the abdomen and for a sore throat. The leaf and inflorescence of *T. diversifolia* A. Gray give positive hemolysis tests, but negative tests for the presence of flavonoids, alkaloids, tannins and sterols. The plant yields hydrocyanic acid (Watt & Breyer-Brandwijk 1962). *T. diversifolia* contain sesquiterpene lactones. The leaves possess a ganglionic stimulant property and induce lowering of blood sugar level in animals. For an estimation of sesquiterpene lactones in the different organs, they were converted to hydroxamic acids on treatment with hydroxylamine hydrochloride and alkali and these gave coloured inner complex ferric salts with ferric chloride. The flowers and leaves contained the highest percentage of lactones (3.2 and 2.4 respectively), followed by the fruits (2.3%), while the percentage of the stem was relatively low (0.059%) (Sayed *et al.* 1980)

The sesquiterpene lactones Tagitinin A and C and the flavone hispidulin, isolated from *Tithonia diversifolia* (Hemsl.) Gray, were potent feeding deterrents when evaluated against 4th instar caterpillars of the Eri-silkworm (*Philosamia ricini* Hutt. Lepidoptera: Saturniidae) (Dutta *et al.* 1986). The inhibitory effects of the sesquiterpenes tagitinin A and C and the flavonoid hispidulin were determined on the germination of radish, cucumber and onion seeds. The flavonoid hispidulin was more toxic to the crop seeds tested and the activity of tagitinin C was weaker than that of tagitinin A and hispidulin (Baruah *et al.* 1994).

5.103 TROGLOPHYTON Hilliard & B.L.Burtt

5.103.1 Troglophyton capillaceum (Thunb.) Hilliard & B.L.Burtt subsp. *capillaceum*

(=*Helichrysum capillaceum* (Thunb.) Less.)

(=*Helichrysum oreophilum* Dinter)

It is a Southern Sotho remedy for chest troubles in children (Watt & Breyer-Brandwijk 1962).

5.104 TRIPTERIS Less.

An infusion of *Tripteris* sp. is taken by the Zulu as an emetic in biliousness (Watt & Breyer-Brandwijk 1962).

5.105 URSINIA Gaertn.

***5.105.1 Ursinia abrotanifolia* (R.Br.) Spreng.**

(=*Sphenogyne abrotanifolia* R.Br.)

A brandy tincture of *Ursinia abrotanifolia* Spreng is used as a medicine. The leaf is a cough remedy. Both the leaf and the stem contain a volatile oil, the leaf yielding 0.58% The oil has a pleasant somewhat camphoraceous odour and a burning bitter taste (Watt & Breyer-Brandwijk 1962).

***5.105.2 Ursinia nana* DC.** subsp. *nana*

(=*U. abyssinica* Sch.Bip. ex Walp.)

(=*U. affinis* Harv.)

(=*U. annua* Less. ex Harv.)

(=*U. engleriana* Muschl.)

(=*U. indecora* DC.)

(=*U. matricariifolia* Dinter)

(=*U. schinzii* Dinter)

The Southern Sotho make an ointment for the use of women and girls from *Ursinia nana* DC. (Watt & Breyer-Brandwijk 1962).

***5.105.3 Ursinia tenuiloba* DC.**

(=*U. montana* DC. subsp. *tenuiloba* (DC.) Prassler)

(=*U. natalensis* (Sch.Bip.) N.E.Br.)

(=*U. tysoniana* E.Phillips)

The Zulu use a hot milk decoction of the root of *Ursinia tenuiloba* DC., drunk slowly while hot, as a cough remedy (Watt & Breyer-Brandwijk 1962).

5.106 VERNONIA Schreb.

From the large genus *Vernonia*, with more than 1000 taxa, a considerable number of species have been investigated chemically. The most widespread compounds are highly oxygenated germacranolides. While previous investigations indicated clear differences between the New World and Old World members, more recent studies show a closer relationship. This is particularly indicated by the occurence of the very typical glaucolides and hirsutinolides in both South American and South African *Vernonia* species (Bohlmann, Gören & Jakupovic 1983).

***5.106.1 Vernonia amygdalina* Delile**

(=*V. randii* S.Moore)

Vernonia amygdalina grows throughout tropical Africa. It is used as a 'leafy vegetable' for preparing bitter-leaf soup (Iwu 1993). The leaf contains 18% crude protein, 5.3% reducing sugars, 5.85% fat

and 8.5% fibre in dry matter, and a good composition of macroelements and microelements (Igile *et al.* 1995). The plant is used by the Pedi as a foodstuff and is well known in West Africa as a foodstuff and as a medicine. Both the root and the twig are used as a chew stick and the leaf, although bitter, is used as a foodstuff. The West African woman eats the leaf in the belief that it renders her sexually more attractive (Watt & Breyer-Brandwijk 1962). The leaves are reputed to be effective remedies for gastrointestinal disorders (Iwu 1993), the juice and the extract serves as a tonic drink (Igile 1994) and in Nigeria as an appetizer, to treat malaria and fevers, as a laxative and it is also used as an antidiabetic (Akah & Ekekwe 1995) and as anthelmints (Igile *et al.* 1995). Pharmacological screening of the leaves proved that they possess a ganglionic stimulant property and induce lowering of the blood sugar level in animals (Sayed *et al.* 1980). The dried leaves are also chewed for the treatment of fevers, and by pregnant woman to check nausea. The fresh leaves are, however, believed to be abortifacient (Iwu 1993). The extract of the leaves has broad spectrum antimicrobial activity and has been shown to produce abortion in goats. The methyl alcohol extract of the leaves when administered to 12-13 days pregnant mice caused abortion within 24 hours of the last dose in a 3-day regimen. *Vernonia amygdalina* is generally nontoxic, but excessive consumption of the leaves is purgative (Iwu 1993). The decoction of the root and stem bark is also used as febrifuge and anti-diarrhoea (Akah & Ekekwe 1995). The bark is administered for venereal diseases and for diarrhea and the peeled stem is used for cleaning teeth (Iwu. 1993). The bitterness of the leaf is often exploited by nursing mothers to assist weaning by rubbing the juice on their breasts (Akah & Ekekwe 1995). The bitterness of the the leaves is usually reduced by boiling, and by soaking in water followed by several washings with fresh water. The soup prepared with the washed leaves is believed to improve lactation (Iwu 1993). It has been used in traditional medicine as an anthelmint, antimalarial and a laxative herb (Igile 1994). It is also used against conditions such as schistosomiases, fever and gastrointestinal upset (Laekeman 1983). A cold infusion of the root bark of *Vernonia amygdalina* Del., made with *Vigna sinensis*, is drunk by the Zezuru in a daily dose of one pint for schistosomiasis. They also eat the fruit for schistosomiasis. In Angola the bark of the root and stem, which is very bitter, is used in a tonic in fevers and as a remedy for intestinal upsets (Watt & Breyer-Brandwijk 1962). It was observed that an apparently sick female wild chimpanzee chewed and suck out the juice from the young piths of the plant. Within 24 hours, her condition greatly improved and she resumed her normal activity. In another field observation, an unusual drop in parasite level was detected by fecal analysis (Ohigashi *et al.* 1993).

Vernonia contains highly oxygenated sesquiterpene lactones, cardiac glycosides, saponins and flavonoids. The major constituents include the saponin vernonin, the sesquiterpenes vernolepin and vernodalin, and the ubiquitous flavonoid, kaempferol (Iwu 1993; Zdero 1991). Kaempferol is known to inhibit platelet aggregation.

Two classes of bitter and related constituents have been isolated: One class, obtained from an ethyl acetate-soluble part of acetone (or methanol) extract included the germacrane and elemane type sesquiterpene lactones, vernodalin, vernodalol, vernolide and hydroxyvernolide. The other class, obtained from an n-butanol-soluble part of the extract was a series of stigmastane-type steroid glucosides, named vernonioside A_1, A_2, A_3 and A_4. Additionally, related nonbitter glucosides,

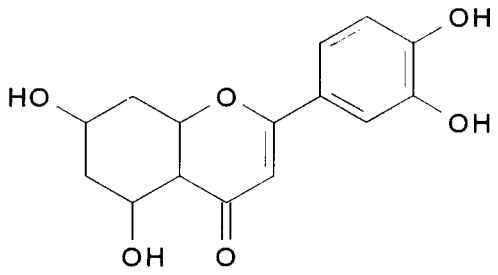
vernonioside B_1, B_2 and B_3, together with vernoniol A_4, the primary aglycone of vernonioside A_4 were isolated (Ohigashi *et al.* 1993).

It was observed that an ill female chimpanzee removed the bark and leaves of the young aerial shoots of *Vernonia amygdalina*, chewed the exposed pith and swallowed only the bitter tasting juice. The sesquiterpene lactones, vernodalin, vernolide and hydroxyvernolide and stigmane type steroid glucosides (vernonioside A_1-A_4: for bitter tasting constituents and veminioside B_1-B_3: for non-bitter relating constituents were isolated. Antiparasitic activity tests of these constituents, together with quantitative analysis of the major active components, vernodalin and veminioside B1, supported the hypothesis that Mahale chimpanzees control parasite related diseases by ingesting the pith of this plant, found to contain several steroid related constituents (Koshimizu *et al.* 1994). Method: Dried whole plant was extracted first with acetone for 7 days and then with methanol for 7 days. Both extracts were separately partitioned between ethyl acetate and water. The ethyl acetate soluble part of the acetone extract (highly bitter), exhibited potent *in vitro* antitumoral activities against P-388 and L-1210, and antibacterial activities against Gram-positive *Bacilus subtilus* and *Micrococcus lutea*. The sesquiterpene lactones vernodalin, vernolide and hydroxyvernolide were isolated as bitter principals from this fraction. The water soluble parts of the of the acetone and methanol extracts were combined. From this the stigmastane type steroid glucosides were isolated. Of these glucosides, vernonioside B_1 was the major constituent (Koshimizu *et al.* 1994).

Different solvent extracts of fresh leaves of *Vernonia amygdalina* (Del.) were tested for their abortifacient properties in 12-13 days pregnant albino mice. The mice treated with methyl alchol extract (75 mg and 150 mg) aborted within 24 hours after the last dose. The chloroform extract was found toxic at relatively low doses and the animals treated with aqueous extracts littered normally (Ojukwu & Onuora 1982). Cytotoxic compounds, vernodalin and vernomygdin have been isolated from the chloroform extract of the leaves and could be responsible for the deaths seen in mice to which the chloroform extract was administered (Kupchan *et al.* 1969).

Flavonoids: Three flavones were isolated from the leaves of *Vernonia amygdalina* and identified as luteolin, luteolin-7-O-βglucuronoside, and luteolin-7-O-β-glucoside. The antioxidant activity of the three flavones was determined by measuring the coupled oxidation of β-carotene and linoleic acid. Luteolin is a significant more potent antioxidant than the synthetic antioxidant butylated hydroxytoluene (BHT) at the same concentration (15 mg/l). The two glycosides showed similar but significantly lower activities than luteolin or BHT. Antioxidant activity of flavonoids is well documented. There is a general agreement that ortho-dihydroxylation of the B ring contributes markedly to the antioxidant activity of flavonoids, and all the components with the 3',4'-dihydroxy configuration studied thus far possessed antioxidant activity (Igile 1994). Method: The air-dried leaves were finely powdered and macerated in aqueous MeOH. The mixture was centrifuged, and the supernatant evaporated until the MeOH was almost removed. This solution was then loaded on a LiChroprep RP18 column, preconditioned with water and washed with water to remove sugars and then succesively with 30%, 40% and 50% MeOH. The 30% MeOH fraction, showing a flavonoid spot

on TLC, was again loaded on the column. The fractions showing the presence of flavonoids were combined, MeOH was removed *in vacuo*, and the flavonoids was extracted into EtOAc. The solvent was evaporated, residue dissolved in MeOH and loaded on a polyamide column preconditioned with water. It was washed with water, then MeOH, followed by EtOH. The EtOH eluate, showing a single spot on TLC, was evaporated, redissolved in MeOH and crystallized. The compounds forming a single spot were separated by reversed phase C18 and polyamide preparative chromatography. Their structures were confirmed by chemical, chromatographic and spectroscopic analysis (Igile 1994).



Luteolin

Luteolin has anti-inflammatory and antibacterial activities. It inhibits iodothyronine deiodinase, proteien kinase C, NADH-oxidase, succinoxidase, lens aldose reductase, etc. (Harborne & Baxter 1993).

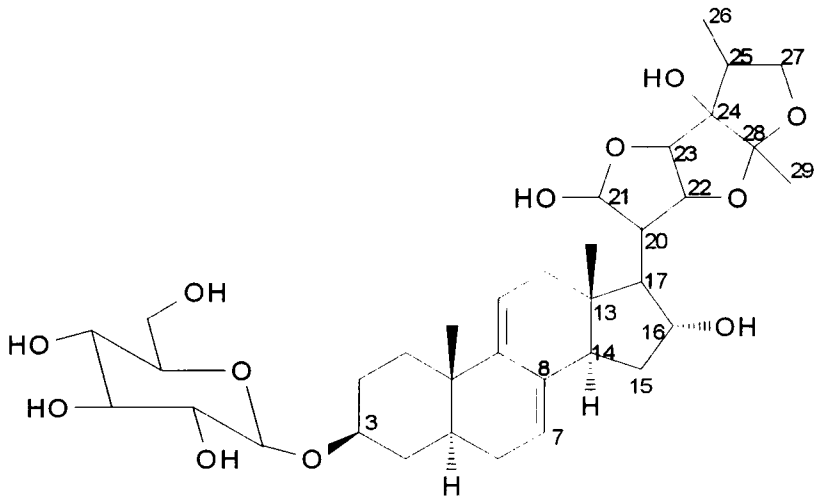
Saponins: The saponin, vernonin, has been shown to exert hypotensive activity and mild cardiotonic effects when injected in dogs. A leaf extract of the plant reduced the rate and force of contraction of the isolated frog heart, and in cats caused a marked fall in blood pressure, as well as a reduction in heart rate; it also caused strong stimulation of the isolated rabbit intestine (Iwu 1993).

The leaves of *V. amygdalina* is used in Nigeria as a green vegetable or as a spice in soup, especially the popular bitter-leaf soup. To prepare such soups, the freshly harvested leaves are macerated with either cold or hot water to reduce the bitterness of the leaves to a desired level. The bitter water extract is taken as a tonic to prevent certain illnesses. Igile *et al.* (1995) studied the nutritional performance of the leaves and its saponin constituents in laboratory mice. The dried powdered leaves was exhaustively extracted with MeOH for 60 hours in a Soxhlet apparatus. The methanolic extract was dried *in vacuo.* Half of this was directly lyophilized. The remaining half was semi-purified by column chromatography. It was loaded onto a C18 column and washed with 30% MeOH. The 30% MeOH eluate contained no saponins, as monitored with thin layer chromatography and was discarded. (TLC was performed on silica gel ready to use plates, developed in ethyl acetate:acetic acid:water (7:2:2) or chloroform:methanol:water (65:30:5), and saponins were made visible by spraying with methanol:sulphuric acid:acetic anhydride (5:1:1. L-B reagent) followed by heating at 105°C.) Saponins retained on the column were washed out with MeOH. Evaporation of the solvent yielded a brownish powder recognized as crude saponins. The crude saponins were further purified on a C18 column washed subsequently with 200ml of methanol:water mixtures (50:50; 60:40, and 70:30 v/v). The 50% MeOH eluted a single compound identified as vernioside D by FAB-MS and

NMR. This saponin was strongly bitter. The 60% and 70% MeOH also eluted mixtures of other compounds also identified to be saponins. The total amount of saponins in the dry matter of *V. amygdalina* was found to be around 2.8% (Igile *et al.* 1995).

Feeding 2-week old growing mice of both sexes with the standard diets amended with 25% dry *V. amygdalina* leaves or equivalent amounts of alcohol extracts or crude or purified saponins for 14 days did not alter their feeding performance. At the lowest concentration (0.33%) of both the crude saponins and vernonioside D, the body weights were stable and the urinary and fecal output showed similar patterns as in the control group. However, liver weights, plasma and liver cholesterol concentrations were significantly reduced, and these effects were more pronounced for the crude saponins than for Vernonioside D. At higher saponin concentrations (0.7%), these treatments caused significant reduction in body weight gains accompanied by increased urinary and fecal output, compared with the control group. At the highest saponin concentration (1.07%), the measured parameters had values similar to those obtained for plant material and crude extract treatments. At necropsy, the liver weights, plasma and liver cholesterol levels were drastically reduced. The stomachs and small intestines were enlarged, compared to the control groups. These symptoms may reflect perturbations in cholesterol and lipid metabolism, as well as in nutrient absorption along the gut. It was concluded that care has to be taken when using the leaves for cooking soups and that saponins should be thoroughly washed out during the debittering process since *V. amygdalina* saponins are sparingly soluble in water. Consumption of tonics containing *V. amygdalina* saponins may create some health hazard. The long term effect of the use of these compounds or extracts need further study to precisely establish a safe level (Igile *et al.* 1995).

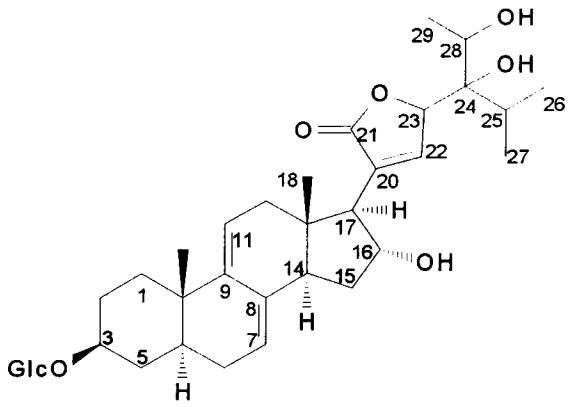
Morgan *et al.* (1972) found that *Gypsophila* saponin precipitated cholesterol from an ethanolic solution only to the extent of about 20%, while digitonin, under the same conditions, gave complete precipitation. When these two saponins were fed to one week old chicks for three weeks (0.25%), both depressed growth and the depression were reversed to a large extent by dietary cholesterol. These two saponins also lowered serum cholesterol in chicks. Although other investigators suggested that saponins might be hypocholesterolaemic, they could not demonstrate this satisfactorily. It had been suggested that the reversal of growth inhibition by cholesterol is due to the formation of a non-absorbable cholesterol saponide in the intestinal tract. If this were so, then it could also account for the hypocholesterolaemic effects of dietary saponin. However no interference of absorption of [^{14}C] cholesterol from the digestive tract were found and no cholesterol digitonide could be isolated from the intestines of the chick. The hypocholesterolaemic effect of saponins could perhaps be due to their causing an increasing excretion of sterol or bile acids (Morgan *et al.* 1972).



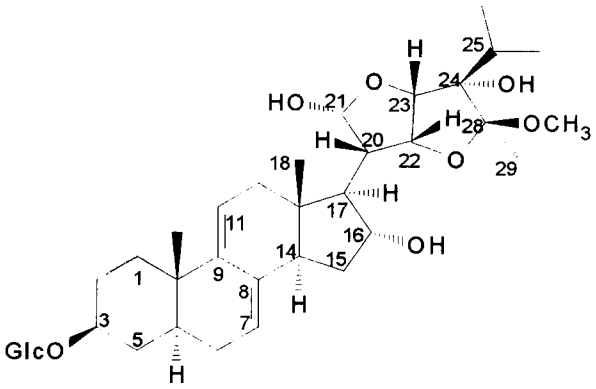
Vernonioside D

Steroid glycosides

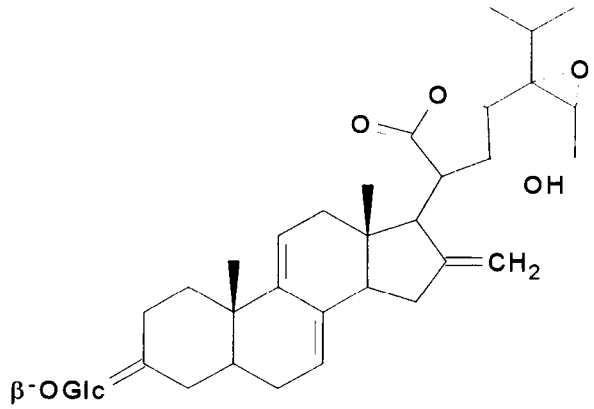
The stigmanetype steroid glucosides vernonioside, A_1, A_2, A_3 and A_4 and related nonbitter glucosides, vernonioside B_1, B_2 and B_3, together with vernoniol A_4, the primary aglycone of vernonioside A_4 have been isolated from the n-butanol-soluble part of the acetone extract (Ohigashi *et al.* 1993). Antischistosomal activity was found for the major steroid glucoside, vernonioside B1. At 200μg/ml, vernonioside B1 was the only steroid glucoside that showed significant inhibitory activity against the movements and egg-laying of the adult. The schistosome movement inhibition was, however, not observed at 20μg/ml, while the inhibitory effect on egg-laying still remains active at 2μg/ml. Vernonioside A_4 seems to be slightly active against egg-laying of the schistosome. A trend in the glucosides to show significant antischistosomal, plasmocidal and amebicidal activities when the sugar moiety was removed, was observed. Antischistosomal activity of vernonioside B_1 was enhanced when the glucose moiety was removed as observed in its primary aglycone B_1 which showed inhibitory effects on schistosome movement and egg-laying at 2μg/ml. Such activity was also detected in the conversion of vernonioside B_4 into primary aglycone vernoniol A_4, whose natural occurrence has been confirmed. Plasmocidal activities of vernoniosides are far weaker than those of the sesquiterpene lactones of *V. amygdalina*. However, the general trend for enhancement of activity upon elimination of the sugar moiety from the respective glucoside was again detected in both plasmocidal and amebicidal activities (Ogihashi *et al.* 1993).



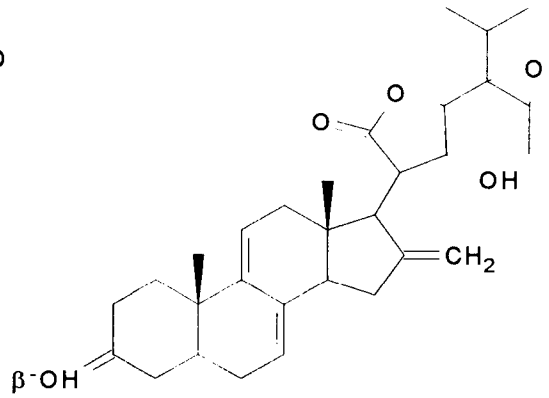
Vernonioside A_4



Vernonioside B_2 (Jisaka *et al.* 1993)



Vernonioside B_1



Vernoniol B_1

(Ohigashi *et al.* 1993)

Sesquiterpene lactones

Several sesquiterpene lactones have been isolated from *Vernonia amygdalina*. Sayed *et al.* (1980), utilizing hydroxylamine-ferric chloride reagent for estimation of sesquiterpene lactones in different organs of *V. amygdalina* (cultivated in Egypt), revealed that the highest content was observed in fruits and flowers (3.5 and 3.3% respectively) followed by the leaves (1.45%), while the percentage in the stem is relatively low (0.8%) (Sayed *et al.* 1980). All the sesquiterpenoids completely inhibited the movement and egg-laying of schistosomes at a concentration of 200µg/ml. At 20µg/ml, vernodalin and vernolide inhibited both functions. All sesquiterpene lactones, however, showed no remarkable antischistosomal activities at 2µg/ml, at which the known schistosomacides, praziquantel and niridazol, showed significant activities. Vernodalin was indicated to be the most active constituent in the sesquiterpene lactone class of compounds. The sesquiterpene lactones showed significant plasmocidal activities, although the IC_{50} values were more than 20 times higher than that of the common antimalarial agent chloroquine (Ohigashi *et al.* 1993). The IC_{50} values of vernodalin, vernolide, hydroxyvernolide and vernodalol against *Plasmodium falciparum* (K1) *in vitro* were 4.0, 8.4, 11.4 and 4.2µg/ml. Vernodalin and vernolide were active against *Leishmania infantum* amastigotes with minimum inhibitory concentrations of 0.5 and <10µg/ml respectively (Phillipson *et*

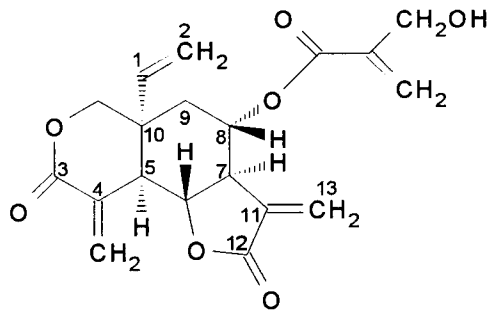
al. 1995). Vernodalin was then tested *in vivo* for antischistosomal activity, but it was lethal to cercaria-infected mouse when orally administered at 5 mg/mouse and injected abdominally at 2 mg, or subcutaneously or intramuscularly at 5 mg per mouse. Upon oral administration of 2.5 mg of vernodalin to cercaria-infected mice with an average body weight of 40g, no effects were observed on the number of recovered schistosomes and egg-laying capability of the schistosomes (Ohigashi *et al.* 1993).

Vernodalin and vernomygdin have been shown to have significant inhibitory activity *in vitro* against the cells derived from human carcinoma of the nasopharynx carried in tissue culture. Similar compounds, vernolepin and vernemenin, which have been isolated from *V. hymenolepis* A. Rich; also show tumor inhibitory activity in the same tissue culture model. The sesquiterpene lactones have *in vitro* cytotoxic activity against KB tumor cells and Wilme's myeloma (Iwu 1993).

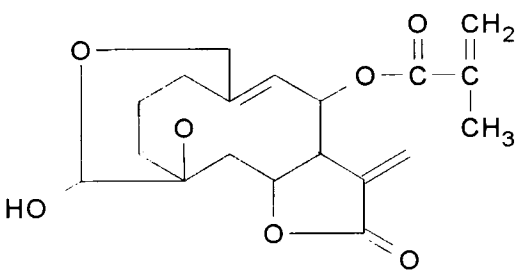
The lactones occur widely in the genus *Vernonia* and are reported to possess a variety of biological activities including cytotoxicity, insect antifeedant and anthelmintic activities. It was found that vernodalin and vernolide were the constituents of the ethyl acetate soluble part of the acetone extract mainly responsible for the antitumor and antibacterial activities. A complete saturation (octahydrovernodalin) of the C-C double bonds resulted in a loss of activity. This may demonstrate that the α, β-unsaturated γ-lactone and δ-lactone are important for the activies against P-338 and L-1210 cells and for the cytotoxic activities against KB cells (Koshimizu *et al.* 1994).

All the sesquiterpene lactones completely inhibited both movement and egg-laying of schistosomes at a concentration of 200μg/ml. At 20μg/ml vernodalin and vernolide inhibited both functions. All lactones however showed no remarkable activities at 2μg/ml, at which the known schistosomacides, praziquantel and niridazol showed significant activities. Of the steroid glucosides, only vernonioside B_1 showed inhibitory activiy at 200μg/ml. Antischistosomal activity of vernonioside B_1 was enhanced when the glucose moiety was removed (Koshimizu *et al.* 1994).

Vernodalin showed extremely high leishmanicidal activity. Its MIC was 10 times lower than that of pentamidine, a common antileishmanial agent. Based on this, the *in vivo* antischistosomal activity of vernodalin was tested. It was however lethal to the cercaria-infected mouse. Upon oral administration at a nonlethal dose (2.5 mg), no effects were observed on the schistosomes (Koshimizu *et al.* 1994).



Vernodalin



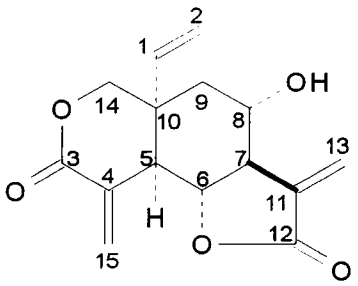
Vernolide

Vernodalin and vernomygdin were isolated from a chloroform extract of *Vernonia amygdalina* Del. which showed significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) carried in tissue culture. The dried ground leaves were extracted continuously with chloroform partition of the extract between 10% aqueous methanol and petroleum ether resulted in the concentration of activity in the aqueous methanol fraction. This was fractioned to give two main cytotoxic fractions. On further chromatography, one fraction yielded vernodalin and the other fraction yielded two compounds with very similar R_f values, vernolide and vernomygdin. Acidic hydrolysis of vernodalin in methanol gave a methanol adduct identical to the methanol adduct of vernolepin (Kupchan *et al.* 1969b).

Vernolepin, a sesquiterpene lactone was isolated from the dried fruit of *V. amygdalina* Del. The different steps used during the extraction were continuous extraction with chloroform, partition of the chloroform extract between petroleum ether and 10% aqueous methanol, column chromatography of the methanol extract, isolation of the active fractions by pharmacological and chemical characterization. Vernolepin was obtained as colourless prisms and identified by melting point, UV, IR, ^1H NMR, optical rotation and mass spectrometry. The total content of the dried fruit was 0.09% vernolepin. The first pharmacological characterization revealed: (1) a competitive antagonism against histamine in guinea pig ileum (pA_2=5.61; 15 min. incubation): (2) a biphasic enhancement/inhibition of coaxial stimulation of guinea pig ileum; (3) an antiaggregating and disaggregating activity against rabbit platelet aggregation induced by arachidonic acid ($1x10^{-4}$g/ml; $3.3x10^{-4}$M) or ADP ($4x10^{-6}$g/ml; $1x10^{-5}$M) without inhibition of cyclo-oxygenase or lipoxygenase. All these reactions were time dependent and occurred at concentrations of $5x10^{-6}$ to $1x10^{-5}$g/ml vernolepin (1.8 to $3.5x10^{-5}$M) The inhibitory effects on neurotransmission are probably due to postsynaptic mechanisms since contractions produced by exogenous acetylcholine were also blocked. The mechanisms of the antiaggregating and disaggregating activity need to be elucidated. The incubations with washed platelets revealed no deactivation of cyclo-oxygenase, different prostoglandin isomers and lipoxygenase by 30 min incubations with vernolepin $1x10^{-5}$g/ml. The cytotoxic activity of vernolepin overshadows the result and one must always be aware of the "alkylating functions" of vernolepin (Laekeman *et al.* 1983).

Vernolepin was first isolated from the chloroform extract of dried leaves of *V. hymenolepis.* (Kupchan *et al.* 1969a). Vernolepin showed significant *in vitro* cytotoxicity (KB) and *in vivo* tumor inhibitory activity against Walker intramuscular carcinosarcoma in rats at 12 mg/kg (Kupchan *et al.* 1968; Kupchan *et al.* 1969a). Vernolepin readily undergoes reaction with methanol in the presence of a trace of acid to afford a methanol adduct, $C_{16}H_{20}O_6$. This conversion during chromatography can be avoided by the use of chloroform-acetone mixtures. Vernolepin has the unusual property of significant solubility both in water and in many organic solvents. Kupchan *et al.* (1969a) report that germacranolide precursors could be transformed to elemanolides by heating, but that vernolepin is indeed a naturally occuring compound. All the unsaturated lactones which show significant *in vivo*

tumor-inhibitory activity possess at least two "alkylating" functions, i.e., structural moieties readily sensitive to attack by nucleophiles (Kupchan *et al.* 1969a).



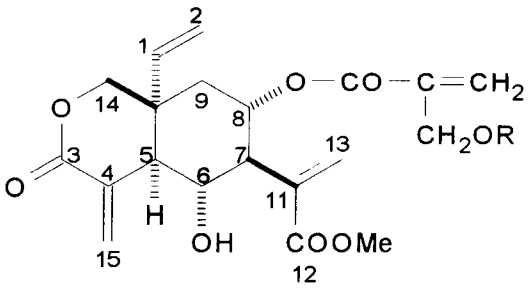
Vernolepin (Kupchan *et al.* 1969)

The water extract of the leaves of *Vernonia amygdalina* cause a decrease in the number of dividing cells of the onion roots (*Allium cepa*). The fresh mature leaves (200g) of *V. amygdalina* were made up to 1l with distilled water and ground in an electric grinder. After two filtrations, through a cheese cloth and glass wool, the liquid was centrifuged for 20min at 3000 r.p.m. The supernatant was taken as a 20% stock and diluted to the required concentrations with distilled water. Germinating onion bulbs with root measuring 2-4 cm were placed in the extracts of 1% 4%, 9%, 13% and 20% under three durations of treatment, 4, 8 and 24 hours. The root tips were fixed, hydrolized and stained in the slide preparation. The number of cells going through the mitotic cycle steadily decreased with the increase in concentration of the extract until nuclear disintegration and cell death occurred at 9% concentration. The toxic effects are probably due to the presence of the sesquiterpene lactones, vernodalin and vernomygdin. Another effect was changes to the chromosome structure leading to stickiness. Under low concentrations or under short periods of treatment, DNA depolymerisation may be somewhat localized producing sticky effects on chromosomes during cell division (Ene-Obong & Amadi 1987).

Chemical investigation of insect antifeedants from bitter tasting leaves of *Vernonia amygdalina* by application of semi-preparative reversed phase HPLC has led to the isolation and characterisation of vernodalin, vernodalol and the elemanolide sesquiterpene lactone, 11,13-dihydrovernodalin. This new compound exhibited *in vitro* cytotoxicity and antifeedant activity agaist the African armyworm *Spodoptera exempta*. The structure was determined by spectroscopic data (Ganjian, Kubo & Fludzinski 1983).

5.106.2 Vernonia anthelmintica (L.) Willd.

Repeated chromatography of the ether extracts of the dried seeds of *V. anthelmintica* on silica gel gave vernodalol, a new elemanolide (Asaka *et al.* 1977).



Vernodalol (Asaka *et al.* 1977)

The volatile oil of *Vernonia anthelmintica* Willd was analized by GS/MS/DS and 24 principal components constituting 91.4% of the oil, were identified. They are caryophyllene (43.08%), β-pinene (21.66%), ethyl buthyl ether (6.4%), silinene (3.51%), bornylene (2.87%), 4-carene (2.67%), isocaryophyllene (1.52%), α-terpineol (1.45%), 2-ethoxy-butane (1.44%), ethyl acetate (1.3%), phenylacetaldehyde (1.07%), as well as 2-methyl propanoic acid, 1.2-dimethyl imidazole, ethyl benzene, camphene, benzaldehyde, 2-carene, sabinene, isolimonene, β-terpineol, terpineol-4, carvone, anise camphor and 4-methyl-phenyl phenyl ether (Fu *et al.* 1986).

5.106.3 Vernonia cinerea Less

V. cinerea (L.) Less. var. *cinerea*

(=*Conyza cinerea* L.)

Vernonia cinerea is an annual herb that is used as a tonic, stomachic, an astringent and is also a known cure for tridosa, consumption, asthma and bronchitis (Misra *et al.* 1984). The flowers are administered for conjuctivitis while the plant juice is given for piles (Gunasingh & Nagarajan 1981). The leaf, flower and twig of *V. cinerea* Less. is a Swahili stomachic. The plant is one of the Pedi food plants. In Senegal and French Guinea an infusion of the plant is used to wash a newborn infant and is given to children with incontinence of urine. The plant has been used in baths and as a fomentation. The root, which is bitter, is a vermifuge and the leaf is used in soup. In East Africa it is used for roundworm. In the Philippines the plant is used in the treatment of cough, as a remedy for skin diseases, and as a dressing on wounds. Among the Hindu it is used as an antifebrile to promote perspiration and the expressed juice as a remedy for haemmorrhoids. In Patna the seed is used as an anthelmintic and as an alexipharmic. In India the flower is administered for conjunctivitis (Watt & Breyer-Brandwijk 1962). The bark and leaves of *V. cinerea* are used as stomachic and for roundworms (TRAMED database, index card 1547).

The leaf has given weakly positive antibiotic tests and the whole plant negative tests for antimalarial action (Watt & Breyer-Brandwijk 1962).

An aqueous ethanolic (50%) extract of the plant showed activity against Rhanikhet-virus disease. It also showed anticancer activity against Sarcoma 180 in mice. The root is bitter and is used as an anthelmintic and diuretic. Fresh juice of the leaves is given to treat dysentery and is locally applied for the extraction of guineaworms. The seeds are also used as anthelmintic and alexipharmic, and they are quite effective against roundworms and threadworms. They are also given for coughs, flatulence, intestinal colic and chronic skin diseases. A paste of the seeds with lime juice is used to

destroy pediculi. The flowers are used to treat conjuctivitis, fever and rheumatism. β-Amyrin, lupeol and their acetates, β-spinasterol, phenolic resin and KCl have been isolated from the whole plant. The roots of *V. cinerea* have yielded six triterpenes, δ-amyrin acetate, α-amyrin acetate, 3β -acetoxyurs-13(18)-ene, β-amyrin acetate, β-amyrin and α-amyrin. Identification of all six compounds have been established with the help of mp, optical rotation, IR, ^{1}H-NMR, ms and chemical reactions. 3 -Acetoxyurs-13(18)-ene gave a deep red colour with Liebermann-Burchard reagent, and a yellow, (turning to violet) colour with Noller's reagent, suggesting that it is a triterpenoid (Misra *et al.* 1984).

The whole plant of *V. cineria* Less. was collected in India, dried, ground and extracted in 50% ethanol. The ethanol extract was screened for antibacterial, antifungal, antiprotozoal, antianthelmintic, antiviral, hypoglyceamic and anticancer activity and for effects on respiration, isolated tissues (contraction of guinea pig ileum and rat uterus) and the central nervous system. It was found to be antiviral against Ranikhet disease virus *in vitro* with 0.5 mg/ml of the extract and 0.192 HA unit/ml of the virus but not against *Vaccinia* virus. It also affected contraction of the isolated guinea pig ileum but it had no effect on the rat uterus. In the anticancer screen it was active in the sarcoma 180 in the mouse but not in the following other anticancer tests done; the human epidermoid carcinoma of the naso-pharynx in tissue culture, the L-1210 lymphoid leukemia in the mouse and the Lewis lung carcinoma in the mouse. The maximum tolerated dose were 500 mg/kg body weight given intraperitoneally (Dhar *et al.* 1968).

The whole plant is reported to contain triterpenoids, sterols and potassium chloride. Luteolin, luteolin-7-glucoside, quercetin-3-methyl ether, isoorientin and chrysoeriol have been isolated from the fresh flowers of *Vernonia cinerea* (L.) Less. (Gunasingh & Nagarajan 1981). From the roots of *Vernonia cinerea* a natural sterol (stigmast-5,17(20)-dien-3β-ol) and an aliphatic acid (26-methylheptasanoic acid) have been isolated together with stigmasterol and sisterol. The plants were collected in India and the roots air-dried and ground to a coarse powder (Misra *et al.* 1984).

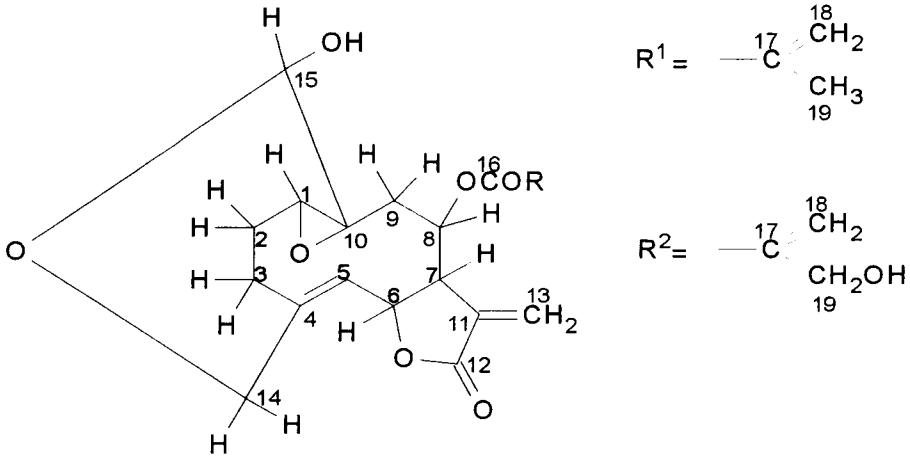
5.106.4 Vernonia colorata (Willd.)Drake subsp. colorata

(=*V. senegalensis* (Pers.) Less.)

In Angola *Vernonia colorata* Drake is taken as a tonic and stimulant. The bark is very bitter. In West Africa, the root, which is thought to contain an alkaloid, is used as a tonic, as an emetic, an antifebrile and as a cough remedy (Watt & Breyer-Brandwijk 1962). In Cental Africa, the root is used to prepare an ointment for parasites of the skin. The root causes poisoning (TRAMED database, index card 9374).

Two lactones were isolated form *Vernonia colorata* leaves and identified as vernolid and hydroxyvernolid by IR, NMR (at 250 MHz), spectroscopy and mass spectroscopy. These lactones have anthelmintic and amoebicidal properties. Vernolid is 5 tot 10 times more active than hydroxyvernolid, *in vitro*, and has a level of action comparable to the product used as reference,

metronidazole. In contrast, only hydroxyvernolide revealed a significant *in vivo* amoebicidal action (Gasquet *et al.* 1985).



R^1 - vernolid R^2 - Hydroxyvernolid (Gasquet *et al.* 1985)

From the aerial parts of the Madagascar *V. colorata* subsp. *grandis* (DC.)C. Jeffrey, the known sesquiterpene lacones, vernodalin, 19-hydroxyvernodalin and the corresponding isobutyrate were isolated. Furthermore, germacrene D, caryophyllene, lupeylacetate and 19-hydroxyglaucolide A were present. This was the first case of co-occurence of a glaucolide with vernodalin and its derivatives. African species of *Vernonia* contain elemanolides like vernolepin and germacranolides like vernodalin, glaucolides are mostly isolated from New World species (Zdero 1991). The LD_{50} of *Vernonia colorata* in mice is about 10g/kg (Iwu 1993).

The anti-inflammatory activity of an ethanol extract of stem/bark and of the leaf of *Vernonia colorata* (Willd.) Drake. (which was treated to remove pigments with petroleum ether) was evaluated in rats using the carrageenin-induced pedal edema assay. A dose of 100 mg/kg x2 resulted in a 19% and 11% inhibition respectively (Benoit *et al.* 1976).

5.106.5 Vernonia fastigiata Oliv. & Hiern

(=*V. schinzii* O.Hoffm.)

The Pedi use the tender leaf of *V. fastigiata* Oliv. & Hiern. as a pot herb. The vitamin C content of the leaf is 6 mg/100g calculated on dry basis (Watt & Breyer-Brandwijk 1962).

5.106.6 Vernonia hirsuta (DC.) Sch.Bip. ex Walp.

(=*V. hirsuta* (DC.) Sch.Bip. ex Walp. var. *obtusifolia* Harv.)

The Southern Sotho use *V. hirsuta* Sch. Bip. as an ingredient of a colic remedy and a root decoction for many diseases. In the Western Transvaal the Blacks (probably Tswana) use the plant as a stomachic bitter. The plant is also a South African antifebrile (Watt & Breyer-Brandwijk 1962). It is used in southern Africa for the relief of colic (TRAMED database, index card 1547).

5.106.7 Vernonia mespilifolia Less.

The root is eaten by the Xhosa for rash or itch on the body. A decoction of the leaves and bark is drunk for infection of the respiratory system (TRAMED database, index card 684).

5.106.8 Vernonia myriantha Hook.f.

(=*V. ampla* O.Hoffm.)

(=*V. podocoma* Sch.Bip. ex Vatke)

(=*V. stipulacea* Klatt)

The VhaVenda drink an infusion of soaked or boiled root *V. stipulacea* Klatt. as a contraceptive two or three times a day. It is normally kept in a bottle or clay pot for daily use. Termination of use is said to result in the immediate end of contraception (Mabogo 1990).

The aerial parts of *V. myriantha* yielded dehyrocostus lactone, 3-O-methylquercetin and various triterpenes. Two collections of *V. stipulacea* Klatt which is a synonym for *V. myriantha*, have yielded a variety of sesquiterpenes and in one instance, the sesquiterpene lactone, parthenolide (Abegaz, *et al.* 1994). The roots of *V. stipulacea* afforded tridecapentaynene, linolenic acid, α-humulene, lupeol, stigmasterol, caryophyllene, a dimeric isovalerate, ferulic acid, two isomeric sesquiterpene aldehydes vernostipulal A and vernostipulal B, several hydrocarbons and a triacetylene, while the aerial parts yielded lupeyl acetate and its Δ^{12}-isomer, linolenic acid and the same triacetylene as the roots. The air-dried plant material, collected in February in the Transvaal was extracted with Et_2O:petrol (1:2) and the resulting extracts were separated first by CC (Si gel) and further by repeated TLC (Si gel). Known compounds were identified by comparing the ^1H NMR spectra with those of authentic material (Bohlmann & Zdero 1982c).

5.106.9 Vernonia natalensis Sch. Bip. ex Walp.

(=*V. pseudonatalensis* Wild)

The Swazi use the powdered bark of *Vernonia natalensis* Sch. Bip. as a remedy for malaria and other febrile conditions. It produces emesis. They also take the powder for cough and inject it in the form of an enema to relief pains in the loins and inhale the smoke from burning it for headache. Among the Whites of the Lydenburg district, an infusion is used as a lotion for bathing haemorrhoids (Watt & Breyer-Brandwijk 1962). In southern Africa the bark is used for fever or malaria (TRAMED database, index card 1547).

An extract of this plant made by Noristan was chromatographed and fractionated. Similar fractions were combined to form 10 fractions which were recombined to form 3 groups. Group 1 affected a 66% inhibition in the writhing test, $p<0.001$ @ 500 mg/kg p.o. Group 2 was inactive. Group 3 was 38% effective in the writhing test, $p<0.01$, @ 500 mg/kg p.o. It also had an analgesic effect (2/4) at a dose of 300 mg/kg i.p. On secondary pharmacological evaluation, one fraction gave 91.9% inhibition in the writhing test at 200 mg/kg p.o. (Noristan not published).

The aerial parts of *Vernonia natalensis* gave germacrene D, bicyclogermacrene, lupeol, lupeyl acetate together with the Δ12-isomers, β-amyrin acetate, lupenone, stigmasterol, spathulenol and four glaucolides which includes 1,10-desoxidoglaucolide E and natalensolide. The air-dried plant material, collected in February in the Transvaal was extracted with Et_2O-petrol (1:2) and the resulting extracts were separated first by CC (Si gel) and furhter by repeated TLC (Si gel). Known compounds were

identified by comparing the ^{1}H NMR spectra with those of authentic material (Bohlmann & Zdero 1982c).

5.106.10 Vernonia oligocephala (DC.) Sch.Bip. ex Walp.

(=*V. kraussii* Sch.Bip. ex Walp.)

In the Transvaal the African (probably the Tswana) administer a decoction of *V. oligocephalus* Sch. Bip. ex Walp. for the relief of abdominal pain during the course of pregnancy and as a stomachic bitter. The Pedi use the plant as a dysentery remedy, while the African in the Filabusi district of Zambia take a decoction for rheumatism. In the Bethlehem district of the Free State Province a decoction of the plant is used as a diabetes remedy and its use apparently reduces the sugar level in the urine. The Southern Sotho, Tswana and Kgatla use an infusion of the leaf as a purgative. The root has been used, with great improvement, in serious chronic illness including ulcerative colitis. The plant has also been used as a colic remedy. As much as 1.4kg of the fresh plant over thirteen days has resulted in no ill effect in sheep (Watt & Breyer-Brandwijk 1962). It is used in southern Africa for the relief of colic (TRAMED database, index card 1547).

Extraction of the plant and separation was done in the same manner as *Vernonia natalensis*. Similar fractions were combined to form 10 fractions. Fractions 1-5 were combined to form group 1 and fractions 6-19 were combined to form group 2. Group 1 was found to be hypoglycaemic and caused a 13,33% reduction in the blood glucose concentration at 300 mg/kg. Group 2 was active in the writhing test with 45% inhibition, $p<0.1$ @ 500 mg/kg p.o. and diuretic with 33% increase in Na^+ excretion, $p<0.2$ @ 500 mg/kg p.o. No hypoglycaemic activity was observed with group 2 (Noristan not published).

The aerial parts of *Vernonia oligocephala* afforded in addition to widespread compounds, minute amounts of three sesquiterpene lactones, 8 -(2-hydroxymethyl acryloyloxy)-hirsutinolide-13-O-acetate and the glaucolides 17,18-epoxyvernonataloide and stilpnotomentolide-8-O-[4-hydroxymethacrylate]. The plant material was collected in the Transvaal and air-dried and worked up in the usual fashion (Bohlmann, Scheidges, Misra & Jakupovic 1984).

5.106.11 Vernonia shirensis Oliv. & Hiern.

An infusion of *Vernonia shirensis* Oliv. & Hiern. is a Zulu influenza remedy. Another mode of treatment is to rub the flower into scarifications in various positions on the body. The Zulu also use the plant for the relief of stomachache, an infusion of the leaf for chronic cough, and a decoction of the root for pain in the chest. They inject the infusion as an enema in feverish conditions, and use preparations of the plant as an parasiticide in the hair. The Jindwe rub the powder of the burnt wood into incisions in the skin to relieve rheumatism (Watt & Breyer-Brandwijk 1962).

5.106.12 Vernonia tigna Klatt

(=*V. corymbosa* (L.f.) Less.)

(=*V. neocorymbosa* Hilliard)

An infusion of the pounded leaf of the root as well as softer parts of the stem is used by the VhaVenda as a remedy against intestinal worms in domestic animals. An infusion is also taken to

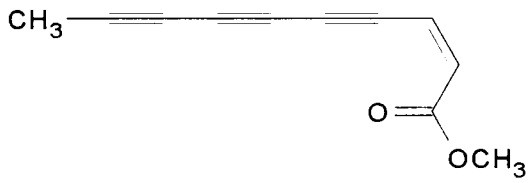
facilitate abortion, but it may have fatal side effects if not properly used (Mabogo 1990). The macerated leaf of *V. corymbosa* Less. is a Swazi remedy for epilepsy (Watt 1967). A Zulu woman takes a decoction of the bulb of *V. corymbosa* Less. and the root of *Pteridium aquilinum*, for menstrual irregularity and as abortifacient. *V. corymbosa* is used alone to facilitate delivery or to determine its onset. Among the Lobedu a decoction of the root, mixed with maize meal to make a thin porrage, is taken for dysentery and for dinohana, a "white worm" in the intestinal tract. The Lobedu administer a sweetened decoction of the root to the donkey as an anthelminthic (Watt & Breyer-Brandwijk 1962).

The aerial parts of *V. neocorymbosa* Hilliard afforded squalene, vernolide and vernodalin while the roots contained the 13-hydroxybisabol-2-en-1-one and 13-hydroxybisabol-2,10-dien-1-one and its acetate as well as small amounts of onopordopicrin (Bohlmann, Gören & Jakupovic 1983).

5.107 XANTHIUM L.

5.107.1 Xanthium canadense

Two polyacetylenes have been reported to be ovicidal to both the fruit fly, *Drosophila melanogaster* and the house fly, *Musca domestica*. The two compounds are cis-dehydromatricaria ester and tri-dec-1-ene 3,5,7,9,11, pentayne from *Xanthium canadense* and some compounds demonstrated phototoxicity against the larvae of the mosquito *Aedes aegypti* (McLachlan, Arnason, Philogene & Champagne 1982)



Dehydromatricaria ester
(Harborne & Baxter 1993)

5.107.2 Xanthium spinosum L.

Xanthium spinosum is toxic to domestic stock, especially the immature plant when the cotyledons have emerged before the first leaves are formed. When they eat the bur, it may cause mechanical injury and form a ball which causes intestinal obstruction. Symptoms of poisoning are depression, nausea accompanied by vomiting, weakness, unsteady gait, laboured breathing and low temperature. Post-mortem examination reveals signs of gastro-enteritis, an unusual amount of serum in the abdomina cavity and frequently a jelly-like accumulation around the gall-blader and bile ducts. For sheep and pigs, the lethal dose is 1.5% of the animals weight, and for cattle it is 3% of the weight. The toxic principal is said to be the glucoside xanthostrumin but there is evidence that this is pharmacologically inert. Other evidence implicates choline as the toxic principal in *Xanthium spinosum* (Watt & Breyer-Brandwijk 1962). It has been long recognized as a folk remedy in the treatment of diabetes, intermittent fever, rabies and as stimulant to the secretion of saliva and urine (Metwally *et al.* 1974).

Two crystalline xanthanolides (xanthitin and xanthatin) were isolated from a light petroleum extract of the plant and β-sisterol was isolated from the unsaponifiable fraction of the same extract. A crystalline diterpene alcohol $C_{30}H_{50}O_5$ was isolated from the ether extract (Metwally *et al.* 1974). In a phytobiochemical study of the chemical composition of *Xanthium spinosum* L., the presence of phenyl-propanoic derivatives of the caffeic and chlorogenic acids type, as well as of flavones, phytosterols, nonhemolytic triterpene saponins, tannins and volatile oils were revealed (Petcu *et al.* 1981).

5.107.3 Xanthium strumarium L.

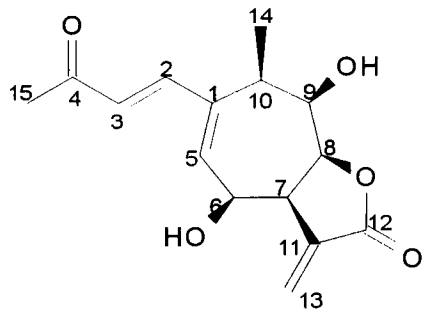
(=*X. natalense* Widder)

(=*X. pungens* Wallr.)

The plant has been used in Ayurvedic and Tibbi systems of medicine as a diaphoretic and sedative. In certain parts of Assam the indigenous people eat the young flowering top and two leaves immediately below as a pot-herb. In South Europe the leaf, fruit and root have been used as remedies for cattarrh, scrofula, leprosy, tubercular and other skin conditions, cancer, dysenteries and bladder ailments and as diaphoretic (Watt & Breyer-Brandwijk 1962). *Xanthium strumarium* Linn. is reputed in the treatment of leucodermia, fever, scrofula, herpes and cancer (Saxena & Mondal 1994).

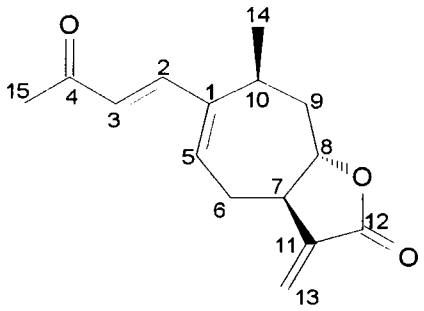
An infusion of the leaf, stalk and seed increases peristalsis in isolated rabbit intestine. In suitable concentrations, the infusion inhibits the frog heart, even producing block, and produces dilation of the blood vessels of the rabbit ear and first dilation and then constriction of the blood vessels of the frog. A tincture of the same parts of the plant, injected intravenously in the cat, produces a transient reduction in blood pressure and depression of the spinal reflexes. A tincture of the seed, injected into the frog, first stimulates and then depresses the respiratory movements. The plant is said to be an active styptic. The plant is reputed to be poisonous to cattle and to swine in the USA and in Australia (Watt & Breyer-Brandwijk 1962).

The anticancerous activity of *X. strumarium* could be linked to the xanthanolides that is structurally related to other antitumor and cytotoxic sesquiterpene lactones (Saxena & Mondal 1994). The xanthanolides xanthinin, xanthumin, xanthinosin, xanthatin, xanthanol and xanthumanol have been isolated from *X. strumarium* L. (Swain & Williams 1977). Saxena & Mondal (1994) isolated one more xanthanolide, 6β,9β-dihydroxy-8-epi-xanthatin, from *X. strumarium*.

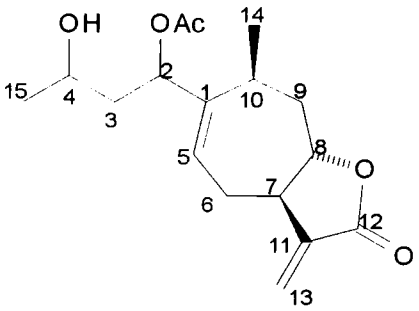


6β,9β-dihydroxy-8-epi-xanthatin (Saxena & Mondal 1994)

Sesquiterpene lactones with guaiane or secoguaiane frameworks are the main secondary metabolites of *Xanthium* species but other skeletal types have also been occasionally found. From the aerial parts of *X. strumarium* and *X. spinosum*, 4,5-secoguaiane derivatives have been isolated. The aerial parts of *X. spinosum* yielded the new compounds anhydrodehydroivalbin and cyclospinosolide and the widespread metabolites, loliolide, sesamin, and coniferyl alcohol and the xanthanolides, xanthatin, xanthanol and isoxanthanol. The arial parts of *Xanthium strumarium* subsp. *italicum* yielded the new xanthanolide, 4,*O*-dihydroinusoniolide and the xanthanolide, xanthinosin (Marco *et al.* 1993).

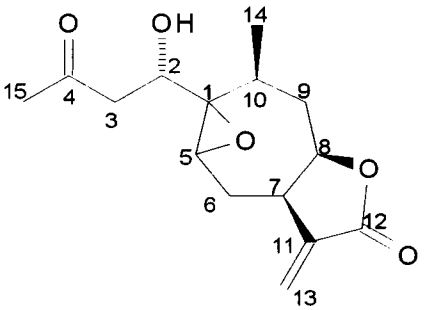


Xanthatin (Marco *et al.* 1993)



Xanthanol (Malik *et al.* 1993)

An Et_2O petrol extract of the aerial parts of *Xanthium strumarium* afforded one new sesquiterpene lactone, 2-hydroxytomentosin-1β,5β-epoxide, in addition to the known tomentosin, 8-epi-xanthatin and 2-hydroxytomentosin (Malik *et al.* 1993).



2-hydroxytomentosin (Malik *et al.* 1993).

Carboxyatractyloside was isolated from cocklebur, *Xanthium strumarium* L. and was shown to be a potent hypoglycemic agent. Later it was also demonstrated that it was the toxic agent responsible for cocklebur poisoning in pigs in South Georgia (Cutler 1983). Potassium carboxyatractylate (LD_{50} = 10.7 mg/kg, ip in mice) strongly inhibits translocation of adenine nucleotides across the mitochondrial membrane (Craig *et al.* 1976). Cutler (1983) demonstrated that potassium carboxyatractyloside exhibited plant growth regulating properties in bioassays. It significantly inhibited growth in wheat coleoptiles at 10^{-3}, 10^{-4} and 10^{-5}M ($p<0.01$). One week after treatment, 15-day-old corn seedlings were stunted and necrotic at 10^{-2}M, and there was chlorosis within the leaf whorls at 10^{-3} and 10^{-4}M. Six-week-old tobacco plants exhibited slight malformations of the leaves

one week after treatment at 10^{-2} and 10^{-3}M. One-week-old bean plants were unaffected by carboxyatractyloside (Cutler 1983).

The whole plant of *Xanthium strumarium* Linn. was collected in India, dried, ground and extracted in 50% ethanol. The ethanol extract was screened for antibacterial, antifungal, antiprotozoal, antianthelmintic, antiviral, hypoglyceamic and anticancer activity and for effects on respiration, isolated tissues and the central nervous system. It displayed only hypoglyceamic activity with a single dose of 250 mg/kg administered orally to rats. The maximum tolerated dose was 100 mg/kg administered intraperitoneally (Dhar *et al.* 1968).

In an antifeedant experiment, the leaves of *Xanthium strumarium* were totally rejected as food by *Earias vitella* larvae, even in the absence of natural food and that the solvent ether extract of the leaves showed strong antifeedant activity when applied to the leaves of 'Empire glandless' (*Gossypium hirsitum*), an ideal food substrate for this insect. The influence of *X. strumarium* leaf extract was evaluated as ovipositional deterrents. Okra fruits were treated by uniformly dispensing over them 0.5ml of 6% and 12% concentration solution of the extract prepared in acetone. The females laid their eggs on the treated fruit but with a progressive decrease as the extract concentration was increased (Dongre & Rahalkar 1984).

The plant contains essential oil, sesquiterpenes, sisterol, stigmasterol and campesterol (Craig *et al.* 1976). The polyphenols, 1,3,5-tri-O-caffeoylquinic acid and 3,5-di-O-caffeoylquinic acid were isolated from the fruit of *Xanthium strumarium*. The air-dried fruits were powdered and homogenized in 70% acetone. The filtrate was concentrated and the separated oily material was removed from the aqueous solution using a separatory funnel. The aqueous solution was then extracted with Et_2O and EtOAc, succesively. The EtOAc extract was chromatographed over Sephadex LH-20 with 70% acetone, and the fraction containing poliphenolic compounds was further chromatographed over Sephadex LH-20 with 60% acetonitrile, to give 3,5-di-O-caffeoylquinic acid and a fraction that was purified on a Sep-Pak C_{18} cartridge using acetonitrile-H_2O to yield 1,3,5-tri-O-caffeoylquinic acid (Agata *et al.* 1993). Peluso *et al.* (1995) isolated caffeoylquinic acids from other plants and found that 3,5-di-O-caffeoylquinic acid exhibited appreciable anti-inflammatory activity *in vitro*.

5.108 INDEX TO CHAPTER 5

CHAPTER 6: DISCUSSION

The Asteraceae is a large cosmopolitan family of about 900 genera and over 17000 species. In this study only about 280 species of 107 southern African genera (2245 species in southern Africa) were found in scientific literature as being used in traditional medicine or with pharmacological effect.

The Asteraceae contains diverse secondary metabolites. Although the major types of compounds are pharmacologically active, two main groups of compounds which are also pharmacologically active, seem to be typical of the Asteraceae . They are the photosensitizers (phototoxic compounds) and the sesquiterpene lactones.

Phototoxic compounds inhibits growth of micro-organisms only after incubation in near UV light (300-400nm), but not after dark incubation. (Arnason *et al.* 1980) Phototoxic compounds include polyacetylenes like phenylheptatryine and thiophenes like α-terthienyl.

Phenylheptatriyne (PHT) found in the leaves of *Bidens pilosa* is a UV mediated antibiotic which is effective in low concentration against *Candida albicans*, some other yeasts and pathogenic bacteria and fungi. In the light of the toxic photodermatitis caused by α-terthienyl (α-T) and 8-methoxypsoralen (8-MOP) and other psoralens (8-methoxypsoralen and other psoralens are used in photochemotherapy in psoriasis), on human skin, Wat *et al.* (1979) tested a number of polyacetylenes on the skin of adults. Many of the tested polyacetylenes were shown to be phototoxic or antibiotic against *Candida albicans*. The lack of apparent activity of photoactive polyacetylenes towards the human skin, coupled with their phototoxic effects on *Candida albicans* and other microorganisms, warrants further investigation into their use as UV-mediated antibiotics and in the topical treatment of dermatosis, and even perhaps psoriasis. 8-MOP and UV-A treatment of lymphocytes *in vitro* gives rise to chromosomal aberrations. Unlike psoralens, PHT does not form interstrand cross-linkages with the calf thymus DNA. (Wat *et al.* 1979)

Many polyacetylenes and in particular PHT show potent phototoxic activity against filamentous fungi, various yeasts including *Candida albicans*, membrane containing viruses, gram-positive bacteria including *Staphylococcus* and *Streptococcus* and to a lesser extent gram-negative bacteria. PHT deserve further attention as a topical antibiotic: like α-T, it is not carcinogenic or mutagenic, it does not induce photodermatitis in man, and there is no evidence to implicate it as a contact allergen. (Towers & Champagne 1977)

It is therefore interesting to note the frequent occurrence of the external use of plants (for skin and eye complaints) that contain phototoxic compounds. The majority of the plants used, contain polyacetylenes. See table 6.1.

Table 6.1: Correlation between plants used for eye and skin diseases and the presence of phototoxic compounds.

Plant name	Medicinal use	Phototoxic compounds
Artemisia afra Jacq. ex Willd.	An infusion has been used in the Western Cape as an eye lotion, and the leaf and stalk have been used as a discutient. The Southern Sotho make a lotion from the plant for washing the body.	polyacetylenes triyne-triene (7) and its derivative pontica epoxide
ASPILIA Thouars *Aspilia eenii* S.Moore *Aspilia pluriseta* Schweinf.	skin infections and eye infections. eye infections skin disease or onto fresh wounds	thiarubrines traces of two thiophenes
BERKHEYA Ehrh. *Berkheya carduoides* (Less.) Hutch. *Berkheya decurrens* (Thunb.) Willd. *Berkheya setifera* DC. *Berkheya speciosa* (DC.) O.Hoffm.	 The Xhosa grind the leaves to a paste and apply it to pimples and drink the ground root in water for relief of rash or itch they get after visiting or crossing the river. The Xhosa apply the pounded leaves externally to the skin when they get rash/itch after visiting the river. The root is used for ophthalmia. The roots are used for ophthalmia	The roots contain as a rule thiophene acetyl compounds thiophene derivatives. The major compound was found to be α-Terthienyl. thiophene derivatives
Bidens pilosa L.	Fresh juice is used for conjunctivitis and burns and in the treatment of wounds.	polyacetylenes, the principle photoactive compound in the leaf is phenylheptatriyne (PHT)
Centaurea cyanus L.	eye wash	polyenes
Chromolaena odorata (L.) R.M.King & H.Rob.	The leaf juice is a good antiseptic and is used in wound dressing and skin infections.	
Chrysocoma ciliata L.	lotion of the root for wounds especially varicose ulcer. The plant is taken for erysipelas (an acute contagious disease caused by *Streptococcus pyogenes*, marked by a circumscribed red eruption on the skin, chills and fever)	The aerial parts contain a C_{16}-acetylenic ester, the enynediene, methyl hexadeca-6,8,12-trien-10-ynoate and two other polyacetylenes.
Cichorium intybus Linn.	local application in the treatment of acne, ophthalmia	

Eclipta prostrata (L.) L.	The juice of the leaves mixed with sesame oil is considered an efficacious application in the treatment of vitigilo, athlete's foot, ringworm and some chronic skin diseases. The leaves are used in central Africa for ringworm and diarrhea.	Thiophenes derivatives (α-Terthienyl) occur in the leaves and other aerial parts as well as polyacetylene derivatives.
Leucanthemum vulgare Lam.	Antibacterial	furanopolyine
Senecio deltoideus Less.	A paste of the leaves are externally applied for inflammation of the eyes and on the skin for rash or itch	C_{11}-acetylenes, C_{17}-acetylenes
Tagetes minuta L.	The oil has insecticidal and anti-inflammatory activity.	Thiophenes such as α-terthienyl

It is clear from table 6.1 that plants containing phototoxic compounds such as PHT or α-terthienyl (αT) are used topically in traditional medicine as antibiotics. It would be interesting to substantiate the use of these plants to specific phototoxic compounds. In the pharmacological tests done by Noristan on *Bidens pilosa*, no antibacterial activity was observed against *Candida albicans*. This may be due to the fact that the phototoxicity was not taken into account. However, it is more likely that the phototoxicity was lost due to the drying of the plant material. Acetylenic compounds are much more labile than most other plant substances and they can only be isolated successfully from fresh plant material. Other plant species that are used in traditional medicine may also have given negative results because air-dried material were used.

There are some Asteraceae species which contain acetylenes but which are apparently not used externally. One explanation may be that the acetylenes in these species are less phototoxic or not phototoxic at all. Another explanation is that other plants which are more phototoxic are available. The amount of acetylenes present may also be a factor determining its use. It is also to be determined if the amounts present in the plants are sufficient to produce the wanted effect as indicated in the traditional use. Species which contain acetylenes but which are not used externally include; *Arctotis grandis*, *Cirsium arvensis*, *Cineraria* spp., *Conyza pinnata*, *Felicia filifolia* and *Schistostephium crataegifolium*.

There are quite a few species which are used externally for eye or skin ailments, but from which polyacetylenes have not been isolated. (Table 6.2) It is not yet confirmed that the plant extracts are effective as indicated by their traditional use. If they are active it may be due to other compounds (not polyacetylenes) or it may be possible still to find polyacetylenes or phototoxic compounds in some of them.

Table 6.2: Plant species which are used externally for eye or skin ailments, from which polyacetylenes have not been isolated:

Plant species	Traditional use
Conyza canadiensis	ringworm, eczema, wounds
Conyza podocephala	lotion for chafing
Cotula villosa	scalds and skin diseases
Emillia sagitata	juice for eye conditions and contusions
Emillia sonchifolia	conjunctivitis
Erlangea misera	inflammation of the eyes
Haplocarpha scaposa	wounds and sores
Helichrysum foetidum	festering sore
Helichrysum gerberifolium	wounds
Helichrysum pedunculatum	wounds (circumcision wounds)
Matricaria nigellifolia	skin infection, rash, wounds
Melanthera scandens	wounds (circumcision wounds), eye drops
Othonna furcata	wound dressing
Pentzia globosa	wound salve

α-Terthienyl, a thiophene of *Tagetes* spp. is phototoxic. α-Terthienyl and other thiophenes show pronounced phytotoxic activity against a diversity of fungi, including the pathogenic yeast *Candida albicans*, gram-positive bacteria, and to a lesser extent gram-negative bacteria. α-Terthienyl is also phototoxic to membrane-bound viruses. However, α-terthienyl in the presence of long wave UV can evoke photodermatitis in human skin. α-Terthienyl was evaluated for activity against the human immunodeficiency virus (HIV-1). HIV-1 was very susceptible to α-T, and the effect was almost totally dependent on UVA radiation. The efficacy was decreased to some extent by the presence of bovine serum in the reactions. Unsaturated compounds in the serum can quench singlet oxygen and thereby reduce the effect of the antiviral agent. Some photodynamic dyes, such as porphyrins and cyanins can bind to serum proteins or lipoproteins and can facilitate the penetration of the agents into the cells. Several phytodynamic agents have been proposed for the use in decontamination of blood products, where a number of viruses constitute potential hazards. Furanocoumarins, in particular 8-methoxypsoralen, have been advocated for this and similar applications and are in use as a treatment mode, the so-called photopheresis, for some blood disorders in UV radiation patients. (Hudson *et al.* 1993)

One of the objectives of this study was to validate the use of indigenous Asteraceae species in traditional medicine. This was difficult to achieve due to the lack of pharmacological and chemical information on the indigenous Asteraceae. From the little data available, interesting conclusions were made. In many of the species used, there is a remarkable correlation between the observed pharmacological action of the plants and the traditional medicinal uses. (Table 6.3) Many of these plant species include introduced or cosmopolitan species and relatively few endemic species. The reason for this may be that little research has been done on the indigenous or endemic species.

Extracts of many plant species, or chemical compounds isolated from them, display remarkable pharmacological action, but no traditional medicinal use was found for them. (Table 6.4) One can therefore infer that most of the plant species would have some positive pharmacological action,

whether they are used traditionally or not. It is more likely that they are/were used, traditionally, but that the use has not been not recorded.

It is evident that much work is stil needed in this field. No research data is available on far too many species. The research data available concerns in most cases only one or two aspects of the biological activity of the plant extract. There is however, a revival in interest in phytotherapy and with it the increase in research.

Table 6.3: Correlation between the traditional medicinal uses of some Southern African Asteraceae and observed pharmacological actvivity.

Plant name	Traditional uses	Pharmacological activity
Acanthospermum australe (Loefl.) Kuntze	Regulating fertility (Paraguay)	Two diterpene lactones with oxepane skeletal types, montanol and zoapatanol both have contragestational activity.
Achillea millefolium L. sens. lat.	analgesic and anti-inflammatory effects	Pronounced anti-inflammatory activity is associated with the oil and azulene-like compounds and with water soluble glycoprotein extracted from flower heads.
	cancer	sesquiterpenoids, achimilic acids A, B and C were found to be active against mouse P-388 leukemia cells *in vivo*.
	a number of ailments involving nerves and muscles	Spasmolytic activity has been attributed to the flavonoids apigenin 7-O-glucoside (cosmosiin) and luteolin 7-O-glucoside.
	insect repellant	N-(2-methylpropyl)-(E,E)-2,4-decadien-amide displays mosquito larvicidal action.
	to check bleeding wounds and sores	The alkaloid, achilleine, is an active hemostatic agent.
	antipyretic activity	Salicylic acid derivatives, chamuzulene
	emenagogue	Thujone is a known abortifacient.
	colds and influenza	Carminative, expectorant, analgesic and diaphoretic properties of several of the constituents of the volatile oil.
Ageratum conyzoides L.	colds and fevers, pneumonia	Broad spectrum antimicrobial activity.
	treatment of wounds and burns and leg ulcers	An extract shows wound healing properties in rabbits.
	to arrest bleeding, epistaxis	Hemostatic effect of the extract probably as result of vaso-constriction and the formation of an artificial clot due to its high tannin content.
	rheumatism, fever	anti-inflammatory activity of an extract.
Artemisia afra Jacq. ex Willd.	colds, influenza	The cold-relieving effects of the aqueous extract of the plant has been ascribed to cineole.
	bronchial troubles	The oil is antimicrobial and inhibits the growth of *Klebsiella pneumoniae*

Artemisia vulgaris L.	mosquito repellant	Essential oil shows 91% repellancy (0.4mg/cm^2). Terpinen-4-ol is the most active compound of the oil.
Aspilia mossambicensis (Oliv.) Wild.	galactogogue and to alleviate menstrual cramps, treatment of eclampsia	Kaurenoic acid and grandiflorenic acid are potnet stimulators of uterine contraction. Ent-kaur-16-en-15β-ol (kaurenol) stimulates progesterone production alone but attenuates follicle stimulating hormone and luteinizing hormone-stimulated progesterone production.
Aspilia pluriseta Schweinf. subsp. pluriseta	skin disease or on fresh wounds	Kaurene diterpenoids are antibacterial.
Athrixia phylicoides DC.	for the relief of sore feet, the Southern Sotho bathe them after scarification with a decoction	Fractions of the extract are anti-inflammatory, antihypertensive and display a narcotic analgesic effect.
Bidens pilosa L.	Zulus chew young shoots as a remedy for rheumatism; a strong decoction of the leaf is taken for the treatment of any inflammation enteritis, bacillary dysentery and pharangitis to treat conjunctivitis, eye irritations and otitis, thrush and oral candidiasis. In the treatment of wounds and ulcers. intestinal worms	Anti-inflammatory activity of aqueous extracts (500mg/kg i.p.) are apparent as early as two days after injection of adjuvant. On day 16, aqueous extracts produced 43.4% inhibition of edema in the injected paw. The ethanolic extract of the leaves caused a 90% inhibition of cyclooxygenase. The antimicrobial activity of the petrol ether extract is due to its content of phenylheptatriyne (PHT), linoleic acid and linolenic acid. The latter two are known bacteriostatics even at concentrations as low as 5-50ppm. PHT is antibacterial to gram-positive bacteria. PHT is phototoxic (UV mediated antibiotic) which is effective in low concentrations against *Candida albicans*, some other yeasts and pathogenic bacteria and fungi. PHT has anthelmintic and protozoacidal properties *in vitro* and in infected mice. Cercaries of schistosomal and echinostomal trematodes are paralyzed irreversably in the dark or under UV light within 5 to 15 min. at concentrations of 0.3ppm.
Brachylaena elliptica (Thunb.) DC.	The Zulu take an infusion of the decorticated root as an emetic for pains in the side and whenever breathing is not normal (pneumonia?), and inject as an enema an infusion of the leaf for biliousness and back ache. The Xhosa use a decoction of the leaf as a gargle for sore throat.	Extracts were only moderatly active in the writhing test.

Calendula officinales	Anti-inflammatory	Triterpenoids, especially faradiol, monoester dislay anti-inflammatory action.
Chromolaena odorata (L.) R.M. King & H. Rob	The leaf extract is a very popular hemostatic agent, arresting bleeding from cuts. The leaf juice is used as an antiseptic and in wound dressing and skin infections	The potent hemostatic activity may be accounted for by the alpha adrenoceptor mediated vasoconstriction - a property well established for adrenaline. The active substances have not yet been isolated and identified. An ethanolic extract possesses some antibacterial activity against *Pseudomonas aeruginosa* and *Streptococcus faecalis* although the minimum inhibitory concentration is large.
Chrysanthemum cinerariiifolium (Trevir.) Vis.	Fly powder	The insecticidal activity is due to the presence of pyrethroids.
Conyza scabrida DC.	Charred root powder is rubbed into cuts made in the chest for pleuretic pain by the Zulu. A poultice of the leaf is often applied to inflammations, especially inflammations within the obdomen.	An extract causes a 41.6% inhibition of writhes in the writhing test at a dose of 500mg/kg p.o. ($p<0.025$). Another extract displayed anti-inflammatory activity; 20.4% inhibition of carrageenan induced oedema at 500mg/kg p.o.
Dicoma zeyheri Sond.	The Xhosa and Mfengu take a decoction of the root for lumbago and other pains in the back.	A fraction of an extract showed a 65% inhibition in the writhing test at 500mg/kg p.o.
Eclipta prostrata (L.)L.	It is present in three Indian preparations for liver ailments. In India the juice of the leaves is considered an efficacious application in the treatment of vitigilo, athlete's foot, ringworm and some chronic skin diseases. The leaves are used in central Africa for ringworm.	A liquid extract afforded significant protection in guinea pigs on hepatic damage caused by carbon tetrachloride. The ether extract containing wedelolactone and ethyl acetate fractions showed pronounced activity. Thiophenes occur in the leaves and other aerial parts. α-Terthienyl is antimicrobial and strongly phototoxic.
Ethulia conyzoides L.	intestinal parasites, roundworm	Ethuliacoumarin A is anthelmintic
Gazania krebsiana Less.	Toothache and earache	Two of the four mice administered with 300mg/kg i.p. of an extract, did not show any pain reaction in the tail clip experiment. It was slightly active in the writhing test and showed signs of weak central nervous system depression.
Helichrysum aureonitens Sch.Bip.	skin infections	The dichloromethane extract is active against all five gram-positive bacteria tested, including *Bacillus subtilis* and *Staphylococcus aureus*.

Helichrysum aureonitens Sch.Bip.	cold sore	The crude aqueous extract from shoots showed significant antiviral activity on herpes simplex type 1 (HSV-1) in human lung fibroblasts (HF).
Helichrysum caespititum (DC.) Harv.	anti-infective	Caespitin (a phloroglucinol derivative) shows antimicrobial activity with significant inhibition against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Cryptococcus neoformans*, *Trichophyton rubrum*, *T. mentagrophytes* and *Microsporum canis*.
Helichrysum nudifolium (L.) Less.	Smoke from the plant is inhaled by the Zulu for relief of headaches.	Anti-inflammatory. Three extracts inhibited oedema by 24%, 28.5% and 30.8% (500mg/kg). Ethanolic extract of the leaves caused a 96% inhibition of cyclooxygenase.
Osmitopsis asteriscoides (P.J.Bergius) Less.	To relieve body aches and pains.	Extracts are active in the writhing test, and have an analgesic effect.
Silybum marianum Gaertn.	Remedy for hepatic diseases.	The liver protective action of silybin and of silymarin have been established *in vitro* and in many *in vivo* liver damage models.
Spilanthes mauritiana (Pers.) DC	Toothache and sore throat.	Spilanthol has strong local anaesthetic action.
Tagetes minuta L.	Intestinal parasites and insecticides (mosquito repellant) Nematocide Applied externally for skin and eye infections.	The root extract which contains photoactive components could be used for mosquito control. (5E)-ocimenone is the factor responsible for mosquito larvicidal activity. α-Terthienyl, a phototoxic thiophene had an LC_{50} of 19ppb for *A. aegypti* larvae when combined with near UV radiation. Thiophenes such as α-terthienyl have a high level of photo-toxicity to herbivorous insects and phytopathogenic fungi. Non-light-mediated ("dark") toxicity of thiophenes has also been reported against insects, crustaceans, nematodes and cultured mammalian cells. The essential oil caused a complete inhibition of 85% of gram-positive strains and 100% of gram negative strains while the multiplication of fungi was 100% inhibited by *T. minuta* oil.
Tarchonanthus camphoratus L.	An infusion of the leaf is taken for abdominal pains, and the plant is used as a toothache remedy. The Southern Sotho inhale the smoke from the burning green branch for the relief of headache.	A fraction of the petroleum ether extract, cause a 39.3% inhibition in writhes at 300mg/kg p.o., $p<0.2$.
Vernonia natalensis Sch. Bip. ex Walp.	The Swazi inject the powdered bark in the form of an enema to relief pains in the loins and inhale the smoke from burning it, for headaches.	Extracts are active in the writhing tests and one fraction also had an analgesic effect.

Vernonia oligocephala (DC.) Schh.Bip. ex Walp.	In the Free State a decoction of the plant is used as a diabetes remedy and its use apparently reduces the sugar level in the urine.	A fraction of an extract was found to be hypoglycaemic and caused a 13.33% reduction in the blood glucose concentration at 300mg/kg.

Table 6.4: The pharmacological action of extracts of plants not used traditionally or chemical compounds isolated from plants not used traditionally.

Plant name	**Active chemical compound**	**Pharmacological action**
Acanthospermum australe (L.) Kuntze	5,7,4'-trihydroxy-3,6-dimethoxyflavone	Inhibitory activity toward rat lens aldose reductase (IC_{50} = $1x10^{-7}$M)
	thymol	antiseptic (20 times more active than phenol) and antifungal.
	isothymol (carvacrol)	antiseptic (1.5 times the activity of phenol). Antifungal and anthelmintic.
Acanthospermum glabratum (DC.) Wild.	sesquiterpene lactones in the melampolide series 3,6-dimethoxy-4',5,7-trihydroxyflavone	cytotoxic, antitumour activity
Ageratum haustonianum Mill.	Chromenes, prococene II	antifeedant to larvae of *Spodoptera*
	Essential oil	mycotoxic
Arctotis auriculata Jacq.	lipophilic extracts	antimycobacterial activity
	thiarubrine A	antifungal against *Candida albicans* and *Saccharomyces cerevisiae* which is enhanced by UV-A
Bidens pilosa L.	PHT	mosquito larvae (*A. aegypti*) were killed after 4.5 minutes exposure to sunlight and at 2ppm PHT; in the dark 80% were dead after 48 hours.
	ethanolic extract	active against *M. tuberculosis* at 500µg/ml against two strains tested.
Calendula arvensis L.	oleanolic acid glycosides	active against vesicular stomatitis virus (VSV)
	50% ethanol extract	antiprotozoal activity was observed against *Entamoeba hystolica* at concentrations of less than 125µg/kg *in vivo*.
Cichorium intybus Linn.	alcoholic and aqueous extracts from the dried and roasted roots	applied as a gum massage, as an antimicrobial adjuvant with dentrifice, against gingival inflammation and as an anti-plaque agent
	ethanol extract	anti-inflammatory effect. A dose of 100mg/kg x2 resulted in 50% inhibition.
Dittrichia graveolens (L.) Greuter	ivalin	shows cytotoxic activity against cultured P-388 (murine lymphocytic leukemia), KB-3 (nasopharangeal carcinoma) and KB-V1 (vinblastine resistant cells)
Eclipta prostrata (L.) L.	wedelolactone	inhibits 5-lipoxygenase (5-LO) by an oxygen radical scavenger mechanism

Elytropappus rhinocerotis (L.f.) Less.	rhinocerotic acid (a labdane diterpene)	anti-inflammatory; causes 50% inhibition of the carrageenan-induced oedema in rats at a dose of 150mg/kg
Felicia erigoides DC.	extracts of all the plant organs	antibiotic activity against *Pseudomonas aeruginosa* and *Candida albicans*
Flaveria bidentis (L.) Kuntze	an ethanol extract of the aerial parts	antiviral activity against *Herpes simplex* type 1.
Grangea maderaspatana (L.) Poir.	a mixture of flavonoids (flavones)	posessoestrogenicity and antiimplantational activities in the mouse
Haplocarpha scaposa Harv.	combined benzene, ethylacetate and methanol extract	active in the writhing test
Helianthus annuus L.	helangolides 15-hydroxy-3-dehydrodesoxyfruticin and niveucin C, niveucin B and 3-ethoxy-niveucin-B ethanol extract	antibiotic effect on gram negative and gram positive bacteria as well as on some fungi as well as cytotoxic effects on mouse myeloma cells anti-inflammatory activity: a dose of 100mg/kg x2 resulted in a 26% inhibition in the carrageenan-induced pedal assay
Helianthus debilis Nutt. subsp. *cucumerifolius* (Torr. & A.Gray) Heiser	the furanoheliangolide, 17,18-dihydrobudlein A	showed complete protection against insect predation in choice experiments with larvae *of Locusta migratoria* and also shows strong antimicrobial activity and is able to inhibit auxin-induced plant growth at a concentration of 10μM and more
Helichrysum odoratissimum (L.) Sweet	3-O-methylquercetin in the flower	antimicrobial activity. The minimum inhibitory concentration (MIC) for *Staphylococcus aureus* was 6.25μg/ml and for *Candida albicans* 12.5μg/ml.
Helichrysum panduratum O.Hoffm.	extracts	anti-inflammatory, active in the writhing test
Helichrysum petiolare Hilliard & B.L.Burtt.	methanol and dichloromethane extract	antihypertensive activity
Helichrysum platypterum DC.	the flavone, chrysin galangin	anti-inflammatory, inhibits iodothyronine deidonase, lens aldose reductase and histamine release form rat peritoneal mast cells antibacterial activity and is a potent inhibitor of bull seminal cyclo-oxygenase activity
Leucanthemum vulgare Lam.	a furanopolyine	phototoxic against yeast, three gram-positive bacteria and three gram-negative bacteria. Active against sinbis (a Togavirus) and murine cytomegallovirus (herpes virus) and cytotoxic in UVA
Melanthera biflora (L.) Wild	16-methylkaur-15-en-19-oic acid, 24-ethylcoprostanone, stigmasterol, grandifloric acid and *ent*-kauradienoic acid	antifeedant and-or antifungal activity
Mikania coordata (Burm. f.) B.L. Robinson	the methanolic fraction of the root extract	antihepatotoxic. Significant normalization of lipid peroxidation and related enzymatic makeup in tetrachloride (CCl_4)-induced hepatotoxicity in mice and protection of liver cells against CCl_4-intoxication.

Mikania coordata (Burm. f.) B.L. Robinson	the germacranolides, mikanolide and dihydromikanolide	antibacterial and antifungal activities; they inhibit the growth in culture of *Staphylococcus aureus* and also of the yeast *Candida albicans*
	an extract of the root	central nervous system depressant. Anti-inflammatory. Significantly inhibited carrageenan-oedema in rats and also showed significant inhibition of formaldehyde-induced arthritis in rats.
	scandenolide	inhibits in a dose dependant manner the formation of the lipoxygenase products leukotriene B_4 and 5-HETE
Parthenium hysterophorus L.	parthenin	active *against Plasmodium falciparum* (K1) *in vitro* with an IC_{50} value of 1.29μg/ml but considerably less active than artemisinin
Pentzia incana (Thunb.) Kuntze	extract	antihypertensive activity with a 18.08% reduction in mean blood pressure and analgesic activity with 2/4 mice not showing any pain reaction in the tail clip experiment
Schistostephium heptalobum (DC.) Oliv. & Hiern	extract	antihypertensive and diuretic with an increase in Na^+ excretion with no increase in volume
Senecio barbertonicus Klatt.	extract	anti-inflammatory, antihypertensive and anti-ulcer activity
Senecio cinerascens Aiton	extract	A fraction inhibited oedema in the anti-inflamatory test and caused inhibition in the writhing test and was active in the antiarrhythmia test. Another fraction was active in the antihypertenxive and anti-ulcer test.
Senecio tamoides DC.	extract	anti-inflammatory, antihypertensive and antimicrobial. A fraction is active in the writhing test.
Sigesbeckia orientalis L.	50% ethanol extract	anti-acetylcholine activity
Tagetes minuta L.	α-terthienyl (in the presence of UVA)	rapidly and efficiently inactivated viruses with membranes. It retained its integrity but did not replicate. HIV-1 was also very susceptible to α-T, and the effect was almost totally dependant on UVA radiation. In contrast the non-membrane containing viruses, poliovirus and Coxsackievirus, infectivity were relatively resistant to α-T + UVA.
Tithonia diversifolia (Hemsl.) A.Gray	sesquiterpene lactones Tagitinin A and C and the flavone hispidulin	potent feeding deterrents of the Eri-silkworm
Vernonia amygdalina Delile	The ethyl acetate soluble part of the acetone extract contain the sesquiterpene lactones vernodalin, vernolide and hydroxyvernolide	exhibited potent *in vitro* antitumoral activities against P-388 and L-1210, and antibacterial activities against gram-positive *Bacillus subtilis*, and *Micrococcus lutea*
	luteolin and two glycosides	potent antioxidant
	the saponin,vernonin	exert hypotensive activity and have mild cardiotonic effects

Vernonia amygdalina Delile	the saponin vernonioside	significantly reduced liver weights, plasma and liver cholesterol concentrations
	the major steroid glucoside, vernonioside B1	antischistosomal activity
	sesquiterpenoids (vernodalin)	inhibited the movement and egg-laying of schistosomes, high leismanicidal activity, significant plasmocidal activities and shoe tumor inhibitory activity in tissue culture, insect antifeedants
	(vernolepin)	a competitive antagonism against histamine; a biphasic enhancement of guinea pig ileum; an antiaggregating and disaggregating activity against rabbit platelet aggregation induced by arachidonic acid or ADP without inhibition of cyclo-oxygenase or lipoxygenase; cytotoxic activity
Vernonia cinerea Less	50% ethanol extract of the whole plant	antiviral against Ranikhet disease virus *in vitro* anticancer - active against sarcoma 180 in the mouse
Vernonia colorata (Willd.)Drake subsp. *colorata*	two lactones, vernolid and hydroxyvernolid	anthelmintic and amoebicidal
	ethanol extract of the stem/bark	slight anti-inflammatory activity
Xanthium canadense	two polyacetylenes, cis-dehydromatricaria ester and tri-dec-1-ene-3,5,7,9,11,pentayne	ovicidal to both the fruit fly, *Drosophila melanogaster* and the house fly, *Musca domestica*
Xanthium strumarium L.	carboxyatractyloside	potent hypoglycemic agent and toxic
	50% methanol extract of the whole plant	hypoglycemic activity with a single dose of 250mg/kg administered orally to rats

CHAPTER 7: SUMMARY

There has been a renewed interest in the medicinal value of plants. Some of the reasons are that research could possibly lead to the development of new drugs, especially in cases where organisms have become resistant to drugs currently being used and in the appearance of new diseases like AIDS. Furthermore, millions of South Africans still depend on traditional herbal medicine. There is also a movement towards the use of natural products like aromatherapy. Screening methods and isolation techniques have made it possible to elucidate the mode of action of old herbal medicines and thereby reintroduce them to modern therapy.

This dissertation comprises a literature study on the medicinal value of the southern African Asteraceae. One of the objectives of this study was to validate the use of indigenous Asteraceae species in traditional medicine. This was difficult to achieve due to the lack of pharmacological and chemical information on the indigenous Asteraceae. From the little data available, interesting conclusions were made. In many of the species used, there is a remarkable correlation between the observed pharmacological action of the plants and the traditional medicinal uses. (Table 6.3) Many of these plant species include introduced or cosmopolitan species and relatively few endemic species. The reason for this may be that little research has been done on the indigenous or endemic species.

Extracts of many plant species, or chemical compounds isolated from them, display remarkable pharmacological action, but no traditional medicinal use was found for them. (Table 6.4) One can therefore infer that most of the plant species would have some positive pharmacological action, whether they are used traditionally or not. It is more likely that they are/were used, traditionally, but that the use has not been not recorded.

It is evident that much work is stil needed in this field. No research data is available on far too many species. The research data available concerns in most cases only one or two aspects of the biological activity of the plant extract. There is however, a revival in interest in phytotherapy and with it the increase in research.

A computer search of two databases, the Science Citation Index and an international database, the dialog Service was used to find the relevant published information. The database of the Traditional Medicines Programe (TRAMED) at the medical school of the University of Cape Town and the research done by Noristan were also used. The medicinal uses of the relevant species, their active ingredients and/or pharmacological affects were included when available.

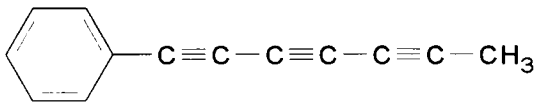
The Asteraceae are exceptionally rich, both in the range of secondary compounds present and also in the number of complex structures known of any one class (Heywood *et al.* 1977). The combined occurrence of sesquiterpene lactones, acetylenic compounds and inulin-type fructans is characteristic of the Asteraceae (Hegnauer 1977).

Both polyacetylenes (acetylenes) and thiophenes are phototoxic. Plant materials which cause inhibition of growth in *Candida albicans* after incubation in near UV light (300-400nm), but not after dark incubation, are called phototoxic (Towers 1980). A correlation between phototoxicity and the reported occurrences of polyacetylenes and thiophenes have been reported (Towers *et al.* 1977).

Most of the known natural acetylenes have been isolated from the Asteraceae (Heywood, Harborne & Turner 1977). Studies have implicated phototoxic compounds as active constituents in Asteraceae used in folk medicine. In a survey of 42 species of Asteraceae used in traditional medicine to treat skin diseases, 20 species were found to be phototoxic or antibiotic, and their activity correlated with the presence of polyacetylenes or thiophenes (Towers & Champagne 1977). This correlation was also found in this study. 15 Species which are used for eye and skin diseases contain phototoxic compounds.

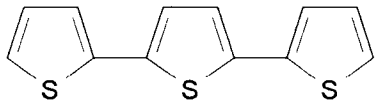
Acetylenic compounds are much more labile than other plant substances and can only be isolated successfully from fresh plant material (Heywood, Harborne & Turner 1977). Negative results obtained in antibiotic screens done with extracts of dried plant material, could therefore be misleading.

Many polyacetylenes and in particular phenylheptatriyne (PHT), found in the leaves of *B. pilosa,* show potent phototoxic activity against filamentous fungi, various yeasts including *Candida albicans*, membrane containing viruses, gram-positive bacteria including *Staphylococcus* and *Streptococcus* and to a lesser extent gram-negative bacteria. PHT deserves further attention as a topical antibiotic: like α-T, it is not carcinogenic or mutagenic, it does not induce photodermatitis in man, and there is no evidence to implicate it as a contact allergen. (Towers & Champagne 1977)



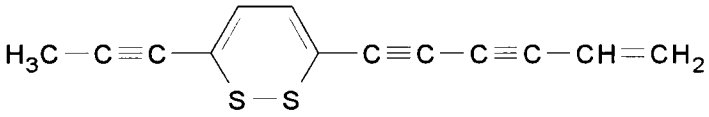
Phenylheptatriyne (PHT)

Thiophenes, such as α-terthienyl (α-T) are also phototoxic and occur in a number of medicinal species such as *Tagetes* and *Eclipta*. α-Terthienyl and other thiophenes show pronounced phytotoxic activity against a diversity of fungi, including the pathogenic yeast *Candida albicans*, gram-positive bacteria, and to a lesser extent gram-negative bacteria. α-Terthienyl is also phototoxic to membrane-bound viruses. However, α-terthienyl in the presence of long wave UV light can evoke photodermatitis in human skin. α-T and its carboxylic acid derivatives were found to possess impressive UVA-dependant activity against the human immunodeficiency virus (HIV-1), but only when assayed in the absence of serum (Hudson *et al.* 1994). 8-Methoxypsoralen (8-MOP) with UVA has been used as a treatment (photopheresis) for some blood disorders and it has recently been used in AIDS patients (Hudson *et al.* 1993). Unlike 8-MOP, α-T does not exhibit mutagenic or carcinogenic activity. α-T may therefore provide an alternative to 8-MOP.



α-Terthienyl

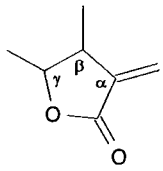
Thiarubrines are found in ten genera of the Asteraeae, including *Aspilia* which is important in the traditional medicine of African countries. Thiarubrines, such as thiarubrine A are strongly antibiotic against a number of micro-organisms. The phototoxic activity appears to be more significant at low thiarubrine concentrations. The antiviral activity of thiarubrine is similar to that of α-T, but it is also toxic to mamalian cells.



Thiarubrine A

Monoterpenes are the major components of essential oils. Monoterpenes are extensively used as disinfectants. The essential oil of *Artemisia afra* displayed antimicrobial activity against 15 bacteria of the 25 tested. The oil also exerted considerable antioxidant effect (Graven *et al.* 1992).

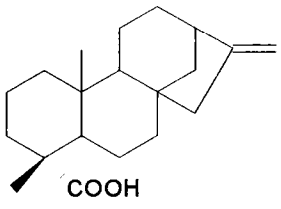
Sesquiterpene lactones are characteristic constituents of the Asteraceae. These bitter substances contain the major structural feature α,β-unsaturated-γ-lactone, which in studies has been shown to be associated with anti-tumor, cytotoxic, antimicrobial and phytotoxic activity (Rodriguez 1976).



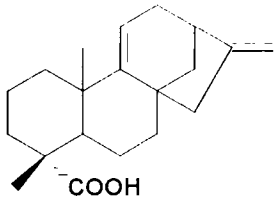
α-Methylene-γ-lactone, the functional group for biological activity of sesquiterpene lactones.

Vernodalin, isolated from *Vernonia amygdalina*, displays antischistosomal activity and inhibitory activity *in vitro* against cells derived from the human carcinoma of the nasopharynx.

Two diterpenes, kaurenoic acid and grandiflorenic acid which were isolated from the leaves of *Aspilia mosambicensis* are potent stimulators of uterine contraction. This supports a hypothesis that wild chimpanzees consume *Aspilia* species for their pharmacological properties and may explain why female chimpanzees consume *Aspilia* leaves more frequently than do males. It is used in traditional medicine as a galactogogue and to alleviate menstrual cramps. (Page *et al.* 1992).



Kaurenoic acid

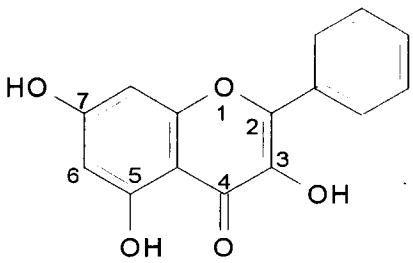


Grandiflorenic acid

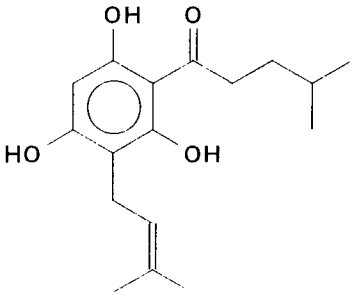
The stigmane-type steroid glucoside, vernonioside B1, isolated from *Vernonia amygdalina* display andtischistosomal activity (Ogihashi *et al.* 1993)

Pyrrolizidine alkaloids are found in two tribes of the Asteraceae, the Eupatorieae and the Senecioceae. Pyrrolizidine alkaloids are probably the most poisonous group of alkaloids. There has recently been an increase in interest in the potential antitumour activity of pyrrolizidine alkaloids because of their cytotoxic and antimitotic properties (Mattocks 1986)

Flavonoids are universal in green land plants. Several plant flavonoids have long been known to possess antiviral properties (Vlietinck *et al.* 1988). A number of flavonoids have anti-inflammatory effects (Gabor 1986). Flavonoids have been shown to inhibit a wide range of enzymes, including mitochondrial electron transport which may contribute to their cytotoxic and antineoplastic activities (Hodnick *et al.* 1986). 3,5,7-Trihydroxyflavone (galangin) from *Helichrysum aureonitens* displays significant antimicrobial activity against all the Gram-positive bacteria tested (*Bacillus cereus*, *Bacillus pumilus*, *B. subtilits, Staphylococcus aureus* and *Micrococcus kristinae*). Galangin indicated considerable activity against the fungi tested with the exception of *Cladosporium herbarum* (Afolayan & Meyer 1997).



Galangin



Caespitin

Caespitin, a phloroglucinol derivative, extracted from *Helichrysum caespitium* shows antimicrobial activity with significant inhibition against *Staphylococcus aureus, Streptococcus pyogenes, Cryptococcus neoformans, Trichophyton rubrum, T. mentagrophytes and Microsporum canis* (Dekker *et al.* 1983).

The active compounds of the majority of Asteraceae species used medicinally, have not yet been identified, although the extracts of some species have been shown to be pharmacologically active. For example, extracts of *Bidens pilosa* display anti-inflammatory activity in adjuvant-induced arthritis and carrageenan-induced oedema in rats (Chih *et al.* 1995) and an ethanolic extract of *B. pilosa* caused a 90% inhibition in prostaglandin synthesis. Prostaglandins are involved in the complex process of inflammation and are responsible for the sensation of pain (Jäger *et al.* 1996)

Many plant species which are traditionally taken as a herbal medicine, were found not to be effective in curing the ailment for which they were taken. Some are even poisonous and are responsible for the deaths of many people. "Impila", for example, the root of *Callilepis laureola*, contains a diterpene glycoside, atractyloside, which has been identified as a nephrotoxin.

REFERENCES

ABEGAZ, B.M., KEIGE, A.W., DÍAZ, J.D. & HERZ, W. 1994. Sesquiterpene lactones and other constituents of *Vernonia* species from Ethiopia. *Phytochemistry*. 37(1):191-196.

ADESOGAN, E.K. & OKUNADE, A.L. 1979. A new flavone from *Ageratum conyzoides*. *Phytochemistry*. 18:1863-1864.

AFOLAYAN, A.J. & MEYER, J.J.M. 1997. The antimicrobial activity of 3,5,7-trihydroxyflavone isolated from the shoots of *Helichrysum aureonitens*. *Journal of Ethnopharmacology. In press*.

AGATA, I., GOTO, S., HATANO, T., NISHIBE, S. & OKUDA, T. 1993. 1,3,5-tri-O-caffeoylquinic acid from *Xanthium strumarium*. *Phytochemistry*. 33: 508-509.

AGUINALDO, A.M., ABE, F., YAMAUCHI, T., PADOLINA, W.G. 1995. Germacranolides of *Mikania cordata*. *Phytochemistry*. 38: 1441-1443.

AHMED, MISRA, L.N. 1994. Terpenoids from *Artemisia annua* and constituents of its essential oil. *Phytochemistry*. 37(1):183-186.

AKAH, P.A. & EKEKWE, R.K. 1995. Ethnopharmacology of some Asteraceae family used in Nigerian traditional medicine. *Fitoterapia*. 66(4):351-355.

AKAH, P.A. 1990. Mechanism of hemostatic activity of *Eupatorium odoratum*. *International Journal of Crude Drug Research*. 28:253-256.

ALLEN, E.H. & THOMAS, C.A. 1971. *Trans-trans*-3,11-tridecadiene-5,7,9-triyne-1,2-dio, an antifungal polyacetylene from diseased Safflower (*Carthamus tinctorius*). *Phytochemistry*. 10:1579-1582.

ANSARI, S., JAIN, P., TYAGI, R.P., JOSHI, B.C. & BARAR, F.S.K. 1983. Phytochemical and pharmaceutical studies of the aerial parts of *Eupatorium adenophorum* L. *Herba Polonica*. 29(2):93-96.

AQUINO, R., DE SIMONE, F., DE TOMMASI, N., PIACENTE, S. & PIZZA, C. 1995. Structure and biological activity of sesquiterpene and diterpene derivatives from medicinal plants. In: Phytochemsitry of Plants Used in Traditional Medicine, eds. Hostettmann, K., Marston, A., Maillard, M. & Hamburger, M., pp. 247-278. Clarendon Press. Oxford.

ARENE, E.O., PETTIT, G.R. & ODE, R.H. 1978. The isolation of isosakuranetin methyl ether from *Eupatorium odoratum*. *Lloydia*. 41(1):68-70.

ARISAWA, M., FUJITA, A. & MORITA, N. 1991. Inhibition of tumor-promoter-enhanced ^{3}H-choline incorporation into cellular phospholipids by phloroglucinolderivatives from *Mallotus japonicus*. *Journal of Natural Products*. 54(5):1409-1412.

ARNASON, T., WAT, C-K., DOWNUM, K., YAMAMOTO, E., GRAHAM, E. & TOWERS, G.H.N. 1980. Photosensitization of *Eschericia coli* and *Saccharomyces cerevisiae* by phenylheptatriyne from *Bidens pilosa*. *Canadian Journal of Microbiology*. 26:698-705.

ARNOLD, T.H. & DE WET, B.C. (Eds) 1993. Plants of southern Africa: names and distribution. *Memoirs of the Botanical Survey of South Africa* No. 62.

ASAKA. Y., KUBOTA, T. & KULKARNI, A.B. 1977. Studies on a bitter principle from *Vernonia anthelmintica*. *Phytochemistry*. 16:1838-1839.

BACHNER-JANSCHKE, I. & KOCH, H. 1979. Die binding der Silymarin-Substanzen an Plasmaproteine und synthetixche Polymere. *Archiv der Pharmazie*. 312(11):954-958.

BALBAA, S.I., HALIM, A.F. & HALAWEISH, F.T. 1980. New 5-methylcoumarin derivatives from *Ethulia conyzoides*. *Phytochemistry*. 19:1519-1522.

BALBAA, S.I., HALIM, A.F. & HALAWEISH, F.T. 1981. Constituents of the aerial parts of *Ethulia conyzoides*. *Fitoterapia*. 52(2):75-76.

BANH-NHU, C., GÁCS-BAITZ, E., RADICS, L., TAMÁS, J., UJSZÁSZY, K. & VERZÁR-PETRI, G. 1979. Achillicin, the first proazulene from *Achillea millefolium*. *Phytochemistry*. 18:331-332.

BARUA, R.N., SHARMA, R.P., THYAGARAJAN, G., HERZ, W. & GOVINDAN, S.V. 1980. New melampolides and darutigenol from Sigesbeckia orientalis. Phytochemsitry. 19:323-325.

BARUAH, N.C., SARMA, J.C., BARUA, N.C., SARMA, S. & SHARMA, R.P. 1994. Germination and growth inhibitory sesquiterpene lactones and a flavone from *Tithonia diversifolia*. *Phytochemistry*. 36(1):29-36.

BENOIT, P.S., FONG, H.H.S., SVOBODA, G.H. & FARNSWORTH, N.R. 1976. Biological and phytochemical evaluation of plants. XIV. Anti-inflammatory evaluation of 163 species of plants. *Lloydia*. 39(2-3):160-171.

BERETZ, A. & CAZENAVE, J-P. 1988. The effect of flavonoids on blood-vessel wall interactions. In: Plant Flavonoids in Biology and Medicine II, eds. V. Cody, E. Middleton, J.B. Harborne & A. Beretz, pp. 187-200. Alan R. Liss, Inc., New York.

BHATTACHARYA, S. & CHAUDHURI, A.K.N. 1987. Preliminary studies on anti-inflammatory and analgesic activities of *Mikania cordata* (Burm) B.L. Robinson root extract. *Medical Science Research*. 15:507-508.

BHATTACHARYA, S., PAL, S & CHAUDHURI, A.K.N. 1988. Neuropharmacological studies on *Mikania cordata* root extract. *Planta Medica*. 6:483-487.

BHOOLA, K.D., COOVADIA, H.M., WATSON, A.R. 1983. Toxic hepato-renal disease in South Africa due to the administration of *Callilepis laureola* extracts. *European Journal of Pediatrics*. 140: 155-155.

BISHAYEE, A., CHATTERJEE, M. 1994a. Anticarcinogenic biological response of *Mikania cordata*: reflections in hepatic biotransormation systems *Cancer Letters* 81: 193-200

BISHAYEE, A., CHATTERJEE, M. 1994b. Protective effects of *Mikania cordata* root extract against physical and chemical factors - Induced gastric erosions in experimental animals. *Planta Medica*. 60(2):110-113.

BOHLMANN, F. & ABRAHAM, W-R. 1979a. Neue diterpene und weitere inhaltstoffe aus *Helichrysum calliconum* und *Helichrysum heterolasium*. *Phytochemistry*. 18:889-891.

BOHLMANN, F. & ABRAHAM, W-R. 1979b. Neue chlorsubstituierte thiopeneacetyleneverbindungen mit unggewönlicher struktur aus *Helichrysum*-arten. *Phytochemistry*. 18:839-842.

BOHLMANN, F., ABRAHAM, W-F. & SHELDRICK, W.S. 1980. Weitere diterpene mit helifulvan-gerüst und andere inhaltstoffe aus *Helichrysum chionosphaerum*. *Phytochemistry*. 19:869-871.

BOHLMANN, F & AHMED, M. 1982. Methyl hexadeca-6,8,12-trien-10-ynoate from *Chrysocoma tenuifolia*. *Phytochemistry*. 21(11):2742-2743.

BOHLMANN, F., AHMED, M. & JAKUPOVIC, J. 1982. Caryophyllane derivatives from *Pulicaria scabrida*. *Phytochemistry*. 21(7):1659-1661.

BOHLMANN, F., BURKHARDT, T. & ZDERO, C. 1973. Naturally Occuring Acetylenes. Academic Press. London.

BOHLMANN, F. & FRITZ, U. 1979. Neue Acetylenverbindingen aus *Felicia filifolia*. *Phytochemistry*. 18:1221-1222.

BOHLMANN, F., GÖREN, N.A. & JAKUPOVIC, J. 1983. Hirsutinolides from South African *Vernonia* species. *Phytochemistry*. 22(5):1159-1162.

BOHLMANN, F. & GRENZ, M. 1972. Notiz über die Isolering von Hautrixa-Säure as *Conyza ivaefolia* Less. *Chemische Berichte*. 105:3123-3125.

BOHLMANN, F. & GRENZ, M. 1978. Diterpene vom sandarocopimaren-typ aus *Chrysanthemoides*-arten. *Phytochemistry*. 18:683-684.

BOHLMANN, F., GRENZ, M., WEGNER, P. & JAKUPOVIC, J. 1983. Clerodan-derivate und neuartige Diterpene aus *Conyza scabrida* DC. *Liebigs Annalen der Chemie*. 11:2008-2020.

BOHLMANN, F., GRENZ, M. & ZDERO, C. 1975. Neue Cumarine aus *Peucedanum*- und *Pteronia* arten. Chemische Berichte. 108:2955-2958.

BOHLMANN, F. & JAKUPOVIC, J. 1979. 8-Oxo-selinen und neue scopoletin-derivate aus *Conyza*-arten. *Phytochemistry*. 19:1367-1370.

BOHLMANN, F., JAKUPOVIC, J., AHMED, M. & SCHUSTER, A. 1983. Sesquiterpene lactones and other constituents from *Schistostephium* species. *Phytochemistry*. 22(7):1623-1636.

BOHLMANN, F., JAKUPOVIC, J., ATES, N., SCHUSTER, A., PICKARDT, J., KING, R.M. & ROBINSON, H. 1983. Steiractinolide, eine neue Gruppe von Sesquiterpenlactonen. *Liebigs Annalen der Chemie*. 0(6):962-973.

BOHLMANN, F., JAKUPOVIC, J., DHAR, A.K., KING, R.M. & ROBINSON, H. 1981. Two sesquiterpene and three diterpene lactones from *Acanthospermum australe*. *Phytochemistry*. 20(5):1081-1083.

BOHLMANN, F. & KNOLL, K-H. 1978. Weitere furanoeremophilane aus *Othonna*-arten. *Phytochemistry*. 17:461-465.

BOHLMANN, F. & LE VAN, N. 1977. Sesquiterpenlactone und polyine aus der gattung *Arctotis*. *Phytochemistry*. 16:487-488.

BOHLMANN, F. & LE VAN, N. 1978a. Ein neues bisabolen-derivat aus *Arctotis grandis*. *Phytochemistry*. 17:1666-1667.

BOHLMANN, F. & LE VAN, N. 1978b. New germacranolides from *Dicoma anomala*. *Phytochemistry*. 17:570-571.

BOHLMANN, F., LE VAN, N., PHAM, T.V.C., JAKUPOVIC, J., SCHUSTER, A., ZABEL, V. & WATSON, W.H. 1979. β-Isocomen, ein neues sesquiterpen aus *Berkheya*-arten. *Phytochemistry*. 18:1831-1834.

BOHLMANN, F., MAHANTA, P.K. & ZDERO, C. 1978. Neue chalkon-derivate aus Südafrikanishen *Helichrysum*-arten. *Phytochemistry*. 17:1935-1937.

BOHLMANN, F., MAHANTA, P.K., SUWITA, A., SUWITA, A., NATU, A.A., ZDERO, C., DORNER, W., EHLERS, D. & GRENZ, M. 1977. Neue sesquiterpenlactone und andere inhaltstoffe aus vertretern der *Eupatorium*-gruppe. *Phytochemistry*. 16:1973-1981.

BOHLMANN, F., METWALLY, M.A, & JAKUPOVIC, J. 1984. Eudesmanolides from *Pluchea dioscoridis*. *Phytochemistry*. 23(9):1975-1977.

BOHLMANN, F & MISRA, L.N. 1984. New prenylflavanones and chalcones from *Helichrysum rugulosum*. *Planta Medica*. 50(3):271-272.

BOHLMANN, F & MOHAMMADI, D. 1983. A further bithienyl derivative from *Berkheya zeyheri*. *Phytochemistry*. 22(12):2856-2857.

BOHLMANN, F., MOHAMMADI, D. & JAKUPOVIC, J. 1984. Sesquiterpene lactones from *Berkheya* species. *Planta Medica*. 50(2):192-193.

BOHLMANN, F., NATU, A.A. & MAHANTA. P.K. 1978. Neue Diterpene und Germacranolide aus *Mikania*-arten. *Phytochemistry*. 17:483-485.

BOHLMANN, F., SCHEIDGES, C., MISRA, L.N. & JAKUPOVIC, J. 1984a. Further glaucolides from South African *Vernonia* species. *Phytochemistry*. 23(8):1795-1798.

BOHLMANN, F., SCHMEDA-HIRSCHMANN, G. & JAKUPOVIC, J. 1984b. New Melampolides from *Acanthospermum australe*. *Planta Medica*. 0(1):37-39.

BOHLMANN, F., SINGH, P. & JAKUPOVIC, J. 1982a. Sesquiterpenes and a dimeric spiroketone from *Cineraria fruticulorum*. *Phytochemistry*. 21(10):2531-2535.

BOHLMANN, F., SINGH, P. & JAKUPOVIC, J. 1982b. New germacranolides and other sesquiterpene lactones from *Dicoma* species. *Phytochemistry*. 21(8):2029-2033.

BOHLMANN, F. & SUWITA, A. 1979a. Ein neues guaianolide und ein secoguaianolide aus *Helichrysum splendidum*. *Phytochemistry*. 18:885-886.

BOHLMANN, F. & SUWITA, A. 1979b. Weitere phloroglucin-derivate aus *Helichrysum*-arten. *Phytochemistry*. 18:2046-2049.

BOHLMANN, F. & WALLMEYER, M. 1982. Sesquisabinene derivatives from *Haplocarpha* species. Phytochemistry. 21(5): 1157-1158.

BOHLMANN, F., WALLMEYER, M. & JAKUPOVIC, J. !982. A new seco-labdane derivative from *Athrixia elata*. *Phytochemistry*. 21(7):1806-1807.

BOHLMANN, F., WALLMEYER, M., JAKUPOVIC, J., GERKE, T., KING, R.M. & ROBINSON, H. 1985. Cuauthemone sesquiterpenoids from *Blumea alata*. *Phytochemistry*. 24(3):505-509.

BOHLMANN, F. & WEGNER, P. 1982a. Three diterpenes from *Conyza podocephala*. *Phytochemistry*. 21(7):1693-1695.

BOHLMANN, F. & WEGNER, P. 1982b. Ent-beyer-15-ene derivatives from *Nidorella anomala*. *Phytochemistry*. 21(5):1109-1114.

BOHLMANN, F. & ZDERO, C. 1972. Constituents of *Artemisia afra*. *Phytochemistry*. 11:2329-2330.

BOHLMANN, F. & ZDERO, C. 1977a. Neuartige cumarin-derivate aus *Ethulia conyzoides*. *Phytochemistry*. 16:1092-1095.

BOHLMANN, F. & ZDERO, C. 1977b. Ein neues thymol-derivat aus *Callilepis laureola*. *Phytochemistry*. 16:1854-1855.

BOHLMANN, F. & ZDERO, C. 1977c. Neue norkauren- und thymol-derivate aus *Athrixia*-arten. *Phytochemistry*. 16:1773-1776.

BOHLMANN, F. & ZDERO, C. 1977d. Neuartige cumarin-derivate aus *Ethulia conyzoides*. *Phytochemistry*. 16:1092-1095.

BOHLMANN, F. ZDERO, C. 1977e. Neue nerolderivate und ein neuartiges dihydrozimtalkohol-derivat aus *Schkuhria*-arten. *Phytochemistry*. 16:780-781.

BOHLMANN, F. & ZDERO, C. 1978a. New furanoeremophilanes from South African *Senecio* species. *Phytochemistry*. 17:1161-1164.

BOHLMANN, F. & ZDERO, C. 1978b. Neue furanoeremophilane und andere sesquiterpene aus vertretern der Gattung *Euryops*. *Phytochemistry*. 17:1135-1153.

BOHLMANN, F. & ZDERO, C. 1979b. 3β-Isovaleroxycostunolid, ein Neues Germacranolid aus *Cotula hispida*. *Phytochemistry*. 18:336-337.

BOHLMANN, F. & ZDERO, C. 1980a. Neue geranylphloroglucin-derivate aus *Helichrysum monticola*. *Phytochemistry*. 19:683-684.

BOHLMANN, F & ZDERO, C. 1980b. Neue phloglucin-derivate aus *Helichrysum*-arten. *Phytochemistry*. 19:153-155.

BOHLMANN, F. & ZDERO, C. 1980c. Neue obliquin-derivate aus *Helichrysum serpyllifolium*. *Phytochemistry*. 19:331-332.

BOHLMANN, F & ZDERO, C. 1981. A heliangolide from *Schkuhria pinnata*. *Phytochemistry*. 20(10):2431-2432.

BOHLMANN, F & ZDERO, C. 1982a. Sesquiterpene lactones from *Brachylaena* species. *Phytochemistry*. 21(3):647-651.

BOHLMANN, F. & ZDERO, C. 1982b. Five tricyclic sesquiterpenes from *Callilepis salicifolia*. *Phytochemistry*. 21(1):139-142.

BOHLMANN, F. & ZDERO, C. 1982c. Glaucolides and other constituents from South African *Vernonia* species. *Phytochemistry*. 21(9):2263-2267.

BOHLMANN, F., ZDERO, C. & AHMED, M. 1982. New sesquiterpene lactones, geranyllinalol derivatives and other constituents from *Geigeria* species. *Phytochemistry*. 21(7):1679-1691.

BOHLMANN, F., ZDERO, C., ABRAHAM, W-R., SUWITA, A. & GRENZ, M. 1980. Neue diterpene und neue dihydrochalkon-derivate sowie weitere inhlatstoffe aus *Helichrysum*-arten. *Phytochemistry*. 19:873-879.

BOHLMANN, F., ZDERO, C., BERGER, D., SUWITA, A., MAHANTA, P. & JEFFREY, C. 1979. Neue furanoeremophilane und weitere inhaltstoffe aus Südafrikanishen *Senecio*-arten. *Phytochemistry*. 18:79-93.

BOHLMANN, F., ZDERO, C., HOFFMANN, E., MAHANTA, P.K. & DORNER, W. 1978. Neue diterpene und sesquiterpene aus Südafrikanishen *Helichrysum*-arten. *Phytochemistry*. 17:1917-1922.

BOHLMANN, F. & ZIESCHE, J. 1979. Ein ungewöhnliches tetrahydrofuran-derivat aus *Helichrysum aureo-nitens*. *Phytochemistry*. 18:664-665.

BOHLMANN, F. & ZIESCHE, J. 1980. New diterpenes from *Gnaphalium* species. *Phytochemsitry*. 19:71-74.

BOHLMANN, F., ZIESCHE, J., KING, R.M. & ROBINSON, H. 1981. Eudesmanolides and diterpenes from *Wedelia trilobata* and an ent-kaurenic acid derivative from *Aspilia parvifolia*. *Phytochemistry*. 20(4):751-756.

BRANDÃO, M.G.L., GRANDI, T.S.M., ROCHA, E.M.M., SAWYER, D.R. & KRETTLI, A.U. 1992. Survey of medicinal plants used as antimalarials in the Amazon. *Journal of Ethnopharmacology*. 36(2):175-182.

BRIDLE, P., LOEFFLER, R.S.T., TIMBERLAKE, C.F. & SELF, R. 1984. Cyanidin 3-malonylglucoside in *Cichorium intybus*. *Phytochemistry*. 23(12):2968-2969.

BROOKES, B.K., CANDY, H.A. & PEGEL, K.H. 1985. Two thymol derivatives from *Callilepis laureola*. *Planta Medica*. (1):32-34.

BROOKES, B.K., CANDY, H.A., PEGEL, K.H. 1983. Atractylosides in *Callilepis laureola* (Asteraceae). *South African Journal of Chemistry*. 36: 65-68.

BUCKINGHAM, J. & MACDONALD, F. (executive eds) 1996. Dictionary of Organic Compounds. Vol. 6. 6th edition. Chapman & Hall. London.

BYE, S.N., COETZER,T.H.T. & DUTTON, M.F. 1990. An enzyme immunoassay for atractyloside, the nephrotoxin of *Callilepis laureola* (Impila). *Toxicon*. 28(8):997-1000.

CAMM, E.L., TOWERS, G.H.N. & MITCHELL, J.C. 1975. UV-mediated antibiotic acitivity of some Compositae species. *Phytochemistry*. 14:2007-2011.

CANDY, H.A., PEGEL, K.H., BROOKES, B. & RODWELL, M. 1977. The occurance of atractyloside in *Callilepis laureola*. *Phytochemistry*. 16:1308-1309.

CARDELLINA, J.H. & BOYD, M.R. 1995. Persuit of new leads to antitumour and anti-HIV agents from plants. In: Phytochemsitry of Plants Used in Traditional Medicine, eds. Hostettmann, K., Marston, A., Maillard, M. & Hamburger, M., pp. 81-93. Clarendon Press. Oxford.

CARLSON, K.D. & CHANG, S.P. 1984. Chemical epoxydation of *Vernonia galamensis* oil, a natural epoxy seed oil. *JOACS*. 61(4):676.

CARSON, C.F. & RILEY, T.V. 1995. Antimicrobial activity of the major components of the essential oil of *Melaleuca alternifolia*. *Journal of Applied Bacteriology*. 78(3):264-269.

CASSADY, J.M., CHANG, C.-J., MCLAUGHLIN, J.L. 1981. Recent Advances in the Isolation of Structural Elucidation of Antineoplastic Agents of Higher Plants. In: Natural Products as Medicinal Agents, eds. J.I. Beal & E. Reinhard, pp. 217-242. Hippokrates Verlag, Stuttgart.

CHAGNON, M., NDIBWAMI, A., DUBÉ, S. & BUMAYA, A. 1983. Anti-inflammatory action of an extract from *Crassocephalum multicorymbosum*. *Planta Medica*. 49(4):255-256.

CHANDLER, R.F., HOOPER, S.N. & HARVEY. M.J. 1982a. Ethnobotany and phytochemistry of Yarrow, *Achillea millefolium*, Compositae. *Economic Botany*. 36(2):203-223.

CHANDLER, R.F., HOOPER, S.N., HOOPER, D.L., JAMIESON,W.D., FLINN, C.G. & SAFE, L.M. 1982b. Herbal remedies of Maritime Indians: Sterols and Triterpenes of *Achillea millefolium* L. *Journal of Pharmaceutical Sciences*. 71(6):690-693.

CHIAPPINI, I. & FARDELLA, G. 1980. Isolation of a new sesquiterpene lactone from *Dittrichia graveolens*. *Fitoterapia*. 51(3):161-162.

CHIH, H-W., LIN, C-C. & TANG, K-S. 1995. Anti-inflammatory activity of Taiwan folk medicine "Ham-Hong-Chho" in rats. *American Journal of Chinese Medicine*. 23(3-4):273-278.

COLEMAN, P.C., POTGIETER, D.J.J., VAN ASWEGEN, C.H. & VERMEULEN, N.M.J. 1984. Flavonoids of *Geigeria*. *Phytochemistry*. 23(5):1202-1203.

CONRADIE, E.A., STRAUGHAN, J.L. 1988. South African Medicines Formulary. CTP Book Printers. Parrow.

CONSTABEL, C.P. & TOWERS, G.H.N. 1989. The complex nature of the mechanism of toxicity of antibiotic dithiacyclohexadiene poyines (Thiarubrines) from the Asteraceae. *Planta Medica*. 55(1):35-37.

CORDELL, G.A. 1977. Recent Experimental and Clinical Data Concerning Antitumor and Cytotoxic Agents from Plants. In: New Natural Products and Drugs with Pharmalogical or Biological or Therapeutic Activity, eds. H. Wagner & P. Wolff, pp. 54-81. Springer-Verlag, Berlin.

CRAIG, J.C., MOLE, M.L., BILLETS, S. & EL-FERALY, F. 1976. Isolation and identification of the hypoglycemic agent, carboxyatractylate, from *Xanthium strumarium*. *Phytochemistry*. 15:1178.

CUTLER, H.G. 1983. Carboxyatractyloside: A compound from *Xanthium strumarium* and *Atractylis gummifera* with plant growth inhibiting properties. The probable "inhibitor A". *Journal of Natural Products*. 46(5):609-613.

DE KOCK, W.T., PACHLER, K.G.R. & WESSELS, P.L. 1968. Griesenin and dihydrogriesenin, two new sesquiterpenoid lactones from *Geigeria africana* Gries-II. *Tetrahedron*. 24:6045-6052.

DEBENEDETTI, S., MARTINO, V., PALACIOS, P. & COUSSIO, J.D. 1987. 6-Methoxy flavonoids from *Acanthospermum australe*. *Journal of Natural Products*. 50(2):325.

DELAVEAU, P. 1981 Evaluation of Traditional Pharmacopeias. In: Natural Products as Medicinal Agents, eds. J.I. Beal & E. Reinhard, pp. 217-242. Hippokrates Verlag, Stuttgart.

DELLA LOGGIA, R., TUBARO, A., SOSA, S., BECKER, H., SAAR, St. & ISAAC, O. 1994. The role of triterpenoids in the topical inflammatory activity of *Calendula officinales* flowers. *Planta Medica*. 60:516-520.

DEKKER, T.G., FOURIE, T.G., SNYCKERS, F.O., VAN DER SCHYF, C.J. 1983. Studies of South African medicinal plants. Part 2. Caespitin, a new phloroglucinol derivative with antimicrobial properties from *Helichrysum caespitium*. *South African Journal of Chemistry*. 36: 114-116.

DEKKER, T.G., FOURIE, T.G., SNYCKERS, F.O., VAN DER SCHYF, C.J. 1988. Studies of South African medicinal plants. Part 7. Rhinocerotinoic acid: a labdane diterpene with anti-inflammatory properties from *Elytropappus rhinocerotis*. *South African Journal of Chemistry*. 41(1):33-35.

DHAR, M.L., DHAR, M.M., DHAWAN, B.N., MEHROTRA, B.N. & RAY, C. 1968. Screening of Indian plants for biological activity: Part I. *Indian Journal of Experimental Biology*. 6:232-247.

DOIREAU, P., QUEMERAIS, D. & VERGER, A. 1983. Occurance of amyrenyl and germanicyl acetates as major amyrenyl and germanicyl compounds in *Lactuva sativa* L. taproot. *Biochemical Society Transactions*. 11(5):595

DOMBROWICZ, E., SWIATEK, L. & KOPYCKI, W. 1992. Phenolic acids in Inflorescentia Helichrysi and Herba Hieracii pilosellae. *Pharmazie*. 47(6):469-470.

DOMÍNGUEZ, X.A. 1977. Eupatorieae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume I, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 488-502. Academic Press. London.

DONGRE, T.K. & RAHALKAR, G.W. 1984. Ovipositional deterrents for *Earias vitella* F. in leaves of *Xanthium strumarium* (Compositae). *Indian Journal of Entomology*. 46(1):111-112.

DUKE, S.O., LEE, S.M. & PAUL, R.N. 1988. Terpenoids from the genus *Artemisia* as potential pesticides. *ACS Symposium series*. 380:318-334.

DURADOLA, J.I. 1977. Antibacterial property of crude extracts from a herbal wound healing remedy - *Ageratum conyzoides* L. *Planta Medica*. 32:338-390.

DUTTA, P., BHATTACHARYYA, P.R., RABHA, L.C., BORDOLOI, D.N., BARUA, N.C., CHOWDHURY, P.K., SHARMA, R.P. & BARUA, J.N. 1986. Feeding deterrents for *Philosamia ricini* (*Samia cynthia* subsp. *ricini*) from *Tithonia diversifolia*. *Phytoparasitica*. 14(1):77-80.

EL DAHMY, S., SARG, T., SALEM., S.A., JAKUPOVIC, J. & BOHLMANN, F. 1986. New guaianolides and farnesol derivatives from *Arctotis arctotoides*. *Planta Medica*. (5):365-367.

EL-EMARY, N.A. & ALI, A.A. 1983. Revised phytochemical study of *Tagetes erecta*. *Fitoterapia*. 54(1):9-12.

EL-KAREMY, Z.A.R., MANSOUR, R.M.A., FAYED, A.A. & SALEH, N.A.M. 1987. The flavonoids of local members of the Asteraceae (Compositae). *Biochemical Systematics and Ecology*. 15(1):53-55.

EL-MASRY, S., ABOU-DONIA, A.H.A., DARWISH, F.D., ABOU-KARAM, M.A., GRENZ, M. & BOHLMANN, F. 1984. Sesquiterpene lactones from *Chrysanthemum coronarium*. *Phytochemistry*. 23(12):2953-2954.

ENE-OBONG, E.E. & AMADI, O.C. 1987. Contributions to the Cytological effects of Medicinal plants. 1. The mitodepressive effects of water extracts of *Boerhavia diffusa* and *Vernonia amygdalina* on *Allium cepa* root tip mitosis. *Cytologia*. 52:(3):469-474.

FALK, A.J., BAUER, L. & BELL, C.L. 1974. The constituents of the essential oil from *Achillea millefolium* L. *Lloydia*. 37(4):598-602.

FARNSWORTH, N.R. & BINGEL, A.S. 1977. Problems and Prospects of Discovering New Drugs from Higher Plants by Pharmacological Screening. In: New Natural Products and Drugs with Pharmalogical or Biological or Therapeutic Activity, eds. H. Wagner & P. Wolff, pp. 1-22. Springer-Verlag, Berlin.

FIEBIG, M. & WAGNER, H. 1984. Neue antihepatotoxisch wirksame flavonolignane aus einer weißblühenden *Silybum*-varietät. *Planta Medica*. 50(4):310-313.

FRANCIS, M.J.O. 1971. Monoterpene Biosynthesis. In: Aspects of Terpenoid Chemistry and Biochemistry, ed. T.W. Goodwin, pp. 29-51. Academic Press, London.

FU, G., XU, Y., RUI, H. & XIN, X. 1986. Chemical compositions of the volatile oil from *Vernonia anthelmintica* Willd. *Youji Huaxue*. 5:379-382.

GÁBOR, M. 1986. Anti-inflammatory and anti-allergic properties of flavonoids. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 471-480. Alan R. Liss, Inc., New York.

GANJIAN, I., KUBO, I. & FLUDZINSKI, P. 1983. Insect antifeedant elemanolide lactones from *Vernonia amygdalina*. *Phytochemistry*. 22(11):2525-2526.

GARCIA, G.H., CAMPOS, R., DE TORRES, R.A., BROUSSALIS, A., FERRARO, G., MARTINO, V. & COUSSIO, J. 1990. Antiherpetic activity of some Argentine medicinal plants. *Fitoterapia*. 61(6):542-546.

GASPAR, A.R.M.D., POTGIETER, D.J.J. & VERMEULEN, N.M.J. 1986. The effect of the sesquiterpene lactones from *Geigeria* on glycolytic enzymes. *Phytochemsitry*. 35(3):493-497.

GASPAR, A.R.M.D., VERSCHOOR, J.A., NEITZ, A.W.H. & VERMEULEN, N.M.J. 1987. The influence of sesquiterpene lactones from *Geigeria* on mast cell degranulation. *Biochemical Pharmacology*. 36(15):2461-2465.

GASQUET, M., BAMBA, D., BABADJAMIAN, A., BALANSARD, G., TIMON-DAVID, P. & METZER, J. 1985. Action amoebicide et anthelminthique du vernolide et de l'hydroxyvernolide isolés des feuilles de *Vernonia colorata* (Willd.)Drake. *European Journal of Medicinal Chemistry*. 20(2):111-115

GEDA, A. & BOKADIA, M.M. 1982. Spectroscopic characterisation of a rare monoterpene from *Blumea mollis*. *Perfumery and Flavorist*. 7(1):27-29.

GEDA, A., BOKADIA, M.M. & DHAR, K.L. 1981. Essential oil of *Blumea mollis*. *Chemistry of Natural Compounds*. 17(1):43-49.

GEISSBERGER, P., SEQUIN, U. 1991. Constituents of Bidens pilosa L.: Do the components found so far explain the use of this plant in traditional medicine? *Acta Tropica* 48: 251-261.

GIANNASI, D.E. 1988. Flavonoids and evolution in the dicotyledons. In: The Flavonoids. Advances in research since 1980, ed. J.B. Harborne, 479-504. Chapmann & Hall, London.

GIESBRECHT, A.M., LOPES, J.L.C., LOPES, J.N.C. & WICHNERWSKI, W. 1985. Antibiotic activity of extracts of constituents of Compositae species. *Brazilian Journal of Medical and Biological research*. 18(5-6):727A.

GLENNIE, C.W., HARBORNE, J.B., ROWLEY, G.D. & MARCHANT, C.J. 1971. Correlations between flavonoid chemistry and plant geography in the *Senecio radicans* complex. *Phytochemistry*. 10:2413-2417.

GLENNIE, C.W., HARBORNE, J.B., ROWLEY, G.D. & MARCHANT, C.J. 1971. Correlations between flavonoid chemistry and plant geography in the *Senecio radicans* complex. *Phytochemistry*. 10:2413-2417.

GONZÁLEZ, A.G. 1977. Lactuceae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume II, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 1081-1095. Academic Press. London.

GRAVEN, E.H., DEANS, S.G., SVOBODA, K.P., MAVI, S. & GUNDIDZA, M.G. 1992. Antimicrobial and antioxidative properties of volatile (essential) oil of *Artemisia afra* Jacq. *Flavour and Fragrance Journal.* 7(3):121-123.

GREGER, H. 1977. Anthemideae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume II, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 899-941. Academic Press. London.

GROENEWEGEN, W.A., KNIGHT, D.W. & HEPTINSTALL, S. 1986. Compounds extracted from feverfew that have anti-secretory activity contain an α-methylene butyrolactone unit. *Journal of Pharmacy and Pharmacology.* 38(9):709-712.

GUÉDON, D., ABBE, P. & LAMAISON, J.L. 1993. Leaf and flower head flavonoids of *Achillea millefolium. Biochemical Systematics and Ecology.* 21: 607-611.

GUNASINGH, C.B.G. & NAGARAJAN, S. 1981. Flavonoids of the flowers of *Vernonia cinerea. Indian Journal of Pharmaceutical Sciences.* 43(3):114.

HACKETT, A.M. 1986. The metabolism of flavonoid compounds in mammals. In: Pant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 15-24. Alan R. Liss, Inc., New York.

HALIM, A.F. & ZAGHOUL, A.M. 1981. Constituents of *Arctotis grandis* leaves. *Fitoterapia.* 52(1):7-8.

HALIM, A.F., ZAGHLOUL, A.M. & BOHLMANN, F. 1980. A further guaianolide from *Arctotis grandis. Phytochemistry.* 19:2767-2768.

HALL, I.H., LEE, K.H., STARNES, C.O., SUMIDA, J.W., WU, R.Y., WADDELL, T.G., COCHRAN, J.W. & GERHART,K.G. 1979. Anti-inflammatory activity of sesquiterpene lactones and related compounds. *Journal of Pharmaceutical Sciences.* 68(5):537-542.

HANDA, S.S., PRAKASH, P. & ROY, B. 1984. Bioactivity directed extraction and fractionation of *Eclipta alba* - an antihepatotoxic drug of Indian origin. *Indian Journal of Pharmaceutical Sciences.* 46(1):50.

HARBORNE J.B. 1986. Nature, distribution and function of plant flavonoids. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 15-24. Alan R. Liss, Inc., New York.

HARBORNE, J.B. & BAXTER, H. 1993. Phytochemical Dictionary. A Handbook of Bioactive Compounds from Plants. Taylor & Francis, London.

HARBORNE, J.B. & WILLIAMS, C.A. 1977. Vernonieae - chemical review. In: The Biology and Chemistry of the Compositae, Volume 1, eds. V.H. Heywood, J.B. Harborne & B.L. Turner, pp. 523-537. Academic Press, London.

HARBORNE, J.B. 1977. Inuleae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume I, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 603-619. Academic Press. London.

HAUSEN, B.M. & HELMKE, B. 1995. Butenylbithiopene, α-terthienyl and hydroxytremetone as contact allergens in cultivars of marigold (*Tagetes* sp.). *Contact Dermatitis.* 33:33-37.

HAUSEN, B.M., BUSKER, E. & CARLE, R. 1984. The sensitizing capacity of Compositae plants. *Planta Medica.* 50(3):229-234.

HAYES, N.A. & FOREMAN, J.C. 1987. The activity of compounds extracted from feverfew on histaine release from rat mast cells. *Journal of Pharmacy and Pharmacology.* 39(6):466-470.

HEDIN, P.A. & WAAGE, S.K. 1986. Roles of flavonoids in plant resistance to insects. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 15-24. Alan R. Liss, Inc., New York.

HEGNAUER, R. 1977. The Chemistry of the Compositae. In: The Biology and Chemistry of the Compositae, Volume 1, eds. V.H. Heywood, J.B. Harborne & B.L. Turner, pp. 283-335. Academic Press, London.

HEINRICH, M., RIMPLER, H. & BARRERA, N.A. 1992. Indigenous Phytotherapy of gastrointestinal disorders in a Lowland mixed community (Oaxaca, Mexico) - Ethnopharmacological evaluation. *Journal of Ethnopharmacology*. 36(1):63-80.

HEROUT, V. 1971. Biochemistry of Sesquiterpenoids. In: Aspects of Terpenoid Chemistry and Biochemistry, ed. T.W. Goodwin, pp. 53-94. Academic Press, London.

HERZ, W. 1977. Astereae - chemical review. In: The Biology and Chemistry of the Compositae, Volume 1, eds. V.H. Heywood, J.B. Harborne & B.L. Turner, pp. 567-576. Academic Press, London.

HERZ, W. & GOVINDAN, S.V. 1980. Eucannabinolide and other constituents of *Schkuhria virgata*. *Phytochemistry*. 19:1234-1236.

HERZ, W., KULANTHAIVEL, P. & WATANABE, K. 1983. *Ent*-kauranes and other constituents of three *Helianthus* species. *Phytochemistry*. 22(9):2021-2025.

HÉTHELYI, E., KOCZKA, I. & TÉTÉNYI, P. 1989. Phytochemical and antimicrobial analysis of essential oils. *Herba Hungarica*. 28(1-2):99-116.

HEYWOOD, V.H., HARBORNE, J.B. & TURNER, B.L. 1977. An overture to the Compositae. In: The Biology and Chemistry of the Compositae, Vol. 1., eds. V.H. Heywood, J.B. Harborne & B.L. Turner, pp. 1-20. Academic Press, London.

HIKINO, H., KISO, Y., WAGNER, H. & FIEBIG, M. 1984. Antihepatotoxic Actions Of Flavonolignans From *Silybum marianum* Fruits. *Planta Medica*. 50(3):248-250.

HODNICK, W.F., ROETTGER, W.J., KUNG, F.S., BOHMONT, C.W. & PARDINI, R.S. 1986. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 249-252. Alan R. Liss, Inc., New York.

HUDSON, J.B., BALZA, F., HARRIS, L. & TOWERS, G.H.N. 1993. Light-mediated activities of thiarubrines against human immunodeficiency virus. *Photochemistry and Photobiology*. 57(4):675-680.

HUDSON, J.B., HARRIS, L., TEEPLE, A. & TOWERS, G.H.N. 1993. The anti-HIV activity of the phytochemical α-terthienyl. *Antiviral Research*. 20(1):33-43.

HUDSON, J.B., MARLES, R.J., SOUCY-BREAU, C., HARRIS, L. & ARNASON, J.T. 1994. Photoactive terthiophenes: The influence of serum on anti-HIV (Human Immunodefficiency virus) activities. *Photochemistry and Photobiology*. 60(6):591-593.

HUTCHINGS, A. & VAN STADEN, J. 1994. Plants used for stress-related ailments in traditional Zulu, Xhosa and Sotho medicine. Part 1: Plants used for headaches. *Journal of Ethnopharmacology*. 43:89-124.

HUDSON, J.B., GRAHAM, E.A., LAM, J. TOWERS, G.H.N. 1991. Ultraviolet-Dependant Biological Activities of Selected Polyines of the Asteraceae. *Planta Medica* 57: 69.

HWANG, Y., WU, K., KUMAMOTO, J., AXELROD, H. & MULLA, M.S. 1985a. Isolation and identification of mosquito repellents in *Artemisia vulgaris*. *Journal of Chemical Ecology*. 11(9):1297-1306.

HWANG, Y-S., WU, K-H. & KUMATO, J. 1985b. Mosquito repellents form *Artemisia* plants. *Proceedings and Papers. Annual Conference. California Mosquito and Vector Control Association.* 52:74-75.

IGILE, G.O., OLESZEK, W., BURDA, S., JURZYSTA, M. 1995. Nutritional assessment of *Vernonia amygdalina* leaves in growing mice. *Journal of Agricultural and Food Chemistry.* 43(8):2162-2166.

IGILE, G.O., OLESZEK, W., JURZYSTA, M., BURDA, S., FAFUNSO, M., FASANMADE, A.A. 1994. Flavonoids from *Vernonia amygdalina* and their antioxidant activities. *Journal of Agricultural and Food Chemistry.* 42: 2445-2448.

INDAP, M.A. & GOKHALE, S.V. 1986. Combined effect of cyclophosphamide and extracts of *Crotalaria* and *Senecio* plants on experimental tumours. *Indian Journal of Physiology and Pharmacology.* 30(2):182-186.

IROBI, O.N. (1992) Activities of *Chromolaena odorata* (Compositae) leaf extract against *Pseudomonas aeruginosa* and *Streptococcus faecalis. Journal of Ethnopharmacology* : 81-83.

IWU, M.M. 1993. Handbook Of African Medicinal Plants. CRC Press. Boca Raton. Florida

IYER, C.S.R. & IYER, P.R. 1978. Steroids from *Grangea maderaspatana. Phytochemistry.* 17:2036-2037.

IYER, C.S.R., IYER, P.R. & VISWANATHAN, N. 1979. Isolation of strictic acid from *Grangea maderaspatana* Poir: Identity of methyl strictate with methyl seconidoresedate. *Indian Journal of Chemistry.* 18B:529-538.

JÄGER, A.K., HUTCHINGS, A. & VAN STADEN, J. 1996. Screening of Zulu medicinal plants for prostoglandin-synthesis inhibitors. *Journal of Ethnopharmacology.* 52(2):95-100.

JAIN, S., SAREEN, V & NARULA A. 1993. Oestrogenic and pregnancy interceptory efficacy of a flavonoid mixture from *Grangea maderaspatana* Poir (*Artemisia maderaspatana*) in the mouse. *Phytotherapy Research.* 7(5):381-383.

JAKUPOVIC, J., JIA, Y., PATHAK, V.P., BOHLMANN, F. & KING, R.M. 1986. Bisabolone derivatives and sesquiterpene lactones from *Centaurea* species. *Planta Medica.* 5:399-401.

JAKUPOVIC, J., KLEMEYER, H., BOHLMANN, F. & GRAVEN, E.H. 1988. Glaucolides and guaianolides from Artemisia afra. *Phytocchemistry.* 27(4):1129-1133.

JAKUPOVIC, J., KUHNKE, J., SCHUSTER, A., METWALLY, M.A. & BOHLMANN, F. 1986. Phloroglucinol derivatives and other constituents from South African *Helichrysum* species. *Phytochemistry.* 25(5):1133-1142.

JAKUPOVIC, J., PATHAK, V.P., GRENZ, M., BANERJEE, S., WOLFRUM, C., BARUAH, R.N. & BOHLMANN, F. 1987. Sesquiterpene derivatives from *Othonna* and related species. *Phytochemistry.* 26(4): 1049-1052.

JAKUPOVIC, J., ZDERO, C., PAREDES, L. & BOHLMANN, F. 1988. Sesquiterpene glycosides and ohther constituents from *Osteospermum* species. *Phytochemistry.* 27(9):2881-2886.

JANISKOWSKA, W., SOBOCINSKA, E. & KASPRZYK, Z. 1979. Distribution of different forms of sterols in three cellular subfractions of *Calendula officinalis* leaves. *Phytochemistry.* 18:427-430.

KASTURI, T.R. & MANITHOMAS, T. 1967. Essential oil of *Ageratum conyzoides* - Isolation and structure of two new constituents. *Tetrahedron.* 27:2573-575.

KHAN, I.A., RALI, T. & STICHER O. 1993. Flavonoids and caffeic acid esters from *Dichrocephala bicolor. Planta Medica.* 59 (3):288.

KHANNA, A.K. & SEHAJPAL, P.K. 1980. Lectins: A new thought. *Vox Sanguinis.* 39(1):44-45.

KIANG, A.K., SIM, K.Y. & YOONG, S.W. 1968. Constituents of Mikania cordata (Burm. f.) B.L. Robinson (Compositae)-II. Phytochemistry. 7:1035-1037.

KOEHRLE, J., AUF'MKOLK, M., SPANKA, M., IRMSCHER, K., CODY, V. & HESCH, R-D. 1986. Iodothyroninr deiodinase is inhibited by plant flavonoids. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 359-371. Alan R. Liss, Inc., New York.

KOSHIMIZU, K., OHIGASHI, H., HUFFMAN, M.A. 1994. Use of *Vernonia amygdalina* by wild chimpanzee - Possible roles of its bitter and related constituents. *Physiology and Behavior*. 56: 1209-1216.

KRISHNASWAMY, N.R., PRASANNA, S., SESHADRI, T.R. & VEDENTHAM, T.N.C. 1975. α- and β-amyrin esters and sisterol glucoside from *Spilanthes acmella*. *Phytochemistry*. 14:1666-1667.

KUBO, I. & HANKE, F.J. 1986. A possible new role for the flavan3-ol (-)-epicatechin in plants. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 15-24. Alan R. Liss, Inc., New York.

KUPCHAN, S.M., HEMINGWAY, R.J., WERNER, D. & KARIM, A. 1968. Vernolepin, a novel elemanolide dilactone tumor inhibitor from *Vernonia hymenolepis*. *Journal of the American Chemical Society*. 90(13):358.

KUPCHAN, S.M., HEMINGWAY, R.J., WERNER, D. & KARIM, A. 1969a. Tumor inhibitors. XLVI. Vernolepin, a novel sesquiterpene dilactone tumor inhibitor from *Vernonia hymenolepis* A. Rich. *Journal of Organic Chemistry*. 34(12):3903-3908.

KUPCHAN, S.M., HEMINGWAY, R.J., WERNER, D. & KARIM, A. & WERNER, D. 1969b. Tumor inhibitors. XLVII. Vernodalin and vernomygdin, two new cytotoxic sesquiterpene lactones from *Vernonia amygdalina* Del. *The Journal of Organic Chemistry*. 34(12):3908-3911.

LAEKEMAN, G.M., MERTENS, J., TOTTÉ, J., BULT, H., VLIETINK, A.J. & HERMAN, A.G. 1983. Isolation and pharmacological characterization of vernolepin. *Journal of Natural Products*. 46(2):161-169.

LALONDE, R.T., WONG, C.F., HOFSTEAD, S.J., MORRIS, C.D. & GARDNER, L.C. 1980. N-(2Methylpropyl)-(E,E)-2,4-decadienamide. A mosquito larvicide from *Achillea millefolium* L. *Journal of Chemical Ecology*. 6(1):35-48.

LANZETTA, R., LAMA, G., MAURIELLO, G., PARRILLI, M., RACIOPPI, R. & SODANO, G. 1991. Ichthyotoxic sesquiterpenes and xanthanolides from *Dittrichia graveolens*. *Phytochemistry*. 30(4):1121-1124.

LAYCHOCK, S.G. 1986. The biochemistry of cell activation as related to the putative actions of flavonoids. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 215-229. Alan R. Liss, Inc., New York.

LEMONICA, I.P. & ALVARENGA, C.M.D. 1994. Abortive and teratogenic effect of *Acanthospermum hispidum* DC. and *Cajanus cajan* (L.) Millps. in pregnant rats. *Journal of Ethnopharmacology*. 43(1):39-44.

LWANDE, W., MACFOY, C., OKECJ, M., DELLE MONACHE, F. & MARINI BETTOLO, G.B. 1985. Kaurenic Acids from *Aspillia pluriseta*. *Fitoterapia*. LVI: 126-128.

MA-MA, K., NYUNT, N. & TIN, K.M. 1978. The protective effect of *Aclipta alba* on carbon tetrachloride induced acute liver damage. *Toxicology and Applied Pharmacology*. 45:723-728.

MABOGO, D.E.N. 1990. The Ethnobotany of the VhaVenda. Magister Scientiae. Department of Botany. University of Pretoria. Pretoria.

MABRY, T.J. & BOHLMANN, F. 1977. Summary of the chemistry of the Compositae. In.: The Biology and Chemistry of the Compositae. Volume II, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 1097-1104. Academic Press. London.

MACLEOD, A.J., PIERIS, N.M. & DE TRONCONIS, N.G. 1982. Aroma volatiles of *Cynara scolymus* and *Helianthus tuberosus*. *Phytochemistry*. 21(7):1647-1651.

MACMILLAN, J. 1971. Diterpenes - The Gibberellins. In: Aspects of Terpenoid Chemistry and Biochemistry, ed. T.W. Goodwin, pp.154-180. Academic Press, London.

MAHMOUD, Z.F., SARG, T.M., AMER, M.E. & KHAFAGY, S.M. 1983. Anthelmintic coumarin from *Ethulia conyzoides* var. *gracilis* Asch. & Schweinf. *Pharmazie*. 38(7):486-487.

MAHMOUD, Z.F., SARG, T.M., AMER, M.E., KHAFAGY, S.M. & BOHLMAN, F. 1980. A 5-methylcoumarin glucoside from *Ethulia conyzoides*. *Phytochemistry*. 19:2029-2030.

MALIK, M.S., SANGWAN, N.K. & DHINDSA, K.S. 1993. Xanthanolides from *Xanthium strumarium*. *Phytochemistry*. 32(1):206-207.

MANDAL, P.K., BISHAYEE, A. AND CHATTERJEE, M. 1993. Stimulation of tissue repair by *Mikania cordata* root extract in carbon tetrachloride-induced liver injury in mice. *Phytotherapy research*. 7(1):103-105.

MARADUFU, A., LUBEGA, R. & DORN, F. 1978. Isolation of (5E)-Ocimenone, a mosquito larvicide from *Tagetes minuta*. *Lloydia*. 41(2):181-183.

MARCO, J.A., SANZ-CERVERA, J., CORRAL, J., CARDA, M. & JAKUPOVIC, J. 1993. Xanthanolides from *Xanthium*: Absolute configuration of xanthanol, isoxanthanol and their C-4 epimers. *Phytochemistry*. 34(6):1569-1576.

MARLES, R.J., HUDSON, J.B., GRAHAM, E.A., SOUCY-BREAU, C., MORAND, P., COMPADRE, R.L., COMPADRE, C.M., TOWERS, G.H.N., ARNASON, T. 1992. Structure-activity photoactivated antiviral and cytotoxic tricyclic thiophenes. *Photochemsitry and Photobiology*. 56: 479-487.

MATHELA, D.K., PANT, A.K. & MATHELA, C.S. 1984. A pyrone glycoside from *Erigeron karwinskyanus*. Phytochemistry. 23(9):2090-2091)

MATTOCKS, A.R., 1986. Chemistry and Toxicology of Pyrrolizidine Alkaloids. Academic Press, London.

MCLACHLAN,D., ARNASON, J.T., PHILOGENE, B.J.R., CHAMPAGNE, D. 1982. Antifeedant activity of the polyacetylene, phenylheptatriyne (PHT), from the Asteraceae to *Euxoa messoria* (Lepidoptera: Noctae) *Experientia*. 38: 1061.

MERRIL, G.B. & STEVENS, K.L. 1985. Sesquiterpene lactones from *Centaurea solstitialis*. *Phytochemistry*. 24(9):2013-2018.

METWALLY, A.M., KHAFAGY, S.M. & EL-NAGGAR, S.F. 1974. Phytochemical investigation of *Xanthium spinosum* L. *Pharmazie*. 29:415-417.

METWALLY, M.A. & DAWIDAR, A.A.M. 1984. Constituents of *Conyza aegyptica* L. *Pakistan Journal of Scientific and Industrial Research*. 27(4):213-214.

MEYER, J.J.M. & DILIKA, F. 1996. Antibacterial activity of *Helichrysum pedunculatum* used in circumcision rites. Journal of *Ethnopharmacology*. 53:51-54.

MEYER, J.J.M., AFOLAYAN, A.J. 1995. Antibacterial activity of *Helichrysum aureonitens* (Asteraceae). *Journal of Ethnopharmacology*. 47: 109-111.

MEYER, J.J.M., AFOLAYAN, A.J., TAYLOR, M.B. & ENGELBRECHT, L. 1996. Inhibition of herpes simplex type 1 by aqueous extracts from shoots of *Helichrysum aureonitens* (Asteraceae). *Journal of Ethnopharmacology*. 52:41-43.

MIDDLETON, E. 1986. Effect of flavonoids on basophil histamine release and other secretory systems. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 493-506. Alan R. Liss, Inc., New York.

MIDDLETON, E., FADEN, H., DRZEWIECKI, G. & PERRISSOUD, D. 1986. Correlation of antiviral and histamine release-inhibitory activity of several synthetic flavonoids. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 541-544. Alan R. Liss, Inc., New York.

MILES, D.H., VALLAPA, C., HEDIN, P.A. & KOKPOL, U. 1993. Potential agrochemicals from leaves of *Wedelia biflora*. *Phytochemistry*. 32(6):1427-1429.

MIRVISH, S.S., SALMASI, S., LAWSON, T.A., POUR, P. & SUTHERLAND, D. 1985. Test of catechol, tannic acid, *Bidens pilosa*, Croton oil and phorbol for cocarcinogenesis of esophageal tumors induced in rats by methyl-n-amylnitrosamine. *Journal of the National Cancer Institute*. 74(6):1283-1290.

MISRA, T.N., SINGH, R.M., UPADHYAY, J. & SRIVASTAVA, R. 1984a. Isolation of a natural sterol and an aliphatic acid from *Vernonia cinerea*. *Phytochemistry*. 23(2):415-417.

MISRA, T.N., SINGH, R.S., UPADHYAY, J. & SRIVASTAVA, R. 1984b. Chemical constituents of *Vernonia cinerea*, part 1. Isolation and spectral studies of triterpenes. *Journal of Natural Products*. 47(2):368-372.

MORGAN, B., HEALD, M., BROOKS, S.G., TEE, J.L. & GREEN, J. 1972. The interactions between dietary saponin, cholesterol and related sterols in the chick. *Poultry Science*. 51:677-682.

NAIR, A.G.R., SUBRAMANAN, S.S., BOHLMANN, F., SCHÖNEWEISS, S. & MABRY, T.J. 1976. A new diterpene galactoside from *Acanthospermum hispidum*. *Phytochemistry*. 15:1776-1778.

NAKANE, H., ARISAWA, M., FUJITA, A., KOSHIMURA, S. & ONO, K. 1991. Inhibition of HIV-reverse transcriptase activity by some phloroglucinol derivatives. *FEBS Letters*. 286(1,2):83-85.

OCHOCKA, R.J., RAJZER, D., KOWALSKI, P. & LAMPARCZYK, H. 1995. Determination of coumarins from *Chrysanthemum segetum* L. by capillary elecrophoresis. *Journal of Chromatography A*. 709:197-202.

ODUOR-OWINO, P. & WAUDO, S.W. 1994. Comparative efficacy of nematicides and nematicidal plants on root-knot nematodes. *Tropical Agriculture*. 71(4):272-274.

OHIGASHI, H., HUFFMAN, M.A., IZUTSU, D., KOSHIMIZU, K., KAWANAKA, M., SUGIYAMA, H., KIRBY, G.C., WARHURST, D.C., ALLEN, D., WRIGHT, C.W., PHILLIPSON, J.D., TIMON-DAVID, P., DELMAS, F., ELIAS, R. & BALANSARD, G. 1993. Toward the chemical ecology of medicinal plant use in chimpanzees: A plant used by wild chimpanzees possibly for parasite-related diseases. *Journal of chemical ecology*. 20:541-553.

OJHA, J.K., SHARMA, P.V. & BAJPAI, H.S. 1978. *Inula racemosa* as a lipid lowering agent. Diabetes. 27(2):495.

OJUKWA, E.M. & ONUORA, G.I. 1982. The effects of extracts of fresh leaves of *Vernonia amygdalina* (Del.) in pregnant local albino mice. *Bulletin of Animal Health and Production in Africa*. 30:257-260.

OMAR, A.A., SARG, T.M., KHAFAGY, M., IBRAHIM, Y.E., ZDERO, C. & BOHLMANN, F. A eudesmanolide from *Pluchea dioscoridis*. *Phytochemistry*. 22(3):779-780.

PACCIARONI, A.C.V, SOSA, V.E., ESPINAR, L.A. & OBERTI, J.C. 1995. Sesquiterpene lactones from *Schkuhria pinnata*. *Phytochemistry*. 39(1):127-131.

PAGE, J. E., BALZA, F., NISHIDA, T., TOWERS, G.H.N. 1992. Biologically active diterpenes from *Aspillia mossambicensis*, a chimpanzee medicinal plant. *Phytochemistry*. 31: 3437-3439.

PAL, R., MOITRA, S.K., CHAKRAVARTI, N.N. & ADHYA, R.N. 1972. Campesterol from *Blumea lacera*. *Phytochemistry*. 11:1855.

PANDEY, D.K., CHANDRA, H., TRIPATHI, N.N. & DIXIT, S.N. 1983. Mycotoxicity in leaves of some higher plants with special reference to that of *Ageratum houstonianum* Mill. *Mykosen*. 26(11):565-573.

PANDEY, U.C., SINGHAL, A.K., BARUA, N.C., SHARMA, R.P., BARUAH, J.N., WATANABE, K., KULANTHAIVEL, P. & HERZ, W. 1984. Stereochemistry of strictic acid and related furano-diterpenes from *Conyza japonica* and *Grangea maderaspatana*. *Phytochemistry*. 23(2):391-397.

PARRY, D.W., O'NEILL, C.H., HODSON, M.J. 1986. Opaline Silica Deposists in the leaves of *Bidens pilosa* L. and their Possible Significance in Cancer. *Annals of Botany*. 58: 641-647.

PATEL, V.K. & VENKATAKRISHNA-BHATT, H. 1983. *Chichorium intibus* Linn - A novel herbal preparation as a gum massage, dentrifice, anti-inflammatory and antiplaque agent. *Therapie*. 38(4):405-414.

PELUSO, G., DEFEO, V., DESIMONE, F., BRESCIANO,E. & VUOTTO, M.L. 1995. Studies on the Inhibitory effects of Caffeoylquinic Acids on Monocyte Migration and superoxide Ion Production. *Journal of Natural Products*. 58: 639-646.

PETCU, P., ANDRONESCU, E., BEDELEANU, D. & BORZA, V. 1981. Phytobiochemical investigations on *Xanthium spinosum* L. *Studii si Cercetari de Biochimie*. 24(1):85-90.

PHILLIPSON,J.D., WRIGHT, C.W., KIRBY, G.C. & WARHURST, D.C. 1995. Phytochemistry of some plants used in traditional medicine for the treatment of protozoal diseases. In: Phytochemsitry of Plants Used in Traditional Medicine, eds. Hostettmann, K., Marston, A., Maillard, M. & Hamburger, M., pp. 95-135. Clarendon Press. Oxford.

PICMAN, A.K., TOWERS, G.H.N. & SUBBA ROA, P.V. 1980. Coronopilin - another major sesquiterpene lactone in *Parthenium hysterophorus*. *Phytochemistry*. 19:2206-2207.

PIERIBATTESTI, J.C., MONDON, J.M., GAYDOU, E.M. & VINCENT, E.J. 1988. Constituents of the essential oil of *Erigeron karwinskyanus*. *Agricultural and Biological Chemistry*. 52(2):599-600.

PROKSCH, P. & RODRIGUEZ, E. 1983. Chromenes and benzofurans of the Asteraceae, their chemistry and biological significance. *Phytochemistry*. 22(11):2335-2348.

QUERCIA, V., PIERINI, N., INCARNATO, G., TERRACCIANO, M. & PAPETTI, P. 1981. Identification and assay by HPLC of the flavonoid components of *Silybum marianum* in medicinal specialities. *Fitoterapia*. 51(2):83-88.

QUIJANO, L., CALDERÓN, J.S., GÓMEZ, F. & RÍOS, T. 1982. Two polymethoxyflavones from *Ageratum houstonianum*. *Phytochemistry*. 21(12):2965-2967.

QUIJANO, L., CALDERÓN, J.S., GÓMEZ, F., ESCOBAR, E. & RÍOS, T. 1985. Octasubstituted flavones from *Ageratum houstonianum*. *Phytochemistry*. 24(5):1085-1088.

RASZEJA, W. & GILL, S.T. 1977. Isolation and identification of psilostachyin B from *Ambrosia artemisiifolia* L. *Planta Medica*. 32(4):319-322.

ROBINS, D.J. 1977. Senecioneae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume II, eds. V.H. Heywood, J.B. Harborne & B.L. Turner, pp. 831-850. Academic Press, London.

RODIN, R.J., 1985. The Ethnobotany of the Kwanyama Ovambos. Allen Press Inc., Lawrence, Kansas.

RODRÍGUEZ, E. & MABRY, T.J. 1977. Tageteae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume II, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 785-797. Academic Press. London.

RODRIGUEZ, E., TOWERS, G.H.N. & MITCHELL, J.C. 1976. Biological activities of sesquiterpene lactones. *Phytochemistry*. 15:1573-1580.

ROMO DE VIVAR, A., PÉREZ C., A.L., LEÓN N., C. & DELGADO, G. 1982. 11,13-dehydroeriolin, schkuhrioidin and schkuhriolid germacranolides from *Schkuhria* species. *Phytochemistry*. 21(12):2905-2908.

ROSS, S.A., SAYED, H.M. & EL-SAYYED, S.M. 1984. Phytochemical studies ofn *Aster squamatus* L. Part 1: Flavonoid constituents of the flowers. *Egyptian Journal of Pharmaceutical Science*. 25(1-4):195-202.

SALEH, A.A., CORDELL, G.A. & FARNSWORTH, N.R. 1976. Isolation of 3,6-dimethoxy-4',5,7-trihydroxyflavone from *Acanthospermum glabratum*. *Lloydia*. 39(6):456-458.

SALEH, A.A., CORDELL, G.A. & FARNSWORTH, N.R. 1977. Acanthamolide, a melampolide amide from *Acanthospermum glabratum* (Compositae). *Journal of the Chemical Society. Chemical Communications*. 11:376-377.

SALEH, A.A., CORDELL, G.A. & FARNSWORTH, N.R. 1980. Potential anticancer agents. Part 13. Cytotoxic constituents of *Acanthospermum glabratum* (Asteraceae). *Journal of the Chemical Society. Perkin Transactions I*. 0(5):1090-1097.

SALIE, F., EAGLES, P.F.K. & LENG, H.M.J. 1996. Preliminary antimicrobial screening of four South African Asteraceae species. *Journal of Ethnopharmacology*. 52:27-33.

SAMEK, Z., HOLUB, M., DROZDZ, B. & GRABARCZYK, H. 1977. Arctolide - A new sesquiterpenic lactone from *Arctotis grandis* Thunb. *Collection of Czechoslovak Chemical Communications*. 42(7):2217-2223.

SARG, T.M., SALAM, N.A.A., EL-DOMIATY, M. & KHAFAGY, S.M. 1981. The steroid, triterpenoid and flavonoid constituents of *Eclipta alba* (L.) Hassk. (Compositae) grown in Egypt. *Scientia Pharmaceutica*. 49(3):262-264.

SASHIDA, Y., NAKATA, H., SHIMOMURA, H. & KAGAYA N. 1983. Sesquiterpene lactones from Pyrethrum flowers. *Phytochemistry*. 22(5):1219-1222.

SAXENA, V.K. & MONDAL, S.K. 1994. A xanthanolide from *Xanthium strumarium*. *Phytochemistry*. 35(4):1080-1082.

SAYED, M.D., ZAKI, A.Y. & DOSS, S.L. 1980. Quantitative estimation of the sesquiterpene lactones of *Vernonia amygdalina* (Del.) and *Tithonia diversifolia* (Gray) cultivated in Egypt. *Egyptian Journal of Pharmaceutical Sciences*. 21(1-2):125-130.

SCALBERT, A. 1991. Antimicrobial properties of tannins. *Phytochemistry*. 30(12):3875-3883.

SCHWARTING, A.E. 1977. Dimeric natural compounds with Pharmacological Activity. In: New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity, eds. H. Wagner & P. Wolff, pp. 197-211. Springer-Verlag, Berlin.

SELWAY, J.W.T. 1986. Antiviral activity of flavones and flavans. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton & J.B. Harborne, pp. 521-535. Alan R. Liss, Inc., New York.

SETO, M., MIYASE, T., UMEHARA, K., UENO, A., HIRANO, Y. & OTANI, N. 1988. Sesquiterpene lactones from *Cichorium endiva* L. and *C. intybus* L. and cytotoxic activity. *Chemical and Pharmaceutical Bulletin*. 36(7):2423-2429.

SHARMA, G.L. & BHUTANI, K.K. 1988. Plant based antiamoebic drugs; part II. Amoebicidal activity of parthenin isolated form *Parthenium hysterophorus*. *Planta Medica*. 54:120-122.

SHIBATA,S. 1977. Saponins with biological and pharmalogical activity. In: New Natural Products and Plant Drugs with Pharmalogical, Biological or Therapeutical Activity, eds. H.Wagner & P. Wolff, pp. 177-196. Springer-Verlag, Berlin.

SHIMIZU, M., HORIE, S., ARISAWA, M., HAYASHI, T., SUZUKI, S., YOSHIZAKI, M., KAWASAKI, M., TERASHIMA, S., TSUJI, H., WADA, S., UENO, H., MORITA, N., BERGANZA, L.H., FERRO, E. & BASUALSO, I. 1987. Chemical and pharmaceutical studies on medicinal plants in Paraguay. I. Isolation and identification of Lens Aldose Reductase Inhibitor from "Tapecué", *Acanthospermum australe* O.K. *Chemical and Pharmaceutidal Bulletin*. 35(3):1234-1237.

SØRENSEN, N.A. 1977. Polycetylenes and conservatism of chemical characters in the Compositae. In.: The Biology and Chemistry of the Compositae. Volume I, eds. V.H. Heywood, J.B. Harborne & B.L. turner., pp. 385-409. Academic Press. London.

SPRING, O., KLEMT, V., ALBERT, K. & HAGER, A. 1986. A furanoheliangolide in Helianthus debilis: implications for chemotaxonomy of the genus *Helianthus*. *Zeitschrift fuer Naturforschung. Section C. Biosciences*. 41(7-8):695-698.

SPRING, O., KUPKA, J., MAIER, B. & HAGER, A. 1982. Biological activities of sesquiterpene lactones from *Helianthus annuus*: Antimicrobial and cytotoxic porperties; influence on DNA, RNA, and protein synthesis. *Zeitschrift fuer Naturforschung. Section C. Biosciences*. 37c(11-12):1087-1091.

SRIVASTAVA, A.K. & CHIASSON, Q. 1986. Effect of quercetin on serine/threonine and tyrosine protein kinases. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 541-544. Alan R. Liss, Inc., New York.

SRIVASTAVA, R.P. & PROKSCH, P. 1993. Insecticidal and antifeedant effects of compounds of plant origin against insect pests. *Indian Journal of Plant Protection*. 21(2):234-239.

ST. PYREK. 1985. Sesquiterpene lactones of *Cichorium intybus* and *Leontodon autumnalis*. *Phytochemistry*. 24(1):186-188.

STEVENS, G.A. & TANG, C-S. 1985. Inhibiting of seedling growth of crop species by recirculating root exudates of *Bidens pilosa* L. *Journal of Chemical Ecology*. 11(10):1411.

STEVENS, K.L. & MERRIL, G.B. 1985. Sesquiterpene lactones and allelochemicals from *Centaurea* species. *ACS Symposium Series*. 268:83-98.

STICHER, O. 1977. Plant mono-, di- and sesquiterpenoids with pharmalogical or therapeutic activity. In: New Natural Products and Plant Drugs with Pharmalogical, Biological or Therapeutical Activity, eds. H.Wagner & P. Wolff, pp. 137-176. Springer-Verlag, Berlin.

STIPANOVIC, R.D., MILLER, R.B. & HOPE, H. 1985. Argophyllone-B, a sesquiterpene lactone from *Helianthus argophyllus*. *Phytochemistry*. 24(2):358-359.

SURESH, B., KALYANARAMAN, V.R., DHANASEKARAN, S., ANNADURAI, K., DHABARAJ, S.A. & BALASUBRAMANIAN, S. 1995. Evaluation of *Santolina* oil in search of new drugs against candidiasis. *Indian Journal of Pharmacology*. 27(3):171-177.

SWAIN, T. & WILLIAMS, C.A. 1977. Helianthae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume II, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 673-697. Academic Press. London.

TADA, M., CHIBA, K., YAMADA, H. & MARUYAMA, H. 1991. Phloroglucinol derivatives as competitive inhibitors against thromboxane A_2 and leukotriene D_4 from *Hypericum erectum*. *Phytochemistry*. 30(8):2559-2562.

TALAPATRA, S.K., BHAR, D.S. & TALAPATRA, B. 1977. Terpenoids and related compounds: Part XIII - Epoxylupeol, a new triterpenoid from *Eupatorium odoratum*. *Indian Journal of Chemistry*. 15B(9):806-807.

TARIQ, M., MOSSA, J.S., AL-YAHYA, M.A., AL-MESHAL, I.A. & AL-DABAR, A.A. 1987. Phytochemical and biological screening of Saudi medicinal plants. part 10. A study on Saudi plants of family Compositae. *International Journal of Crude Drug Research*. 25(1):17-25.

TING, I.P. 1982. Plant physiology. Addison-Wesley Publishing Company, Reading, Massachusetts.

TOMÁS-BARBERÁN, F.A., MSONTHI,J.D. & HOSTETTMANN, K. 1988. Antifungal epicuticular methylated flavonoids from *Helichrysum nitens*. *Phytochemistry*. 27(3):753-755.

TOMÁS-LORENTE, F., INIESTA-SANMARTÍN, E., TOMÁS-BARBERÁN, F.A., TROWITZSH-KIENAST, W. & WRAY, V. 1989. Antifungal phloroglucinol derivatives and lipophilic flavonoids from *Helichrysum decumbens*. *Phytochemistry*. 28(6):1613-1615.

TOMASSINI, T.C.B. & MATOS, M.E.O. 1979. On the natural occurance of 15α-tiglinoyloxy-kaur-16-en-19-oic acid. *Phytochemistry*. 18:664-665.

TOPCU, G., ÖKSÜZ, S., SHIEH, H., CORDELL, G.A., PEZZUTO, J.M., BOZOK-JOHANSSON, C. 1993. Cytotoxic and antibacterial sesquiterpenes from *Inula graveolens*. *Phytochemistry* 33: 407-410.

TOWERS, G.H.N. 1980. Photosensitizers from plants and their photodynamic action. *Progress in Phytochemistry*. 6:183-202.

TOWERS, G.N.H., ARNASON, T., WAT, C-K., GRAHAM, E.A., LAM, J. & MITCHELL, J.C. 1979. Phototoxic polyacetylenes and their thiophene derivatives (Effects on human skin). *Contact Dermatitis*. 5(3):140-144.

TOWERS, G.H.N. & CHAMPAGNE, D.E. 1977. Medicinal photochemistry of the Compositae: The activities of selected acetylenes and their sulphur derivatives. In: Chemistry and Biology of Naturally-occurring Acetylenes and Related Compounds (NOARC), eds, J. Lam, H. Breteler, T. Arnason & L. Hansen, pp. 139-149. Elsevier, Amsterdam.

TOWERS, G.H.N., WAT, C-K., GRAHAM, E. & BANDONI, R.J. 1977. Ultraviolet-mediated antibiotic activity of species of Compositae caused by Polyacetylenic compounds. Lloydia. 40(5):487-498.

TOZYO, T., YOSHIMULA, Y., SAKURAI, K., UCHIDA, N., TAKEDA, Y., NAKAI, H. & ISHII, H. 1994. Novel antitumor sesquiterpenoids in *Achillea millefolium*. *Chem. Pharm. Bul.* 42: 1096-1099.

TSANKOVA, E. & BOHLMANN, F. 1983. A monoterpene from *Aster bakerianus*. *Phytochemistry*. 22(5):1285-1286.

VAN ASWEGEN, C.H., POTGIETER, D.J.J. & VERMEULEN, N.M.J. 1982. Site of respiratory inhibition by sesquiterpene lactones from *Geigeria*. *South African Journal of Scinece*. 78:125-127.

VAN PUYVELDE, L., DE KIMPE, N., COSTA, J., MUNYJABO, V., NYIRANKULIZA, S., HAKIZAMUNGU, E. & SCHAMP, N. 1989. Isolation of flavonoids and a chalcone from *Helichrysum odoratissimum* and synthesis of helichrysetin. *Journal of Natural Products*. 52(3):629-633.

VAN PUYVELDE, L., NTAWUKILIYAYO, J.D., PORTAELS, F. & HAKIZAMUNGU, E. 1994. *In vitro* inhibition of Mycobacteria by Rwandese medicinal plants. *Phytotherapy Research*. 8(2):65-69.

VANHAELEN, M. & VANHAELEN-FASTRÉ, R. 1975. Lactonic lignans from *Cnicus benedictus*. *Phytochemistry*. 14:2709.

VARMA, P.N., TALWAR, S.K. & GARG, G.P. 1980. Chemical investigation of *Silybum marianum*. *Planta Medica*. 38(4):377-378.

VARMA, S.D. 1986. Inhibition of aldose reductase by flavonoids: Possible attenuation of diabetic complications. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 343-358. Alan R. Liss, Inc., New York.

VERZÁR-PETRI, G., CUONG, B.N., RADICS, L. & ÚJSZÁSZI, K. 1979. Isolation of azulene from yarrow oil (*Achillea millefolium* L. species complex) and its identification. *Herba Hungarica*. 18(2):83096.

VLIETINCK, A.J., VANDEN BERGHE, D.A. & HAEMERS, A. 1988. Present status and prospects of flavonoids as anti-viral agents. In: Plant Flavonoids in Biology and Medicine II, eds. V. Cody, E. Middleton, J.B. Harborne & A. Beretz, pp. 283-299. Alan R. Liss, Inc., New York.

VYAS, A.V. & MULCHANDANI, N.B. 1984. Structure reinvestigation of Conyzorigun, a new chromone form *Ageratum conyzoides*. *Journal of the Chemical Society. Perkin Transactions I.* 12:2945-2947.

VYAS, V.V. & MULCHANDANI, N.B. 1986. Polyoxygenated flavones from *Ageratum conyzoides*. *Phytochemistry*. 25(11):2625-2627.

WAGNER, H. 1977a. Cynaraceae - chemical review. In.: The Biology and Chemistry of the Compositae. Volume II, eds. V.H. Heywood, J.B. Harborne & B.L. Turner., pp. 1017-1038. Academic Press. London.

WAGNER, H. 1977b. Pharmaceutical and economic uses of the Compositae. In: The Biology and Chemistry of the Compositae, Volume I. eds, V.H. Heywood, J.B. Harborne & Turner, B.L. Academic Press, London.

WAGNER, H. 1981. Plant constituents with Antihepatotoxic Activity. In: Natural Products as Medicinal Agents, eds. J.I. Beal & E. Reinhard, pp. 217-242. Hippokrates Verlag, Stuttgart.

WAGNER, H. & FESSLER, B. 1986. *In vitro* 5-Lipoxygenase inhibition by Eclipta alba extracts and the coumestan derivative wedelolactone. Planta Medica. 5:374-377.

WAGNER, H., GERHÄUSER, C. & SAMTLEBEN, R. 1995. Bioactive polymers from higher plants. In: Phytochemsitry of Plants Used in Traditional Medicine, eds. Hostettmann, K., Marston, A., Maillard, M. & Hamburger, M., pp. 205-225. Clarendon Press. Oxford.

WAT, C-K., BISWAS, R.K., GRAHAM, E.A., BOHM, L. & TOWERS, G.H.N. 1979b. Ultraviolet-mediated cytotoxic activity of phenylpeptatriyne from *Bidens pilosa* L. *Journal of Natural Products*. 42(1):103-111.

WAT, C-K., JOHNS, T., TOWERS, G.H.N. 1980. Phototoxic and antibiotic activities of plants of the Asteraceae used in folk medicine. *Journal of Ethnopharmacology*. 2: 279-290.

WATANABE, K., OHNO, N., YOSHIOKA, H., GERSHENZON, J. & MABRY, T.J. 1982. Sesquiterpene lactones and diterpenes from *Helianthus argophyllus*. *Phytochemistry*. 21(3):709-713.

WATT, J.M. 1967. African plants potentially useful in mental health. *Lloydia*. 30(1):1-22.

WATT, J.W. & BREYER-BRANDWIJK, M.G. 1962. The Medicinal and Poisonoud Plants of Southern and Eastern Africa. E. & S. Livingstone Ltd., Edinburgh.

WEAVER, D.K., WELLS, C.D., DUNKEL, F.V., BERTSCH, W., SING, S.E. & SRIHARAH, S. 1994. Insecticidal activity of floral, foliar, and root extracts of *Tagetes minuta* (Asterales: Asteraceae) against adult Mexican Bean Weavils (Coleoptera: Bruchidae). *Journal of Economic Entomology*. 87(6):1718-1725.

WELTON, A.F., TOBIAS, L.D., FRIEDLER-NAGY, C., ANDERSON, W., HOPE, W., MEYERS, K. & COFFEY, J.W. 1986. Effect of flavonoids on arachidonic acid metabolism. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 231-242. Alan R. Liss, Inc., New York.

WENKERT, E. & ARRHENIUS, S.T. 1983. Direct stereocontrolled Synthesis of Isocomene. *Journal of the American Chemical Society*. 105(7):2030-2033.

WHITTLE, S.R. & TURNER, A.J. 1981. Anti-convulsants and brain aldehyde metabolism. *Biochemical Pharmacology*. 30(11):1191-1196.

WILLIAMS, V.L. 1996. The Witwatersrand muti trade. *Veld & Flora*. 82(1):12-14.

WOLLENWEBER, E. & MANN, K. 1989. Exudate flavonoids of three essential oil plants from the Ciskei (South Africa). *Fitoterapia*. 60(3):249-251.

WOOD, A.W., SMITH, D.S., CHANG, R.L., HUANG, M-T. & CONNEY, A.H. 1986. Effects of flavonoids on the metabolism of xenobiotics. In: Plant Flavonoids in Biology and Medicine, eds. V. Cody, E. Middleton, & J.B. Harborne, pp. 15-24. Alan R. Liss, Inc., New York.

WRANG, P.A. & LAM, J. 1975. Polyacetylenes from *Chrysanthemum leucanthemum*. *Phytochemistry*. 14:1027-1035.

WRIGHT, W.G. 1976. South African Plant Extractives. Part III. Helichrysin, a new chalcone glucoside from *Helichrysin* species. *Journal of the Chemical Society. Perkin Transactions*. 16:1819-1820.

XIAO, P.G. 1981. Traditional Experience of Chinese Herb Medicine Its Application in Drug Research and New Drug Searching. In: Natural Products as Medicinal Agents, eds. J.I. Beal & E. Reinhard, pp. 217-242. Hippokrates Verlag, Stuttgart.

YAMANE, M.A., WILLIAMS, A.C. & BARRY, B.W. 1995. Effects of terpenes and oleic acid as skin penetration enhancers towards 5-fluorouracil as assessed with time-permeation, partitioning and differential scanning calorimetry. *International Journal of Pharmaceutics*. 116(2):237-251.

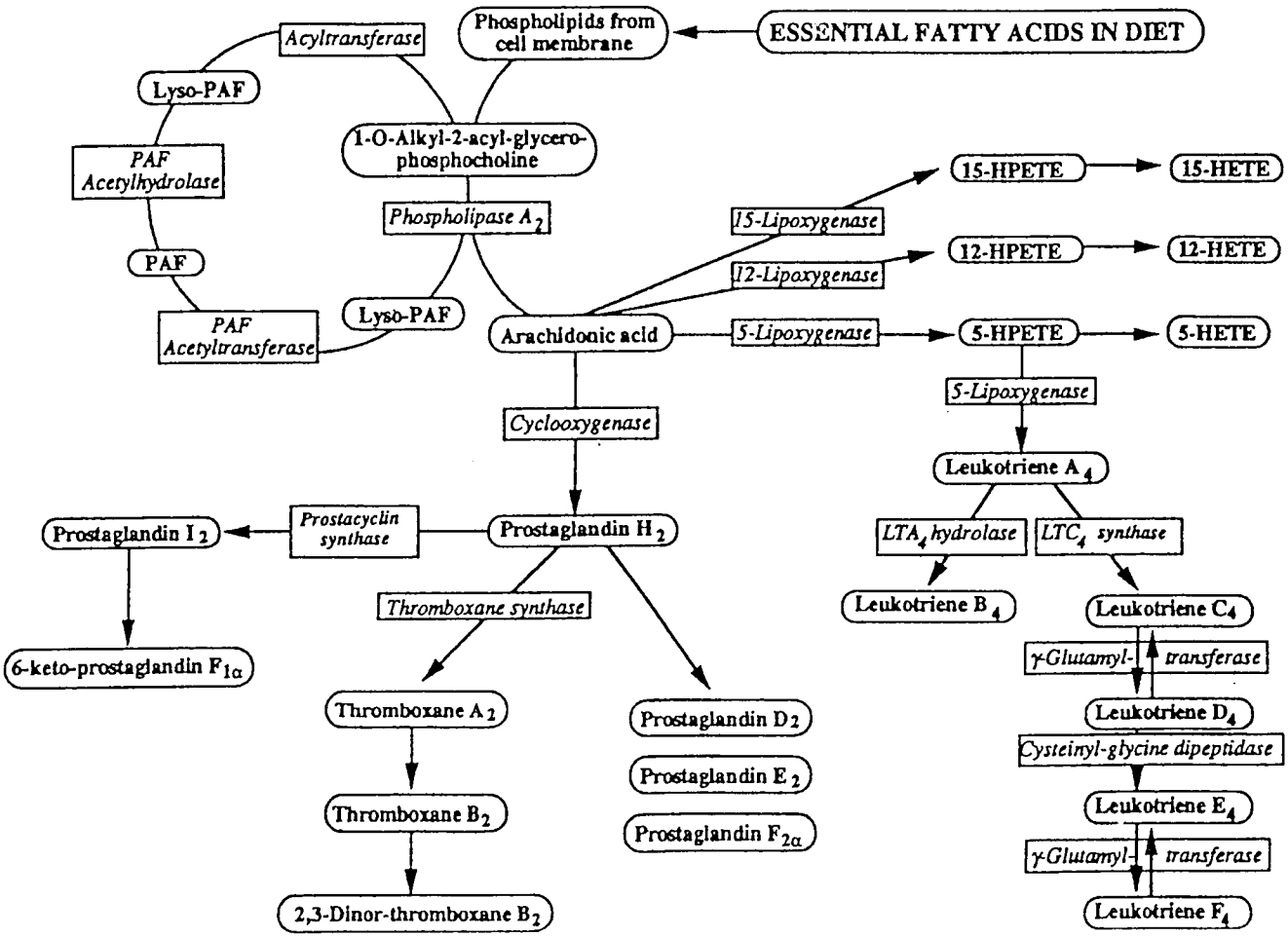
YSREAL, M.C. & CROFT, K.D. 1990. Inhibition of leukotriene and platelet activating factor synthesis in leukocytes by the sesquiterpene lactone scandenolide. *Planta Medica*. 56:485-489.

ZDERO, C., BOHLMANN, F., WASSHAUSEN, D.C. & MUNGA, M.G. 1991. Glaucolides from Old World *Vernonia* species. *Phytochemistry*. 30(12):4025-4028.

ZHOA, X-L., CHAN, M-Y. & OGLE, C.W. 1989. The identification of pyrrolizidine alkaloid-containing plants - A study on 20 herbs of the Compositae family. *American Journal of Chinese Medicine*. 17(1-2):71-78.

ZULUETA, M.C.A., TADA, M. & RAGASA, C.Y. 1995. A diterpene from *Bidens pilosa*. *Phytochemistry*. 38(6):1449-1450.

APPENDIX 1: Pathways of phospholipid-derived inflammatory mediators.



APPENDIX 2: Glossary

alexia. A form of aphasia in which brain damage causes inability to grasp the meaning of written or printed words, also called visual aphasia or word blindness.
amenorrhea. Absence of menstruation.
anthelmintic, anthelminthic, antihelminthic. Able to destroy or expel intestinal worms.
anthracosis. Disease caused by accumulation of carbon in the lungs.
anthrax. An acute infectious disease of wild and domesticated animals which may be transmitted to man either directly or by contact with hides or hair infected with the anthrax bacillus; the characteristic lesion in man resembles a carbuncle.
antipruritic. Relieving itching.
antipyretic. Reducing or tending to reduce fever.
antiseptic. A germicide, or under special conditions, a bacteriostat, generally used on living tissue.
atrophic. Characterized by atrophy.
atrophy. A wasting, progressive degeneration and loss of function of any part of the body.
Bacillus. A genus of rod-shaped bacteria.
B. anthracis, a causative agent of anthrax.
B. cereus, a saprophytic, spore-forming bacillus with peritrichous flagella; thought to be responsible for some outbreaks of food poisoning.
B. subtilis, a widely distributed saprophytic, spore-forming, gram-positive bacillus found in soil and decomposing organic matter; a source of antibiotics; also called hay or grass bacillus.
Candida. Yeastlike fungi.
C. albicans, the saprophyte which most commonly is responsible for monilial infections, such as thrush, vaginitis and sometimes systemic infection.
candidiasis. Infection with microorganisms of the genus *Candida*.
carminative. Acting/medicine to remedy colic and flatulence.
catarrh. Inflammation of a mucous membrane, especially of the nose and throat, with a discharge.
cathartic. A drug that promotes evacuation of intestinal contents of a more or less fluid state, by increasing motor activity of the intestine, either directly or reflexly; distinguished from a laxative which produces a milder effect; also called purgative.
caustic. Corrosive; capable of burning.
cholagogue. Any agent that promotes the flow of bile.
cholecystitis. Inflammation of the gallbladder.
choleretic. The secretion of bile by the liver.
cicatrization. The formation of scar tissue.
colic. 1. Relating to the colon. 2. Acute abdominal pain. 3. A symptom complex seen in infants under three months of age, characterized by paroxysmal abdominal pain and frantic crying.
colitis. inflammation of the colon.
conjunctivitis. Inflammation of the conjunctiva resulting from bacterial, viral or allergic agents; acute catchall conjunctivitis is caused by a bacterium (usually pneumococcus), epidemic keratoconjunctivitis is caused by a virus (adenovirus 8), vernal catarrh is caused by hypersensitivity to exogenous allergens.
contusion. A superficial injury or bruise.
convalescence. A stage in recovery between abatement of a disease or injury and complete health.
Cryptococcus. A genus of yeastlike fungi.
C. neoformans, species commonly found in pigeon droppings and causing cryptococcosis in man.
Cryptococcosis. A chronic disseminated disease caused by the fungus *Cryptococcus neoformans*; it causes a respiratory infection often overlooked until it spreads to other areas of the body, particularly to the central nervous system where it causes meningitis; also called torulosis.
cystitis. Inflammation of the urinary bladder.
diaphoretic. 1. An agent that causes sweating, especially profuse sweating. 2. Perspiring.
diarrhoea. Abnormally frequent passage of loose stools.
diphtheria. An acute contagious disease caused by a bacillus, *Corynebacterium diphtheriae*; marked by inflammation of the upper respiratory tract, fibrin formation (false membrane) of mucous membranes, an elaboration of soluble exotoxin which acts on the heart and cranial or peripheral nerve cells.
discutient. Denoting an agent that causes the dispersal of a tumor or any pathologic accumulation.
dropsy. Obsolete term to describe heart failure, chronic renal disease and other fluid-retaining states.
dysmenorrhoea. Painful menstrual periods.
dyspepsia. Indigestion.

dysuria. Difficulty of pain in urination.
emmenagogue. 1. Increasing or producing menstrual flow. 2. Any agent producing such an effect.
emetic. Causing vomiting.
emollient. 1. Soothing. 2. An agent that softens and soothes the skin and mucous membranes.
epistaxis. nosebleed.
erysipelas. An acute contagious disease caused by *Streptococcus pyogenes*, marked by a circumscribed red eruption on the skin, chills and fever.
expectorant. 1. Promoting the expulsion of mucus or other material from the air passages.
febrifuge. Febrile. Having fever.
gonorrhea. A common contagious disease caused by *Neisseria gonorrhoeae* and transmitted chiefly by intercourse.
gripe. Colic; sharp pain in the intestines.
halitosis. Unpleasant breath; some causes are poor mouth hygiene, infection in the oronasopharyngeal structures, and lung abscess.
hemorrhoid. A dilated (varicose) vein situated at or near the anus.
hemostatic. 1. Arresting hemorrhage. 2. Any agent that stops bleeding.
indigestion. 1. Discomfort caused by a temporary inability to digest food properly. 2. Failure of digestion.
inflammation. A tissue reaction to irritation, infection or injury, marked by localized heat, swelling, redness, pain and sometimes loss of function.
inflammatory. Relating to, marked by, resulting from or causing inflammation.
i.p. Intraperitoneal.
i.v. Intravenously
jaundice. Yellow pigmentation of the skin and/or sclera caused by high levels of bilirubin in the blood.
keratolytic. Causing scaling of the epidermis.
leucodermia. Absence of pigment in the skin.
leukorrhea. An abnormal white or yellowish discharge from the vagina, containing mucus and puss cells.
lumbago. Backache in the lumbar region.
Micrococcus. A genus of bacteria characterized by a spherical shape and occurring singly, in pairs and in irregular clusters.
Microsporum. A genus of fungi causing skin infections.
mast. Combining form denoting breast.
neuralgia. Severe pain along the course of a nerve.
nidation. The embedding or implantation of the fluid-filled blastocyst in the uterine mucosa during pregnancy.
oestrogenic. Inducing oestrus.
oestrus. The recurrent period of sexual excitement in the female mammals, also called heat.
oxytocic. 1. Relating to rapid child birth. 2. An agent that hastens the process of childbirth, especially by stimulating contraction of uterine muscle.
pediculus. A genus of lice of the family Pediculidae.
periodontitis. A disease of the periodontium manifested by inflammation of the gums, loss of bone tissue around the teeth, degeneration of the periodontal membrane of ligament, and the formation of pockets between the teeth and the surrounding bone; also called pyorrhea.
phthisis. 1. Tuberculosis. 2. A wasting away of tissue.
phytoalexins. A group of antibiotics produced by plants in response to damage or infection which help disease resistance to micro-organisms or environmental accidents.
p.o. *per os*. By mouth.
purgative. See cathartic.
pus. A thick, viscous yellowish fluid, product of inflammation, composed chiefly of dead white blood cells (leukocytes) and a thin liquid (liquor puris), and often a microbiologic agent responsible for the inflammation.
pyorrhea. See periodontitis.
sciatica. Any condition characterized by pain along the course of the sciatic nerve; usually a neuritis and generally caused by mechanical compression or irritation of the 5th lumbar spinal root.
scrofula. Tuberculous inflammation of lymph nodes in the neck of children, caused by *Myobacterium bovis*; relatively rare in the United states as a result of elimination of tuberculous cattle and pasteurization of milk.
seborrhoeic. Dermatitis. Inflammation of the skin.

Staphylococcus. A genus of gram-positive, nonmotile, usually pathogenic bacteria which tend to aggregate in grapelike clusters.
S. aureus, a species containing the pigmented, coagulase positive variety which causes boils, carbuncles, abscesses, and other suppurative inflammations.

Streptococcus. A genus of gram-positive , round or ovoid bacteria, pathogenic and/or nonpathogenic in man, occurring in pairs or chains; medically classified according to their hemolytic activity on blood agar as α-hemolytic streptococci, which produce a zone of incomplete hemolysis and green discoloration adjacent to the colony, β-hemolytic streptococci, which produce a clear zone of hemolysis around the colony, and γ-streptococci, which produce no hemolysis.
S. pneumoniae, a rarely spherical species which causes lobar pneumonia and other acute pus-forming conditions such as middle ear infections and meningitis.
S. pyogenes, a species which is the cause of several acute pyogenic (pus-forming) infections in man, such as scarlet fever, erysipelas and sore throat.

sudorific. Causing perspiration; also called diaphoretic and sudoriferous.

t.d.s. *Ter die sumendum*. Latin for to be taken three times a day; used in prescription writing.

tonic. A remedy that is supposed to restore vigour.

Trichophyton. A genus of pathogenic ringworm fungi being parasitic in the skin, nails and hair follicles of man.
T. mentagrophytes causes ectothrix infections of the scalp and beard hair.
T. rubrum, the cause of superficial infections of the skin and nails.

tussive. Relating to or caused by a cough.

vermifuge. An agent that expels intestinal worms.

vitiligo. Sharply demarcated milky-white patches on the skin, usually on the face, neck, hands, lower abdomen, and thighs, caused by the absence of melanin; also called acquired leukoderma.