Medicinal Applications and Toxicological Activities of *Aloe* Products

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Abstract

Aloe (Lilliaceae) has long been used as a remedy in many cultures. *Aloe* products, which include the latex, gel, and whole leaf, are used, among other reasons, as laxatives, in creams for skin ailments, and as a treatment for a wide range of diseases, respectively. The heterogeneous nature of *Aloe* products may contribute to the diverse biological and therapeutic activities that have been observed. Variations in the composition of *Aloe* can result in products with different chemical and physical properties, making the comparison of products difficult. In this article, the chemistry, uses, pharmacological activity, and toxicity of *Aloe* gel, latex, and isolated compounds are reviewed. This article is confined to literature pertaining to *Aloe vera* (L.) Burm.f. (also known as *A. barbadensis* Miller) and *Aloe ferox* Miller since they are the most widely used species both commercially and for their therapeutic properties.

Introduction

There are approximately 500 species of the genus *Aloe* (Lilliaceae) (Swanson, 1995), of which 160 are indigenous to South Africa. Many of these are used in traditional healing (Lindsey et al., 2002). "Aloes" is the generic name for the solid residue obtained by boiling and cooling the latex of *Aloe ferox* Miller, its hybrids, and *A. vera* (L.) Burm.f. (also known as *A. barbadensis* Miller). *Aloe* has long been used as a remedy in many cultures. There are anecdotal references to its use in ancient Egypt in 1500 B.C., and it is mentioned in the pharmacopoeia produced by Dioscorides in the first century A.D. (Castleman, 1991). *Aloe* gel, the clear jelly-like substance obtained from the parenchymatous cells in the inner leaf, was first used clinically in the 1930s for the treatment of radiation burns (Tyler et al., 1981). Today, *Aloe* gel is a familiar ingredient used in ointments and the cosmetic industries. The latex, found in the pericyclic cells in the margins of the leaves, is mainly used for its laxative effect. In this paper, the chemistry, uses, pharmacological activity, and toxicity of *Aloe* gel, latex, and isolated compounds are reviewed. This article is confined to literature pertaining to *Aloe vera* and *Aloe ferox* since they are the most widely used species both commercially and for their therapeutic properties.

Botany of the *Aloe* plant

Aloe ferox and *A. vera* belong to the family Liliaceae and the tribe Aloineae. *Aloe* are perennial succulents and are characterized by stemless large, thick, fleshy leaves that are lance shaped and have a sharp apex and a spiny margin. *Aloe* leaves have a yellow latex, which is referred to as *Aloe* juice or sap and has a bitter taste. The leaf pulp is the innermost portion of the leaf and is composed of the parenchyma cells that contain the gel. Although *A. vera* originated in the warm, dry climates of Africa, the plant is readily adaptable and occurs naturally worldwide.

Chemistry

Aloe gel contains polysaccharides, primarily of β-(1,4)-linked, polydispersed, highly acetylated mannans (hence "acemannan") with an average molecular weight of 1000 kDa (Femenia et al., 1999). The polysaccharides are unstable and are affected by acidity, certain enzymes, and heat (Femenia et al., 2003). *A. vera* gel contains three malic acid acylated carbohydrates: Veracylglucans A, B, and C. All three compounds demonstrate anti-inflammatory effects, but whereas Veracylglucan A and Veraglucan B possess anti-proliferative effects, Veraglucan C enhances cell proliferation (Esua & Rauwald, 2006).

The main active constituents of the latex are anthraquinones, which include aloins A and B, barbaloin, isobarbaloin, and emodin (Wichtl & Bisset, 1994). Also included are aloe-emodin, resins, aloesin and its aglycone, aloesone, and chromone derivatives (Wichtl & Bisset, 1994). Other potentially active constituents are lipids, amino acids, enzymes, and sterols (Bruneton, 1995).

Aloe contains the enzymes carboxypeptidase and bradykinase, both of which have been shown to relieve pain and decrease inflammation and swelling (Duke, 1997). Salicylic acid has also been detected in *A. vera* (Robson et al., 1982), as has a relatively high concentration of mannose 6-phosphate (Davis et al., 1994). The potent anti-oxidative compound 8-C-β-D-glucopyranosyl-2-propyl-7-methoxy-5-methylchromone, has been isolated from a methanol extract of *A. vera* (Lee, 2000) and iso-aloesin (2-acetonyl-6-C-β-D-glucopyranosyl-7-hydroxy-5-methylchromone) from the leaves this plant (Yuan, 1993; Yuan et al., 1991). The anti-inflammatory compound aloeresin I was recently isolated from *A. ferox* (Speranza et al., 2005). The presence of two dihydrocoumarins with immunomodulatory and antioxidative properties has also been reported (Zhang et al., 2006).

Studies of the concentrations of the major compounds in fresh *A. ferox* leaf exudates have shown them to be remarkably consistent, with aloeresin A, aloesin, and aloin (both epimers A and B) contributing between 70 and 97% of total dry weight, in a ratio of approximately 4:3:2, respectively (van Wyk et al., 1997). The age of the plant plays a role in the levels of polysaccharides and flavonoids (Hu et al., 2003), as do climatic conditions. The concentrations in the final products depend on the preparation technique used (Reynolds & Dweck, 1999).

Methods of Detection

In body fluids

Detection of aloin and its metabolites in urine is possible using thin-layer chromatography (Perkins & Livesey, 1993). In plasma, High-performance liquid chromatography (HPLC) is more sensitive, with a limit of detection (LOD) of 4.5 ng/ml (Zaffaroni et al., 2003).

In plant material

Methods reported include micellar electrokinetic chromatography (Kuzuya et al., 2001), Gas chromatography-mass spectrometry (GC-MS) (Saccu et al., 2001), capillary zone electrophoresis (Wang et al., 2000), HPLC (Cao & Liu 2003), and size exclusion chromatography with refractive index detection (Turner et al., 2004).

In pharmaceuticals

HPLC has been used to quantitate barbaloin in *Aloe* capsules, with an LOD of 0.002 µg (Chen et al., 2002) and for the detection of *Aloe* components in creams (Yamamoto et al., 1985). A quantitative colorimetric assay for glucomannan in *Aloe* products was described by Eberendu et al. (2005); this method showed negligible interference by non-*Aloe* polysaccharides and was rapid, producing results within 5 min. GC-MS with a LOD of 0.005 ppm for aloe-emodin and 0.05 ppm for aloin (ElSohly et al., 2004) and size exclusion chromatography with refractive index detection (Turner et al., 2004) may also be used. GC-MS has been employed to detect *Aloe* components in cosmetic products (Nakamura & Okuyama, 1990).

Food

An HPLC method (Yamamoto et al., 1985) and an interesting rapid amplified polymorphic DNA method (Shioda et al., 2003) have been applied to detect *Aloe* compounds in food.

Herbal remedies

Micellar electrokinetic chromatography with an LOD of 10 µg/ml has been applied to Chinese teas (Zheng et al., 2004). Capillary zone electrophoresis has also been used to detect *Aloe* components in Chinese medicine (Wang et al., 2004). HPLC was employed to detect the presence of aloesin and aloeresin A in an African traditional remedy (Wang et al., 2003).

Uses

Medicinal

Although the use of *Aloe* was recorded by the Egyptians, Assyrians, and Mediterranean peoples as far back as 1500 B.C., the Greek physician Dioscorides was the first to describe the use of *Aloe* to treat mouth infections, sores, and wounds and as a purgative. *Aloe* has been used in India as a cathartic, stomachic, emmenagogue, and anthelmintic and more recently in England and in the USA and Mexico for the treatment of diseases of the immune system (Oronzo-Barocio et al., 1999). Today *Aloe* is still a popular folk medicine among peoples of Indian, Chinese, and Mexican origin. Recent surveys have indicated that it is one of the three most used botanicals of middle-aged Mexican women (Zenk et al., 2001); elderly Hispanic and non-Hispanic patients (Zeilmann et al., 2003); asthmatic patients in Trinidad (Clement et al., 2005); low-income, nutritionally vulnerable children in Kansas and Wisconsin (Lohse et al., 2006), Italian women (Zaffani et al., 2006); and households in Texas (Rivera et al., 2002) and Europe (Pahor, 1995).

Gastrointestinal effects

A. vera gel has a prophylactic and curative effect on gastric lesions (Kandil & Gobran, 1982) and irritable bowel disease (Robinson, 1998). The anti-inflammatory action of *A. vera* gel *in vitro* supports the proposal that it may have a therapeutic effect in inflammatory bowel disease (Langmead et al., 2004).

Laxative effects

The anthraquinones, which are poorly absorbed from the GIT, are cleaved by gut bacteria to produce aloe-emodin, which is more readily absorbed and responsible for the purgative properties of these preparations (Blumenthal et al., 1998). The laxative effect is believed to take place through water accumulation in the intestine via active Na + transport (Ishii et al., 1990) or by water secretion due to a prostaglandin-dependent mechanism (Capasso et al., 1983). The mechanism of the cathartic effect has been studied in a series of papers by Iishii et al. (1981, 1988, 1990, 1994).

Skin and wound healing

Several studies have shown that *A. vera* gel components can prevent UV or γ-radiation-induced skin reactions in mice and humans, by preventing either the suppression of contact hypersensitivity or the immune suppression induced by the radiation (Williams et al., 1996; Roberts & Travis, 1995; Lee et al., 1997). Wound-healing activity has been partially attributed to the presence of mannose-6-phosphate (Davis et al., 1994). However, the polysaccharides in *A. vera* act as immunostimulants, enhancing the release of cytokines, which, in turn, stimulate an increase in the replication of the fibroblasts that are partially responsible for wound healing (Yates et al., 1992). In an *in vitro* wound-migration assay, purified β-sitosterol from *A. vera* stimulated neovascularization in the mouse Matrigel plug assay and motility of human umbilical vein endothelial cells (Moon et al., 1999).

Aloe also encourages wound contraction caused by increased collagen activity (Heggers et al., 1996). A glycoprotein fraction from *A. vera* was found to accelerate wound healing in a monolayer of human keratinocytes and increase expression of proliferation markers at the immunohistochemical level (Choi et

al., 2001). *A. vera* inhibits inflammation in a dose-response manner and improves wound healing in diabetic mice (Davis & Maro, 1989; Chithra et al., 1998).

Diabetes

Extracts of *Aloe* gum increases glucose tolerance in both normal and diabetic rats (Al-Awadi & Gumaa, 1987), and *A. vera* sap taken for 4-14 weeks has shown a significant hypoglycaemic effect both clinically and experimentally (Ghannam et al., 1986). *A. vera* leaf pulp and gel extracts were ineffective in lowering the blood sugar level of nondiabetic rats, but the leaf pulp extract showed hypoglycaemic activity in type I and II diabetic rats (Okyar et al., 2001). A significant decrease in blood glucose levels after oral administration of the ethanol extract of *A. vera* gel in streptozotocin-induced diabetic rats was ascribed to the antioxidant effect of the extract (Rajasekaran et al., 2005).

Anti-inflammatory effects

The anti-inflammatory activity of *A. vera* gel may be due to inhibition of the arachidonic acid pathway through cyclo-oxygenase (Vazquez et al., 1996). Penneys (1981) found that *A. vera* gel and extract inhibited oxidation of arachidonic acid *in vitro*. In *A. vera*-treated burn wounds, PGF2x levels decreased while PGE2 levels increased compared to controls (Heggers et al., 1979). An aqueous extract from *Aloe* gel inhibited the production of prostaglandin E2 from arachidonic acid *in vitro* (Vazquez et al., 1996). Yagi et al. (2003) isolated a radical scavenging glycoprotein from *A. vera* gel that inhibits cyclooxygenase-2 and thromboxane A2 synthase. The aloesin derivatives of *A. vera* possess strong DPPH radical and superoxide anion scavenging activities (Yagi et al., 2002).

Antineoplastic activity

In vitro, aloe-emodin inhibits the growth of Merkel carcinoma cells (Wasserman et al., 2002; Fenig et al., 2004), liver cancer cell lines (Hep G2 and Hep 3B; Kuo et al., 2002), and human promyelocytic leukaemia HL-60 cells (Chen et al., 2004); has antineuroectodermal tumor activity (Pecere et al., 2000); and induces apoptosis in lung carcinoma cell lines (Lee, 2001). Lectin-like substances from the leaves of *A. vera* have been shown to promote the growth of normal human cells in culture but inhibit tumor cell growth (Winters et al., 1981). However, in contrast, aloesin has been shown to stimulate the proliferation of cultured hepatoma SK-Hep 1 cells (Yagi & Takeo, 2003).

The anticancer activity of aloe-emodin is based on its promoting cell death by a neuroectodermal tumor-specific drug uptake (Pecere et al., 2003). Aloe-emodin displays a reduced growth inhibitory and pro-apoptotic activity in p53 mutant cells with respect to the p53 wild-type line. After aloe-emodin treatment, p53 translocates to the mitochondria inter-membrane space in both neuroblastoma cell lines. Due to its high accumulation in neuroectodermal tumor cells, aloe-emodin could kill tumor cells harboring p53 mutant genes. This property would further contribute to aloe-emodin's specific antitumor activity (Pecere et al., 2003).

Mijatovic et al. (2004) investigated aloe-emodin's ability to modulate survival of mouse L929 fibrosarcoma and rat C6 astrocytoma cells through interference with the activation of inducible nitric oxide synthase and subsequent production of tumoricidal free radical nitric oxide. Aloe-emodin rescued interferon-γ interleukin-1-stimulated L929 cells from nitric oxide-dependent killing by reducing their autotoxic nitric oxide release. Aloe-emodin inhibition of tumor cell nitric oxide release coincided with a reduction in cytokine-induced accumulation of transcription and translation products of genes encoding inducible nitric oxide synthase and its transcription factor IRF-1. Aloe-emodin has the capacity to directly kill tumor cells but also to protect them from nitric oxide-mediated toxicity. *In vivo*, *Aloe* polysaccharides have antitumor effects in both Sarcoma 180- and Hepatoma 22-bearing mice, the effect possibly being derived from inducing IL-2 and TNF production and thus improving the immune response (Wang et al., 2001).

Other medicinal applications

Immunostimulation

Aloeride from *A. vera* has been shown to activate macrophages (Pugh et al., 2001), whereas the polysaccharides have been noted to display adjuvant activity on specific antibody production (t'Hart et al., 1989) and enhance the release of cytokines (Peng et al., 1991). Oronzo-Barocio et al. (1999) observed that immunosuppressed mice treated with *Aloe* gel showed restoration of cellular immune response. Aloesin appears to prevent UV-B-induced immune suppression (Yagi & Takeo, 2003).

Protection of the liver and kidney

Liver

Intraperitoneal injections of aloe-emodin protected the livers of rats treated with CCl_4, as shown by a reduction in the elevation of ALT and AST (Arosio et al., 2000). *A. vera* gel decreased the damage to the liver in neonatal streptozotocin-induced type II diabetic rats (Can et al., 2004). *Aloe* injections lowered the ALT by 87% in 38 HbsAg-positive patients with chronic hepatitis (Fan et al., 1989).

Woo et al. (2002) determined that aloe-emodin is a potent inhibitor of hepatic stellate cell activation and proliferation, although the mechanism has not been elucidated. *Aloe* extract has a cytoprotective effect against 1,4-naphthoquinone-induced hepatotoxicity in primary cultured rat hepatocytes (Norikura et al., 2002).

Kidney

In rat kidneys with mild damage caused by type II diabetes, *A. vera* gel extract led to improvement in both histological and biochemical parameters, suggesting a protective effect (Bolkent et al., 2004).

Hematological

Two lectin glycoproteins, Aloctin I and Aloctin II, isolated from the leaf pulp showed hemagglutinating activity against rabbit erythrocytes *in vitro* (Winters et al., 1981; Akev & Can, 1999). However, *Aloe* whole-leaf powder fed to rats for 90 days showed no adverse effects on hematological parameters (Zhou et al., 2003). The carbohydrate fraction of *A. vera* has been shown to have hematopoietic activity (Talmadge et al., 2004).

Hormonal

Aloe-emodin is a potent hypotensive agent leading to a 79% fall in arterial blood pressure at a dose of 3 mg/kg (Saleem et al., 2001).

A. vera leaf extracts (125 mg/kg) reduced the serum levels of both T3 and T4 in male mice, suggesting a possible use in the regulation of hyperthyroidism (Kar et al., 2002).

Anthraquinones have been traditionally used for the prevention and palliation of menoxenia and postmenopausal disease and, in an *in vitro* study, Matsuda et al. (2001) found that *A. ferox* extracts enhanced proliferation of MCF-7 cells, indicating that they do, indeed, have estrogenic activity.

Neural

Diabetes mellitus has been reported to impair memory function in experimental animals. Since the mammalian hippocampus and cerebral cortex play a pivotal role in memory, Parihar et al. (2004) examined the vulnerability of these regions of the brain to oxidative damage in streptozotocin-diabetic

mice. When supplemented with *A. vera* extracts, the oxidative damage in both brain regions was reduced, as shown by a significant decline in both lipid peroxidation and protein carbonyl. Memory impairment and motor dysfunction were also improved.

Eyes

Biopharmaceutical studies by Kodym and Bujak (2002) concluded that the addition of *Aloe* extract to eye drops containing neomycin sulphate increased the permeation of the drug through the cornea, suggesting that it may have a role to play in the treatment of inflammations and infections of the eye.

Cosmetics

In cosmetics, *Aloe* gel is added to cleansers, moisturizers, shampoos, suntan lotions, and sunburn screens. Aloesin modulates melanogenesis via competitive inhibition of tyrosinase, thus holding promise as a pigmentation-altering agent for cosmetic and therapeutic applications (Jones et al., 2002; Yagi & Takeo, 2003). When considering the physicochemical and microbiological stability of *Aloe* components, Kodym and Bujak (2002) determined that the most advisable base for such ointments is white vaseline, liquid paraffin, solid paraffin, or cholesterol.

Food supplements

Aloe is a popular supplement in health foods, sold for the treatment of obesity, hyperlipidaemia, and acne (Wang et al., 2002). The internal use of the gel is regulated as a dietary supplement in the USA (Code of Federal Regulations, 1991) and Europe (Council of Europe, 1981). Use of the juice and integument of leaves of *A. vera* and *A. ferox* as food, however, is not permitted in Japan (Shioda et al., 2003). An edible coating based on *A. vera* gel has been shown to increase the cold storage and subsequent shelf life of grapes and, in addition, reduces the microbial counts of the stored product (Valverde et al., 2005).

Pharmacological Activity

The pharmacological difference between the gel and the latex is that the gel does not contain anthraquinone compounds and does not therefore exert laxative action (Newall et al., 1996). Aloemannan is catabolized by human intestinal mucosa or by intestinal microflora to two metabolites, which accumulate mainly in the kidneys (Yagi et al., 2001). Aqueous extracts of *Aloe* enhance the oxidation rate of ethanol rate *in vivo* (Chung et al., 1996).

Aloin can be hydrolyzed in the gut to form aloe-emodin anthrone, which autooxidizes to a quinone, aloe-emodin. Barbaloin in *Aloe* drinks is converted to aloin-dimers and trimers during storage (Shindo et al., 2002).

Adverse effects/toxicity

Hypersensitivity (Morrow et al., 1980) and allergic conditions to *Aloe* preparations have been reported (Ernst, 2000).

Exposure of rats to emodin resulted in an increased incidence of renal tubule pigmentation and nephropathy in mice (National Toxicology Program, 2001). In rats that were fed *Aloe* whole leaf powder for 90 days, the kidney weight was significantly increased and, in males, testis weights were significantly increased. Additionally, the pigmentation in renal tubular, mesenteric lymph nodes, and lamina propria of the colonic mucosa were also significantly increased compared to the controls, and proliferation of mesenteric lymph nodes was observed (Zhou et al., 2003).

In humans, there are no published controlled toxicology studies *in vivo*, although several single-case reports are available. One patient experienced massive intraoperative bleeding after consumption of *A. vera* tablets. The cause seems to have been a possible herb-drug interaction between *A. vera* and sevoflurane (Lee et al., 2004). Luyckx (2002) reported a patient with acute renal failure following *Aloe* ingestion where no other cause could be found. A case of severe vomiting after *Aloe* ingestion was reported by Wang et al. (2003), and Willems et al. (2003) published a case of melanosis coli that developed after prolonged anthranoid self-medication. Acute hepatitis has been observed following *A. vera* ingestion (Rabe et al., 2005) and Henoch-Schonlein purpura after an *A. vera* herbal remedy juice was taken for back pain (Evangelos et al., 2005).

Deaths have been reported following the use of *Aloe* as abortifacients. However, there is no evidence that the deaths were due to *Aloe* toxicity (Vago, 1969). Adverse effects of *Aloe* whole-leaf powder have been reported at concentrations of 2 g/kg BW, and the LOAEL for aloin is estimated at 11.8 g/kg BW (Zhou et al., 2003). Pregnant women are advised not to take *Aloe* latex because of its cathartic action, which may cause severe uterine contractions and increase the risk of miscarriage. It should also not be ingested by nursing mothers because of the possibility of causing severe cramps and diarrhea in the infant (Brinker, 1998).

Conclusion

Aloe has been traditionally used worldwide as a folk remedy for various diseases because of its multiple biological activities. The number of preparations containing *Aloe* extracts is vast and consists of pills, capsules, creams, powders, and aqueous solutions. In South Africa, the preparations are often crude, consisting of the plant itself or aqueous infusions, but in the commercial products now available worldwide, the preparations often contain stabilizers and preservatives, since some components are subject to oxidation. The heterogeneous nature of *A. vera* products may contribute to the diverse biologic and therapeutic activities that have been observed. The variations in the composition of *A. vera* often results in products with different chemical and physical properties, making the comparison of products virtually impossible.

The FDA has approved the internal use of the gel only as a dietary supplement and its external use only as a cosmetic ingredient. In general, caution is warranted for internal, long-term use (Shah et al., 1989), although Ikeno et al. (2002) have stated that lifelong *A. vera* ingestion does not cause any obvious harmful and deleterious side effects and could be beneficial for the prevention of age-related pathology. *In vitro* and *in vivo* tests have demonstrated and confirmed the activity of *A. vera* gel; however, there are a number of discrepancies about its therapeutic properties, and clinical studies have not always found it to be effective. It is of concern, however, that there are reports of adverse effects.

A metaanalysis of 10 studies covering a number of the putative therapeutic effects of *Aloe* preparations prompted Vogler and Ernst (1999) to conclude that: "Even though there are some promising results, the clinical effectiveness of oral or topical *A. vera* is not sufficiently defined at present." It is vital that *Aloe* products be certified as to content and identification of compounds. Only then will this allow for an accurate comparison of products as well as their efficacy in the clinical setting.

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