In vivo Studies on Antidiabetic Plants Used in South African Herbal Medicine

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Summary **Diabetes is one of the most common metabolic disorders worldwide. It is a major health problem with its frequency increasing every day in most countries. The disease is generally believed to be incurable; and the few orthodox drugs available to manage the disease are not readily affordable to the poor. Based on the historical success of natural products as antidiabetic agents and the ever increasing need for new antidiabetics, a number of South African medicinal plants have been evaluated for their antidiabetic properties. In this article, we review the major studies conducted based on ethnobotanical surveys carried out between 2005 and 2008 in South Africa on plants that are traditionally used for the treatment of diabetes. Overall, the results of the studies conducted confirmed the potential of South African medicinal plants in antidiabetic drug discovery and identified a number of promising taxa for further *in vivo* investigation as plant-based antidiabetic agents.**

Key Words**: diabetes, herbal medicines, antidiabetic, plant extract, blood glucose**

Introduction

The word *diabetes* is borrowed from the Greek word meaning *a siphon* because the affected individuals experience polyuria and *pass water like a siphon*. Diabetes could either be mellitus or less often, insipidus. However, when the term is used without qualification, it usually refers to diabetes mellitus.

Diabetes mellitus is a metabolic disease characterized by high blood glucose level resulting from defects in insulin secretion, insulin action or both [*1*]. It is a chronic disorder that affects the metabolism of carbohydrates, fats, proteins and electrolytes in the body, leading to severe complications which are classified into acute, sub-acute and chronic [*2*]. Acute complications include hypoglycemia, diabetic ketoacidosis, hyperosmolar and hyperglycaemic non-ketotic syndrome [*3*] while sub acute complications include thirst, polyuria, lack of energy, visual blurriness and weight loss [*4*]. Chronic hyperglycemia causes glycation of body proteins which in turn leads to complications that may affect the eyes, kidneys, nerves and arteries [*5*].

Diabetes insipidus, on the other hand, is a disorder that is associated with lack of vasopressin and characterized by an abnormal increase in urine output, fluid intake, frequent urination and excessive thirst [*6*]. Vasopressin is an antidiuretic hormone formed in the hypothalamus and secreted by the pituitary gland. The hormone is used primarily to control water retention through the reduction in urine output. Although both diabetes mellitus and insipidus share some common symptoms such as frequent urination and excessive thirst, the diagnosis and treatment are not the same [*6*].

On the basis of aetiology and clinical presentation, diabetes mellitus is classified into two. Type 1, known as insulin-dependent diabetes mellitus (IDDM) is caused by immunological destruction of pancreatic β cells resulting in insulin deficiency [*7*]. Its pathogenesis involves environmental triggers that may activate autoimmune mechanisms in genetically susceptible individuals, leading to progressive loss of pancreatic islet β cells [*8*]. Many of the acute effects of this disease can be controlled by insulin replacement therapy; however it has long term adverse effects on blood

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vessels, nerves and other organs of the body [*9*].

Type 2, also known as non insulin-dependent diabetes mellitus (NIDDM) is characterized by both impaired insulin secretion and insulin resistance, which is often associated with obesity and hereditary disposition [*10*]. It is increasing rapidly and is becoming a significant global health problem [*11*]. Type 2 diabetes can lead to cardiovascular damage through a number of mechanisms, each of which in turn may accelerate or worsen the others [*12*]. Despite numerous research efforts, the nature of the defect is yet to be determined. Some patients have abnormal insulin receptor and/or defective insulin signaling while no defects have been identified in others. Generally, NIDDM is controlled through dietary therapy, exercise and hypoglycemic agents [*13–15*].

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects [*16*]. Herbal medicines continue to play an important role in diabetic therapy, particularly in the developing countries where most people have limited resources and do not have access to modern treatment [*17*]. WHO has also authenticated the use of herbal remedies for the treatment of diabetes [*18*]. The increase in demand for the use of plant based medicines to treat diabetes may be due to the side effects associated with the use of orthodox drugs such as insulin and oral hypoglycemic agents [*19*]. Another important factor that strengthens the use of plant materials as antidiabetics could be attributed to the belief that herbs do provide some benefits over and above allopathic medicine and allow the users to feel that they have some control in their choice of medication [*20*].

In South Africa, 32 plant species have been identified for the treatment of diabetes based on the major ethnobotanical surveys documented by Erasto *et al.* [*21*]; Thring and Weitz [*22*]; Van Wyk *et al.* [*23*]; van de Venter *et al.* [*24*] and Van Wyk [*25*, *26*] (Table 1). These surveys covered the Eastern and Western Cape Provinces, Southeastern Karoo, Khoi-San and Cape Dutch regions which are recognized as the richest flora communities in South Africa. Out of these flora, only nine species have been documented in scientific literature to possess *in vivo* antidiabetic activity. Basic researches relating to these plants are reviewed in this paper with a view to highlighting the potential of South African medicinal plants in antidiabetic drug discovery and the need for further *in vivo* investigations on antidiabetic plants.

Prevalence of Diabetes among Human Populations

Diabetes is a common and very prevalent disease affecting the citizens of both developed and developing countries. The WHO estimated the disease in adults to be around 173 million in 2000, two-thirds of which live in developing countries [*27*]. The prevalence of diabetes mellitus is on the increase worldwide and it is still expected to increase by 5.4% in 2025 [*28*]. Increase in sedentary lifestyle, consumption of energy-rich diet and obesity are some of the factors causing the rise in the number of diabetics. According to the American Diabetes Association [*29*], Asia and Africa are regions with greatest potential where diabetics could rise to two or threefold above the present level. In South Africa, the number of people suffering from diabetes has been rising steadily over the past two decades. Several reports have stressed the high mortality from diabetes especially among the black populations [*30*, *31*]. Despite these alarming statistics, diabetes still remain one of the age long chronic diseases of human race and its frontiers are expanding by the day.

Relevance of *in vivo* Study in Diabetic Research

Diabetes affects many metabolic pathways in human tissues, many of which are potential targets for drug treatment [*24*]. Most of the studies on antidiabetic plants are focused on *in vitro* analysis. Unfortunately, this approach complicates the identification of new treatments, as most *in vitro* screening models consider single cell types, metabolic pathway or enzyme; thus greatly reducing the possibility of identifying antidiabetic plant extracts or compounds. Another disadvantage of *in vitro* studies is that only acute or immediate effects are measured, whilst effects that may only be apparent after chronic exposure to the antidiabetic compounds are overlooked [*24*]. In this regard, animal models are more appropriate for the evaluation of antidiabetic properties of medicinal plants.

South Africa is home to over 30,000 species of higher plants and 3,000 of these species are used in traditional medicine across the country [*32*]. According to Mander, there are over 27 million users of indigenous medicine [*33*]; and an estimated 200,000 indigenous traditional healers that treat up to 60% of the population [*32*]. Hence, there is the need to carry out *in vivo* studies on medicinal plants with a view to validating their acclaimed efficacy and evaluating their toxic potentials.

Plants with Documented *in vivo* Antidiabetic Activities

Vernonia amygdalina Del. (Asteraceae)

Vernonia amygdalina commonly known as bitter leaf, is a small tree growing up to 3 m high. It occurs wild in most countries of tropical Africa. In South Africa, the plant is found in KwaZulu Natal, Mpumalanga, Eastern and Northern Cape Provinces [*34*]. It is probably the most used plant in the genus *Vernonia*. The common and documented medicinal uses include the treatment of schistomiasis, amoebic dysentery and gastrointestinal problems [*35*]. It is

Table 1. Documented antidiabetic plants used in South African herbal medicine

Species	Parts used	References
Artemisia afra Jacq. Ex Willd.	Leaves, roots	Erasto *et al.*, 2005
	Leaves	Thring and Weitz, 2006
	Leaves	Van Wyk, 2008b
Brachylaena discolor DC.	Leaves,	Erasto *et al.*, 2005
	Leaves, roots, stem	van de Venter *et al.*, 2008
Brachylaena elliptica Thunb.	Leaves	Van Wyk, 2008a
Bulbine natalensis Mill.	Roots	Erasto *et al.*, 2005
Bulbine frutescens L.	Roots	Erasto *et al.*, 2005
Cannabis sativa L.	Leaves	van de Venter *et al.*, 2008
Catha edulis Forrsk. Ex Endl.	Leaves, stems, roots	van de Venter *et al.*, 2008
Catharanthus roseus (L) G. Don.	Leaves	Erasto *et al.*, 2005
	Leaves, twigs	van de Venter *et al.*, 2008
Chilianthus olearaceus Burch.	Leaves, twigs	Erasto *et al.*, 2005
Chironia baccifera L.	Whole plant	van de Venter *et al.*, 2008
Cissampelos capensis L.f.	Leaves	van de Venter *et al.*, 2008
Conyza scabrida DC.	Leaves	Thring and Weitz, 2006
Elytropappus rhinocerotis (L.f.)	Leaves	Thring and Weitz, 2006
Galium tomentosum Thunb.	Roots	Van Wyk *et al.*, 2008
Herichrysum nudifolium L.	Leaves, roots	Erasto *et al.*, 2005
Herichrysum odoratissimum L.	whole plant	Erasto *et al.*, 2005
Herichrysum petiolare H & B.L.	whole plant	Erasto *et al.*, 2005
Heteromorphica arborescens H.	Leaves, roots	Erasto *et al.*, 2005
Hypoxis colchicifolia Bak.	Corms	Erasto *et al.*, 2005
Hypoxis hemerocallidea Fisch.	Corms	Erasto *et al.*, 2005
Leonotis leonurus L.	Leaves, flowers	Thring and Weitz, 2006
Momordica balsamina L.	Stem, flowers	van de Venter *et al.*, 2008
Momordica foetida Schumach.	Whole plant	van de Venter *et al.*, 2008
Petroselenium crispum (Mill)	Leaves	Thring and Weitz, 2006
Psidium guajava L.	Leaves, roots	van de Venter *et al.*, 2008
Ricinus communis L.	Leaves	Thring and Weitz, 2006
Ruta graveolens L.	Leaves	Thring and Weitz, 2006
	Leaves	Van Wyk, 2008a
Sclerocarya birrea Hochst.	Stem, bark, roots	van de Venter *et al.*, 2008
	Stem, bark	Van Wyk, 2008b
Sutherlandia frutescens L.	Leaves	Van Wyk, 2008b
Vinca major L.	Leaves, roots, stem	van de Venter *et al.*, 2008
Vernonia oligocephala Sch. Bip.	Leaves, twigs, roots	Erasto *et al.*, 2005
	Leaves	Thring and Weitz, 2006
Vernonia amygdalina Del.	Leaves	Erasto *et al.*, 2005

also used in the treatment of malaria, venereal diseases, wounds, hepatitis and diabetes [*36–41*]. The leaves may be consumed either as a vegetable or aqueous extracts as tonics for the treatment of various illnesses.

Until the last decade, there were only anecdotal reports and claims to support the antidiabetic activity *V. amygdalina*. Gyang *et al.* [*42*] reported that chloroform extract of the plant has hypoglycaemic activity in both normoglycemic and alloxan-induced hyperglycemic rats. Ebong *et al.* [*43*] also reported the antidiabetic efficacy of combined ethanolic extracts of *Azadirachta indica* (neem) and *V. amygdalina* in rats. The decrease in blood glucose for the animals treated with combined extracts and bitter leaf only compared well with chlorpropamide and non-diabetic control, but not with neem alone. This finding corroborated the report of Atangwho *et al.* [*44*] who observed significant hypoglycemic

activity in diabetic rats treated with *V. amygdalina*. Osinubi [*45*] also reported that the extract of *V. amygdalina* produced significant reductions in the blood glucose concentrations of normal and diabetic rats; 1 to 12 h after the acute treatment. In another study involving healthy human subjects, Okolie *et al.* [*46*] investigated the hypoglycemic effects of the plant and observed a positive disposition of the plant extract towards the treatment of diabetes. Hence, the authors encouraged diabetic patients to consume the vegetable for therapeutic purposes.

Hypoxis hemerocallidea Fisch. (Hypoxidaceae)

Hypoxis hemerocallidea is one of the frequently used African medicinal plants. The plant grows in the wild in the area stretching from the Eastern Cape through to KwaZulu-Natal Provinces, Lesotho, Gauteng, Mozambique, Limpopo, Zimbabwe and even further north into East Africa [*32*]. This medicinal plant of southern Africa origin is a tuberous, perennial herb with long, strap-shaped leaves and yellow, star-shaped flowers. The broad and slightly hairy leaves of *H. hemerocallidea* are arranged one above the other to form three distinct groups of leaves spreading outwards from the centre of the plant, while the bright yellow, star-shaped flowers are borne on long, slender stalks [*47*]. The tuberous rootstock (corm) of the herb, which is commonly known as 'African Potato', is widely used in southern African traditional medicine as a remedy for an array of human ailments. The plant is claimed to be an effective remedy against HIV/AIDS-related diseases, arthritis, yuppie flu, hypertension, diabetes mellitus, cancer, psoriasis, gastric and duodenal ulcers, tuberculosis, urinary tract infections, asthma, and some central nervous system disorders especially epilepsy and childhood convulsions [*47–52*].

Very little scientific reports are available on the anecdotal claim of the antidiabetic property of *H. hemerocallidea*. In separate studies by Zibula & Ojewole and Ojewole, evaluation of the antidiabetic activity of aqueous extracts of the plant on streptozotocin (STZ) induced diabetic rats revealed significant reductions in the blood glucose concentration of the animals [*53*, *54*]. It was concluded that the plant extract, like glibenclamide, induces hypoglycemia by stimulating insulin release thereby enhancing the cellular uptake and utilization of glucose in the animals. In another study by Mahomed and Ojewole, aqueous extract of the plant caused 30.20% and 48.54% reductions in the blood glucose concentrations of fasted normal and STZ-treated diabetic rats. The authors attributed the hypoglycemic effect of the plant extract to its phytosterols and/or sterolin contents [*55*]. The results of these animal studies indicate that African potato possesses hypoglycemic activity; and thus lends credence to the suggested folkloric use of the herb in the control and/or management of diabetes mellitus in some communities of South Africa. Another report by Musabayane *et al.* however, suggested that aqueous extract of the plant may impair kidney function [*56*].

Catharanthus roseus (L) G. Don (Apocynaceae)

Catharanthus roseus (also known as *Vinca rosea* or *Vinca multiflora*) originated from Madagascar, hence the name Madagascar periwinkle. However, the plant has now spread throughout the tropics and subtropics (including South Africa) by human activities. It has readily naturalized in most places where it was introduced [*32*]. When it was discovered by the Europeans, the plant was wrongly classed as *Vinca* or true periwinkle. This error was later corrected, and the plant was put in its own genus (Catharanthus). It is a semiwoody evergreen perennial, usually cultivated as annual in flower beds. In frostfree climates, it develops a woody stem near the base and can grow up to 1 m tall and spread just as wide [*47*]. The plant is grown commercially for its medicinal uses in Australia, Africa, India and southern Europe where it is used primarily in the traditional setting to treat diabetes.

Numerous animal studies have shown that ethanolic extracts of the leaves and flowers of *C. roseus* lower blood glucose levels [*57–59*]. Research findings have also shown that while the aqueous leaf extract of the herb could lower blood glucose by about 20% in diabetic rats, dichloromethane and methanol extracts lowered blood glucose by 49–58% [*60*]. Significant increase in glucokinase activity was reported in the liver of rats treated with the leaf extract of *C. roseus* and it was suggested that the increase in glucose utilization could be the mechanism of antidiabetic activity of the extract [*60*]. Rats pretreated with the alcoholic extract became completely immune to the diabetes-inducing effect of streptozotocin, while the aqueous extract had only minor preventive effect [*58*]. The hypoglycemic effects appeared to be the result of increased glucose utilization in the liver. No adverse effects were observed in the animals treated with the extract of the plant except that serum acid and alkaline phosphatase levels were elevated in both untreated diabetic and treated diabetic rats. The 70% ethanolic leaf extract of the herb given orally at 400 mg/kg was 20% as effective as tolbutamide in diabetic rats, though the extract was much safer [*61*]. The sap from fresh leaves of this plant was also reported to reduce blood glucose in alloxan-treated rabbits [*62*]. Overall, no major toxicity was observed in the diabetic rats treated with the extract from *C. roseus* [*60*]. However, the duration of treatment was short and the authors suggested that chronic toxicity should be investigated for human use.

Leonotis leonurus L. (Lamiaceae)

Leonotis leonurus is also known as lion's tail, lion's ear or wild dagga. It is native to southern Africa; common at forest

margins, on rocky hillsides, river banks and in tall grassland especially in the Eastern and Western Cape, Kwazulu-Natal and Mpumalanga Provinces [*63*]. It is a shrub of 2–5 m tall, branching from a thick woody base with a pale brown and densely pubescent stem. The leaves are simple, opposite, petiolate, coriaceous, linear, acute at apex and base; and serrate in the distal half. The upper surface of the leaf is bright green and the lower surface densely pubescent [*63*]. Traditionally, the plant is used for the treatment of cough, cold, influenza, chest infections, diabetes, hypertension, eczema, epilepsy, delayed menstruation, intestinal worms, constipation, spider bites, scorpion stings and as an antidote for snakebite.

Not much has been done to validate the reported *in vivo* antidiabetic activity of *L. leonorus*. Ojewole reported that aqueous leaf extract of the plant caused significant hypoglycemic effect in rats which was attributed to the different flavonoids, diterpenoids, polyphenolics and other chemical constituents of the extract [*64*]. It is pertinent to state that the results of this study lend pharmacological credence to the folkloric use of the herb in the management and/or control of diabetes in some communities in South Africa. Maphosa *et al.* [*65*] however reported that the aqueous shoot extract of the herb produced adverse hematological, biochemical and histopathological changes in rats. The authors therefore concluded that caution must be exercised in the use of the plant for medicinal purposes.

Catha edulis Forrsk. Ex Endl. (Celastraceae)

Catha edulis popularly called *khat* is an evergreen shrub of the tropics [*66*, *67*]. The fresh leaf is traditionally chewed by some people in East Africa and the Arabian Peninsula to attain a state of euphoria and stimulation [*68*, *69*]. Since the leaf rapidly loses its effect upon wilting, the chewing habit has remained endemic to the areas where the plant is cultivated. During the last decades, however, due to the development of road networks and the availability of air transport, the habit has spread considerably in those regions and countries where the plant does not grow. This is probably the means by which the herb found its way into South Africa.

Although van de Venter *et al.* [*24*] reported moderate *in vitro* antidiabetic property of *C. edulis*, there is no published scientific article substantiating this claim in animal models. Contrary to this, Saif-Ali *et al.* [*70*] in a study involving human subjects, observed an insignificant increase in blood glucose concentration in type 2 diabetic *khat* chewers. The authors attributed the effect to an indirect sympathomimetic action.

Momordica foetida Schumach. (Cucurbitaceae)

Momordica foetida is a perennial climbing herb with tendrils. The flowers are cream, often with a reddish or orange centre, having the male and female flowers on the same plant. The characteristic fruit is bright orange with prickles and the plant has a strong unpleasant smell [*71*]. The herb is used to treat a number of ailments including hypertension, diabetes mellitus, fever and symptoms of malaria [*72*].

Very little has been done to establish the *in vivo* antidiabetic property of *M. foetida*. Marquis *et al.* [*73*] investigated the effect of foetidin, isolated from the plant on blood glucose levels of fasting and alloxan-treated rats. The authors reported that the compound exhibited hypoglycemic effect in normal but not in diabetic rats. The unsatisfactory action in alloxan-treated rats was attributed to the absence of synergistic compounds which may be present in the whole plant or fruits as used in folkloric medicinal preparations.

Sclerocarya birrea (A. Rich.) Hochst. (Anacardiaceae)

Sclerocarya birrea is one of the most highly valued indigenous trees in southern Africa [*74*]. It grows up to 15 m high with grey fissured bark, stout branchlets and pale foliage. The leaves are compound, pinnate and the flowers greenish-white or reddish. The fruits are yellow and closely resemble the mango fruits. The pulp of the fruit is delicious and the large nut is also edible. In Africa, the tree is commonly found in savannah regions and its geographical distribution stretches from Gambia in the west across to Nigeria and Cameroon, in Central Africa, and to Ethiopia and Sudan in the east [*75*]. In South Africa, the plant is commonly found in the Northern Province [*76*]. The Zulu people use the bark decoction to treat diarrhoea, dysentery, fevers, stomach ailments, ulcers and bacterial-related diseases [*48*, *52*, *74*]. Traditional Zulu healers wash in bark decoctions before treating patients with gangrenous rectitis and also administer the decoction to the patient [*77*].

Quite a number of studies have been carried out to establish the antidiabetic activity of *S. birrea* in animal models. Ojewole reported the hypoglycemic effect of aqueous stem-bark extract of the plant in normal and STZ-treated diabetic rats [*78*]. In another study by Dimo *et al.*, a methanol/methylene chloride (1:1) extract of the plant reduced blood glucose and increased plasma insulin levels in diabetic rats [*79*]. The extract also prevented body weight loss and reduced plasma cholesterol, while the triglyceride and urea levels tended towards normal levels. The diabetic rats also showed significant improvement in glucose tolerance following the administration of the extract. Gondwe *et al.* also investigated the hypoglycemic effect of the stem bark extract of the herb in normal and diabetic rats alongside the major complications of diabetes. Whereas the extract exhibited dose-dependent reduction in blood glucose level, the same extract did not significantly alter kidney function; and the blood pressure was reduced in all the animals. The authors concluded that stem bark extract of

S. birrea has reno- and cardio-protective effects in diabetic animals [*80*]. These observations thus lend credence to the folkloric use of the plant in the management and/or control of adult-onset diabetes in some African communities.

Psidium guajava Linn. (Myrtaceae)

Psidium guajava is a tree of about 10 m high with thin, smooth, patchy and peeling bark. Its leaves are opposite with short-petiolates and the blades are oval with prominent pinnate veins about 5–15 cm long. Flowers are somewhat showy, petals are whitish and up to 2 cm long with numerous stamens [*81*]. Fruits are fleshy and about 5 cm in diameter with edible pink mesocarp containing numerous small hard white seeds. The plant is considered a native to Mexico [*82*], however it has extended throughout the South America, Europe, Africa and Asia. Based on archaeological evidence, the plant has been used widely and known in Peru since pre-Columbian times [*81*]. It grows in all the tropical and subtropical areas of the world, and adapts to different climatic conditions but prefers dry climates.

The antidiabetic property of *P. guajava* bark, leaves and fruits has been studied by several authors. The aqueous leaf extract was tested by Mukhtar *et al.* [*83*] and Ojewole [*84*] in alloxan-induced and STZ-induced diabetic rats respectively. The authors attributed the observed hypoglycemic effect of the extract to tannins, flavonoids, pentacyclic triterpenoids, guiajaverin, quercetin and other chemical compounds present in the plant. In another study, Mukhtar *et al.* [*85*] examined the anti-hyperglycemic activity of the ethanol extract obtained from the stem bark of the plant on blood glucose levels of normal, alloxan-induced hyperglycemic and normal glucose loaded rats. The results showed that the extract exhibited significant hypoglycemic activity but was devoid of hypoglycemic effect in normal and glucose loaded rats. The butanol-soluble fraction of the leaves also demonstrated antidiabetic property in $Lepr^{db}/Lepr^{db}$ mice [*86*]. Another study by Wang *et al.* [*87*] revealed significant inhibition of alpha-glucosidase activity in the small intestine of diabetic mice that were administered with the leaf extract of the herb.

Sutherlandia frutescens Linn. (Fabaceae)

Sutherlandia frutescens is a popular plant in traditional medicine. It is indigenous to South Africa, Lesotho, southern Namibia and southeastern Botswana. In South Africa, it is widespread in the drier areas of the South Western and Northern Cape Provinces [*88*]. The plant belongs to the Legume family which is the third largest family of flowering plants. It is a lax spreading shrub and approximately 1.2 m in height, with prostrate to erect stems. The leaves are compound pinnate with leaflets oblong to linear-elliptic, slightly to densely hairy, the latter silvery in appearance. *S. frutescens* flowers between July and December and the flowers are bright scarlet. The fruits are inflated leathery pods, bearing persistent upturned style; and seeds are black and flattened. The plant is generally regarded as the most beneficial of the medicinal plants in southern Africa, and has thus been used by all cultures including the San, Khoi, Sotho and Nguni-speaking people [*88*].

Very little has been reported on the antidiabetic activity of *S. frutescens*. Ojewole reported the hypoglycemic effect of aqueous shoot extract of the plant in STZ-induced diabetic rats [*89*]. Similar finding was reported by Chadwick *et al.* in rats fed with diabetogenic diet. The extract demonstrated ability to normalize insulin levels and glucose uptake in peripheral tissues and suppresses intestinal glucose uptake [*90*].

Conclusion

In South Africa, the number of people suffering from diabetes has been rising steadily over the past two decades. This high prevalence deserves special attention towards the treatment of diabetes. The few orthodox management options available are expensive and often associated with negative side effects; therefore, the use of indigenous medicinal plants provides better alternative which are usually less toxic and affordable. Out of the 32 identified medicinal plants traditionally used in South Africa for the treatment of diabetes, only nine have been documented in scientific literature to have demonstrated some *in vivo* antidiabetic activity. Considering the rich cultural traditions of plant use and the high prevalence of diabetes mellitus in South Africa, more *in vivo* investigations should be encouraged in order to validate the antidiabetic activity of the identified plants as claimed by the traditional healers.

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References

[1] Khan, A., Zaman, G., and Anderson, R.A.: Bay leaves improve glucose and lipid profile of people with Type 2 diabetes. *J. Clin. Biochem. Nutr.*, **44**, 52–56, 2009.

[2] Rang, H.P., Dale, M.M., and Ritters, J.M.: The endocrine pancreas and the control of blood glucose, *in Pharmacology*, eds. By Simmons, B. and Beasley, S., U.K. Longman group Ltd., pp. 403–410, 1991.

[3] Knentz, A.J. and Nattras, M.: Diabetic ketoacidosis, non

ketotic hyperosmolar coma and lactic acidosis, *in Handbook of diabetes*, eds. By Pickup, J.C. and Williams, G., (2nd edition). Blackwell Science, pp. 479–494, 1991.

[4] Kumar, P.J. and Clark, M.: *Textbook of Clinical Medicine*, Saunders, London, pp. 1099–1121, 2002.

[5] Sharma, A.K.: Diabetes mellitus and its complications: An Update, *in Macmillan*, eds. By Galadari, E.O., Behara, I., Manchandra, M., Adbulrazzaq, S.K., and Mehra, M. K., New Delhi, 1993.

[6] Perkins, R.M., Yuan, C.M., and Welch, P.G.: Dispogenic diabetes insipidus: Report of a novel treatment strategy and literature review. *Clin. Exp. Nephrol.*, **10**, 63–67, 2006.

[7] Notkins, A.L.: Immunologic and genetic factors in type 1 diabetes. *J. Biol. Chem.*, **277**, 43545–43548, 2002.

[8] Harrison, L.C. and Honeyman, M.C.: Cow's milk and type 1 diabetes: the real debate is about mucosal immune function. *Diabetes*, **48**, 1501–1507, 1999.

[9] Garau, C., Cummings, E., Phoenix, D.A., and Singh, J.: Beneficial effect and mechanism of action of *Momordica charantia* in the treatment of diabetes mellitus: A mini review. *Int. J. Diabet. Metab.*, **11**, 46–55, 2003.

[10] Zimmet, P., Dowse, G., Finch, C., Serjeantson, S., and King, H.: The epidemiology and natural history of NIDDM—Lessons from the South Pacific. *Diabetes Metab. Rev.*, **6**, 91–124, 1990.

[11] Suriyaprom, K., Phonrat, B., Namjuntra, P., Chanchay, S., and Tungtrongchitr, R.: The +299(G>A) resistin gene polymorphism and susceptibility to Type 2 diabetes in Thais. *J. Clin. Biochem. Nutr.*, **44**, 104–110, 2009.

[12] Ahmed, K.A., Muniandy, S., and Ismail, I.S.: N^{ε}-(Carboxymethyl)lysine and coronary atherosclerosis-associated low density lipoprotein abnormalities in Type 2 diabetes: current status. *J. Clin. Biochem. Nutr.*, **44**, 14–27, 2009.

[13] Harris, A. and Zimmet, P.: Classification of diabetes mellitus and other categories of glucose intolerance, *in International Textbook of Diabetes Mellitus*, ed. By Alberti, K.G.M., John Wiley & Sons, NY, pp. 9–23, 1997.

[14] Miller, C.D., Phillips, L.S., Ziemer, D.C., Gallina, D.L., Cook, C.B., and El-Kebbi, I.M.: Hypoglycemia in patients with type 2 diabetes mellitus. *Arch. Intern. Med.*, **161**, 1653–1659, 2001.

[15] Zimmet, P., Alberti, K.G., and Shaw, J.: Global and societal implications of diabetes epidemic. *Nature*, **414**, 782–787, 2001.

[16] Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S., and Devasagayam, T.P.A.: Indian herbs and herbal drugs used for the treatment of diabetes. *J. Clin. Biochem. Nutr.*, **40**, 163–173, 2007.

[17] Ali, H., Houghton, P.J., and Soumyanath, A.: α-amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to *Phyllanthus amarus*. *J. Ethnopharmacol.*, **107**, 449–455, 2006.

[18] Bailey, C.J. and Day, C.: Traditional plant medicines as treatment for diabetes. *Diabetes Care*, **12**, 553–564, 1989.

[19] Marles, R. and Farnsworth, N.R.: Plants as sources of anti-diabetic agents. *in Economic and Medicinal Plant Research*, eds. By Wagner, H. and Farnsworth, N.R., Academic Press Ltd., UK, vol. 6, pp. 149–187, 1994.

[20] Joshi, B.S. and Kaul, P.N.: Alternative medicine: herbal drugs and their critical appraisal—Part I. *Prog. Drug Res.*, **56**, 1–76, 2001.

[21] Erasto, P., Adebola, P.O., Grierson, D.S., and Afolayan, A.J.: An ethnobotanical study of plants used for the treatment of diabetes in Eastern Cape Province, South Africa. *Afr. J. Biotechnol.*, **4**, 1458–1460, 2005.

[22] Thring, T.S. and Weitz, F.M.: Medicinal plants use in the Bredasdorp/Elim region of the southern Overberg in the Western Cape Province of South Africa. *J. Ethnopharmacol.*, **103**, 261–275, 2006.

[23] Van Wyk, B.E., de Wet, H., and Van Heerden, F.R.: An ethnobotanical survey of medicinal plants in the southeastern Karoo, South Africa. *S. Afr. J. Bot.*, **74**, 696–704, 2008.

[24] 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., and Folb, P.: Antidiabetic screening and scoring of 11 plants traditionally used in South Africa. *J. Ethnopharmacol.*, **119**, 81–86, 2008.

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

[26] Van Wyk, B.E.: A broad review of commercially important southern African medicinal plants. *J. Ethnopharmacol.*, **119**, 342–355, 2008.

[27] Wild, S., Roglic, G., Green, A., Sicree, R., and King, H.: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, **27**, 1047–1053, 2004.

[28] Moller, D.E. and Flier, J.S.: Insulin resistance—mechanism, syndromes, and implications. *N. Engl. J. Med.*, **325**, 938–948, 1991.

[29] American Diabetes Association: Standards of medical care for patients with diabetes mellitus (position statement). *Diabetes Care*, **20**, 518–520, 1997.

[30] Levitt, N.S., Katzenellenbongen, J.M., Bradshaw, D., Hoffman, M.N., and Bonnice, F.: The prevalence and identification of risk factor for NIDDM in urban Africans in Cape Town, South Africa. *Diabetes Care*, **16**, 601–607, 1993.

[31] Erasmus, R.T., Blanco, E.B., Okesina, A.B., Gqweta, Z., and Matsha, T.: Assessment of glycaemic control in stable type 2 black South Africans diabetics attending a peri-urban clinic. *Postgrad. Med. J.*, **75**, 603–606, 1999.

[32] Van Wyk, B.E., Van Oudtshoorn, B., and Gericke, N.: *Medicinal Plants of South Africa*, Briza Publications, Pretoria, 1997.

[33] Mander, M.: Marketing of indigenous medicinal plants in South Africa. *A Case study in Kwa-Zulu Natal*, Food and Agricultural Organization of the United Nations, Rome, 1998.

[34] Erasto, P., Grierson, D.S., and Afolayan, A.J.: Bioactive sesquiterpene lactones from the leaves of *Vernonia amygdalina*. *J. Ethnopharmacol.*, **106**, 117–120, 2006.

[35] Huffman, M.A., Page, J.E., Sukhdeo, M.V.K., Gotoh, S.,

Kalunde, M.S., and Towers, G.H.N.: Leaf swallowing by chimpanzees: a behavioral adaptation for the control of strong nematode infections. *Int. J. Primatol.*, **72**, 475–503, 1996.

[36] Riley, H.: *Families of flowering plants of Southern Africa*, University of Kentucky Press, 170, 1963.

[37] Chagnon, M.: General pharmacological inventory of medicinal plants of Rwanda. *J. Ethnopharmacol.*, **12**, 239–251, 1984.

[38] Akah, P.A. and Ekekwe, R.K.: Ethnopharmacology of some Asteraceae family used in Nigerian traditional medicine. *Fitoter*, **66**, 351–355, 1995.

[39] Vlietinck, A.J., Van Hoof, L., Totte, J., Lasure, A., Vanden Berghe, D., Rwangabo, P.C., and Mvukiyumwami, J.: Screening of hundred Rwandese medicinal plants for antimicrobial and antiviral properties. *J. Ethnopharmacol.*, **46**, 31–47, 1995.

[40] Hamill, F.A., Apio, S., Murbiru, N.K., Mosango, M., Bukenya-Ziraba, R., Maganyi, O.W., and Soejarto, D.D.: Traditional herbal drugs of southern Uganda, I. *J. Ethnopharmacol.*, **70**, 281–300, 2000.

[41] Kambizi, L. and Afolayan, A.J.: An ethnobotanical study of plants used for the treatment of sexually transmitted diseases (njovhera) in Guruve District, Zimbabwe. *J. Ethnopharmacol.*, **77**, 5–9, 2001.

[42] Gyang, S.S., Nyam, D.D., and Sokomba, E.N.: Hypoglycaemic activity of *Vernonia amygdalina* (chloroform extract) in normoglycaemic and alloxan-induced hyperglycaemic rats. *J. Pharm. Biores.*, **1**, 61–66, 2004.

[43] Ebong, P.E., Atangwho, I.J., Eyong, E.U., and Egbung, G.E.: The antidiabetic efficacy of combined extracts from two continental plants: *Azadirachta indica* (A. Juss) (Neem) and *Vernonia amygdalina* (Del.) (African Bitter Leaf). *Am. J. Biochem. Biotech.*, **4**, 239–244, 2008.

[44] Atangwho, I.J., Ebong, P.E., Egbung, G.E., Eteng, M.U., and Eyong, E.U.: Effect of *Vernonia amygdalina* Del. on liver function in alloxan-induced hyperglycaemic rats. *J. Pharm. Biores.*, **4**, 27–31, 2007.

[45] Osinubi, A.A.: Effects of *Vernonia amygdalina* and chlorpropamide on blood glucose. *Med. J. Islamic World Acad. Sci.*, **16**, 115–119, 2008.

[46] Okolie, U.V., Okeke, C.E., Oli, J.M., and Ehiemere, I.O.: Hypoglycemic indices of *Vernonia amygdalina* on postprandial blood glucose concentration of healthy humans. *Afr. J. Biotechnol.*, **7**, 4581–4585, 2008.

[47] Van Wyk, B.E., Van Oudtshoorn, B., and Gericke, N.: *Medicinal Plants of South Africa (2nd ed.)*, Briza Publications, Pretoria, pp. 156–157, 2002.

[48] Watt, J.M. and Breyer-Brandwijk, M.G.: *The Medicinal and Poisonous Plants of Southern and Eastern Africa, (2nd ed.)*, Livingstone, London, pp. 39, 1962.

[49] Hutchings, A.: Survey and analysis of traditional medicinal plants as used by the Zulu, Xhosa and Sotho. *Bothalia*, **19**, 111–123, 1989.

[50] Pujol, J.: Naturafrica—*The Herbalist Handbook*, Jean Pujol Natural Healers' Foundation, Durban, South Africa, 1990.

[51] Albrecht, C.F.: Hypoxoside: a putative prodrug for the treatment of malignancies, HIV infections, and inflammatory conditions. *S. Afr. Med. J.*, **85**, 302–307, 1995.

[52] Hutchings, A., Scott, A.H., Lewis, G., and Cunningham, A.B.: *Zulu medicinal plants—An inventory*, University of Natal Press, Pietermaritzburg, South Africa, 1996.

[53] Zibula, S.M.X. and Ojewole, J.A.O.: Hypoglycaemic effects of *Hypoxis hemerocallidea* corm 'African Potato' methanolic extract in rats. *Med. J. Islamic Acad. Sci.*, **13**, 75–78, 2000.

[54] Ojewole, J.A.: Antinociceptive, anti-inflammatory and antidiabetic properties of *Hypoxis hemerocallidea* Fisch. & C.A. Mey. (Hypoxidaceae) corm ['African Potato'] aqueous extract in mice and rats. *J. Ethnopharmacol.*, **103**, 126–134, 2006.

[55] Mahomed, I.M. and Ojewole, J.A.: Hypoglycemic effect of *Hypoxis hemerocallidea* corm (African potato) aqueous extract in rats. *Methods Find. Exp. Clin. Pharmacol.*, **25**, 617–623, 2003.

[56] Musabayane, C.T., Xozwa, K., and Ojewole, J.A.: Effects of *Hypoxis hemerocallidea* (Fisch. & C.A. Mey.) [Hypoxidaceae] corm (African Potato) aqueous extract on renal electrolyte and fluid handling in the rat. *Ren. Fail.*, **27**, 763–770, 2005.

[57] Ghosh, R.K. and Gupta, I.: Effect of *Vinca rosea* and *Ficus racemososus* on hyperglycemia in rats. *Indian J. Animal Health*, **19**, 145–148, 1980.

[58] Chattopadhyay, R.R., Sarkar, S.K., Ganguly, S., Banerjee, R.N., and Basu, T.K.: Hypoglycemic and antihyperglycemic effect of leaves of *Vinca rosea* Linn. *Indian J. Physiol. Pharmacol.*, **35**, 145–151, 1991.

[59] Chattopadhyay, R.R., Banerjee, R.N., Sarkar, S.K., Ganguly, S., and Basu, T.K.: Antiinflammatory and acute toxicity studies with leaves of *Vinca rosea* Linn in experimental animals. *Indian J. Physiol. Pharmacol.*, **36**, 291–292.

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

[61] Chattopadhyay, R.R.: A comparative evaluation of some blood sugar lowering agents of plant origin. *J. Ethnopharmacol.*, **67**, 367–372, 1999.

[62] Nammi, S., Boini, M.K., Lodagala, S.D., and Behara, R.B.S.: The juice of fresh leaves of *Catharanthus roseus* Linn. reduces blood glucose in normal and alloxan diabetic rabbits. *BMC Complement. Altern. Med.*, **3**, 1–4, 2003.

[63] Iwarsson, M.: *Leonotis*, in Flora of Southern Africa. *Botanical Research Institute*, **28**, 31–37, 1985.

[64] Ojewole, J.A.: Antinociceptive, antiinflammatory and antidiabetic effects of *Leonotis leonurus* (L.) R. BR. [Lamiaceae] leaf aqueous extract in mice and rats. *Methods Find. Exp. Clin. Pharmacol.*, **27**, 257–264, 2005.

[65] Maphosa, V., Masika, P., and Adedapo, A.: Safety evaluation of the aqueous extract of *Leonotis leonurus* shoots in rats. *Hum. Exp. Toxicol.*, **27**, 837–843, 2008.

[66] Dagne, E.: Botanical Aspects of "*Khat*" *Catha edulis* (Celastaceae). Addis Ababa. NAPRECA, 1984.

[67] Rudolf, M. and Brenneisn, A.: *Khat: The natural amphetamine. Institute of Pharmacy*, University of Berne,

Baltzerstrasse 5, CH-3012 Berne, Switzerland, 1985.
[68] Al-Meshal, I.A., Ageel, A.M., Parmar, N.S., and Tariq, M.: *Catha edulis* (*Khat*): Use, Abuse and Current Status of Scientific Knowledge. *Fitoter.*, **56**, 131–152, 1985.
[69] Kalix, P.: *Catha edulis*, a plant that has amphetamine effects. *Pharm. World Sci.*, **18**, 69–73, 1996.
[70] Saif-Ali, R., Al-Qirbi, A., Al-Geiry, A., and Al-Habori, M.: Effect of *Catha edulis* on plasma glucose and C-peptide in both type 2 diabetics and non-diabetics. *J. Ethnopharmacol.*, **86**, 45–49, 2003.
[71] Jeffrey, C.: *Cucurbitaceae in Flora of Tropical East Africa*, Crown Agents, London, 1990.
[72] Hakizamungu, E., Van Puyvelde, L., and Wery, M.: Screening of Rwandese medicinal plants for anti-trichomonas activity. *J. Ethnopharmacol.*, **36**, 143–146, 1992.
[73] Marquis, V.O., Adanlawo, T.A., and Olaniyi, A.A.: The effect of foetidin from *Momordica foetida* on blood glucose level of albino rats. *Planta Med.*, **31**, 367–374, 1977.
[74] Eloff, J.N.: Antibacterial activity of Murula (*Sclerocarya birrea* (A. rich) Hochst. Subsp. *Caffra (Sond) Kokwaro) (Anacardiaceae) bark and leaves. J. Ethnopharmacol.*, **76**, 305–308, 2001.
[75] Berhaut, J.: *Flore Illustrée du Sénégal. Dycotylédones. Tome I. Acanthacées à avicenniacées.* Ministère du Développement Rural. Direction des Eaux et Forêt, Dakar, pp. 277–279, 1971.
[76] Shackleton, C.: Growth and fruit production of *Sclerocarya birrea* in the South African lowveld. *Agroforestry Systems*, **55**, 175–180, 2002.
[77] Bryant, A.T.: *Zulu medicine and medicine men*, Cape Town, Struik, 1966.
[78] Ojewole, J.A.O.: Hypoglycemic effect of *Sclerocarya birrea* [(A. Rich.) Hochst.] [Anacardiaceae] stem-bark aqueous extract in rats. *Phytomedicine*, **10**, 675–681, 2003.
[79] Dimo, T., Rakotonirina, S.V., Tan, P.V., Azay, J., Dongo, E., Kamtchouing, P., and Cros, G.: Effect of *Sclerocarya birrea* (Anacardiaceae) stem bark methylene chloride/methanol extract on streptozotocin-diabetic rats. *J. Ethnopharmacol.*, **110**, 434–438, 2007.
[80] Gondwe, M., Kamadyaapa, D.R., Tufts, M., Chuturgoon, A.A., and Musabayane, C.T.: *Sclerocarya birrea* [(A. Rich.) Hochst.] [Anacardiaceae] stem-bark ethanolic extract (SBE) modulates blood glucose, glomerular filtration rate (GFR) and mean arterial blood pressure (MAP) of STZ-induced diabetic rats. *Phytomedicine*, **15**, 699–709, 2008.
[81] Stone, B.: The flora of Guam. *Micronesica*, **6**, 454–455, 1970.
[82] Rios, C.D., Salazar, C.R., Cardona, C., Victoria, K., and Torres, M.: Guayaba. En: Instituto Colombiano Agropecuario. Bogotá (Colombia), second ed. Frutales. *Manual de Asistencia Técnica*, **4**, 221–248, 1977.
[83] Mukhtar, H.M., Ansari, S.H., Ali, M., Naved, T., and Bhat, Z.A.: Effect of water extract of *Psidium guajava* on alloxan-induced diabetic rats. *Pharmazie*, **59**, 734–735, 2004.
[84] Ojewole, J.A.: Hypoglycemic and hypotensive effects of *Psidium guajava* Linn. (Myrtaceae) leaf aqueous extract. *Methods Find. Exp. Clin. Pharmacol.*, **27**, 689–695, 2005.
[85] Mukhtar, H.M., Ansari, S.H., Bhat, Z.A., Naved, T., and Singh, P.: Antidiabetic activity of an ethanol extract obtained from the stem bark of *Psidium guajava* (Myrtaceae). *Pharmazie*, **61**, 725–727, 2006.
[86] Oh, W.K., Lee, C.H., Lee, M.S., Bae, E.Y., Sohn, C.B., Oh, H., Kim, B.Y., and Ahn, J.S.: Antidiabetic effects of extracts from *Psidium guajava*. *J. Ethnopharmacol.*, **96**, 411–415, 2005.
[87] Wang, B., Liu, H.C., Hong, J.R., Li, H.G., and Huang, C.Y.: Effect of *Psidium guajava* leaf extract on alpha-glucosidase activity in small intestine of diabetic mouse. *Sichuan Da Xue Xue Boa Yi Xue Ban*, **38**, 298–301, 2007.
[88] Van Wyk, B.E. and Albrecht, C.: A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Sutherlandia frutescens* (Fabaceae). *J. Ethnopharmacol.*, **119**, 620–629, 2008.
[89] Ojewole, J.A.: Analgesic, antiinflammatory and hypoglycemic effects of *Sutherlandia frutescens* R. BR. (variety Incana E. MEY.) [Fabaceae] shoot aqueous extract. *Methods Find. Exp. Clin. Pharmacol.*, **26**, 409–416, 2004.
[90] Chadwick, W.A., Roux, S., van de Venter, M., Louw, J., and Oelofsen, W.: Anti-diabetic effects of Sutherlandia frutescencs in Wistar rats fed a diabetogenic diet. *J. Ethnopharmacol.*, **109**, 121–127, 2007.