A Review on the anti-hyperglycaemic potential of *Catharanthus roseus* and *Portulacaria afra*

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Highlights

- Traditional medicinal plants' potential in the management of diabetes.
- Documented hypoglycaemic effects of *C. roseus* in diabetic-induced rats.
- *P. afra* is a plant with anti-inflammatory and pain-relieving properties.
- Economic advantages of cost-effective and accessible diabetic treatments in low-income countries.
- Exploring the anti-diabetic activity of *C.roseus: P.afra* (1:1) in the context of their traditional use by South African healers.

Abstract

Diabetes mellitus is a prevalent non-communicable disease affecting individuals in developed and developing countries. However, low-income countries face significant challenges in managing diabetes due to socio-economic factors resulting in high mortality rates annually. The lack of adequate healthcare facilities and resources in low-income countries limits access to synthetic anti-hyperglycaemic medication, leading to an increased reliance on traditional medicinal plants to manage diabetes mellitus. One such traditional remedy is the combination of *Catharanthus roseus* (L.) G. Don and *Portulacaria afra* Jacq. (1:1) used by traditional healers in South Africa to lower blood glucose levels and manage diabetes symptoms. *Catharanthus roseus* has demonstrated anti-hyperglycaemic activity in diabetic-induced rats, while previous studies have identified various pharmacological potentials of *P. afra*, including anti-inflammatory and pain-relieving properties. This review aims to explore the anti-hyperglycaemic potential of *C. roseus* and *P. afra* in the context of their traditional use by South African healers. By examining the existing literature, we aim to provide insights into the potential of these medicinal plants as alternative and complementary treatments for diabetes management. As the global burden of diabetes continues to increase, it is critical to explore cost-effective and accessible treatments, particularly in low-income countries where healthcare resources are limited. This review contributes to the understanding of traditional medicinal plants' potential in the management of diabetes and provides a basis for further research into their use as alternative treatments.

Keywords: Diabetes mellitus; Traditional medicinal plants; South Africa; Catharanthus roseus and Portulacaria afra

1. Introduction

Diabetes mellitus is a metabolic disorder associated with the endocrine system (Li et al., 2004) and characterised by persistent hyperglycaemia with disturbances of protein, carbohydrate and fat metabolism (Bhutkar 2018). Diabetes is also characterised by either a diminished production of insulin from the pancreas (type 1 diabetes mellitus) or insufficient cellular response to adequate amounts of insulin possibly from defective receptors (type 2 diabetes mellitus) (Cantley and Ashcroft 2015; Weinstock 2018., Egan and Dinneen 2019). Type 2 diabetes mellitus (T2DM) is the most common type of diabetes and is considered a chronic metabolic disorder characterized by hyperglycaemia due to the body's inability to produce or use insulin efficiently (Egan and Dinneen 2019). It is a multifactorial disease with a complex pathogenesis, influenced by genetic, environmental, and lifestyle factors. The pathogenesis of T2DM is complex and involves a range of factors, including genetic susceptibility, environmental factors, and lifestyle factors such as diet and physical activity. The underlying mechanisms of T2DM development include insulin resistance, beta-cell dysfunction, and glucose toxicity. Insulin, a hormone produced by the pancreatic beta (β)-cells, plays a crucial role in homoeostasis of blood glucose levels (Gaikwad et al., 2014). Insulin resistance refers to the reduced ability of insulin to promote glucose uptake in peripheral tissues such as muscle, liver, and adipose tissue. It is a characteristic feature of T2DM and is thought to be due to abnormalities in insulin signalling pathways, which impair insulin receptor function and downstream signalling events. In the event of insufficient insulin production by β-cells, glucose will not enter the cells for further metabolism and it builds up in the blood, leading to hyperglycaemia (Belinda 2004). The exact mechanisms underlying insulin resistance are not fully understood, but it is thought to involve factors such as inflammation, oxidative stress, and mitochondrial dysfunction.

Beta-cell dysfunction is another critical factor in the pathogenesis of T2DM and it refers to the inability of pancreatic beta cells to secrete sufficient amounts of insulin to maintain normal glucose homoeostasis (Krentz and Gloyn 2020). Beta-cell dysfunction is thought to occur due to a combination of factors such as chronic hyperglycaemia, lipotoxicity, and glucotoxicity, which result in beta-cell apoptosis and impaired insulin secretion (Hudish et al., 2019). Genetic factors also play a role in beta-cell dysfunction, with mutations in genes involved in insulin synthesis and secretion identified as risk factors for T2DM (Kettunen and Tuomi 2020).

Glucose toxicity refers to the deleterious effects of chronic hyperglycaemia on various organs and tissues, including the pancreatic beta cells, which further exacerbate insulin resistance and beta-cell dysfunction. High glucose levels lead to the accumulation of advanced glycation end-products (AGEs) and activation of protein kinase C (PKC) pathways, which impair insulin signalling and beta-cell function. Hyperglycaemia associated with glucose toxicity contributes to the development of severe complications, such as oxidative stress, abnormally high levels of lipids in the blood (hyperlipidaemia), retinopathy, neuropathy, and nephropathy, cardiovascular diseases (CVDs), such as coronary artery disease, heart attacks, hypertension and enzymatic protein glycation (Firdous 2014; Sagbo et al., 2018).

Type 2 diabetes mellitus has become a major public health burden worldwide due to its rising prevalence, associated complications, and economic impact (Htay et al., 2019). According to the International Diabetes Federation (IDF), the global prevalence of T2DM was estimated to be 9.3 % in 2019, with around 463 million adults aged 20–79 years affected. The prevalence of T2DM is projected to increase to 10.2 % by 2030 and 10.9 % by 2045, with the greatest increase expected in low- and middle-income countries. T2DM management is responsible for

a significant proportion of global healthcare expenditures, with at least USD 966 billion spent on T2DM treatment in 2021 alone (IDF 2021). The aim of the review was to evaluate the current evidence on the anti-hyperglycaemic potential of *Catharanthus roseus* (L.) G.Don and *Portulacaria afra* Jacq.This was achieved through examination of the literature which provided insights into the potential of the two medicinal plants as alternative and complementary treatments for diabetes management.

2. Methods

The present review article was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Literature search strategy

A systematic search was performed using the electronic databases PubMed, Scopus, ScienceDirect and Web of Science from their inception until February 2023. The search strategy was developed by combining the following keywords: ("medicinal plants" OR "herbal medicine" OR "phytotherapy" OR "traditional medicine" OR "*Catharanthus roseus*" OR "*Portulacaria afra*") AND ("diabetes mellitus" OR "hyperglycaemia" OR "glucose metabolism" OR "insulin resistance"). The search was limited to studies conducted on humans, animal models, or *in vitro* systems published in English language.

2.2. Study selection

Four reviewers (BdV, TN, RH and WP) independently screened the titles and abstracts of all retrieved articles to identify potentially relevant studies. Full-text articles were retrieved for studies that met the inclusion criteria and were assessed for eligibility. Inclusion criteria were studies that investigated the anti-hyperglycaemic potential of medicinal plants in humans, animal models, or *in vitro* systems. Exclusion criteria were studies that did not provide sufficient data, were duplicates, or were not published in English language. Disagreements between the reviewers were resolved through discussion or consultation with a fifth reviewer (AN).

2.3. Data extraction

A standardized data extraction form was used to extract data from the included studies. The following data were extracted: study design, study population, intervention, outcomes, and results. Data were extracted independently by three reviewers (BdV, RH and TN), and discrepancies were resolved through discussion or consultation with a fourth and fifth reviewer (AN and WP).

2.4. Quality assessment

The quality of the included studies was assessed using the expertise of four reviewers (BdV, TN, RH and WP) who independently assessed the quality of each study, and any discrepancies were resolved through discussion or consultation with a fifth reviewer (RH).

2.5. Data synthesis

Data from the included studies were synthesized narratively due to heterogeneity of the studies in terms of intervention, population, and outcomes. The studies were grouped according to their study design, population, and intervention.

2.6. Reporting

The present review article was reported according to the PRISMA guidelines. The use of PRISMA guidelines in this review ensured that the search, selection, and synthesis of studies were conducted in a transparent and comprehensive manner, and that the findings were reported in a standardized and clear way.

2.7. Diabetes management strategies

The management of diabetes focus primarily on glycaemic control since diabetes complications increase the probability of microvascular and macrovascular complications (Imran et al., 2018; Harding et al., 2019). The strict and intensive management of blood glucose levels has also been shown to reduce vascular complications associated with T2DM (Cavaiola and Pettus 2017). The three most common management strategies for diabetes include adoption of healthy lifestyle choices, oral anti-hyperglycaemic medication (glipizide, metformin, repaglinide) and insulin treatment (Ganesan and Sultan 2019). For instance, managing dietary intake and increasing physical exercise are two of the basic lifestyle changes that are used for the treatment of T2DM (Marin-Penalver et al., 2016). Physical exercise benefits diabetic patients by improving glycaemic control, increasing insulin sensitivity and maintaining a healthy body weight (Phielix et al., 2010). Several pharmacological agents have also been used in the treatment and management of T2DM (Irons and Minze 2014).

2.8. Pharmacological approaches in the treatment of type 2 diabetes mellitus

The management of type 2 diabetes mellitus (T2DM) involves various pharmacological approaches that aim to control hyperglycaemia and prevent or delay the development of diabetes-related complications (Padhi et al., 2020). The pharmacological treatments available for T2DM can be broadly categorized into oral anti-hyperglycaemic agents and injectable agents (Dowarah and Singh 2020). Oral anti-hyperglycaemic agents include biguanides, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors (Dowarah and Singh 2020). Biguanides such as metformin are the first-line therapy for T2DM as they improve insulin sensitivity, reduce hepatic glucose production, and decrease intestinal glucose absorption. Metformin is derived from the *Galega officinalis* plant and is well known for its anti-hyperglycaemic effects (Goboza et al., 2016) *in vivo* studies (Za'abi et al., 2021) and *in vitro* studies (Akinyede et al., 2021). It is physiologically responsible for decreasing hepatic production by increasing glucose utilisation in the gut. According to Foretz et al. (2014), the hyperglycaemic effect of metformin is exhibited by the inhibition of hepatic gluconeogenesis (the process whereby energy is converted into glucose). Sulfonylureas, meglitinides, and DPP-4 inhibitors stimulate insulin secretion by pancreatic beta cells, while thiazolidinediones improve insulin sensitivity and reduce insulin resistance (Artasensi et al., 2020). SGLT2 inhibitors lower blood glucose levels by increasing renal glucose excretion.

Injectable agents include glucagon-like peptide-1 (GLP-1) receptor agonists and insulin. GLP-1 receptor agonists stimulate insulin secretion, inhibit glucagon secretion, delay gastric emptying, and reduce food intake (Feingold et al., 2020). They also promote weight loss and have a low risk of hypoglycaemia. Insulin therapy is used when oral anti-hyperglycaemic agents fail to achieve glycaemic control, and it can be administered via multiple daily injections or continuous subcutaneous insulin infusion (Feingold et al., 2020). In addition to pharmacological interventions, lifestyle modifications such as weight loss, physical activity, and dietary changes are also important in the management of T2DM. However, pharmacological treatments remain essential for many patients with T2DM.The choice of pharmacological therapy for T2DM depends on various factors such as the patient's age, comorbidities, and risk of hypoglycaemia. Individualized treatment plans should be developed for each patient to achieve optimal glycaemic control while minimizing the risk of adverse effects.

Despite their therapeutic value in the management of type 2 diabetes mellitus, the use of pharmacological agents is associated with several side-effects. Due to the cost and availability of metformin, diabetic patients in developing countries rely on the use of traditional medicinal plants as a cheaper and safer alternative. It is for this reason, that an increasing number of studies on alternative and complementary anti-hyperglycaemic treatments have been initiated (İpek et al., 2018; Sunny et al., 2019).

Despite the numerous pharmacological agents available for the management of type 2 diabetes mellitus (T2DM), there are still a number of challenges, including side- effects, patient non-adherence, inadequate glycaemic control, high cost, comorbidities, and individual variability. To overcome these challenges and minimize negative effects, a safe and affordable, patient-centred strategy that takes into account patients circumstances is necessary. Medicinal plants have been proposed as safe and affordable alternatives.

2.9. Therapeutic value of medicinal plants

Medicinal plants have been used for medicine for centuries and the knowledge of their use has been passed down through generations. The Chinese were pioneers in traditional medicine and their use of medicinal plants has led to their continued use today. Indigenous knowledge of medicinal plants is important for many African communities and enhances traditional health delivery. The therapeutic value of medicinal plants has been attributed to the presence of biologically active phytochemicals or secondary metabolites such as flavonoids, saponins, alkaloids and glycosides (Bacanli et al., 2019; Srivastava et al., 2019; Teffo et al., 2022). These compounds are known to be healthy and treat or prevent diseases such as diabetes by improving insulin sensitivity and combating complications associated with diabetes (Teffo et al., 2022; Bacanli et al., 2019). Moreover, the combination of phytoconstituents are also known to have synergistic effects that are useful in the treatment of several human diseases (Zhao et al., 2020). Therefore, the medicinal and therapeutic potentials of plants are attributed to several phytochemical constituents each comprising of numerous biological activities (Mehwish et al., 2019).

A summary of these phytochemical compounds, found in medicinal plants and their biological potentials, is given in Table 1, below.

Table 1. Phytochemicals and their role in health care.

Phytochemical Classes	Phytoconstituents	Role in healthcare (Biological potentials)	Reference
Phenolic compounds	Flavonoids	Anti-oxidant, anti-bacterial, anti-inflammatory, anti-cancer, anti-hyperglycaemic and anti-microbial activities	(Urzua et al., 2008; Olaokun et al., 2017; Koche et al., 2018; Panche et al., 2016)
Phenolic compound	Tannins	Anti-microbial, anti-bacterial, anti-oxidant, anti-cancer, anti-viral and anti-inflammatory	(Singh and Kumar 2019; Sieniawska 2015; Koche et al., 2018; Urzua et al., 2008)
Nitrogen compounds	Alkaloids	Anti-hyperglycaemic, anti-cancer, anti-malarial, anti-microbial and analgesic	(Koche et al., 2018; Othman et al., 2019)
Triterpene glycoside compounds	Saponins	Anti-oxidant, anti-bacterial, anti-microbial, anti-cancer, anti-hyperglycaemic -inflammatory	(Koche et al., 2018; Jin et al., 2017; Sparg et al., 2004; Urzua et al., 2008)
Phenolic compounds	Polyphenols	Anti-oxidant, anti-inflammatory, anti-hyperglycaemic, anti-microbial and metabolic regulation functions	(Ly et al., 2014; Othman et al., 2019; Wang et al., 2018)
	Glycosides	Anti-inflammatory, anti-fungal, anti-cancer,anti-tumour, anti-oxidant, anti-hyperglycaemic, anti-bacterial and antiviral	(Xiao et al., 2016; Khan et al., 2019; Gangasani et al., 2022)
Phenolics compounds	Terpenoids	Anti-microbial, anti-hyperglycaemic, anti-malarial, detoxifying agents and anti-carcinogenic	(Koche et al., 2018; Gutiérrez-del-Río et al. 2018; Gaikwad et al., 2014)

2.10. Common medicinal plant-based anti-hyperglycaemic treatments in South Africa

The floral biodiversity of South Africa expanded the cultural traditions of medicinal plant use (Van de Venter et al. 2008). South Africa encompasses over 30,000 higher plant species from which 3000 are being used in traditional medicines (Van Wyk et al. 1997). A wide variety of these plants have been reported to possess anti-hyperglycaemic properties (Afolayan and Sunmonu 2010; Davids et al., 2016). Table 2 shows the most commonly used medicinal plants in the management of diabetes mellitus. Most of these plants were evaluated for anti-hyperglycaemic activities using only *in vitro* screening models. The main disadvantage of using *in vitro* screening models is the use of a single cell line which may not mimic the inherent complexity of organ systems. Over the years local South Africa communities in rural and urban areas use different plant species in combination possibly to benefit from the potential synergistic effects of the phytoconstituents. Some studies have shown that the combination of phytochemicals may affect or alter the intensity of their bioactivities by modifying the bioavailability of the compounds (Ioannides 2003; Phan et al., 2018).

3. Anti-hyperglycaemic potential of *Catharanthus roseus* and *Portulacaria afra*

Although there are many medicinal plants available (see Table 2) for the management of diabetes, two of them, *Catharanthus roseus* and *Portulacaria afra* have not been extensively studied in relation to their effects on diabetes. The role of *P. afra* and *C. roseus* and their potential therapeutic effects on diabetes, such as their ability to lower blood glucose levels, improve insulin sensitivity, and reduce inflammation is not fully understood. There is anecdotal evidence on how these two medicinal plants have been used in combination to manage T2DM. It is possible that *P. afra* and *C. roseus* exerts a synergistic effect when combined leading to better glycaemic control in individuals with diabetes. Therefore, the review aims to fill this gap in knowledge by exploring the potential benefits of using these plants individually and in combination for diabetes management and to identify areas for future research.

3.1. The potential role of *Catharanthus roseus* in the management of diabetes

Catharanthus roseus (L.) G. Don, commonly known as the Madagascar periwinkle (English), Kanniedood (Afrikaans) and *Isishushlungu* (*isiZulu*) belongs to the Apocynaceae family (Fapohunda et al., 2018). This plant can grow 30–100 cm in diameter, the flower itself consists of five petals, forming a variety of pink-, white- or purple-coloured flowers (Nisar et al., 2016; Fapohunda et al., 2018). This plant has been widely used traditionally in herbal medicine for their medicinal properties. The leaf decoction of *C. roseus* is used to treat a wide variety of human diseases, such as hypertension, asthma, menstrual irregularities, chronic constipation, diarrhoea, indigestion, malaria, dengue fever, diabetes, cancer and skin diseases (Fern 2022). *Catharanthus roseus* was first discovered by the Europeans and then used as a traditional cure for diabetes (Afolayan and Sunmonu 2010; Swanston-Flatt et al., 1989). It can be found in South Africa near the coast and inland on riverbanks, in open forests or scrubs (Henderson 2001). *Catharanthus roseus* is native and endemic to Madagascar (Mishra and Verma 2017) and can be found as an invasive species in the provinces of Limpopo (Maema et al., 2016), Gauteng, North West Province and KwaZulu-Natal, South Africa (Henderson 2001).

In countries such as Australia, Brazil, Thailand, England, South Africa, Pakistan and Jamaica, dried leaves of *C. roseus* is consumed as a water decoction for the treatment of diabetes, cancer and menorrhagia (Nisar et al., 2016; Cock et al., 2021). In China, the whole plant is used as a menstrual regulator, cough medicine, diuretic and an astringent (Farnsworth 1961; Virmani et

Table 2. Medicinal plants used for the treatment of diabetes in South Africa, reporting the family names, species with common names, and the part of the plants used during treatments.

Family	Species	Common names	Part of plant used	Reference
Aizoaceae	*Carpobrotus edulis* (L.) N.E.Br.	Freeway iceplant	Leaves, juice, fruit	(Davids et al., 2016)
Aizoaceae	*Sceletium tortuosum* (L.) N.E. Br.	Kougoed[a]	Leaves, roots	(Davids et al., 2016)
Alliaceae	*Tulbaghia violacea* Harv.	Wild garlic, wildeknoffel[a]	Leaves, roots	(Davids et al., 2016)
Anacardiaceae	*Sclerocarya birrea* Hochst.*	Marula	Stem, bark, roots	(Van de Venter et al. 2008)
			Stem, bark	(Van Wyk 2008a)
Anacardiaceae	*Searsia burchellii* (Sond. Ex Engl.) Moffett.	Karroo Kuni-bush	Leaves, roots, stem	(Davids et al., 2016)
Apiaceae	*Heteromorphica arborescens* H.	Parsley tree, pietersieliebos[a]	Leaves, roots	(Erasto et al., 2005)
Apiaceae	*Lichtensteinia lacera* Cham. & Schltdl.		Leaves, stem	(Davids et al., 2016)
Apiaceae or Umbelliferae	*Petroselenium crispum* (Mill)	Parsley	Leaves	(Thring and Weitz 2006)
Apocynaceae	*Catharanthus roseus* (L) G. Don*	Madagascar Periwinkle, Jasmine	Leaves	(Erasto et al., 2005)
			Leaves, twigs	(Van de Venter et al. 2008)
Apocynaceae	*Hoodia gordonii* (Masson) Sweet ex Decne*	Bitter ghaap[e]	Inner stem	(Davids et al., 2016)
Apocynaceae	*Vinca major* L.	Greater periwinkle or bigleaf periwinkle	Leaves, roots, stem	(Van de Venter et al. 2008)
Asphodelaceae	*Aloe ferox* Mill. *	Bitter aloe, cape aloe or red aloe	Leaves/juice	(Davids et al., 2016)
Asphodelaceae	*Bulbine natalensis* Mill.	Bulbine, Rooiwortel[a]	Roots	(Erasto et al., 2005)
Asphodelaceae	*Bulbine frutescens* L.	Stalked bulbine, snake flower, cat's tail or geelkatstert[a]	Roots	(Erasto et al., 2005)
Asteraceae	*Artemisia afra* Jacq. Ex Willd.*	Wormwood or Bitterals[a], Wildealsem	Leaves, roots	(Erasto et al., 2005)
			Leaves	(Davids et al., 2016)
			Leaves	(Thring and Weitz 2006)
			Leaves	(Van Wyk 2008a)
Asteraceae	*Brachylaena discolour* DC.*	Coastal Silver-oak or Vaalbos[a]	Leaves	(Erasto et al., 2005)
			Leaves, roots, stem	(Van de Venter et al. 2008)
Asteraceae	*Brachylaena elliptica* Thunb.	Pepperbark tree	Leaves	(Van Wyk 2008b)
Asteraceae	*Chrysocoma ciliate* L.	Bitter bush or bitterbos[a]	Leaves, roots	(Davids et al., 2016)
Asteraceae	*Conyza scabrida* DC.	Oven Bush	Leaves	(Thring and Weitz 2006)

Asteraceae	*Elytropappus rhinocerotis* (L.f.)	Rhinoceros bush	Leaves	(Thring and Weitz 2006)
Asteraceae	*Euryops abrotanifolius* (L.) DC.	Lace-leaf euryops, mountain resin bush	Leaves, stem	(Davids et al., 2016)
Asteraceae	*Helichrysum nudifolium* L.	Hottentot's tea	Leaves, roots	(Erasto et al., 2005)
Asteraceae	*Helichrysum odoratissimum* L.	Everlasting	Whole plant	(Erasto et al., 2005)
Asteraceae	*Helichrysum petiolare* H & B.L	Silver bush everlasting	Whole plant	(Erasto et al., 2005)
Asteraceae	*Tagetes minuta* L.	Khaki bush	Leaves	(Davids et al., 2016)
Asteraceae	*Vernonia oligocephala* Sch. Bip.	Bicoloured-leaved vernonia	Leaves, roots, stem	(Erasto et al., 2005)
			Leaves	(Thring and Weitz 2006)
Asteraceae	*Vernonia amygdalina* Del.	English bitter leaf	Leaves	(Erasto et al., 2005)
Brassicaceae	*Cadaba aphylla* (Thunb.) Wild	Leafless wormbush, desert spray	Leaves, Stem	(Davids et al., 2016)
Buddlejaceae	*Chilianthus olearaceus* Burch.	Wild elder	Leaves, twigs	(Erasto et al., 2005)
Cannabaceae	*Cannabis sativa* L.	Cannabis	Leaves	(Van de Venter et al. 2008)
Celastraceae	*Catha edulis Forsk*. Ex Endl.	Somali tea	Leaves, roots, stem	(Van de Venter et al. 2008)
Compositae	*Dicerothamnus rhinocerotis* (L.f.) Koek.	Rhinoceros bush	Leaves, stem	(Davids et al., 2016)
Convolvulaceae	*Convolvulus capensis* Burm. f.	Cape Bindweed or Bobbejaantou[a]	Bulb	(Davids et al., 2016)
Crassulaceae	*Crassula muscosa* L.	Lizard's tail	Leaves, stem, roots, flower	(Davids et al., 2016)
Crassulaceae	*Tylecodon paniculatus* (L.f.) Toelken	Butter bush	Leaves, stem	(Davids et al., 2016)
Cucurbitaceae	*Momordica balsamina* L.*	African Cucumber, balsam Apple	Stem, flowers	(Van de Venter et al. 2008)
Cucurbitaceae	*Momordica foetida* Schumach.	Gifappel[a]	Whole plant	(Van de Venter et al. 2008)
Euphorbiaceae	*Ricinus communis* L.	Castor bean	Leaves	(Thring and Weitz 2006)
Fabaceae	*Lessertia frutescens* L.*	Cancer bush	Leaves	(Van Wyk 2008a)
Fabaceae Lindl.	*Lessertia frutescens* (L.) Golblatt & J.C. Manning	Balloon Pea, Cancer bush	Leaves	(Davids et al., 2016)
Gentianaceae	*Chironia baccifera* L.	Christmas berry or bitterbossie[a]	Whole plant	(Van de Venter et al. 2008)
Geraniaceae	*Pelargonium antidysentericum* (Eckl. & Zeyh.) Kostel.	Rooistorm[a]	Roots	(Davids et al., 2016)
Hypoxidaceae	*Hypoxis colchicifolia* Bak.	Broad-leaved hypoxis	Corms	(Erasto et al., 2005)
Hypoxidaceae	*Hypoxis hemerocallidea* Fisch.*	Star flower, yellow star or sterblom[a]	Corms	(Erasto et al., 2005)
Lamiaceae	*Ballota africana* (L.) Benth	Cat herb	Leaves	(Davids et al., 2016)

Lamiaceae	*Leonotis leonurus* L.	Cape hemp	Leaves, flowers	(Thring and Weitz 2006)
Lamiaceae	*Leonotis leonurus* (L.) R.Br.	Lion's tail, lion's ear, wild dagga or rooidagga[a]	Leaves, roots, flower	(Davids et al., 2016)
Lamiaceae	*Mentha longifolia* (L.) L.	Wild mint	Leaves, stem	(Davids et al., 2016)
Lamiaceae	*Salvia africana-caerulea* L.	Blue sage, wild sage, purple sage or blousalie[a]	Leaves	(Davids et al., 2016)
Menispermaceae	Cissampelos *capensis* L.f.	Davidjies[a]	Leaves	(Van de Venter et al. 2008)
Myrtaceae	*Psidium guajava* L.	Guava	Leaves	(Van de Venter et al. 2008)
Portulacaceae	*Portulacaria afra*	Spekboom[a], Elephant bush	Leaves	(Hulley and Van Wyk 2019)
Rubiaceae	*Galium tomentosum* Thunb.	Old Man's Beard or Rooivergeet[a]	Roots	(Van Wyk et al. 2008)
Rutaceae	*Diosma oppositifolia* L.	Bitter buchu	Leaves, stem, flower	(Davids et al., 2016)
Rutaceae	*Ruta graveolens* L.	Rue, common rue or herb-of-grace	Leaves	(Thring and Weitz 2006)
			Leaves	(Van Wyk 2008b)
Thymelaeaceae	*Gnidia deserticola* Gilg.	Night- or evening- scented bush	Leaves, stem, roots	(Davids et al., 2016)

∗ Used *in vivo* (evaluated efficacy using animal models).
[a] *Afrikaans*.
[e] *English*.

al., 1978). In India, the plant is boiled in water and administered orally for cancer treatment (Virmani et al., 1978). Previous studies have shown evidence of anti-oxidant, anti-microbial, anti-inflammatory as well as anti-hyperglycaemic potential in plant extracts of *Catharanthus roseus* (Oluwaseun and Saliu 2018).

3.1.1. Phytochemical constituents of Catharanthus roseus

Catharanthus roseus (L.) G. Don., a plant species, has been found to have therapeutic potential due to its various bioactive compounds (Ponnusamy et al., 2011). These compounds include flavones, phenols, tannins, glycosides, reducing sugars, and other phytochemicals (Malathi et al., 2010). Over 120 alkaloids have been identified in *C. roseus*, of which 70 are pharmacologically active (Barrales-Cureño 2015). *Catharanthus roseus* (L.) G. Don. has also been reported to contain various alkaloids, including vinblastine and vincristine, which have been shown to possess anti-hyperglycaemic activity in animal models. Vincristine and vinblastine, two alkaloids found in *C. roseus*, are potent chemotherapeutic agents used in cancer management (Van Der Heijden et al. 2004). Vindogentianine, another alkaloid found in the leaves of *C. roseus*, has potential anti-hyperglycaemic activity against type 2 diabetes (Tiong et al., 2015). The plant's medicinal potential needs further exploration. These compounds were found to increase glucose uptake and glycogen synthesis in skeletal muscle and adipose tissues, resulting in improved glucose homoeostasis (Pham et al., 2020).

The anti-hyperglycaemic potential of *C. roseus* has been recorded in several *in vivo* studies with blood glucose reductions varying anywhere from 13 % up to 78 % (Table 3). The only solvent that caused animal deaths were recorded for the chloroform treated groups (Table 3) and it was speculated that the deaths were due to the presence of some toxic alkaloids such as tropane, piperidine, pyrrolizidine and indolizidine (Thawabteh et al., 2019; Islam et al., 2009). More *in vivo* studies are listed in Table 3.

The effectiveness of *C. roseus* as a anti-hyperglycaemic treatment, is clearly supported by scientific evidence for the management of diabetes mellitus.

3.2. The potential role of *Portulacaria afra* in the management of diabetes mellitus

Portulacaria afra Jacq., also known as the Porkbush, Elephant bush/food (English) (Khanyile et al., 2021), *Spekboom* (Afrikaans) (Hulley and Van Wyk 2019), *iNtelezi, isAmnilane, isiCococo* (isiZulu) and *iGqwanitsha* (isiXhosa) (Maroyi 2020), belongs to the Portulacaceae family and is widely found in the southern and south- eastern regions of South Africa (Guralnick and Ting 1987; Hankey 2009; Van Jaarsveld and Le Roux 2021). This plant is used as a garden ornament or as a medicinal agent for the treatment of skin disorders, toothaches, colds, coughs, pain, constipation, high blood pressure, obesity, cancer, and diabetes mellitus (De Wet et al. 2013; Dlova and Ollengo 2018; Hulley and Van Wyk 2019; Olaokun et al., 2017). he leaves of *P. afra* are considered the most preferable part of the plant and can be characterised by a sour or bitter taste (Hankey 2009; De Wet et al. 2013). Traditional use of *P. afra* has been associated with treating skin-related ailments due to its anti-microbial properties (De Wet et al. 2013; Hulley and Van Wyk 2019; Nciki et al., 2016). However, a recent *in vivo* study revealed that *P. afra* extract exhibited anti-inflammatory activity and had potential in the prevention of inflammation (Tabassum et al., 2022).

Table 3. A list of recent *in vivo* studies that evaluated the anti-hyperglycaemic effects of *Catharanthus roseus* and its potency as represented by the percentage (%) reduction in blood glucose levels by making use of various plant parts, solvents, oral dosages (unless specified otherwise), animal strains and chemically-induced diabetic models (Alloxan or STZ).

Treatment of *C. roseus*	**Dose (mg/kg or mL/Kg)**	**Period (days)**	**Animal**	**Diabetes induction method**	**Percentage reduction in blood glucose levels (BGL)**	**Reference**
Methanolic leaf	250 mg/kg	7	Male Albino rats	Alloxan	69 %	(Aruljothi and Samipillai 2016)
Aqueous flower, root, leaf and stem	250 mg/kg	6h	Male mice: *Mus musculus* CD-1 strain	Alloxan	~50 % (reduction in fasting BGL)	(Vega-Avila et al., 2012)
Fresh leaf juice	1.0 mL/Kg	20h	Rabbits	Alloxan	36.5 ± 4.8 %, ($p < 0.001$)	(Nammi et al., 2003)
Methanolic whole plant	300 and 500 mg/kg	14	Wistar rats (Male & Female)	Alloxan	25–50 %	(Ahmed et al., 2010)
DCM: methanol (1:1) leaves and twigs	500 mg/kg	7 and 15	Male Sprague Dawley rats	STZ	49 % (7 days) and 58 % (15 days)	(Singh et al., 2001; Salehi et al., 2019)
Aqueous	1000 mg/kg	21	Male Sprague Dawley rats	STZ	20.2 %	(Singh et al., 2001)
Aqueous leaf	1000 mg/kg	14	Albino rats (Male & Female)	STZ	~13 %	(Mostofa et al., 2007)
Ethanolic leaf (Petroleum ether,Chloroform & Ethyl acetate)	150 mg/kg	1	Long-Evans female Rats	STZ	52 % petroleum ether 0 % (chloroform) and 50 % ethyl acetate	(Islam et al., 2009)
Ethanolic leaf	100 and 200 mg/kg	28	Male Wistar rats	STZ	46 % (100 mg/kg) and 54 %	(Al-Shaqha et al., 2015; Salehi et al., 2019)
Methanolic leaf	200 and 400 mg/kg	13	Mice	STZ	58 % (200 mg/kg) and 59 %	(Singh et al., 2014)
Methanol leaf	250 mg/kg	7	Albino rats	Alloxan	37 %	(Ohadoma and Michael 2011)
Aqueous leaf	100 mg/kg	60	Male albino Wistar rats	STZ	78 %	(Rasineni et al., 2010)
DCM: methanol (1:1) leaf	500 mg/kg	20	Male albino Wistar rats	Alloxan	54 %	(Jayanthi et al., 2010)
Dry leaf powder	1.5 and 3.0 mg/kg	45	Male albino Wistar rats	STZ	59 % and 61 % (3.0 mg/kg)	(Chauhan et al., 2012)
Aqueous leaf	500 mg/kg	15	Albino rats	STZ	46.5 %	(Prasad et al., 2009)

Ethanolic leaf	300 mg/kg	45	Male albino Wistar rats	Alloxan	53 %	(Manoharan et al., 2011)
Ethanolic leaf	300 mg/kg	14	Albino rats	Alloxan	74 %	(Mohan et al., 2015)
Aqueous leaf, flower and stems	25 mg/kg	7	Male albino Wistar rats	Alloxan	18 %	(Iweala and Okeke 2005)
Leaf juice	500, 750 and 1000 mg/kg	1	Rabbits	Alloxan	17 %, 29 % and 39 % (1000 mg/kg)	(Satyanarayana et al., 2008)
Ethanolic leaf	150 mg/kg	14	Male and female albino rats	Alloxan	49 %	(Akhtar et al., 2007)
Aqueous leaf	0.1 mg/kg (IP)	30	Albino Wistar rats	Alloxan	51 %	(Muralidharan 2014)
Aqueous stems	250 mg/kg	6h	Male mice, *M. musculus* CD-1	STZ (single 135 mg/kg)	51.2 ± 19.3 %	(Espejel-Nava et al., 2018)

IP=Intraperitoneal administration.

A quantitative ethnobotanical survey by Hulley and Van Wyk (2019) revealed that *P. afra* was used for the treatment of high blood pressure and diabetes. While studies have shown the anti-hyperglycaemic potential of *P. afra*, they lack scientific evidence from an *in vivo* source. Therefore, future studies are required to evaluate its application in the management of diabetes as it is being prescribed to patients by traditional healers. Overall, *P. afra* has several medicinal potentials, including anti-hyperglycaemic activity, and further research is required to establish its potential in diabetes management.

3.2.1. Phytochemical constituents and pharmacological evidence of Portulacaria afra: anti-hyperglycaemic activity

Several studies have highlighted the potential of *Portulacaria afra* in the management of diabetes. The plant has been reported to possess anti-hyperglycaemic properties due to the presence of various phytochemicals such as flavonoids, saponins, tannins, phenolic compounds, and terpenoids (Adeleye and Risenga 2022; De Wet et al. 2013; Opabode et al., 2019). Some of the potential anti-hyperglycaemic mechanisms of Spekboom include improving glucose uptake, reducing insulin resistance, and protecting pancreatic beta-cells (Olaokun et al., 2017; Oyenihi et al., 2019; Visagie et al., 2019). Additionally, *P. afra* has been found to have anti-oxidant and anti-inflammatory properties that could contribute to its potential in diabetes management (Opabode et al., 2019; Tabassum et al., 2022; Tabassum et al., 2023). The biological activity of anti-oxidants are well known for their effectiveness in reducing diabetic complications (Bajaj and Khan 2012; Johansen et al., 2005; Krishnaiah et al., 2011). Furthermore, the plant has been reported to have a low glycaemic index and high fibre content, which may help regulate blood glucose levels. However, more research is needed to fully explore the anti-hyperglycaemic potential of Spekboom and its mechanisms of action.

4. Pharmacological potentials of the combination of *Catharanthus roseus* and *Portulacaria afra*

It is accepted that complex mixtures of two medicinal plants is more effective due to beneficial combination interactions (Vaou et al., 2022). However, scientific evidence of their therapeutic properties is lacking. According to our phytochemical analysis report obtained from Agro-processing of Medicinal and Food Crops Lab (Agricultural Research Council (ARC) Roodeplaat: Vegetable and Ornamental Plants), aqueous leave extracts of both *C. roseus* and *P. afra* presented positive results for metabolites of flavonoids and total phenolics. Flavonoids and phenolics (and many other including alkaloids) are active metabolites that are promising sources of natural anti-hyperglycaemic agents and could be the subject in future studies (Oliveira et al., 2014). In fact, the activity of medicinal plants is the result of multiple intra-phytochemical interaction with synergistic or antagonistic activity (Ulrich-Merzenich et al., 2010). The most comprehensive technique used to evaluate the effects of herb-herb interactions is shown *in vivo* model systems (Potts et al., 2013). To date, a sufficient number of *in vivo* reports documented the anti-hyperglycaemic effects of leave extracts of *C. roseus*, however, only *in vitro* anti-microbial, anti-hyperglycaemic and anti-inflammatory (*in vitro* and *in vivo* model) assays have been performed on the leaf extracts of *P. afra* (Teffo et al., 2022). There remains a significant shortage of *in vivo* reports on the pharmacological activity of *P. afra* in the management of diabetes mellitus. Understanding the herb-herb interactions between these two medicinal plants will result in the development of new combination anti-hyperglycaemic therapy. Therefore, it is recommended that a well-designed animal study be performed using a 1:1 combination of aqueous leave extracts of *C. roseus* and *P. afra*. The safety and efficiency of herbal preparations is greatly dependant on *in vivo* research.

5. Conclusion

Currently, diabetes management in South Africa heavily relies on pharmacological agents, which come with a variety of drawbacks such as adverse side-effects, high costs, and their monotherapeutic nature. This issue is especially pronounced in low-income countries due to various socio-economic challenges. However, the rich floral biodiversity of Africa has provided a potential solution through the use of medicinal plant remedies. By combining two medicinal plants that present similar pharmacological properties, in a 1:1 mixture, traditional healers have been able to further increase their synergistic potency for the management of certain chronic diseases. One such combination that has gained attention in the management of diabetes is the mixture of *Catharanthus roseus* and *Portulacaria afra* leave extracts. While anecdotal evidence from traditional healers supports the therapeutic properties of this mixture, there is currently a lack of scientific validation to confirm its anti-hyperglycaemic properties. Despite the extensive ethnobotanical records, *in vitro* and *in vivo* exploration is needed to fully explore the therapeutic benefits of this combination. By further investigating the potential of these plant extracts, we may be able to offer a more accessible and cost-effective solution for the management of diabetes in South Africa and beyond.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Adeleye, O.C., Risenga, I.M., 2022. Screening of phytochemical profile and biological activities in the leaves, stems and roots of South African Portulacaria afra using four extraction solvents. Biomedical Pharmacol. J. 15, 1561–1572.

Afolayan, J., Sunmonu, O., 2010. In vivo studies on antidiabetic plants used in South African herbal medicine. J. Clin. Biochem. Nutr. 47, 98–106.

Ahmed, M.F., Kazim, S.M., Ghori, S.S., Mehjabeen, S.S., Ahmed, S.R., Ali, S.M., Ibrahim, M., 2010. Antidiabetic activity of Vinca Rosea extracts in alloxan-induced diabetic rats. Int. J. Endocrinol. 2010, 841090.

Akhtar, M.A., Rashid, M., Wahed, M.I.I., Islam, M.R., Shaheen, S.M., Islam, M.A., Amran, M.S., Ahmed, M., 2007. Comparison of long-term antihyperglycemic and hypolipidemic effects between Coccinia cordifolia (Linn.) and Catharanthus roseus (Linn.) in alloxan-induced diabetic rats. Res. J. Med. Med. Sci. 2, 29–34.

Akinyede, K.A., Oyewusi, H.A., Hughes, G.D., Ekpo, O.E., Oguntibeju, O.O., 2021. In vitro evaluation of the anti-diabetic potential of aqueous acetone Helichrysum petiolare extract (AAHPE) with molecular docking relevance in diabetes mellitus. Molecules 27.

Al-Shaqha, W.M., Khan, M., Salam, N., Azzi, A., Chaudhary, A.A., 2015. Antidiabetic potential of Catharanthus roseus Linn. and its effect on the glucose transport gene (GLUT-2 and GLUT-4) in streptozotocin induced diabetic Wistar rats. BMC Complement. Altern. Med. 15, 379.

Artasensi, A., Pedretti, A., Vistoli, G., Fumagalli, L., 2020. Type 2 diabetes mellitus: a review of multi-target drugs. Molecules 25, 1987.

Aruljothi, B., Samipillai, S.S., 2016. Antidiabetic activity of Catharanthus roseus in alloxan-induced diabetic rats. Int. J. Modn. Res. Revs. 4, 1121–1124.

Bacanli, M., Dilsiz, S.A., Basaran, N., Basaran, A.A., 2019. Effects of phytochemicals against diabetes. Adv. Food Nutr. Res. 89, 209–238.

Bajaj, S., Khan, A., 2012. Antioxidants and diabetes. Indian J. Endocrinol. Metab. 16, S267–S271.

Barrales-Cure~no, H., 2015. Pharmacological applications and in vitro biotechnological production of anticancer alkaloids of Catharanthus roseus. Biotechnol. Apl. 32, 1101–1110.

Belinda, R., 2004. Gale encyclopaedia of alternative medicine. Gale Encyclopaedia Altern. Med. 2603–2605.

Bhutkar, M.A., 2018. In Vitro studies on alpha amylase inhibitory activity of some indigenous plants. Modern Applications Pharm. Pharmacol. 1.

Cantley, J., Ashcroft, F.M., 2015. Insulin secretion and type 2 diabetes: why do beta-cells fail? BMC Biol. 13, 33.

Cavaiola, T.S., Pettus, J.H. 2017. Management of type 2 diabetes: selecting amongst available pharmacological agents. Endotext [Internet]. MDText. com, Inc.

Chauhan, K., Sharma, S., Rohatgai, K., Chauhan, B., 2012. Antihyperlipidemic and anti-oxidative efficacy of Catharanthus roseus Linn [Sadabahar] in streptozotocin induced diabetic rats. Asian J. Pharmaceutical Health Sci. 2.

Cock, I.E., Ndlovu, N., Van Vuuren, S.F., 2021. The use of South African botanical species for the control of blood sugar. J. Ethnopharmacol. 264, 113234.

Davids, D., Gibson, D., Johnson, Q., 2016. Ethnobotanical survey of medicinal plants used to manage high blood pressure and type 2 diabetes mellitus in Bitterfontein, Western Cape Province, South Africa. J. Ethnopharmacol. 194, 755–766.

De Wet, H., Nciki, S., Van Vuuren, S.F., 2013. Medicinal plants used for the treatment of various skin disorders by a rural community in northern Maputaland, South Africa. J. Ethnobiol. Ethnomed. 9, 51.

Dlova, N.C., Ollengo, M.A., 2018. Traditional and ethnobotanical dermatology practices in Africa. Clin. Dermatol. 36, 353–362.

Dowarah, J., Singh, V.P., 2020. Anti-diabetic drugs recent approaches and advancements. Bioorg. Med. Chem. 28, 115263.

Egan, A.M., Dinneen, S.F., 2019. What is diabetes? Medicine (Baltimore). 47, 1–4.

Erasto, P., Adebola, P., Grierson, D., Afolayan, A., 2005. An ethnobotanical study of plants used for the treatment of diabetes in the Eastern Cape Province, South Africa. Afr. J. Biotechnol. 4.

Espejel-Nava, J.A., Vega-Avila, E., Alarcon-Aguilar, F., Contreras-Ramos, A., Diaz-Rosas, G., Trejo-Aguilar, G., Ortega-Camarillo, C., 2018. A phenolic fraction from Catharanthus roseus L. stems decreases glycemia and stimulates insulin secretion. Evid. Based Complement. Altern. Med. 2018, 7191035.

Fapohunda, O., Saliu, J., Samuel, A. 2018. Antidiabetic potential of aqueous extract of Catharanthus roseus. 1, 81-87.

Farnsworth, N., 1961. Pharmacognosy of Periwinkles-vinca and Catharanthus. Lloydia 24, 105-+.

Feingold, K.R., Anawalt, B., Boyce, A., Chrousos, G., Dungan, K., Grossman, A., Hershman, J., Kaltsas, G., Koch, C., Kopp, P., 2020. Oral and injectable (non-insulin) pharmacological agents for type 2 diabetes. Endotext. South Dartmouth (MA).

Fern, K. 2022. Tropical plants database [Online]. Available: https://tropical.theferns.info/viewtropical.php?id=Catharanthus+roseus [Accessed].

Firdous, S.M., 2014. Phytochemicals for treatment of diabetes. EXCLI J. 13, 451–453.

Foretz, M., Guigas, B., Bertrand, L., Pollak, M., Viollet, B., 2014. Metformin: from mechanisms of action to therapies. Cell Metab. 20, 953–966.

Gaikwad, B.S., Krishna Mohan, G., Rani, M.S., 2014. Phytochemicals for diabetes management. Pharm. Crop 5, 11–28.

Ganesan, K., Sultan, S. 2019. Oral Hypoglycemic medications. StatPearls [Internet]. Stat-Pearls Publishing.

Gangasani, J.K., Pemmaraju, D.B., Murthy, U.S.N., Rengan, A.K., Naidu, V.G.M., 2022. Chapter 4 - Chemistry of herbal biomolecules. In: Mandal, S.C., Nayak, A.K., Dhara, A.K. (Eds.), Herbal Biomolecules in Healthcare Applications. Academic Press.

Goboza, M., Aboua, Y.G., Meyer, S., Oguntibeju, O.O., 2016. Diabetes mellitus: economic and health burden, treatment and the therapeutical effects of Hypoxis hemerrocallidea plant. Medical Technol. South Africa.

Guralnick, L.J., Ting, I.P., 1987. Physiological changes in Portulacaria afra (L.) Jacq. During a summer drought and rewatering. Plant Physiol. 85, 481–486.

Gutiérrez-Del-Río, I., Fernández, J., Lombó, F., 2018. Plant nutraceuticals as antimicrobial agents in food preservation: terpenoids, polyphenols and thiols. Int. J. Antimicrob. Agents 52, 309–315.

Hankey, A. 2009. Portulacaria afra Jacq. [Online]. Available: http://pza.sanbi.org/portulacaria-afra [Accessed].

Harding, J.L., Pavkov, M.E., Magliano, D.J., Shaw, J.E., Gregg, E.W., 2019. Global trends in diabetes complications: a review of current evidence. Diabetologia 62, 3–16.

Henderson, L., 2001. Alien weeds and invasive plants: a complete guide to declared weeds and invaders in South Africa. Plant Protection Research Institute Handbook No.12. Agricultural Research Council, Pretoria.

Htay, T., Soe, K., Lopez-Perez, A., Doan, A.H., Romagosa, M.A., Aung, K., 2019. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Curr. Cardiol. Rep. 21, 45.

Hudish, L.I., Reusch, J.E., Sussel, L., 2019. b-cell dysfunction during progression of metabolic syndrome to type 2 diabetes. J. Clin. Invest. 129, 4001–4008.

Hulley, I.M., Van Wyk, B.E., 2019. Quantitative medicinal ethnobotany of Kannaland (western Little Karoo, South Africa): non-homogeneity amongst villages. S. Afr. J. Bot. 122, 225–265.

Idf, 2021. International Diabetes Federation. Diabetes around the world in 2021. IDF Diabetes Atlas.

Imran, S.A., Agarwal, G., Bajaj, H.S., Ross, S., 2018. Targets for glycemic control. Can. J. Diabetes 42, S42–S46.

Ioannides, C., 2003. Drug-phytochemical interactions. Inflammopharmacology 11, 7–42.

İpek, P., TaşDemir, E., KoçYiğIt, Y.K., 2018. Investigation of possible antidiabetic effects of Potentilla fulgens in diabetic rats and comparison with other antidiabetics. Haydarpasa Numune Training Res. Hospital Med. J.

Irons, B.K., Minze, M.G., 2014. Drug treatment of type 2 diabetes mellitus in patients for whom metformin is contraindicated. Diabetes, Metab. Syndr. Obes. 7, 15–24.

Islam, M., Akhtar, M.A., Islam, M., Hossain, M., Alam, M., Wahed, M., Rahman, B., Anisuzzaman, A., Shaheen, S., Ahmed, M., 2009. Antidiabetic and hypolipidemic effects of different fractions of Catharanthus roseus (Linn.) on normal and streptozotocin-induced diabetic rats. J. Scientific Res. 1, 334–344.

Iweala, E.E., Okeke, C.U., 2005. Comparative study of the hypoglycemic and biochemical effects of Catharanthus roseus (Linn) G. apocynaceae (Madagascar periwinkle) and chlorpropamide (diabenese) on alloxan-induced diabetic rats. Biokemistri 149–156.

Jayanthi, M., Sowbala, N., Rajalakshmi, G., Kanagavalli, U., Sivakumar, V., 2010. Study of anti-hyperglycemic effect of Catharanthus roseus in alloxan-induced diabetic rats. Int. J. Pharm. Pharm. Sci. 2, 114–116.

Jin, Z., Gao, L., Zhang, L., Liu, T., Yu, F., Zhang, Z., Guo, Q., Wang, B., 2017. Antimicrobial activity of saponins produced by two novel endophytic fungi from Panax notoginseng. Nat. Prod. Res. 31, 2700–2703.

Johansen, J.S., Harris, A.K., Rychly, D.J., Ergul, A., 2005. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovasc. Diabetol. 4, 5-5.

Kettunen, J.L., Tuomi, T., 2020. Human physiology of genetic defects causing beta-cell dysfunction. J. Mol. Biol. 432, 1579–1598.

Khan, H., Saeedi, M., Nabavi, S.M., Mubarak, M.S., Bishayee, A., 2019. Glycosides from medicinal plants as potential anticancer agents: emerging trends towards future drugs. Curr. Med. Chem. 26, 2389–2406.

Khanyile, A., Maliehe, T.S., Shandu, J.S., Khan, R., 2021. In vitro antibacterial, antioxidant, anti-quorum sensing and cytotoxic properties of Portulacaria afra leave extract. Biosci. Res. 18, 455–463.

Koche, D., Shirsat, R., Kawale, M. 2018. An overerview of major classes of phytochemicals: their types and role in disease prevention. 9, 2016.

Krentz, N.A., Gloyn, A.L., 2020. Insights into pancreatic islet cell dysfunction from type 2 diabetes mellitus genetics. Nat. Rev. Endocrinol. 16, 202–212.

Krishnaiah, D., Sarbatly, R., Nithyanandam, R., 2011. A review of the antioxidant potential of medicinal plant species. Food Bioprod. Process. 89, 217–233.

Li, W.L., Zheng, H.C., Bukuru, J., De Kimpe, N., 2004. Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J. Ethnopharmacol. 92, 1–21.

Ly, C., Yockell-Leliévre, J., Ferraro, Z.M., Arnason, J.T., Ferrier, J., Gruslin, A., 2014. The effects of dietary polyphenols on reproductive health and early developmenty. Hum. Reprod. Update 21, 228–248.

Maema, L.P., Potgieter, M., Mahlo, S.M., 2016. Invasive alien plant species used for the treatment of various diseases in Limpopo Province, South Africa. Afr. J. Tradit. Complement. Altern. Med. 13, 223–231.

Malathi, V., Devi, S.S., Revathi, K., 2010. Antidiabetic activity by the in vitro alpha-amylase and alpha-glucosidase inhibitory activity of Catharanthus roseus. Bioscan 5, 655–659.

Manoharan, S., Umadevi, S., Jayanthi, S., Baskaran, N., 2011. Anti-hyperglycemic effect of Coscinium fenestratum and Catharanthus roseus in alloxan-induced diabetic rats. Int. J. Nutrition, Pharmacol. Neurolog. Dis. 1.

Marin-Penalver, J.J., Martin-Timon, I., Sevillano-Collantes, C., Del Canizo-Gomez, F.J., 2016. Update on the treatment of type 2 diabetes mellitus. World J. Diabetes 7, 354–395.

Maroyi, A., 2020. Ethnobotanical study of wild and cultivated vegetables in the Eastern Cape Province, South Africa. Biodiversitas J. Biol. Diversity 21.

Mehwish, S., Islam, A., Ullah, I., Wakeel, A., Qasim, M., Khan, M.A., Ahmad, A., Ullah, N., 2019. In vitro antileishmanial and antioxidant potential, cytotoxicity evaluation and phytochemical analysis of extracts from selected medicinally important plants. Biocatal. Agric. Biotechnol. 19.

Mishra, J.N., Verma, N.K., 2017. A brief study on Catharanthus roseus: a review. Intern J. Res. Pharm. Pharmaceut. Sci. 2, 20–23.

Mohan, S., Priyadarshini, G., Balam.urugan, V., 2015. GC-MS analysis of phytochemicals and hypoglycemic effect of Catharathus roseus in alloxan-induced diabetic rats. Int. J. Pharm. Sci. Res. 25, 123–128.

Mostofa, M., Choudhury, M., Hossain, M., Islam, M., Islam, M., Sumon, M., 2007. Antidiabetic effects of Catharanthus roseus, Azadirachta indica, Allium sativum and glimepride in experimentally diabetic induced rat. Bangladesh J. Veterinary Med. 99–102.

Muralidharan, L., 2014. Catharanthus roseus leaves as an antidiabetic and hypolipidemic agents in alloxan-induced diabetic rats. Am. J. Phytomed. Clin. Therapeutics 2, 1393–1396.

Nammi, S., Boini, M.K., Lodagala, S.D., Behara, R.B.S., 2003. The juice of fresh leaves of Catharanthus roseus Linn. reduces blood glucose in normal and alloxan diabetic rabbits. BMC Complement. Altern. Med. 3, 4.

Nciki, S., Vuuren, S., Van Eyk, A., De Wet, H., 2016. Plants used to treat skin diseases in northern Maputaland, South Africa: antimicrobial activity and in vitro permeability studies. Pharm. Biol. 54, 2420–2436.

Nisar, A., Mamat, A., Mohamed Dzahir, M.I.H., Ahmad, M.S., Aslam, M., 2016. An updated review on Catharanthus roseus: phytochemical and pharmacological analysis. Indian Res. J. Pharm. Sci. 3, 631–653.

Ohadoma, S.C., Michael, H.U., 2011. Effects of co-administration of methanol leaf extract of Catharanthus roseus on the hypoglycemic activity of metformin and glibenclamide in rats. Asian Pac. J. Trop. Med. 4, 475–477.

Olaokun, O.O., Mkolo, N.M., Mogale, M.A., King, P.H., 2017. Phytochemical screening, antioxidant, anti-inflammatory, and glucose utilization activities of three South African plants used traditionally to treat diseases. Biol. Med. 09.

Oliveira, L.D.L.D., Carvalho, M.V.D., Melo, L., 2014. Health promoting and sensory properties of phenolic compounds in food. Revista Ceres 61, 764–779.

Oluwaseun, F., Saliu, J. 2018. Antidiabetic potential of aqueous extract of Catharanthus roseus.

Opabode, J.T., Ogundele, O.J., Ashafa, A.O.T., Afolayan, A.J., 2019. In vitro hypoglycemic and anti-oxidant potentials of Portulacaria afra (L.) Jacq. and Helichrysum pedunculatum (Hilliard and Burtt) in human liver hepatocellular carcinoma cell line. J. Basic Clin. Physiol. Pharmacol. 30.

Othman, L., Sleiman, A., Abdel-Massih, R.M., 2019. Antimicrobial activity of polyphenols and alkaloids in middle eastern plants. Front. Microbiol. 10, 911.

Oyenihi, A.B., Afolayan, A.J., Bradley, G., 2019. In vitro anti-diabetic and anti-inflammatory effects of aqueous and methanol extracts of Portulacaria afra Jacq. leaf in insulin-resistant HepG2 cells. S. Afr. J. Bot. 120, 329–335.

Padhi, S., Nayak, A.K., Behera, A., 2020. Type 2 diabetes mellitus: a review on recent drug based therapeutics. Biomed. Pharmacother. 131, 110708.

Panche, A.N., Diwan, A.D., Chandra, S.R., 2016. Flavonoids: an overview. J. Nutr. Sci. 5, e47.

Pham, H.N.T., Vuong, Q.V., Bowyer, M.C., Scarlett, C.J., 2020. Phytochemicals derived from Catharanthus roseus and their health benefits. Technologies 8, 80.

Phan, M.a.T., Paterson, J., Bucknall, M., Arcot, J., 2018. Interactions between phytochemicals from fruits and vegetables: effects on bioactivities and bioavailability. Crit. Rev. Food Sci. Nutr. 58, 1310–1329.

Phielix, E., Meex, R., Moonen-Kornips, E., Hesselink, M.K., Schrauwen, P., 2010. Exercise training increases mitochondrial content and ex vivo mitochondrial function similarly in patients with type 2 diabetes and in control individuals. Diabetologia 53, 1714–1721.

Ponnusamy, S., Ravindran, R., Zinjarde, S., Bhargava, S., Ravi Kumar, A., 2011. Evaluation of traditional Indian anti-diabetic medicinal plants for human pancreatic amylase inhibitory effect in vitro. Evid. Based Complement. Altern. Med. 2011.

Potts, M.B., Kim, H.S., Fisher, K.W., Hu, Y., Carrasco, Y.P., Bulut, G.B., Ou, Y.H., Herrera-Herrera, M.L., Cubillos, F., Mendiratta, S., Xiao, G., Hofree, M., Ideker, T., Xie, Y., Huang, L.J., Lewis, R.E., Macmillan, J.B., White, M.A., 2013. Using functional signature ontology (FUSION) to identify mechanisms of action for natural products. Sci. Signal 6, ra90.

Prasad, S., Kulshreshtha, A., Qureshi, T.N., 2009. Antidiabetic activity of some herbal plants in streptozotocin induced diabetic albino rats. Pak. J. Nutr. 8, 551–557.

Rasineni, K., Bellamkonda, R., Singareddy, S.R., Desireddy, S., 2010. Antihyperglycemic activity of Catharanthus roseus leaf powder in streptozotocin-induced diabetic rats. Pharmacognosy Res. 2, 195–201.

Sagbo, I.J., Van De Venter, M., Koekemoer, T., Bradley, G., 2018. In vitro anti-diabetic activity and mechanism of action of Brachylaena elliptica (Thunb.) DC. Evid. Based Complement. Altern. Med., 4170372 2018.

V.N.C. Salehi, B., Ata, A., Anil Kumar, N., Sharopov, F., Ramírez-Alarcón, K., Ruiz-Ortega, A., Abdulmajid Ayatollahi, S., Valere Tsouh Fokou, P., Kobarfard, F., Amiruddin Zakaria, Z., Iriti, M., Taheri, Y., Martorell, M., Sureda, A., Setzer, W., Durazzo, A., Lucarini, M., Santini, A., Capasso, R., Adrian Ostrander, E., -Ur-Rahman, A., Iqbal Choudhary, M., Cho, W., Sharifi-Rad, J., 2019. Antidiabetic potential of medicinal plants and their active components. Biomolecules 9, 551.

Satyanarayana, S., Sarma, G.S., Ramesh, A., Sushruta, K., Srinivas, N., 2008. Evaluation of herbal preparations for hypoglycemic activity in normal and diabetic rabbits. Pharm. Biol. 41, 466–472.

Sieniawska, E., 2015. Activities of tannins from in vitro studies to clinical trials. Nat. Prod. Commun. 10, 1934578X1501001118.

Singh, A., Kumar, S. 2019. Applications of tannins in industry.

Singh, A., Singh, P.K., Singh, R.K., 2014. Antidiabetic and wound healing activity of Catharanthus roseus L. in streptozotocin-induced diabetic mice. Am. J. Phytomed. Clin. Ther. 2, 686–692.

Singh, S.N., Vats, P., Suri, S., Shyam, R., Kumria, M.M.L., Ranganathan, S., Sridharan, K., 2001. Effect of an antidiabetic extract of Catharanthus roseus on enzymic activities in streptozotocin induced diabetic rats. J. Ethnopharmacol. 76, 269–277.

Sparg, S.G., Light, M.E., Van Staden, J., 2004. Biological activities and distribution of plant saponins. J. Ethnopharmacol. 94, 219–243.

Srivastava, A., Srivastava, P., Pandey, A., Khanna, V.K., Pant, A.B., 2019. Chapter 24 - Phytomedicine: a potential alternative medicine in controlling neurological disorders. In: Ahmad Khan, M.S., Ahmad, I., Chattopadhyay, D. (Eds.), New Look to Phytomedicine. Academic Press.

Sunny, B., Mathews, M.M., Joseph, D., Mathew, F., George, J., Varghese, B., 2019. An in-depth investigation of diverse therapeutic benefits of Psidium Guajava with major emphasis on antidiabetic effect. Res. J. Pharm. Technol. 12.

J Swanston-Flatt, S.K., Day, C., Flatt, P., Gould, B., Bailey, C., 1989. Glycaemic effects of traditional European plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice. Diabetes Res. 10, 69–73.

Tabassum, S., Ahmad, S., Rehman, K.U., Khurshid, U., Rao, H., Alamri, A., Ansari, M., Ali, B., Waqas, M., Saleem, H., Anwar, S., 2022. Phytochemical, biological, and in-silico characterization of Portulacaria afra Jacq.: a possible source of natural products for functional food and medicine. S. Afr. J. Bot. 150, 139–145.

Tabassum, S., Ahmad, S., Ur Rehman Khan, K., Ali, B., Usman, F., Jabeen, Q., Sajid-Ur-Rehman, M., Ahmed, M., Muhammad Zubair, H., Alkazmi, L., El-Saber Batiha, G., Zaman, Q.U., Basit, A., 2023. Chemical profiling and evaluation of toxicological, anti-oxidant, anti-inflammatory, anti-nociceptive and tyrosinase inhibitory potential of Portulacaria afra using in vitro, in vivo and in silico studies. Arabian J. Chem. 16.

Teffo, T.K., Ramalepe, P., Risenga, I., 2022. A short communication on the ethnobotany, phytochemistry, pharmacological evidence and ecosystem restoration potential of South African Portulacaria afra. J. Med. Plants 10, 112–115.

Thawabteh, A., Juma, S., Bader, M., Karaman, D., Scrano, L., Bufo, S.A., Karaman, R., 2019. The biological activity of natural alkaloids against herbivores, cancerous cells and pathogens. Toxins (Basel) 11.

Thring, T., Weitz, F., 2006. Medicinal plant use in the Bredasdorp/Elim region of the Southern Overberg in the Western Cape Province of South Africa. J. Ethnopharmacol. 103, 261–275.

Tiong, S.H., Looi, C.Y., Arya, A., Wong, W.F., Hazni, H., Mustafa, M.R., Awang, K., 2015. Vindogentianine, a hypoglycemic alkaloid from Catharanthus roseus (L.) G. Don (Apocynaceae). Fitoterapia 102, 182–188.

Ulrich-Merzenich, G., Panek, D., Zeitler, H., Vetter, H., Wagner, H. 2010. Drug development from natural products: exploiting synergistic effects.

Urzua, A., Rezende, M.C., Mascayano, C., Vasquez, L., 2008. A structure-activity study of antibacterial diterpenoids. Molecules 13, 882–891.

Van De Venter, M., Roux, S., Bungu, L.C., Louw, J., Crouch, N.R., Grace, O.M., Maharaj, V., Pillay, P., Sewnarian, P., Bhagwandin, N., Folb, P., 2008. Antidiabetic screening and scoring of 11 plants traditionally used in South Africa. J. Ethnopharmacol. 119, 81–86.

Van Der Heijden, R., Jacobs, D.I., Snoeijer, W., Hallard, D., Verpoorte, R., 2004. The Catharanthus alkaloids: pharmacognosy and biotechnology. Curr. Med. Chem. 11, 607–628.

Van Jaarsveld, E., Le Roux, A., 2021. Portulacaria afra (L.) Jacq.: variability and distribution. Bradleya 138–152 2021.

Van Wyk, B.E, 2008a. A broad review of commercially important southern African medicinal plants. J. Ethnopharmacol. 119, 342–355.

Van Wyk, B.E, 2008b. A review of Khoi-San and Cape Dutch medical ethnobotany. J. Ethnopharmacol. 119, 331–341.

Van Wyk, B.E., De Wet, H., Van Heerden, F, 2008. An ethnobotanical survey of medicinal plants in the southeastern Karoo, South Africa. S. Afr. J. Bot. 74, 696–704.

Van Wyk, B.E., Oudtshoorn, B.V., Gericke, N. 1997. Medicinal Plants of South Africa, Briza.

Vaou, N., Stavropoulou, E., Voidarou, C.C., Tsakris, Z., Rozos, G., Tsigalou, C., Bezirtzoglou, E., 2022. Interactions between medical plant-derived bioactive compounds: focus on antimicrobial combination effects. Antibiotics (Basel) 11.

Vega-Avila, E., Cano-Velasco, J.L., Alarcon-Aguilar, F.J., Fajardo Ortiz Mdel, C., Almanza-Perez, J.C., Roman-Ramos, R., 2012. Hypoglycemic activity of aqueous extracts from Catharanthus roseus. Evid. Based Complement. Altern. Med., 934258 2012.

Virmani, O., Srivastava, G., Singh, P., 1978. Catharanthus roseus: the tropical periwinkle. Indian Drugs 231–252.

Visagie, A., Mabasa, L., Oosthuizen, L., 2019. The hypoglycaemic and anti-diabetic activity of South African medicinal plants used traditionally to treat diabetes. J. Med. Plants Res. 13, 322–339.

Wang, T.Y., Li, Q., Bi, K.S., 2018. Bioactive flavonoids in medicinal plants: structure, activity and biological fate. Asian J. Pharm. Sci. 13, 12–23.

Weinstock, R.S. 2018. Patient education: type 1 diabetes: overview (beyond the basics).

Xiao, J., Capanoglu, E., Jassbi, A.R., Miron, A., 2016. Advance on the flavonoid c-glycosides and health benefits. Crit. Rev. Food Sci. Nutr. 56 (Suppl 1), S29–S45.

Za'abi, M.A., Ali, B.H., Al Suleimani, Y., Adham, S.A., Ali, H., Manoj, P., Ashique, M., Nemmar, A., 2021. The effect of metformin in diabetic and non-diabetic rats with experimentally-induced chronic kidney disease. Biomolecules 11.

Zhao, Q., Luan, X., Zheng, M., Tian, X.H., Zhao, J., Zhang, W.D., Ma, B.L., 2020. Synergistic mechanisms of constituents in herbal extracts during intestinal absorption: focus on natural occurring nanoparticles. Pharmaceutics 12.