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The use of South African botanical species for the control of blood sugar

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ABSTRACT

Ethnopharmacological relevance: Diabetes mellitus (DM) is one of the most prevalent diseases globally and is of considerable concern to global health. Approximately 425 million people are estimated to have DM globally and this is predicted to increase to >642 million by 2040. Whilst the prevalence of DM in South Africa is slightly lower than the global average, it is expected to rise rapidly in future years as more South Africans adopt a high calorie "Westernised" diet. Traditional medicines offer an alternative for the development of new medicines to treat DM and the usage of South African plants is relatively well documented.

Aim of the study: To critically review the literature on the anti-diabetic properties of South African plants and to document plant species used for the treatment of DM. Thereafter, a thorough examination of the related research will highlight where research is lacking in the field.

Materials and methods: A review of published ethnobotanical books, reviews and primary scientific studies was undertaken to identify plants used to treat DM in traditional South African healing systems and to identify gaps in the published research. The study was non-biased, without taxonomic preference and included both native and introduced species. To be included, species must be recorded in the pharmacopeia of at least one South African ethnic group for the treatment of DM.

Results: One hundred and thirty-seven species are recorded as therapies for DM, with leaves and roots most commonly used. The activity of only 43 of these species have been verified by rigorous testing, although relatively few studies have examined the mechanism of action.

Conclusion: Despite relatively extensive ethnobotanical records and a diverse flora, the anti-diabetic properties of South African medicinal plants is relatively poorly explored. The efficacy of most plants used traditionally to treat DM are yet to be verified and few mechanistic studies are available. Further research is required in this field.

Keywords:

Diabetes, hyperglycaemia, glycosylated haemoglobin, blood glucose concentration, traditional medicine, ethnomedicine, South African plants

Contents

Abbreviations: DM, diabetes mellitus; (GDM), gestational diabetes mellitus; WHO, The World Health Organisation; UTIs, urinary tract infections.

1. Introduction

Diabetes is a chronic metabolic disease that manifests as hyperglycaemia over prolonged periods. The symptoms of diabetes include frequent urination as well as increased thirst and hunger. If not effectively treated, the elevated blood glucose levels can induce many metabolic and physiological complications including ketoacidosis and serious damage to cardiac, neuronal, hepatic and renal tissue, as well as to the eyes and blood vessels. The disease can arise either through the inability of the pancreas to produce functional insulin, or from an inability to effectively use the insulin that is produced.

Whilst historically, diabetes is well-known, modern lifestyles with their high energy diets and low exercise levels have resulted in a dramatic increase in diabetes associated diseases. The World Health Organisation (WHO) now considers the global burden of diabetes to be of considerable concern (WHO, 2019). In 1980, the WHO estimated the cases of diabetes mellitus (DM) to be 108 million worldwide (WHO, 2019). By 2017, this figure had increased dramatically to 425 million people with diabetes, an increase of almost 400% across that period. This figure equates to approximately 9% of the adult population over 18 years of age globally, with equal representation from both males and females. The increasing rates of diabetes have been most notable in low-middle income developing countries, with rates of increase substantially higher than the global average. Of further concern, the number of people suffering from DM is expected to continue to rise at similar rates and it is estimated that >642 million people will have DM by 2040 (International Diabetes Federation, 2015). Notably, all these figures document the reported number of cases of DM. As many cases remain unreported, particularly in the early phases, the prevalence of diabetic related disease may be substantially under-estimated.

Not only does the disease cause serious morbidities including blindness, coronary and renal disease, stroke and often the need for limb amputation, DM more than doubles an individual's risk of early death (WHO, 2019). Indeed, it was estimated in 2017 that DM was directly responsible for 3.2-5.0 million deaths globally (International Diabetes Federation, 2017). Notably, substantial further deaths that are not directly attributed with DM also result from hyperglycaemia. Indeed, high blood sugar levels were noted in 2.12 million further deaths not attributed to DM in 2012 (WHO, 2019). With current trends, the condition is anticipated to become one of the world's leading causes of disability and death in the next 25 years (Malviya et al., 2010). The high levels of morbidity and mortality caused by DM also place an increasing burden on the health care system, with the global cost of DM estimated to be US$727 billion in 2017 (International Diabetes Federation, 2017). These costs are expected to increase in parallel with the projected increases in DM levels in the future.

In South Africa, the prevalence of DM is estimated to be between 4% and 6% of the adult population (Deutschländer et al., 2009), making it similar to, but slightly below the global average. Furthermore, DM was recorded as the fifth leading cause of death in the country (WHO, 2016). Several reports have highlighted the higher levels of mortality from diabetes amongst black South African populations, compared with other South African ethnic groups (Erasto et al., 2005). Women are of the highest risk group based in part towards sociocultural aspects (Goedecke et al., 2017). It is likely that the prevalence amongst black South Africans will continue to increase at greater rates than the South African average as the economic position of the population improves and more people adopt higher energy diets. In the face of this growing epidemic, new safe and efficient DM treatments are urgently required (Mbanya et al., 2010). A re-examination of traditional therapeutic options is promising for the development of new therapies. Whilst reviews are available on medicinal plants for the control of blood sugar from various countries and geographical areas (Table 1) there has been very little consolidated literature of natural product leads for DM from South Africa and the neighbouring countries. This review focuses on these aspects with the aim to 1.) Provide a background of DM, the treatment options and the need to examine natural products as alternative treatment options. 2.) Document the medicinal plants used in South Africa for the control of blood sugar and lastly 3.) Correlate the scientific findings of traditionally used plants in order to identify frequently used plant species with anti-DM potential and hence stimulate further research in this field.

Table 1

Reviews on diabetes

Subject matter	**Geographical focus**	**Number of plant species covered**	**Recommendations**	**Authors**
In vivo anti-diabetic activity	South Africa	32	1) Identified a number of promising taxa for further investigation.	Afolayan and Sunmonu, 2010
Herbal medicines for diabetes	Global perspective	35	1) Isolation and identification of active constituents. 2) Preparation of standardized doses. 3) Provide Evidence-Based alternative medicine.	Upendra Rao et al., 2010
Antidiabetes activity of African medicinal plants	Africa	42	1) Novel therapeutic agents for diabetes management should be further investigated.	Ndip et al., 2013

Subject matter	Geographical focus	Number of plant species covered	Recommendations	Authors
African medicinal plants with antidiabetic potential	Africa	185	1) Governmental support in research.	Mohammed et al., 2014
Lesser known medicinal plants for diabetes	India and Africa	9	1) Isolation, purification and characterization of the bioactive compounds.	Mohammed et al., 2015

Subject matter	Geographical focus	Number of plant species covered	Recommendations	Authors
Medicinal plants used for management of diabetes in the Eastern Cape	Eastern Cape Province, South Africa	45	1) The identification of the active compounds. 2) Emphasis on neglected botanical families for further studies. 3) Mechanism of action studies and comparison with existing conventional drugs.	Odeyemi and Bradley, 2018
Hypoglycaemic and anti-diabetic activity	Africa	16	1) Identify phytochemical constituents linked to hypoglycaemic and anti-diabetic activity. 2) Conduct clinical trials. 3) Investigate combinations with synthetic drugs.	Oguntibeju, 2019

Subject matter	**Geographical focus**	**Number of plant species covered**	**Recommendations**	**Authors**
			4) Monitor and determine long-term effects of medicinal plants. 5) Investigate inter and intra-species variation of secondary metabolites. 6) Formulation studies. 7) Develop acceptable approach of fortifying local foods with herbal products that have displayed significant hypoglycaemic and anti-diabetic activities.	
Diabetes mellitus and antidiabetic plants	None, but general overview of global perspective		1) More emphasis on medicinal plants to manage diabetes.	Chinsembu, 2019

Subject matter	Geographical focus	Number of plant species covered	Recommendations	Authors
Medicinal plants with concomitant anti-diabetic effects against diabetes	Global perspective	64	1) Need for dual acting anti-diabetic and anti-hypertensive agents. 2) Methodologically-balanced analyses conducted on *in vivo* investigations. 3) Toxicity and safety profile of the majority of the medicinal plants.	Chukwuma et al., 2019
Medicinal herbs, spices, and food plants for diabetes management	Global perspective	94	1) Taxonomic classification should be strictly adhered to. 2) Ethnomedicinal uses more vigorously reported. 3) Attention given to traditional modes of preparation.	Seetaloo et al., 2019

Subject matter	**Geographical focus**	**Number of plant species covered**	**Recommendations**	**Authors**
			4) Interactions and toxicology should be studied. 5) Standard use of methodology.	
Traditional uses with pharmacological and toxicity focus	Nigeria	115 plant species	1) Need for pharmacovigilance and standardization. 2) Clinical evidence.	Ezuruike and Prieto, 2020 in press

1.1. Classes of diabetes

Diabetes mellitus is classified into four broad categories based on causes and physiological and metabolic features:

• Type 1 DM is also called juvenile-onset DM. It is characterised by a loss of insulin producing β-cells in the Islets of Langerhans of the pancreas and is auto-immune related (Shafrir, 1996; American Diabetes Association, 2010; Cock and Cheesman, 2019). Type 1 DM accounts for approximately 10% of the cases of DM in Western countries. This disease may begin in either children or adults.

• Type 2 DM is the most common class of DM with an adult onset. Type 2 DM is caused by the resistance of the body to the action of insulin and is believed to result from non-functional/decreased functional insulin receptors (American Diabetes Association, 2010). This class of DM is most frequently caused by lifestyle factors including obesity, lack of physical activity, poor diet and stress. Genetic factors may also be involved and a higher correlation with obesity has been noted for some ethnic groups.

• Gestational DM (GDM) has features that resemble both type 1 and type 2 DM, with both inadequate levels of insulin secretion and substantially decreased responsiveness. It occurs in up to 10% of pregnancies and the symptoms often disappear following delivery, although the symptoms remain in up to 10% of women with GDM (American Diabetes Association, 2010). Despite the transient nature of this disease, GDM may cause considerable damage to both the mother and foetus if not effectively treated.

• Type 3 DM is a relatively new area of diabetic associated insulin deficiency, where cognitive functions decline. There has been some interlinked association between types 1 and 2 diabetes with a positive correlation to enhancing Alzheimer's disease (Kandimalla et al., 2017).

1.2. Causes of diabetes mellitus

Diabetes is caused by carbohydrate metabolism abnormalities which may be linked to low blood insulin levels or to target organ insensitivity to insulin (Maiti et al., 2004). The key function of insulin is to respond to the combined action of several hyperglycaemia-generating hormones and to maintain glucose levels at a normal level of less than 5.6 mmol/L, particularly in response to food consumption (King, 2014). The increase in the number of people suffering from DM is linked in part to the ageing global population. It is also caused by calorie-rich diet consumption, obesity and a sedentary lifestyle which has resulted from changes that have occurred in the human environment, human behaviour and lifestyle due to globalisation (Zimmet et al., 2001; Oyedemi et al., 2009).

1.3. Symptoms of diabetes mellitus

High blood sugar levels can induce a variety of physiological symptoms. Due to loss of glucose, individuals with untreated DM frequently have sudden and substantial unintentional weight loss. Polyuria (increased urine volume), polydipsia (increased thirst), polyphagia (increased hunger), are all common symptoms (American Diabetes Association, 2010). The onset of symptoms is generally rapid in people with type 1 DM and the symptoms are generally evident within weeks of the onset of the disease. The onset of symptoms is generally substantially slower in people with type 2 DM and may be much more subtle.

Several other signs and symptoms may also manifest in DM, although they are not specific to the disease. These include fatigue, headache, blurred vision, dry, itchy skin and the slow healing of cuts and abrasions. Prolonged hyperglycaemia can also result in high blood pressure. This in turn can cause glucose absorption into the lens in the eye, thereby changing its shape and affecting visual acuity. Long-term hyperglycaemia can cause more severe damage, resulting in vision loss (diabetic retinopathy). Skin rashes (diabetic dermadrones) are also frequently encountered.

1.4. Current treatment options for diabetes mellitus and role of alternate therapies

Several methods are used to treat diabetes. For type 1 DM, treatment with exogenous insulin is usually effective. For type 2 DM, lifestyle modifications including a change of diet and increased exercise are often effective. Pharmacotherapy with drugs such as metformin and selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors are also often effective (Mudaliar and Henry, 2001; Klein et al., 2004; Chao and Henry, 2010). Metformin functions by improving glucose tolerance, lowering both basal and postprandial plasma glucose levels. It decreases the gluconeogenesis production in the liver, lowers absorption of glucose in the intestine and leads to improvement of insulin sensitivity through the increase of peripheral glucose uptake and consumption (Bailey and Turner, 1996). The SGLT2 inhibitors work by inducing glucosuria, resulting in increased excretion of glucose in the urine. When these drugs are co-administered over a longer period, a lower level of glycated haemoglobin is observed (Abdul-Ghani et al., 2012).

Another method used to treat, and control DM is with medicinal plants and traditional medicines. Consultation with traditional and folk medicine healers for the treatment of DM is particularly prevalent among rural patients (Semenya et al., 2012). Modern antidiabetic drug therapy is costly and is not affordable to the people in the low-income groups living in the rural areas such as the Eastern Cape and Limpopo provinces of South Africa (Erasto et al., 2005). Furthermore, inhabitants of these regions may be long distances from medical clinics and allopathic medicines are not always available. Thus, there is a need for cheaper, more readily available therapeutic alternatives. Allopathic drug therapy for DM may also induce a wide range of side effects including hypoglycaemia, weight gain, gastrointestinal discomfort, nausea, liver and heart failure, as well as diarrhoea (Stack, 2008). Conversely, if not effectively treated, the long-term effects of hyperglycaemia may lead to damage, dysfunction and failure of various organs including the eyes, kidneys, nerves, heart and blood vessels and can result in renal failure and amputation (American Diabetes Association, 2010). An examination of the hypoglycaemic effects of traditional medicines may highlight new drug leads with enhanced efficacy and fewer or less severe side effects.

One aspect only recently considered is the role of the gut microflora in the control of DM. Studies have shown that an imbalance in the distribution of microbial communities in the gut can result in a malfunction of bacterial metabolic activity resulting in obesity, insulin resistance and the onset of type 2 diabetes. Prebiotics, probiotics, and feacal microbiota transplantation have been proposed has therapeutic options to correct microbial balance and therefore indirectly control DM (Leylabadlo et al., 2020). From an African perspective (Nigerian context), it has been shown that the gut microbiota of elderly people living with Type 2 diabetes is not consistent with a healthy gut biome, and gut microbiota modification are warranted (Afolayan et al., 2020).

1.5. The use of medicinal plants in diabetes treatment

Prior to the advancements of modern medicine over the last century, plant-based therapies were used for the treatment and maintenance of DM. Their usage dates back to the earliest written records, and likely much earlier. Indeed, the Egyptian Papyrus Ebers (circa 1550 BC) records the usage of various grains in the treatment of DM (Bailey and Day, 1989), and numerous other texts have described the use of herbs, spices and other plant materials for the same purposes (Ryan et al., 2001; Upendra Rao et al., 2010). With the more recent availability of insulin and oral antidiabetic agents (e.g. sulfonylureas, biguanides, α-glucosidease inhibitors, glinides), the use of herbal medicines to treat DM has almost disappeared in Western medicine systems. However, traditional use remains common in developing countries, as well as in rural and isolated areas of more developed countries. Even in Western countries that use allopathic therapies almost exclusively, there has been a recent revival in the use of herbal medicines and some studies have reported that up to a third of people with DM in those countries take herbal medicines, usually as an adjunct to allopathic therapies (Ryan et al, 2001).

It has been estimated that more than 1000 plant remedies are used globally for the treatment and maintenance of DM (Marles and Farnsworth, 1995). However to date, relatively few of these have had their usage validated by rigorous scientific evaluation and fewer have had their mechanisms of action determined. Of these, the therapeutic properties and usage of specific species have been reviewed elsewhere (El Haouari et al, 2019; Yusuf et al, 2012; Baskaran et al 1990). Many of these species are widely distributed and cultivated and have been naturalised globally. For example, *Allium sativum* L (garlic; origin unknown although the high diversity in central Asia indicates China may be the origin), *Annona squamosa* L. (custard apple, sweetsop; origin, tropical region of the Americas). *Berberis vulgaris* L. (sugarbeet, beetroot, chard, spinach beet; origin, Southeast Europe to Western Asia), *Lantana camara* L. (lantana, big-sage; origin, American tropics) and *Momordica charantia* L. (bitter melon; origin, India) are distributed globally and their therapeutic usage is often better known in areas where they have been naturalised than in their area of origin. Notably, several of these species are grown in South Africa and are used in South African traditional medicine systems, including for the treatment of DM. A study group on the management of diabetes among Zulu traditional health practitioners revealed that the majority of treatments involved herbal mixtures referred to as *Amakhambi.* The exact composition is unknown, but plant species dominant to the mixture include *Aloe vera* (L.) Burm.f. and *A. sativum* (Frimpong and Nlooto, 2019)

Many of these species have been relatively well-studied (as reviewed in Upendra Rao et al., 2010) and the major active components have been identified. All have been shown to have hypoglycaemic effects. However, with very few exceptions, the efficacy of these plants (and purified compounds) have been investigated using *in vivo* model systems. Whilst these studies have verified the therapeutic efficacy of these species, they have done little to elucidate the mechanism of action and substantial more work is required in this field. Furthermore, whilst many other species have been recorded in the traditional medicine literature as therapies for diabetes, they are often yet to be evaluated. Future studies to verify the efficacy of these species, and to determine how they decrease blood glucose levels are required.

Interestingly, even in developed countries where allopathic medicine dominates, plant derived compounds are widely used to treat DM. Several biguanide drugs including metformin, phenormin and buformin were initially isolated from *Galega officinalis* L. (commonly known as French lilac, goat's rue). All of these drugs are noted to specifically lower blood glucose levels. Whilst phenormin and buformin were withdrawn from clinical usage in the maintenance of DM in the 1970s due to toxicity concerns (Tonascia and Meinert, 1986), metformin remains a first-line medication for the treatment of type 2 DM (Maruthur et al., 2016). These drugs function via a variety of mechanisms that increase insulin sensitivity, without affecting insulin production and/or secretion. Instead, their therapeutic effects are due to a direct stimulation of glucose uptake and an inhibition of gluconeogenesis, both of which decrease blood glucose levels (Song, 2016). Two recent reviews (Apaya et al., 2020; Rasouli et al., 2020), provide an extensive overview of plant compounds together with emerging trends toward mechanistic studies and clinical perspectives.

2. An overview of diabetes mellitus in South Africa

It was estimated that in 2009, approximately two million South Africans over the age of 30 (9% of that age group nationally) had diabetes (Bertram et al., 2013). This represents an almost doubling in prevalence from nine years earlier, when it was reported that 5.5% of South Africans above the age of 30 had the disease (Bertram et al., 2013). Of concern, the incidence is expected to continue to rise at similar rates in coming years. In part, the South African situation relates to recent economic successes and the upward mobility of the poorer classes into middle- and higher-income brackets. These increases in wealth bring with them associated lifestyle changes including higher food intake and the consumption of an increasing 'Westernised' diet high in fats, coupled with lower levels of activity (Kengne et al., 2013; Peer et al., 2014; Pheiffer et al., 2017). Similarly, greater urbanisation due to the availability of employment opportunities has also accelerated these social and nutritional changes (Steyn et al., 1997; Vorster et al., 2005). These factors are directly related to obesity, which in turn is related to several morbidities, including DM. Indeed, it was estimated in 2000 that 87% of DM cases directly correlated with excess body weight (Joubert et al., 2007). This is particularly concerning as a recent survey estimated that 38% of men and 69% of women in South Africa are overweight or obese (Ng et al., 2014).

Socio-economic status and the level of education are perhaps the factors most correlated with the incidence of DM in South Africa. A recent epidemiological study reported that economic status was the most important factor in the development of DM (Soetedjo et al., 2018). Indeed, the highest prevalence of DM was in South Africans from the richest socio-economic group (42% of all the surveyed South Africans with DM), with individuals in the upper middle (33.3%) and middle-income brackets (14.8%) also having high rates of DM. In contrast, only 9.8% of South Africans with DM were poor. It is evident that the lifestyle changes associated with increased income are largely responsible for the prevalence of DM in South Africa. Educational level was also a major contributing factor to the development of

DM. The same study reported that 74.4% of the South Africans with DM had no formal education, or had only a primary school level of education, whilst a further 17.1% had secondary education. In comparison, 6.1% had completed high school education and only 1% had university education. It is likely that an understanding of DM and the lifestyle factors from formal education significantly decreases the likelihood that South Africans to develop DM.

A correlation between ethnicity and the prevalence of DM is also evident. A higher than average incidence of morbidity and mortality from DM has been reported in black South African populations compared with other South African ethnic groups (Erasto et al., 2005). As DM correlates with economic transition, increased urbanisation and the consumption of high fat, high energy foods, it is likely that the prevalence of DM amongst black South Africans will continue to rise more rapidly than the South African average as their economic conditions continue to improve. A recent survey also highlighted several other risk factors in South Africans with DM and reported that an aging population also contributes to the increased incidence of DM, with a median age of 54 years estimated for South Africans with DM (Soetedjo et al., 2018). With better medical access becoming available to many South Africans, the life expectancy has increased, resulting in an aging population. As DM is most prevalent in the older age groups, it is possible that this increased life expectancy is at least partly responsible for the current South African situation. That study also identified several other risk factors. There was a substantially higher prevalence of women with DM. Indeed, an estimated 65% South Africans with DM are female. This closely correlates with recent estimates of the rates of overweight and obesity in South Africans (38% of men, 69% of women; Ng et al, 2013), further confirming the importance of obesity as a risk factor for DM.

Furthermore, gestational diabetes mellitus (GDM) also occurs at greater prevalence in black South Africans (also in Asian South Africans), than in other ethnic groupings (Macaulay et al., 2018). Indeed, that study reported that 9.1% of pregnant black South African women tested had GDM, a risk factor for the development of type 2 DM in both the mother and the unborn child (Dabelea and Crume, 2011). The higher prevalence of GDM in black South African populations results in further health complications and morbidities, as well as decreased longevity. Furthermore, the increasing prevalence of DM places further burden on the South African healthcare system.

3. Materials and methods

Information presented in this review was sourced from a variety of southern African related ethnobotanical books (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Von Koenen, 1996; Van Wyk et al., 2009) and various ethnobotanical reviews (Erasto et al., 2005; Thring and Wietz, 2006; Afolayan and Mbaebie, 2010; Semenya et al., 2012; Mahwasane et al., 2013; Chauke et al., 2015; Davids et al., 2016; Moteetee et al., 2019; Hulley and Van Wyk, 2019). Original scientific research papers were identified and selected using the Google-Scholar, PubMed, Scopus and Science-Direct electronic databases. The filters used included the following terms, searched either alone or in combinations: “South African”, “medicinal plant”, “traditional medicine”, “ethnobotany”, “diabetes” and “blood sugar”. The study was non-biased, without emphasis on endemic species, date of publishing nor with any taxonomic preference. One hundred and thirty-seven southern African plant species were identified as traditional therapies for the treatment of DM. The vast majority of these are native South African plants, although a few introduced species that are widely cultivated and are now considered an integral part of the pharmacopeia of at least one ethnic group were also included. A thorough literature review was then undertaken on each of the identified plant species to identify any research studies examining the identified species for DM related therapeutic activities. While the authors are cognisant that some literature sources may be of higher credibility than others, the goal here was to provide an unbiased and comprehensive approach.

Criteria for inclusion in this study included ethnomedicine, human usage, medicinal plants of South African and other key words related to DM and treatment. To be included in this study, each plant had to have been recorded as being use traditionally in South Africa to treat DM, or its symptoms. Plants that were used within land locked countries within South Africa such as Lesotho were included, but those that were further scattered into mid-Africa or further afield were excluded. Also excluded were terms such as "diabetic wounds" or "obesity" or other health conditions associated with diabetes complications. Scientific evidence to support traditional use was not included in the initial ethnobotanical literature search but was included in follow-up searches to determine if the traditional usage has been validated. Our study aimed to update these earlier reviews and to take a broader approach to the ethnobotanical usage of South African plants in the treatment of DM, with the hopes of highlighting plant species for future research in this area. All taxonomic revisions were considered by checking with the database "The Plant List. A Working List of All Plant Species" (http://www.theplantlist.org/tpl1.1/search?).

4. South African medicinal plants traditionally used to treat diabetes mellitus

Traditional medicines are often used to target disease symptoms and therefore it may often be difficult to discern between treatments for diseases with similar symptoms. For example, ethnobotanical records may list a traditional medicine as useful in the treatment of increased urine output, which may be a symptom of numerous diseases including DM, benign prostatic hyperplasia, or several urinary tract infections (UTIs). Indeed, in other parts of the world, *U. dioica* is indicated for inflammation and prostatic hyperplasia (Upton, 2013), as well as for diabetes (El Haouari and Rosado, 2019). Whether the usage of *U. dioacia* in traditional South African medicine is due to symptomatic relief, or if its use is targeted more specifically at DM is unclear. Similarly, increased thirst and hunger may also be symptoms of numerous other diseases, such as intestinal worms and helminths (Cock et al., 2018a). Only plant species that were reported to be treatments for DM are included here. Where the basis for the therapeutic usage was ambiguous, the plant species has been excluded from this review.

Reference to a total of 137 plants from 36 families that are used in the management of blood sugar were found in literature (Table 2). Some plant species such as *Aloe ferox* Mill*.*, *Artemisia afra* Jacq. ex Wild., *Dicoma anomala* Sond. subsp. *anomala*, *Momordica balsamina* L, *Opuntia ficus-indica* L., *Pentanisia prunelloides* (Klotzch ex. Edd & Zeyh.) Walp., *Lessertia frutescens* subsp. *frutescens* (L.) Goldblatt & J.C. Manning (previously referred to as *Sutherlandia frutescens*) and *Eriocephalus punctulatus* DC have been cited by various sources providing validity to their traditional use to treat DM, while others (64%) have been only mentioned once. The South African plant species that are commonly used in the treatment of diabetes come from a wide range of families (Figure 1a). The Asteraceae family were consistently the most highly represented family for the treatment and maintenance of DM. Indeed, the usage of 26 species from the Asteraceae family was recorded as treatments for DM (Table 2). This is not unexpected, as a recent family-level floristic study lists Asteraceae as one of the top families represented in African traditional medicine (Van Wyk, 2020)

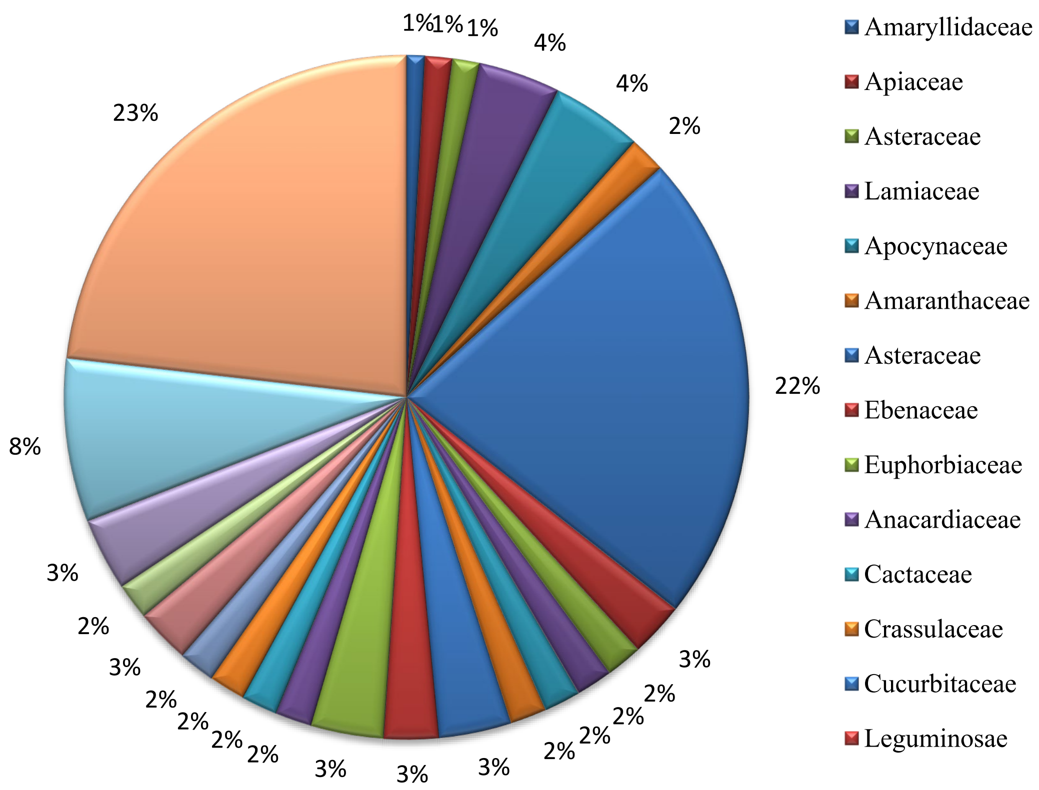
Apocynaceae (10 species), Lamiaceae (nine species) and Xanthorrhoeaceae (nine species) were also well represented. This is consistent with similar reports examining the anti-DM properties of plants in other parts of Africa (Abo et al., 2008; Keter and Mutiso, 2012).

Figure 1b shows the usage distribution of the different plant parts for the treatment of blood sugar. The most common plant part used in the treatment of diabetes is the leaves (39%) (Fig 1b) as the leaves are believed to be the most potent part of many plants (Davids et al., 2016). The leaves of multiple *Aloe* species including *A. arborescens* Mill., *A. ferox* Mill., *A. greatheadii* (Schönland) Glen & D.S.Hardy, *A. maculata* All., *A. marlothii* A. Berger, *A. microstigma* Salm-Dyck and *A. vera* were listed in South African ethnobotanical records as the sole (or main) plant part used to treat DM. Many other studies have documented the use of leaves for medicinal purposes (Nain et al., 2012; Yassa and Tohamy, 2014; Baldissera et al., 2016; Cock and Cheesman, 2018b). Interestingly, for several of these species, the roots, bark, twigs or whole plant were also sometimes used. It is unclear from the published records whether these differences relate to the practices of different ethnic groups, the availability of the plant part, or if they were targeted at different symptoms of DM.

Other parts of the plant used in the treatment of diabetes include roots, bulbs, bark, stems and the whole plant. The roots were particularly widely used, being the sole or main plant part used for approximately 21% of the recorded species. It is believed that the healing power of the plant is often stored in the roots, in the same way that it is stored in the leaves. The roots were the third most frequently used plant part (Fig.1b, Table 2). Fruits and seeds are rarely used because they are only available during certain seasons of the year. Similarly, bark is not always available for wild harvesting as it may often be stripped off by African macro-fauna. Furthermore, bark should only be used sparingly as its removal damages the plant and may kill the more sensitive species. Notably, many herbaceous species are used for the treatment of diabetes (Semenya et al., 2012). The use of these parts of the plant have implications for sustainable harvesting (Davids et al., 2016). Many medicinal plants are endangered and some are close to extinction (Street et al., 2008) and therefore the usage of plant parts where harvesting does not cause extensive damage is encouraged.

For some of the plants (29 %) used to treat DM, we were unable to determine which plant part is traditionally used as it has not been specified in the available literature. It is often difficult to identify the most active part of plant because of the difference in preparation and in the doses and duration that the medicine is used to be effective. Furthermore, variation in methods used to determine the antidiabetic parameters also makes comparisons difficult (Mohammed et al., 2014). Further research is required to determine the part(s) of these species that is best suited for the treatment of DM.

(A)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(B)

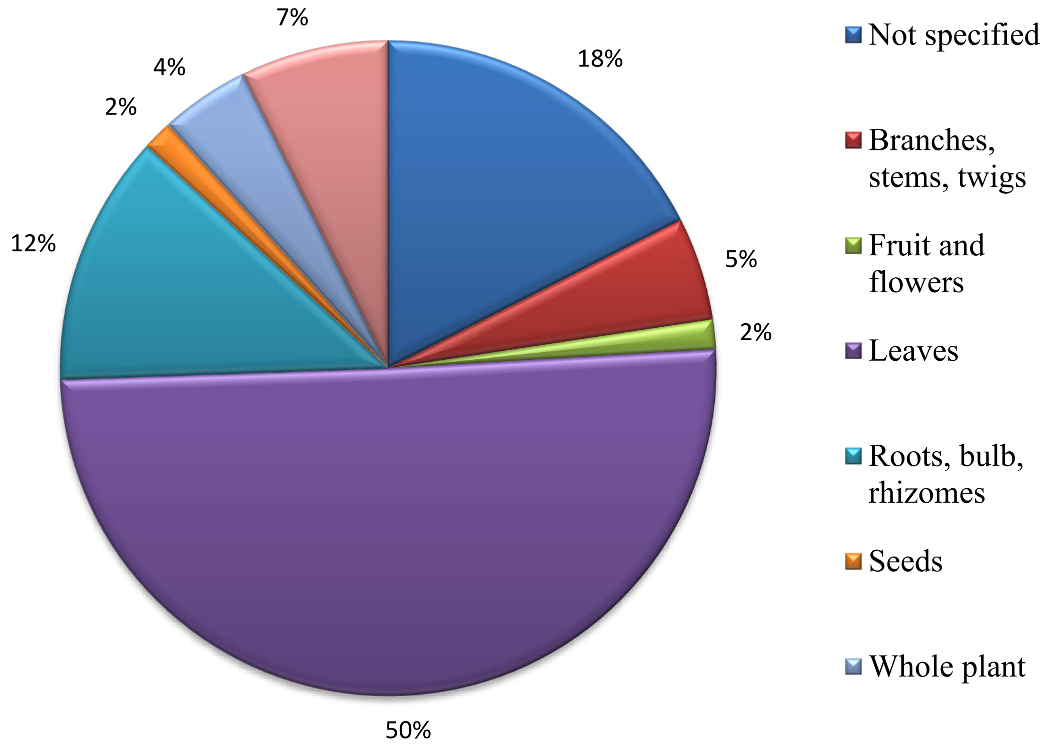

Fig 1. The plant (A) families and (B) parts used traditionally in South Africa to reduce blood glucose concentrations in the treatment of DM.

Table 2

South African plant species used for the treatment of blood sugar.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Acokanthera oblongifolia (Hochst.) Benth. & Hook.f. ex B.D.Jacks.	Apocynaceae	Inhlungunyemba, inhlungunyembe (Zulu)	Not specified	Not specified	Mhlongo and Van Wyk, 2019.
Acokanthera oppositifolia (Lam.) Codd	Apocynaceae	Inhlungunyembe (Zulu)	Not specified	Not specified	Mhlongo and Van Wyk, 2019.
Acorus calamus L.	Acoraceae	Kalmoes (Afrikaans)	Not specified	Infusion	Hulley and Van Wyk, 2019.
Adenia digitata (Harv.) Engl	Passifloraceae	Uthangazane (Zulu)	Not specified	Not specified	Mhlongo and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Allium cepa L.	Amaryllidaceae	Onion (English)	Green top of sprouts, root and bulb.	Fresh juice is taken orally.	Watt and Breyer-Brandwijk et al., 1962.
Aloe arborescens Mill.	Xanthorrhoeaceae	Krantz aloe (English), kransaalwyn (Afrikaans), ikalene (Xhosa), inkalane, umhlabana (Zulu)	Leaves	Decoctions used to treat diabetes.	Amoo et al., 2014; Cock, 2015a.
Aloe ferox Mill.	Xanthorrhoeaceae	Cape aloe (English), bitteraalwyn, winkelaalwyn (Afrikaans), iKhala (Xhosa), iNhlaba (Zulu)	Leaves, Roots	Decoctions are ingested to treat diabetes.	Moffett, 2010; Moteetee and Van Wyk, 2011; Amoo et al., 2014; Nortje and Van Wyk, 2015; Cock, 2015a; Davids et al., 2016; Hulley and Van Wyk, 2019; Moteetee et al., 2019.
Aloe greatheadii var. davyana (Schönland) Glen & D.S.Hardy	Xanthorrhoeaceae	Spotted aloe (English), Transvaalaalwyn, grasaalwyn (Afrikaans)	Leaves	Decoctions are used to treat diabetes.	Amoo et al., 2014; Cock, 2015a.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Aloe maculata All.	Xanthorrhoeaceae	Soap aloe (English), bontaalwyn (Afrikaans), lekhala (southern Sotho)	Leaves	The leaves mixed with roots of *Searsia diviricata* for diabetes.	Moffett, 2010; Moteetee and Van Wyk, 2011; Cock, 2015a.
Aloe marlothii A. Berger	Xanthorrhoeaceae	Sekgopha, kgopha ya go ema (Sepedi), bindamutshe (Tshivenda), mhangani (Tsonga)	Leaves and roots	The thorns are removed from the leaves and the leaves are mixed with water and consumed.	Mogale et al., 2019.
Aloe microstigma Salm-Dyck	Xanthorrhoeaceae	Bitteraalwyn, aalwyn, veldaalwyn, kamiesberg (Afrikaans)	Leaves	Leaf juice used for diabetes.	Nortje and Van Wyk, 2015; Cock, 2015a.
Aloe vera (L.) Burm.f.	Xanthorrhoeaceae	Burn aloe, True aloe, Indian aloe, Barbados aloe (English)	Leaves, gel	Decoctions are ingested to treat diabetes.	Balogun et al., 2016; Cock, 2015a.
Anacardium occidentale L.	Anacardiaceae	Cashew tree, cashew, cashew nut, cashew nut	Bark	Oral administration of a tincture.	Watt and Breyer-Brandwijk, 1962.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		tree, cashew apple (English), Kasjoeneut (Afrikaans)			
Arctopus echinatus L.	Apiaceae	Platdoring (Afrikaans)	Root	Not specified	Philander, 2011.
Aristea africana (L.) Hoffmanns	Iridaceae	Sand moerbos (Afrikaans)	Foliage	Not specified	Philander, 2011.
Artemisia absinthium L.	Asteraceae	Wormwood, grand wormwood, absinthe (English)	Leaves	An infusion is used to lower blood sugar	Nortje and Van Wyk, 2015.
Artemisia afra Jacq. ex Wild.	Asteraceae	Wild wormwood, African wormwood (English), wilde-als (Afrikaans), umhlonyane (Xhosa), mhlonyane (Zulu), lengana (Tswane), zengana (southern Sotho)	Leaves	Decoctions are used to treat diabetes. A small amount of the tea is taken twice daily continuously.	Hutchings et al., 1996; Thring and Wietz, 2006; Nortje and Van Wyk, 2015; Davids et al., 2016; Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Asclepias crispa P.J. Bergius	Apocynaceae	Witvergif, witvergeet, witstorm (Afrikaans)	Not specified	Not specified	Nortje and Van Wyk, 2015.
Asclepias fruticosa L.	Apocynaceae	African milkweed, wild cotton, fire sticks (English), wilde kapok, melkbos, falsche bauwolle (Afrikaans), ulusinga, lwesalukazi (Zulu), lebeyana, modimolo (Sotho)	Dried roots	An infusion prepared from the dried roots is consumed.	Von Koenen, 2001.
Ballota africana (L.) Benth.	Lamiaceae	Kattekruid, kattekruie, salie (Afrikaans)	Leaf	Infusion	Hulley and Van Wyk, 2019.
Brachylaena discolor DC.	Asteraceae	Coastal/Natal silverleaf, silver oak (English), bosvaalbos, kreukelboom, kusvaalbos, vaalbos (Afrikaans), iPhahla, iphahla (Zulu), umPhahla	Leaves	An infusion is used to lower blood sugar.	Hutchings et al., 1996; Corrigan et al., 2010.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		(Xhosa), mpahla (northern Sotho)			
Brachylaena elliptica (Thunb.) DC.	Asteraceae	Bitter-leaf, bitterleafed silver oak, fire sticks (English), bitterblaar, suurbos (Afrikaans), isiduli, isagqeba, igqeba, umphahla (Xhosa), elimnyama, iphahle, isiduli - ehlathi, uhlunguhlungu (Zulu)	Leaves	Decoctions are used to treat diabetes.	Hutchings et al., 1996.
Brachylaena ilicifolia (Lam.) Phill. and Schweick.	Asteraceae	Small bitter-leaf (English), fynbitterblaar (Afrikaans), igqeba (Xhosa)	Leaves	Decoctions are used to treat diabetes.	Hutchings et al., 1996.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Bridelia micrantha (Hochst.) Baill.	Phyllanthaceae	Coastal goldenleaf (English), mitserie, bruin stinhhout (Afrikaans), motsere, munzere (Sotho), ndzerhe (Tswana)	Bark	Decoction is used to treat diabetes.	Khumalo, 2018.
Buddleja salviifolia (L.) Lam.	Scrophulariaceae	Sagewood, butterfly bush, mountain sage (English), saliehout (Afrikaans), lelothwane (southern Sotho), igwangi, iloshane, ilothane, mupambati (Zulu), chipambati (Shona)	Not specified	The part used and the prepartaion method are not specified.	Moffett, 2010.
Bulbine latifolia (L.f.) Spreng.	Xanthorrhoeaceae	Red carrot (English), rooiwortel (Afrikaans)	Root	Not specified	Philander, 2011.
Bulbine narcissifolia Salm-Dyck	Xanthorrhoeaceae	Strap leafed bulbine, snake flower (English), lintblaar bulbine, geelslangkop, wildekopieva (Afrikaans),	Bulb, roots	Decoctions are used to treat diabetes.	Balogun et al., 2016.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		khomo-ea-balisa, serelelile (southern Sotho)			
Cadaba aphylla (Thunb.) Wild.	Capparaceae	Stormwortela, swartstorm (Afrikaans)	Root	Infusion	Davids et al, 2016; Hulley and Van Wyk, 2019.
Cannabis sativa L.	Cannabaceae	Marijuana, Indian hemp (English), dagga (Afrikaans), umya (Xhosa), nsanga, insangu (Zulu)	Leaves	Decoctions are used to treat diabetes.	Hutchings et al., 1996.
Carpobrotus edulis (L.) N.E.Br.	Aizoaceae	Sour fig, Cape fig, Hottentot's fig (English), vyerank, ghaukum, ghoenavy, hotnotsvye, kaapvy, perdevy, rankvy (Afrikaans), ikhambi-lamabulawo, umgongozi (Zulu)	Leaves	Not specified	Nortje and Van Wyk, 2015; Davids et al, 2016; Mogale et al., 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Cassia abbreviate Oliv	Leguminosae	Longtail cassia (English), molomanama (Pedi)	Stem bark	Boiled or soaked in water. Extract drunk.	Chauke et al., 2015; Mongalo and Makhafola, 2018.
Catharanthus roseus (L.) G.Don	Apocynaceae	Madagascar periwinkle (English)	Roots, Leaves	An infusion of the leaf is used to treat diabetes.	Van Wyk et al., 1997; Ndip et al., 2013.
Chamarea capensis (Thunb.) Eckl. & Zeyh.	Apiaceae	Vinkelbol, vinkelwortel (Afrikaans)	Not specified	Infusion	Hulley and Van Wyk, 2019.
Chironia baccifera L.	Gentianaceae	Christmas berry (English), bitterbos, aambeibossie (Afrikaans)	Leaves, whole plant	Decoctions are used to treat diabetes.	Philander, 2011; Nortje and Van Wyk, 2015.
Chrysocoma ciliata L.	Asteraceae	Bitterbos (Afrikaans)	Leaves and roots	Not specified	Davids et al., 2016.
Cissampelos capensis L.f.	Menispermaceae	Dawidtjiewortel, dawidtjie se wortelb (Afrikaans)	Leaves, root	Not specified	Philander, 2011; Hulley and Van Wyk, 2019.
Clutia natalensis Bernh.	Peraceae	Unknown	Roots	Decoctions are used to treat diabetes.	Kose et al., 2015; Moteetee, et al., 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Cnicus benedictus L.	Asteraceae	Holy thistle (English)	Not specified	The plant is powdered, and an infusion is created using boiling water. This infusion is taken orally before meals.	Van Wyk et al., 1997; Hulley and Van Wyk, 2019.
Coleonema album (Thinb.) Bartl. & H.L. Wendl.	Rutaceae	Aasbossie (Afrikaans), confetti bush (English)	Foliage	Not specified	Philander, 2011.
Commelina africana L.	Commelinaceae	Yellow Commelina (English), geeleendagsblom (Afrikaans)	Not specified	Not specified	Balogun et al., 2016.
Commiphora africana (A.Rich.) Endl.	Burseraceae	Hairy corkwood, Namibian corkwood (English), harige kanniedood (Afrikaans)	Bark	A decoction is used to treat diabetes.	Khumalo, 2018.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Conyza scabrida DC.	Asteraceae	Waterbos, vleiwilger, meidebos, medisynebos, slangbos, fonteinbos (Afrikaans)	Foliage	Not specified	Thring and Wietz, 2006; Philander, 2011; Nortje and Van Wyk, 2015.
Crassula muscosa L.	Crassulaceae	Akkedisbos (Afrikaans)	Leaves, stems, roots and flowers	Leaves, stems, roots and flowers	Davids et al., 2016.
Dicerothamnus rhinocerotis (L.f.) Koek.	Asteraceae	Ranosterbos (Afrikaans)	Leaves and stem	Not specified	Davids et al., 2016.
Dicoma anomala Sond.	Asteraceae	Fever bush, stomach bush (English), maagbitterwortel, koorbossie, gyrshout, maagbossie (Afrikaans), hloenya (southern Sotho), inyongana (Xhosa),	Roots, Leaves	Decoctions are used to treat diabetes.	Moffett, 2010; Moteetee and Van Wyk, 2011; Kose et al., 2015; Balogun et al., 2016; Moteetee et al., 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		isihlabamakhondlwane, umuna (Zulu)			
Dicoma carpensis Less.	Asteraceae	Hosabies, hosabie, koorbossie, sandsalie, wilde karmedik, karmadik, vrouensbos, kuniebos, baarbos, hotnotskooigoed, hen-met-kuikens (Afrikaans)	Leaves	A decoction is used to treat diabetes.	Nortje and Van Wyk, 2015.
Dittrichia graveolens (L.) Greuter	Asteraceae	Kakiebos (Afrikaans)	Leaves, twigs	An infusion is used to lower blood sugar levels.	Nortje and Van Wyk, 2015.
Dodonaea viscosa (L.) Jacq.	Sapindaceae	Sand olive (English), sandolien, ysterbos (Afrikaans), mutata-vhana (Venda), mutepipuma (Shona)	Leaves	Crushed leaves are immersed in boiling water and left standing overnight. One cupful is taken daily.	Von Koenen, 2001; Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Elephantorrhiza elephantina (Burch.) Skeels	Leguminosae	Eland's bean, aland's wattle, elephant's root (English), boswortel, eland's-boontjie, leerbossie, looi ersboontjie, olifantswortel (Afrikaans), mupangara (Shona), mositsane (Sotho, Tswana), intolwane (Xhosa, Zulu).	Rhizomes	Decoctions are used for the management of diabetes.	Balogun et al., 2016.
Elytropappus rhinocerotis (L.f.) Less.	Asteraceae	Rhinosaurous bush (English), renosterbos (Afrikaans)	Not specified	Not specified	Thring and Wietz, 2006; Nortje and Van Wyk, 2015; Hulley and Van Wyk, 2019.
Empodium plicatum (Thunb.) Garside	Hypoxidaceae	Golden star (English)	Not specified	Not specified	Balogun et al., 2016.
Englerophytum magalismontanum	Sapotaceae	Mahlatswa a hlateng (Sepedi)	Bark	Not specified	Mhlongo and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
(Sond.) T.D. Penn.					
Eriocephalus ericoides (L.f.) Druce	Asteraceae	Kapokbos, wilderoosmaryn (Afrikaans)	Not specified	Not specified	Hulley and Van Wyk, 2019.
Eriocephalus punctulatus DC.	Asteraceae	Wild rosemary, Cape snowbush (English), kapokbos (Afrikaans)	Leaves	A decoction is used to treat diabetes.	Moffett, 2010; Moteetee and Van Wyk, 2011; Kose et al., 2015; Balogun et al., 2016.
Eriocephalus tenuifolius DC.	Asteraceae	Sehalahala-sa-matlaka (Sesotho)	Not specified	Not specified	Moteetee et al., 2019.
Eucalyptus citriodora Hook.	Myrtaceae	Lemon-scented gum (English)	Not specified	An aqueous extract of the plant is administered orally.	Watt and Breyer-Brandwijk et al., 1962.
Eucalyptus globulus Labill.	Myrtaceae	Ronde bloekomblaar (Afrikaans)	Not specified	Infusion	Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Euclea crispa (Thunb.) Gürke	Ebenaceae	Guarri bush, blue gaurri (English), bloughwarrie (Afrikaans), iyeza-lokuxaxazisa, umgwali (Xhosa), idungamuzi, umgwali (Zulu), gwari (Pedi)	Roots	Dry root powder taken orally.	Gelfand et al. 1985.
Euclea natalensis A.DC.	Ebenaceae	Large-leaved guarri (English), mohlakola	Roots	Boiled and may also be mixed with other plants (not specified).	Chauke et al., 2015.
Euclea undulata Thunb	Ebenaceae	Ghwarrie, ghwarriebos, ghwarrieboom, ghwarriebessie, wildepruim (Afrikaans)	Not specified	Infusion	Hulley and Van Wyk, 2019.
Euphorbia clavariodes Boiss.	Euphorbiaceae	Lions spoor (English), sehlehle, sehloko, thethebale (southern	Whole plant	A decoction is used to treat diabetes.	Kose et al., 2015.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		Sotho), isihlekehleke, isantilele (Zulu)			
Euphorbia prostrata Aiton	Euphorbiaceae	Harige kruipmelkkruid (Afrikaans)	Not specified	Used by South African Indians to treat diabetes.	Von Koenen, 2001.
Euryops abrotanifolius (L.)DC.	Asteraceae	Harpuisbos (Afrikaans)	Stems and leaves	Not specified	Davids et al., 2016.
Exomis microphylla (Thunb.) Aellen	Amaranthaceae	hondepisbos(sie), hondebossie (Afrikaans)	Not specified	Not specified	Hulley and Van Wyk, 2019.
Galium tomentosum Thunb.	Rubiaceae	Rooihoutjie (Afrikaans)	Root	Not specified	Van Wyk et al., 2008; Philander, 2011; Hulley and Van Wyk, 2019.
Gazania krebsiana Less.	Asteraceae	Gousblom, botterblom (Afrikaans)	Leaves	A decoction is used to treat diabetes.	Balogun et al., 2016.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Gnidia deserticola Gilg	Thymelaeaceae	Koorsbos (Afrikaans)	Leaves, stems and roots	Combination with *Lessertia frutescens* and *Ballota africana*	Davids et al., 2016.
Grewia flavescens Juss.	Malvaceae	Sandpaper raisin (English), Mopharantshone (Pedi)	Roots	Used in a mixture (other ingredients not given)	Chauke et al., 2015.
Grewia villosa Willd.	Malvaceae	Mallow raisin (English), Mopharantshone (Pedi)	Roots	Used in a mixture (other ingredients not given)	Chauke et al., 2015.
Gomphrena celosioides Mart.	Amaranthaceae	Soft khaki weed (English), Lebolomo la naga (Pedi)	Roots	Used in a mixture (other ingredients not given)	Chauke et al., 2015.
Gunnera perpensa L.	Gunneraceae	River pumpkin, wild rhubarb (English), rivierpampoen, wilde ramenas (Afrikaans), qobo (Sotho), vqobho (Swati), rambala-vhadzimu, shambala-vhadzimu	Roots, Rhizomes	Decoctions are used to treat diabetes.	Balogun et al., 2016; Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		(Venda), iphuzi lomlambo, igobho (Xhosa), ugobhe, ugobho (Zulu)			
Gymnema sylvestre (Retz.) R.Br. ex Sm.	Apocynaceae	Gymnema, Australian cowplant, periploka of the woods (English), gurmar (Hindi, means sugar destroyer)	Leaves	A decoction is used to treat diabetes.	Von Koenen, 2001.
Haplocarpha scaposa Harv.	Asteraceae	False gerbera (English), melktou (Afrikaans), Khutsana (southern Sotho), isikhali (Xhosa)	Leaves, Roots	Extracts are ingested for the management of diabetes.	Balogun et al., 2016.
Helichrysum caespititium (DC.) Sond. ex Harv.	Asteraceae	Mokgata (Sepedi)	Whole plant	Not specified	Mogale et al., 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Helichrysum crispum (L.) D. Don	Asteraceae	Kooigoedbos (Afrikaans)	Not specified	Infusion	Hulley and Van Wyk, 2019.
Hermannia cuneifolia Jacq.	Malvaceae	Wilde heuning, geneesbossie, pleisterbossie (Afrikaans)	Leaves	An infusion is used to lower blood sugar levels.	De Beer and Van Wyk 2011.
Hermannia pinnata L.	Malvaceae	Doll's rose (English), kwaasblaar, kruip poprosie (Afrikaans).	Not specified	Not specified	Balogun et al., 2016.
Hoodia currori (Hook.) Decne.	Apocynaceae	Hoodia cactus, bitter ghap (English), bitterghaap, muishondghaap, wolweghaap, bobbejaanghaap, bergghaap, bokhorings (Afrikaans), khobab (Khoi)	Little stem	The outer layer of the little stem is scraped off, together with its thorns. A portion of the stem is cut off and eaten in the morning, afternoon and evening.	Von Koenen, 2001.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Hoodia gordonii (Masson) Sweet ex Decne	Apocynaceae	Bitterghaap	Inner stem	Not specified	Davids et al., 2016.
Hypoxis hemerocallidea Fisch. & C.A. Mey & Avé-Lall.	Hypoxiadaceae	Yellow star, star lily, star flower (English), sterblom, geelsterretjie, gifbol (Afrikaans), moli kharatsa, lotsane (southern Sotho); inkomfe, inkomfe enkulu (Zulu), inongwe, ilabatheka, ixhalanxa, ikhubalo lezithunzela (Xhosa), tshuka (Tswana)	Not specified	Not specified	Kose et al., 2015; Ojewole, 2005.
Inula graveolens (L.)Desf.	Asteraceae	Khakibos (Afrikaans)	Foliage	Not specified	Philander, 2011.
Jacobaea maritima (L.) Pelser & Meijden	Asteraceae	Vaalbos (Afrikaans)	Not specified	Not specified	Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Kedrostis africana (L.) Cogn.	Cucurbitaceae	Bojaankamoo (Afrikaans)	Not specified	Not specified	Hulley and Van Wyk, 2019.
Kedrostis nana Cogn.	Cucurbitaceae	Kalmoes, bitterhout (Afrikaans), serekola (Zulu)	Root, tuber	A decoction is used for the management of diabetes.	Van Wyk et al., 2008; Philander, 2011.
Leonotis leonurus (L.) R.Br.	Lamiaceae	Wildedagga (Afrikaans)	Leaves	Infusion.	Nortje and Van Wyk, 2015; Davids et al., 2016; Hulley and Van Wyk, 2019.
Leonotis ocymifolia (Burm.f.) Iwarsson	Lamiaceae	Wildedagga, klipdagga (Afrikaans)	Not specified	Not specified	Hulley and Van Wyk, 2019.
Lessertia frutescens (L.) Goldblatt & J.C. Manning	Leguminosae	Cancer bush, balloon pea (English), kankerbos, blaasbossie, blaas-ertjie, eendjies, gansiekeurtjie, klappers, hoenderbelletjie	Leaves	Decoctions or infusions of the leaves are used to treat diabetes.	Van Wyk, 1997. Thring and Wietz, 2006; De Beer and Van Wyk 2011; Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		(Afrikaans), umnwele (Xhosa, Zulu)			
Limeum aethiopicum Burm.f.	Limeaceae	Koggelmandervoet, boesmandagga (Afrikaans)	Not specified	Infusion	Hulley and Van Wyk, 2019.
Mentha longifolia (L.) L.	Lamiaceae	Wild mint (English), kruisement, balderjan (Afrikaans); Koena-ya-thaba (southern Sotho); inixina, inzinziniba (Xhosa); ufuthana lomhlanga (Zulu)	Leaves	An infusion is used for the management of diabetes.	Nortje and Van Wyk, 2015; Davids et al., 2016.
Merwilla plumbea (Lindl.) Speta.	Asparagaceae	Setsusha (Sepedi), kgerere (South Sotho)	Leaves	Not specified	Mogale et al., 2019.
Mimulus gracilis R.Br.	Phrymaceae	Unknown	Not specified	A decoction is taken orally although the plant part was not specified	Balogun et al., 2016.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Mimusops zeyheri Sond.	Sapotaceae	Mmupudu, mobupudu (Sepedi), mibubulu (Tsonga), mubulu (Tshivenda)	Leaves	Not specified	Mogale et al., 2019.
Momordica balsamina L.	Cucurbitaceae	Balsam pear (English), laloentjie (Afrikaans), mohodu (Sotho), intshungu, intshungwana yehlathi (Zulu)	Not specified	Not specified	Hutchings et al., 1996; Ndip et al., 2013; Chauke et al., 2015; Mogale et al., 2019.
Momordica foetida Schumach.	Cucurbitaceae	Unknown	Leaves and stems	Medicines made from crushed leaves are taken for diabetes.	Hutchings et al., 1996.
Morella serrata (Lam.) Killick	Myricaceae	Lance-leaved strawberry, waxberry, mountain waxberry (English), smalblaarwasbessie, Berg-wasbessie (Afrikaans),	Roots	Decoctions are used for the management of diabetes.	Balogun et al., 2016.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		isibhara, umakhuthula, umaluleka (Xhosa), Iyethi, ulethi, umakhuthula, umlulama (Zulu)			
Moringa oleifera Lam.	Moringaceae	Moringa, makgonatsohle (Sepedi)	Any part or seeds and leaf	Not specified	Mogale et al., 2019.
Notobubon galbanum (L.) Magee	Apiaceae	Berg celery, blister bush (English), bergseldery (Afrikaans)	Foliage	Not specified	Philander, 2011.
Nymphaea caerulea Savigny	Nymphaeaceae	Blue water lily (English), blouwaterlelie (Afrikaans)	Seeds	The ground seed is mixed with water and taken orally weekly.	Von Koenen, 2001.
Olea europaea L.	Oleaceae	Wild olive (English), olienhout, olienhoutboom (Afrikaans), mohlware (Sotho), umnquma (Zulu,	Bark	Decoctions are used for the management of diabetes.	Nortje and Van Wyk, 2015.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		Xhosa, Swati), mutlhwari (Venda), motlhware (Tswana)			
Opuntia ficus-indica (L.) Mill.	Cactaceae	Indian pear, Indian fig, sweet prickly pear (English), boereturksvy, grootdoringturksvy (Afrikaans), umthelekisi (Zulu)	Leaves	Crushed leaves or a leaf decoction may be taken orally for mild diabetes.	Von Koenen, 2001; Chauke et al., 2015; Hulley and Van Wyk, 2019; Mogale et al., 2019.
Opuntia vulgaris Mill.	Cactaceae	Prickly pear (English)	Leaves	A decoction is taken orally for the management of diabetes.	Watt and Breyer-Brandwijk, 1962.
Pegolettia baccharidifolia Less.	Asteraceae	Ghwarrieson, gwarrieson, heuningdou(bos) (Afrikaans)	Foliage	Not specified	Philander, 2011; Hulley and Van Wyk, 2019.
Pelargonium	Geraniaceae	Rooistorm (Afrikaans)	Roots	Not specified	Davids et al., 2016.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
antidysentericum (Eckl. & Zeyh.) Kostel.					
Pentanisia prunelloides (Klotzch) Walp.	Rubiaceae	Wild verbena, broad-leaved Pentanisia (English), sooibrandbossie (Afrikaans), icimamlilo (Zulu)	Roots, leaves	Extracts are used to treat diabetes	Philander, 2011; Kose et al., 2015; Balogun et al., 2016; Moteetee et al., 2019.
Pentzia incana (Thunb.) Kuntze	Asteraceae	Skaapkaroo(bos), ankerkaroo, kleinskaapkaroobos, rambossie (Afrikaans)	Not specified	Not specified	Hulley and Van Wyk, 2019.
Pittosporum viridiflorum Sims	Pittosporaceae	Umkhwenkhwe (Zulu)	Bark	Not specified	Philander, 2011.
Portulacaria afra Jacq.	Didiereaceae	Spekbosb, spekboomblareb, spekboom (Afrikaans)	Not specified	Eaten	Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Psidium guajava L.	Myrtaceae	Guava (English), koejawel (Afrikaans), ugwava (Zulu)	Leaves	An infusion is taken orally for the management of diabetes.	Van Wyk et al., 1997; Hulley and Van Wyk, 2019.
Pteronia cinerea L.f.	Asteraceae	Boegoe, silverboegoe (Afrikaans)	Leaves	Leaf infusion is taken orally.	Nortje and Van Wyk, 2015.
Punica granatum L.	Lythraceae	Granaat, grinaat, wildegranaatbos (Afrikaans)	Root	Infusion	Hulley and Van Wyk, 2019.
Rapanea melanophloeos Mez.	Primulaceae	Cape beech (English), boekenhout, beukehout (Afrikaans), isiCalabi, umaPhipha, iKhubalwane, isiQalaba sehlati (Zulu), isiQwane sehlati (Xhosa)	Not specified	Dried plant material is mixed with food and consumed to treat diabetes.	Adeniji et al., 2001.
Rhamnus prinoides L'Hér.	Rhamnaceae	African dogwood, camdeboo stinkwood, glossy-leaf (English),	Branches	A decoction is prepared and used to treat diabetes.	Kose et al., 2015.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		blinkblaar, camdeboostinkhout (Afrikaans), umGlindi, umlindi (Xhosa), umGilindi, uNyenye, umHlinye (Zulu), Mofifi (southern Sotho)			
Rosmarinus officinalis L.	Lamiaceae	Rosemary (English), roosmaryn (Afrikaans)	Not specified	An infusion is prepared and consumed.	Van Wyk et al., 2008.
Rumex lanceolatus Thunb.	Polygonaceae	Small dock, smooth dock, common dock (English), gladdetongblaar (Afrikaans)	Leaves, roots	Decoctions are used to treat diabetes	Kose et al., 2015; Balogun et al., 2016.
Ruta graveolens L.	Rutaceae	Rue, common rue, herb-of-grace (English), wynruit (Afrikaans)	Leaves	Infusion is used.	Thring and Wietz, 2006; Nortje and Van Wyk, 2015; Van Wyk and Gorelik, 2017.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Salix mucronata Thunb.	Salicaceae	Rivierwilger, rivierwiller, rooisteeltjiewilg, vaalwilger (Afrikaans)	Foliage	Not specified	Philander, 2011; Hulley and Van Wyk, 2019.
Salvia africana-lutea L.	Lamiaceae	Red sage	Foliage	Not specified	Philander, 2011.
Salvia dentata Aiton	Lamiaceae	Toothed sage (English), bergsalie, blousalie, bloublomsalie, salie, sandsalie (Afrikaans)	Not specified	A syrup is prepared and used.	Nortje and Van Wyk, 2015.
Salvia microphylla Kunth	Lamiaceae	Mak salie, rooiblomsalie, pienkblomsalie (Afrikaans)	Not specified	Not specified	Hulley and Van Wyk, 2019.
Schkuhria pinnata (Lam.) Kuntze ex Thell.	Asteraceae	Dwarf Mexican marigold (English), klein-gousblom, kleinkakiebos (Afrikaans), ruhwahwa (Shona)	Whole plant, leaves or roots	The whole plant is boiled and consumed orally.	Mahwasane et al., 2013.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Searsia lancea (L.f) F.A. Barkley	Anacardiaceae	Karee (English), karee, rooikaree (Afrikaans), mokalabata, monhlohlo, motshakhutshakhu (northern Sotho), inhlangutshane (Swati), mosinabele, mosilabele (southern Sotho), mosabele, mosilabele (Tswana), mushakaladza (Venda), umhlakotshane (Xhosa)	Leaves, fruits	Decoctions or infusions are consumed to treat diabetes.	Moteetee and Van Wyk, 2011; Kose *et al*., 2015; Hulley and Van Wyk, 2019.
Stachys hyssopoides Burch. ex Benth	Lamiaceae	Hyssop-leaved hedge nettle (English)	Not specified	Not specified	Moffett, 2010; Moteetee and Van Wyk, 2011; Moteetee et al., 2019.
Strychnos henningsii Gilg.	Loganiaceae	Red bitter berry, coffee hard pear, coffee-bean Strychnos, hard pear	Bark	Powdered bark is consumed for the	Khumalo, 2018.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
		(English), rooibitterbessie, bosolienhout, hardepeer, hardepeerhout, koffiehardepeer, koffiehardepeerhout (Afrikaans), muramba-kolodza (Venda), umanana, umnono (Zulu), umanono, umnonono (Xhosa)		management of diabetes.	
			Leaves	Decoctions or infusions of the leaves are used to treat diabetes.	Van Wyk, 1997. Thring and Wietz, 2006; De Beer and Van Wyk 2011
Tagetes minuta L.	Asteraceae	Koebiebos (Afrikaans)	Leaves	Not specified	Davids et al., 2016.
Teedia Lucida (ex Sol.) Rudolphi	Scrophulariaceae	Hlwenya (Zulu), klipkersie, predikant-op-die-preekstoel, stinkbos (Afrikaans)	Not specified	Not specified	Moffett, 2010; Moteetee et al., 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Terminalia sericea Burchell ex. DC.	Combretaceae	Silver terminalia, silver cluster leaf (English), vaalboom, geelhout, sandvaalboom, (Afrikaans), mususu (Venda)	Bark	The bark is pulverised and mixed with maize meal. This mixture is eaten as a remedy for diabetes.	Van Wyk et al., 1997; Von Koenen, 2001; Hutchings et al., 1996; Cock 2015b.
Thesium lineatum L.f. LEP	Santalaceae	Black storm (English), swartstrom (Afrikaans)	Root	Not specified	Philander, 2011.
Tinospora fragosa Verdoorn & Troupin	Menispermaceaea	Aaron's rod (English), Makgonatsohle (Pedi)	Leaves and stem	Boiled and drunk. May be mixed with tea or juice.	Chauke et al., 2015.
Tulbaghia violacea Harv.	Amaryllidaceae	Wild garlic (English), Wilde knoffel (Afrikaans)	Leaf and root	Not specified	Davids et al., 2017.
Tylecodon paniculatus (L.f.) Toelken	Crassulaceae	Bees se bal (Afrikaans)	Leaves and stem	Not specified	Davids et al., 2017.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Urtica dioica L.	Urticaceae	Common nettle, stinging nettle (English)	Leaf and root	An infusion is prepared and consumed for the management of diabetes	Watt and Breyer-Brandwijk et al., 1962; Moffett, 2010; Moteetee et al., 2019.
Urtica urens L.	Urticaceae	Brandnekel(boom), brandneker, netelbos (English)	Not specified	Infusion	Hulley and Van Wyk, 2019.
Vernonia oligocephala Katt	Asteraceae	Silver leaved vernonia (English)	Not specified	Infusions or decoctions are consumed as a remedy for diabetes.	Watt and Breyer-Brandwijk et al., 1962; Von Koenen, 2001.
Viscum capense L. f.	Santalaceae	Cape mistletoe (English), groen voelent, taaibos (Afrikaans)	Stem	Stem infusions are used to treat diabetes.	Van Wyk, 1997; De Beer and Van Wyk 2011; Hulley and Van Wyk, 2019.
Viscum continuum E. Mey. ex Sprague	Santalaceae	Voëlent, litjiestee (Afrikaans)	Not specified	Infusion	Hulley and Van Wyk, 2019.

Plant species	Family	Common names	Plant part used medicinally	Traditional method of usage	Reference
Xysmalobium indulatum (Schltr.) N.E. Br.	Apocynaceae	Milk bush, milkwort, wild cotton, wave-leaved xysmalobium (English), bitterhout, bitterwortel, bitterhoutwortel, melkbos (Afrkaans), leshokoa, poho-tšehla (southern Sotho), iyeza elimhlophe, nwachaba, iShongwane (Xhosa), iShongwane, iShongwe, iShinga (Zulu)	Roots	Root infusions or decoctions are used to treat diabetes.	Kose et al., 2015; Balogun et al., 2016.
Ziziphus mucronata Willd.	Rhamnaceae	Motalo, mokgalo (Sepedi), makhalu (Tshivenda), nceseni (Tsonga)	Root	Not specified	Mogale et al., 2019.

5. Scientific studies into the anti-diabetes mellitus activity of South African plants

Several laboratory-based studies have aimed to verify the efficacy of South African plant species and to determine to their anti-DM mechanisms (Table 3). Most of these studies have examined the effects in DM-induced animal models, especially in rats, mice and rabbits.

The *Aloe* species have been perhaps the most extensively studied. Administration of 1000 mg/kg body weight of *A. arborescens* juice decreased blood glucose levels by 8.4% after 6 h (Chacko et al., 2008). Continuous administration proved to be effective, with reductions of 26.9% at 200 mg/kg body weight and 42.3% at 1000 mg/kg body weight observed after 18 days. In another study, an *A. arborescens* leaf fraction significantly suppressed blood glucose levels in streptozotocin-induced diabetic mice (Amoo et al., 2014). Similarly, an *A. ferox* leaf extract (300 mg/kg body weight) increased insulin levels in streptozotocin induced diabetic rats (Loots et al., 2011; Amoo et al., 2014). Surprisingly, no changes in the hyperglycaemic state were observed, despite the increased insulin secretion.

The antihyperglycemic activity of *A. cepa* juice has also been particularly well reported. The therapeutic properties have been verified in alloxan-induced rats, lowering of plasma glucose levels by approximately 70% (El-Dermerdash et al., 2005). Similarly, *A. cepa* essential oil substantially reduces blood sugar levels and raises insulin secretion (El-Soud and Khalil, 2010). Upon administration of *A. cepa* to alloxan induced rats for six weeks, it was found that the effect is dose dependant (Ozougwu, 2011). At 200 mg/kg body weight, blood glucose levels were reduced by 62.9%, at 250 mg/kg they were reduced by 69.7% and at 300 mg/kg they were reduced by 75.4%. In another study, *A. cepa* administration resulted in a significant reduction in induced hyperglycaemia by approximately 120 mg/dL after 4 h (Taj Eldin et al., 2010). The administration of 100 mg/kg body weight of crude *A. cepa* extract lowered fasting blood glucose levels in diabetic patients by 40 mg/dL. A relatively gradual decrease in fasting blood glucose was also observed for the same period compared to insulin therapy in type 1 diabetic patients. Administration of an ether extract of *A. cepa* to diabetic rabbits showed antihyperglycemic activity (Ogunmodede et al., 2012). Similarly, increasing dosages (100 and 300 mg/kg body weight) of the aqueous extract of *A. cepa* resulted in significant reductions of fasting glucose levels of 53.3% and 73.3% respectively. The reduction in blood glucose level observed in rabbits treated with *A. cepa* after four weeks of treatment showed potential for complete recovery over an extended period of administration in the same study.

The therapeutic effects of *A. occidentale* stem-bark extracts have been reported in fructose-diabetic rats. Rats receiving a single daily intravenous dose of 200 mg/kg body weight of *A. occidentale* methanol extract had significantly lower plasma glucose levels compared to the control rats on a high-fructose diet (Olatunji et al., 2010). That report linked the antihyperglycemic effect of the extract to high antioxidant capacities. Similarly, the administration of alcoholic *A. occidentale* bark extracts resulted in the reduction of serum glucose levels. Indeed, treatment with 300 mg/kg body weight reduced the blood sugar levels by 18.4%, 200 mg/kg reduced them by 17.3% and 12.8% depending on the weight of the rats, whilst 30 mg/kg produced a reduction of 15.6% (Fagbohun and Odufunwa, 2010; Ukwenya et al., 2012).

Other studies conducted on streptozotocin–induced diabetic rats showed that *A. afra* aqueous extracts significantly reduced blood glucose levels (Afolayan and Sunmonu, 2011; Afolayan and Sunmonu, 2013). Notably, following 21 days of administration, the glucose levels tended towards normalcy. Saponins that have been reported to exhibit hypoglycaemic effects in diabetic rabbits were detected in the *A. afra* aqueous extract and were postulated to be responsible for the activity of that extract. Similarly, *B. discolor* methanolic extracts induced a time dependent decrease in the blood glucose levels in streptozotocin-induced diabetic rats at 200 and 600 mg/kg body weight (Mellem et al., 2013). The higher dose of 600 mg/kg produced more pronounced effects than the reference drug metformin. Similarly, the related species *B. elliptica* also decreased blood glucose levels in L6 myoblast cells (Sagbo et al 2018), suggesting that *B. elliptica* functions by a similar mechanism to metformin. An increase in glucose uptake was reported in HepG2 cells in a dose-dependent manner in that study.

A different study reported that methanolic *C. roseus* leaf extracts significantly reduce blood glucose levels by 41.7% in streptozotocin-induced diabetic mice (Ojewole and Adewumni, 2000). In another study, administration of an aqueous *C. roseus* extract (1g/kg body weight) for 21 days streptozotocin-induced rats decreased blood glucose levels by 20.2% (Singh et al., 2001). Similarly, the same study reported that a dichloromethane/methanol extract (500 mg/kg body weight) decreased blood glucose levels by 48.6% and 57.6% at 7 and 15 days respectively. The extract also resulted in a 30 min delay in peak blood glucose levels reaching a peak.

Administration of *C. africana* extracts to alloxan-induced diabetic rats reduced fasting blood glucose from 408.5 mg/dL (hyperglycaemia) to 90 mg/dL (normoglycemia) (Agunbiande et al., 2012; Balogun et al., 2016). This 78% reduction is comparable to that of glibenclamide, which produced a reduction of 69.2% over a period of seven days. Those studies also determined that the extract inhibited the absorption of glucose through the gut lumen, directly stimulated glycolysis in peripheral tissues, reduced hepatic gluconeogenesis, facilitated glucose entry into peripheral cells and reduced plasma glucagon levels.

The antihyperglycemic properties of aqueous *H. hemerocallidea* corm extracts have also been verified *in vivo* (Ojewole et al., 2005; Street and Prinsloo, 2012; Ncube et al., 2013; Boaduo et al., 2014; Balogun et al.., 2016). The extract (50-800 mg/kg body weight) significantly reduces blood glucose levels in streptozotocin-induced rats (Ojewole et al., 2005). That study identified *Hypoxis* and its aglycone derivative, rooperol in the aqueous extract and have postulated that these compounds contribute to the activity of the extract. *H.*

hemerocallidea corm acetone and ethyl acetate extracts induce higher α-amylase inhibitory effects than the standard drug acarbose (Boaduo et al., 2014). That study also reported that the extract stimulates insulin secretion and it has been suggested that this may be responsible for the blood glucose lowering effects of the extract.

Several studies have compared the efficacy of olive leaf extracts with the standard drug glibenclamide *in vivo* (Eidi et al*.,* 2008; El and Karakaya 2009; El Amin et al*.,* 2013; Hashmi et al*.,* 2015). The extracts and glibenclamide had similar effects when tested at 0.5 g/kg body weight, significantly reducing serum glucose levels and increasing insulin levels in streptozotocin-induced rats towards normal values (Eidi et al*.,* 2008). The decrease in blood glucose levels was comparable to that seen for metformin, with a reduction of 64.6% observed for the *O. europaea* extract (Eidi et al*.* 2008). Further studies identified oleuropein and related secoiridoids in the extracts and postulated that they may be responsible for this activity (El and Karakaya, 2009). In a separate study, pure oleuropein (20 mg/kg body weight) was administered to diabetic rabbits over a 16 week period, resulting in significantly decreased blood glucose levels (Al-Azzawie and Alhamdani, 2006). Oleuropein also accelerated glucose uptake into cells (Sangi et al., 2015).

Administration of aqueous *U. dioica* leaf extracts significantly reduced blood glucose levels in alloxan-induced diabetic rats (Bnouham et al., 2003). A significant reduction (67.9%) in blood sugar levels was observed within 1 h of administration. In contrast, hexane, ethyl acetate and methanol extracts were less effective at lowering blood glucose levels (Ahangarpour et al., 2012; Dar et al., 2013). These studies reported reductions of 28.3% and 40% at 1 and 2 h after administration respectively for the methanol extract. Interestingly, the *U. dioica* leaf extracts also significantly reduced serum insulin secretion and fasting insulin resistance index (Ahangarpour et al., 2012; Dar et al., 2013).

The antidiabetic properties of several other plant species used traditionally in South Africa to treat DM have also been verified *in vivo*. Administration of an aqueous *Eucalyptus citridora* Hook leaf extract at 250 mg/kg and 500 mg/kg body weight significantly reduced blood glucose levels in a diabetic rat model (Arjun et al., 2009). Similarly, *P. guajava* has substantial hypoglycaemic activity in induced diabetic rats, although it was not effective on normal rats (Afolayan and Sunmonu, 2010). Treatment of streptozotocin-induced diabetic rats with *L. leonurus* extracts for 15 days significantly reduced blood glucose levels by a comparable extent to that of the standard drug glibenclamide (Oyedemi et al., 2010). Alcoholic *G. sylvestre* extracts stimulate insulin release from rat pancreatic β-cells by increasing cell permeability (Baskaran et al., 1990; Khan et al., 2011). Furthermore, an ethanolic *G. sylvestre* extract decreases blood glucose levels in a rat model (Baskaran et al., 1990). A clinical study conducted on Type 2 diabetic patients reported that administration of *G. sylvestre* extracts and hypoglycaemic drugs substantially improved blood sugar control at doses of 400-600 mg/day (Khan et al., 2011). *Ruta graveolens* extract administration in streptozotocin-induced diabetic rats induces the β-cells to return to normal functionality, thereby demonstrating an insulinogenic effect (Toserkani et al., 2012). *Lessertia frutescens* also has significant anti-DM effects in rats fed on a high diabetogenic diet. Shoot extracts (0.01 mg/g body weight) returned the rats insulin secretion to normal levels and substantially increased glucose clearance rates (Chadwick et al., 2007). Indeed, the *L. frutescens* extracts returned the experimental rats from a pre-diabetic state to normal and reversed insulin resistance. Several clinical trials have been conducted using *Cinnamomum cassia* Siebold extracts in diabetic patients and have reported substantial blood glucose lowering activity (Khan et al., 2003; Mang et al., 2006; Dugoua et al., 2007; Pham et al., 2007; Boaduo et al., 2013). These studies reported that the *C. cassia* extracts inhibited α-amylase activity to a greater extent that the acarbose control, although the extracts were relatively ineffective against α-glucosidase.

Interestingly there is very little mention of plant combinations or mixtures to treat DM. A study by Matsabisa et al. (2019) examined the anti-diabetic potential of a locally prepared mixture of three plant species (*S. birrea, O. ficus-indica* and *Solanum pimpinellifolium* L). The mixture was shown to have a synergistic anti-hyperglycemic effect via inhibitingα-glucosidase, DPP-IV and glycation activities as well as enhancing glucose utilisation. *In vitro* mechanistic studies are relatively rare for the plants identified in Table 2. The majority of studies have examined the overall efficacy of the extracts without determining the mechanism by which they induce these reductions in blood glucose levels. It is therefore not known whether many of the extracts function via a regulation of insulin synthesis or release, or if their effects are more direct (e.g. via the direct activation of enzymes involved glucose storage and metabolism). Substantially more mechanistic studies are required to understand how these extracts achieve their effects. Indeed, for the majority of the 43 plant species whose blood glucose lowering properties have been verified, the antihyperglycemic mechanisms remain to be determined. *In vitro* assays were carried out to test the effects of *S. pinnata* extracts on the C2C12 myocytes, 3T3-L1 preadipocytes and Chang liver cells (Deutschlander et al., 2009). The ethanolic extract significantly lowered blood sugar levels when tested on the C2C12 cells, although an acetone extract had no effect. When 3T3-L1 preadipocytes were exposed to the extracts, both *S. pinnata* ethanol and acetone extracts lowered blood glucose levels significantly. This decrease was shown to be mediated via stimulation of glucose uptake. However, the *S. pinnata* ethanol and acetone extracts were toxic to 3T3-L1 preadipocytes, raising concerns about their use medicinally. A rise in glucose utilisation was observed in differentiated 3T3-L1 cells treated with

Table 3

Studies conducted on different plants used for the treatment of blood sugar in South Africa.*Bold denotes species found in Table 2 i.e. correlation to traditional use.

Plant species*	**Plant part used medicinally**	**Type of extract tested**	**Outcome of the study**	**Reference**
Allium cepa	Green top of sprouts, root and bulb or leaf	Various solvent and aqueous extracts, leaf juice	Ether extract reduces blood glucose levels *in vivo*. Aqueous extracts significantly reduce fasting glucose levels by up to 73% at 300 mg/kg body weight. Long term reductions in blood glucose levels in rabbits indicated complete recovery. Treatment of alloxan-induced rats with leaf juice resulted in the lowering of plasma glucose levels by 70%.	El-Dermerdash et al., 2005; Ozougwu, 2009; El-Soud and Khalil, 2010; Taj Eldin et al., 2010; Eyo et al., 2011; Khan et al., 2011;

Plant species*	**Plant part used medicinally**	**Type of extract tested**	**Outcome of the study**	**Reference**
	Leaves	Essential oil	Leaf essential oil reduces blood sugar and raises insulin levels *in vivo*. Essential oil treatment of alloxan-induced diabetic rats significantly lowers blood glucose levels by up to 75% (at 300 mg/kg body weigh). Essential oil also reduced *in vivo* hyperglycaemia by 120 mg/dL within four hours of treatment.	Ogunmodede et al., 2012; Yusuf et al.., 2012.
Aloe arborescens	Leaves	Juice	Juice reduced serum glucose levels *in vivo*. A dose of 1000 mg/kg body weight decreased glucose levels by 8% after 6 h. Continuous administration of the same dose produced greater efficacy, with a 42% reduction in blood glucose levels after 18 days.	Chacko et al., 2008.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
	Leaf	Aqueous extract	Extract fraction significantly suppressed blood glucose levels in low-dose streptozotocin-induced diabetes in mice.	Amoo et al., 2014.
Aloe ferox	Leaf	Ethanolic extract	Treatment of streptozotocin-induced diabetic rats with ethanol extract (300 mg/kg body weight) significantly increased insulin levels. However, no change in the hypoglycaemic state was observed.	Loots et al., 2011; Amoo et al., 2014.
Aloe greatheadii var. davyana	Leaf gel	Ethanolic extract	Administration of an ethanolic leaf gel extract to streptozotocin-induced diabetic rats at 300 mg/kg body weight significantly decreased blood glucose concentrations and increased insulin levels.	Loots et al., 2011; Amoo et al., 2014.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Anacardium occidentale	Bark, leaves, stem	Various solvent extracts	An ethanolic bark extract (200 mg/kg) significantly reduced blood glucose concentrations in diabetic rats. Aqueous, ethanol and hexane extracts leaf extracts also reduce blood glucose levels *in viv*o.	Olatunji et al., 2005; Sokeng et al., 2007; Abdullah and Olatunji, 2010; Fagbohun and Odufunwa, 2010; Saidu et al., 2012; Ukwenya et al., 2012.
Artemisia afra	Leaves and isolated saponins	Aqueous extracts	Aqueous extract significantly reduces blood glucose concentrations in streptozotocin-induced diabetic rats. *A. afra* saponins also have hypoglycaemic effects in diabetic rabbits.	Afolayan and Sunmonu, 2011; Afolayan and Sunmonu, 2013.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Aspalathus linearis (Burm.f.) R.Dahlgren	Leaves	Green unfermented extract	The *in vivo* effect was examined using obese diabetic KK-Ay mice. *In vitro* studies on glucose uptake in L6 myotubes and on pancreatic β-cell protective ability from reactive oxygen species (ROS) in RIN-5F cells. Results strongly suggest antidiabetic potential through multiple modes of action.	Kamakura et al., 2015.
Brachylaena discolor	Leaves, root and stem	Solvent and aqueous extracts	Extracts were tested in streptozotocin-induced diabetic rats at two doses of 200 mg/mL and 600 mg/mL over 28 days. Both extracts induced significant decreases in the blood glucose levels. The higher dose of 600 mg/kg produced a higher anti-DM activity than metformin (reference drug). The effect of plant	Van de Venter et al., 2008; Mellem et al., 2013.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
			extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12muscle cells using a scoring system demonstrated excellent activity for root organic extract and very good activity for the other extracts and other plant parts.	
Brachylaena elliptica	Leaves	Aqueous extract	Crude extract decreasing blood glucose levels in L6 myoblast cells. This suggested that *B. elliptica* works in a similar manner to metformin. An increase in the glucose uptake was seen in HepG2 cells in a dose-dependent manner. The plant extract was dosed at 25 and 100 µg/mL.	Sagbo et al., 2018.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Bulbine frutescens (L.) Wild	Whole plant	Aqueous and ethanol extracts	The % glucose uptake for aqueous extracts was 130.1 µg/mL ± 2.43, and for ethanol extracts 128.3 µg/mL ± 6.65. The starting concentration was 0.5 µg/mL. The insulin control at starting concentration of 1 µM demonstrated activities 119.7 µg/mL ± 1.46 and 117.9 µg/mL ± 2.53 respectively.	Van Huyssteen et al., 2011.
Cannabis sativa	leaf	Organic and aqueous extracts	Summary of the effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system demonstrates moderate to poor activity for all extracts tested.	Van de Venter et al., 2008.
Carpobrotus edulis	leaf		*In vitro* studies by measuring the alpha-glucosidase inhibitory activity. Potential	Mulaudzi et al., 2019.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Carpobrotus dimidiatus (Haw.) L. Bolus		Water, 70% acetone, and 50% methanol extracts	demonstrated but *in vivo* studies recommended.	
Catha edulis (Vahl) Endl.	Leaves, roots and stems	Organic and aqueous extracts	Summary of the effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system demonstrates best activity for organic leaf extract.	Van de Venter et al., 2008.
Catharanthus roseus	Leaf	Methanol and dichloromethane extracts	Extracts reduce blood glucose levels in streptozotocin-induced diabetic mice by 42%. Similarly, administration of a dichloromethane-methanol extract (1g/kg body weight) to streptozotocin-induced rats for 21 days decreased blood glucose levels by of	Ojewole and Van de Venter et al., 2008; Adewumni, 2000; Singh et al., 2001.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
			20%. The same study also reported that treatment with 500 mg/kg of the same extract reduced blood glucose levels by 49% and 58% at 7 and 15 days respectively. In another study where the effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system, the leaf organic extract scored highly in terms of efficacy	
Chironia baccifera	Whole plant	Organic and aqueous extracts	The effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system demonstrated very good	Van de Venter et al., 2008.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
			activity for aqueous extract and good activity for organic extract.	
Cinnamomum cassia Siebold	Bark	Methanol extracts	Methanolic bark extracts have been reported to significantly lower blood glucose levels in clinical trials. A methanolic bark extract significantly inhibited α-amylase activity but did not inhibit α-glucosidase activity.	Khan et al., 2003; Mang et al., 2006; Dugoua et al., 2007; Pham et al., 2007; Boaduo et al., 2013.
Cissampelos capensis	Leaf	Organic and aqueous extracts	The effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system demonstrated poor activity for organic extract and a moderate score for the aqueous extract.	Van de Venter et al., 2008.

Plant species*	**Plant part used medicinally**	**Type of extract tested**	**Outcome of the study**	**Reference**
Commelina africana	Leaves	Aqueous extracts	Aqueous extracts (500 mg/kg of body weight) reduced fasting blood glucose levels from 409 mg/dL to 90 mg/dL in alloxan-induced diabetic rats over a 7-day period, compared with a 69 % reduction for glinbeclamide. The extract decreased glucose cellular absorption and stimulated glycolysis in peripheral tissues, as well as reducing hepatic gluconeogenesis and reducing plasma glucagon levels.	Agunbiande et al., 2012; Balogun et al., 2016.
Dicoma anomala	Roots	Water, ethanol, hydro-ethanol and methanol extracts	*In vitro* inhibition ofα-amylase, and α-glucosidase as well as *in vivo* model against streptozotocin (STZ)-induced diabetic Wistar rats. The water extract revealed the most effective inhibition with An IC_{50} of 51.90. It	Balogun and Ashafa, 2017.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
			was observed that STZ administration significantly increased total cholesterol, triglycerides and low-density lipoprotein cholesterol levels with a reduction in high density lipoprotein cholesterol when compared with the control.	
Elephantorrhiza elephantina	Leaf	Aqueous extract	The percentage C2C12 glucose utilisation activity was (69.55±0.36%) at the concentration of 500 mg/mL and was higher than insulin (65.50 ±0.30%) at the concentration of 1mM.	Olaokun et al., 2020.
	Leaf	Aqueous extract		Arjun et al., 2009.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Eucalyptus citridora Hook			The administration of aqueous leaf extract (250 mg/kg and 500 mg/kg body weight) induced significant reductions in blood glucose levels in diabetic rats.	
Euclea undulata var.myrtina	Root bark	Acetone extract	Root bark at a concentration of 100 mg/kg body weight lowered fasting blood glucose levels as well as elevated cholesterol and triglyceride levels to near normal without any weight gain demonstrating antidiabetic activity in type 2 induced diabetic rats.	Deutschländer et al., 2012.
Gymnema sylvestre	Leaf	Ethanolic extract	Ethanolic leaf extract stimulated insulin release from pancreatic β-cells. The extract also decreased blood glucose concentrations in a diabetic rat model. In a clinical study	Baskaran et al., 1990; Khan et al., 2011.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
			conducted on type 2 diabetic patients, administration of extracts substantially improved blood glucose levels at 400-600 mg/day.	
Hypoxis hemerocallidea	Roots, corm	Aqueous, acetone and ethyl acetate extracts	Aqueous extracts (50-800 mg/kg body weight) decrease blood glucose levels in streptozotocin-induced diabetic rats via stimulation of insulin secretion. The bioactive compounds in the extract have been identified as *Hypoxis* and its aglycone derivative, rooperol. Root acetone and ethyl acetate extracts also strongly inhibit α-amylase enzymatic activity.	Ojewole et al., 2005; Street and Prinsloo, 2012; Ncube et al., 2013; Boaduo et al., 2014; Balogun et al.., 2016.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Leonotis leonurus	Leaves	Aqueous extract	Treatment of streptozotocin-induced diabetic rats with aqueous leaf extracts for 15 days significantly reduced blood glucose to levels comparable to those seen for glibenclamide.	Oyedemi et al., 2010.
Lessertia* (previously known as *Sutherlandia*) *frutescens	Leaves	Aqueous infusion	Administration of infusions (0.01 mL/g body weight) in an induced diabetic rat model did not affect insulin levels, but increased blood glucose clearance. It has been suggested that *L. frutescens* infusions can return the pre-diabetic state to normal state and is able to reverse insulin resistance.	Chadwick et al., 2007.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Momordica balsamina	Stems and flowers	Organic and aqueous extracts	The effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system indicated best activity for the organic extract of the stem.	Van de Venter et al., 2008.
Momordica foetida	Fruit	Aqueous extract	Administration of extracts decreased blood glucose levels in normal rats but had no effects in an alloxan-treated diabetic rat model. This was attributed to the lack of synergistic compounds found in the fruits. The effects of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system indicated moderate to poor effects.	Van de Venter et al., 2008; Afolayan and Sunmonu, 2010.

Plant species*	**Plant part used medicinally**	**Type of extract tested**	**Outcome of the study**	**Reference**
Moringa oleifera	Leaf	Methanol extract	*In vivo* study where treatment with methanolic leaf extracts significantly improved weight loss, polydipsia, glucose tolerance and liver function tests in diabetic animals.	Muzumbukilwa et al., 2019.
Olea europaea* subsp. *africana	Leaves	Aqueous extract	Aqueous olive leaf extracts (0.5 g/kg body weight) significantly reduce serum glucose concentrations towards normal values in a streptozotocin-induced diabetic rat model. Indeed, the antidiabetic effect of *O. europa* extract was greater than that of glibenclamide. Blood glucose levels were restored to the basal level in 13 days. The decrease in blood glucose levels was comparable to that of metformin.	Eidi et al., 2008; El and Karakaya 2009; El Amin et al. 2013; Hashmi et al. 2015.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
		Purified oleuropein	Administration of 120 mg/kg body weight of oleuropein for a 16- week period significantly decreased blood glucose levels in an induced diabetes rabbit model. Oleuropein accelerates glucose uptake by the cell.	
Opuntia ficus-indica	Seed	Oil	The administration of extract at a concentration of 2 ml/kg attenuated alloxan-induced death and hyperglycemia ($P<0.001$) in treated mice. It was postulated that the role of synergism of anti-oxidant compounds in quenching free radicals may have resulted in the reduction of Allx-induced diabetes in mice.	Berraaouan et al., 2015.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Ornithogalum longibracteatum Jacq.	Bulb	Aqueous and ethanol extracts	The % glucose uptake for aqueous extracts was 129.2 µg/mL ± 4.19 and for ethanol extracts 118.3 µg/mL ± 5.26. The starting concentration was 0.5 µg/mL. The insulin control at starting concentration of 1 µM demonstrated activities 119.7 µg/mL ± 1.46 and 117.9 µg/mL± 2.53 respectively.	Van Huyssteen et al., 2011.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Psidium guajava	Leaf, root	Aqueous and organic extract	Extract significantly decreased the blood glucose levels in alloxan and streptozotocin induced rats. The aqueous leaf extract also inhibited α-glucosidase activity in the small intestine of diabetic mice at 250 mg/kg body weight. In another study the effects of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system demonstrated a very good score for leaf and root organic and aqueous extracts	Van de Venter et al., 2008; Khan et al., 2011; Rawi et al., 2011.
Punica granatum	Peel	methanolic extract	Oral administration of extract (75 and 150 mg of kg body weight) for 45 days resulted in significant reduction in blood glucose levels	Middha et al., 2012.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
			and was found to alleviate brain oxidative stress in alloxan induced diabetic rats by attenuating lipid and protein oxidation.	
Ruta graveolens	Leaf	Aqueous extract	Administration of an aqueous leaf extract in streptozotocin-induced diabetic rats induced the β-cells to return to normal, demonstrating an insulinogenic effect. In another study, the % glucose uptake for aqueous extracts was 124.7 µg/mL ± 3.30 and for ethanol extracts 136.9 µg/mL ± 10.85. The starting concentration was 0.5 µg/mL. The insulin control at starting concentration of 1 µM demonstrated activities 119.7 µg/mL ± 1.46 and 117.9 µg/mL ± 2.53 respectively.	Van Huyssteen et al., 2011; Toserkani et al., 2012.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Schkuhria pinnata	Not specified in the study	Ethanol and acetone extracts	Extracts increased the uptake of glucose into C2C12 myocytes, 3T3-L1 preadipocytes and Chang liver cells *in vitro* at 50 µg/mL. However, both extracts were toxic on 3T3-L1 preadipocytes so should be used with caution.	Deutschlander et al., 2009.
Sclerocarya birrea (A. Rich.) Hochst. subsp. *caffra* (Sond.)	Stem bark and root	Organic and aqueous extracts	The effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system indicated excellent activity for stem and bark (organic extracts) followed by good activity from the aqueous extracts.	Van de Venter et al., 2008.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Strychnos henningsii	Bark	Aqueous extracts	Treatment of differentiated 3T3-L1 cells with aqueous bark extract reduced hyperglycaemia by increasing cellular uptake and utilisation. However, *S. henningsii* extracts must be used cautiously as the extracts are toxicity. Furthermore, they antagonise the action of metformin. Similar extracts also induce a dose-dependent reduction of blood glucose levels from 13 to 6 mmol in streptozotocin-nicotinamide treated rats.	Oyedemi et al., 2012; Oyedemi et al., 2013.
Tarchonanthus camphoratus L.	Leaves and soft twigs	Aqueous and ethanol extracts	The % glucose uptake for aqueous extracts was 128.4 μg/mL ± 3.27 and for ethanol extracts 131.6 μg/mL ± 6.54. The starting concentration was 0.5 μg/mL. The insulin	Van Huyssteen et al., 2011.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
			control at starting concentration of 1 μM demonstrated activities 119.7 μg/mL ± 1.46 and 117.9 μg/mL ± 2.53 respectively.	
Terminalia sericea	Stem bark	Acetone	The crude extract exhibited a α-glucosidase inhibition of 97.4%. The four isolated compounds namely β-sitosterol, β-sitosterol-3-acetate, lupeol, and stigma-4-ene-3-one, presented with α-glucosidase inhibition values between 54.5-164.9%. In addtion two inseparable sets of mixtures of isomers (epicatechin-catechin and gallocatechin-epigallocatechin) were tested yielding α-glucosidase values of 119.3% and 255.8% respectively.	Nkobole et al., 2011

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
Tulbaghia violacea	Whole plant	Aqueous and ethanol extracts	The % glucose uptake for aqueous extracts was 4.65 µg/mL ± 2.99 and for ethanol extracts 19.38 µg/mL ± 5.19. The starting concentration was 0.5 µg/mL. The insulin control at starting concentration of 1 µM demonstrated activities 119.7 µg/mL ± 1.46 and 117.9 µg/mL ± 2.53 respectively.	Van Huyssteen et al., 2011.
Urtica dioica	Roots and leaves	Aqueous extracts and various solvent extracts	Aqueous extracts (300 mg/kg body weight) reduce blood glucose concentrations by 68% in non-diabetic rats within 1 h of administration. The extracts also significantly reduced serum insulin and fasting insulin resistance index across the range 50-200 mg/kg body weight.	Ahangarpour et al., 2012; Dar et al., 2013.

Plant species*	Plant part used medicinally	Type of extract tested	Outcome of the study	Reference
***Vinca major* L.**	Stems, roots and leaves	Aqueous and organic extracts	The effect of plant extracts on glucose utilisation and toxicity in Chang liver, 3T3-L1 adipose and C2C12 muscle cells using a scoring system where the leaf organic extract demonstrated excellent activity followed by good activity for all the other extracts tested with the exception of the organic root extract which demonstrated a lower score.	Van de Venter et al., 2008.

aqueous *S. henningsii* bark extract (Oyedemi et al 2012; Oyedemi et al 2013). The authors of those studies have suggested that the extract stimulates glucose uptake in the peripheral tissues, thereby lowering blood glucose concentrations. However, there are concerns with regards to the safety of *S. henningsii* in the treatment of diabetes due to toxicity, as well as antagonistic effects when used in combination with metformin and the plant should only be used with caution (Oyedemi et al 2012; Oyedemi et al 2013).

6. Discussion

An effective and targeted way to develop new drugs is through a re-examination of traditionally used medicinal plants for potent, non-toxic and cost-effective DM therapies. South Africa has one of the most diverse floras in the world, with more than 30,000 plant species documented. To date, the therapeutic uses have been recorded in the ethnobotanical literature for approximately 3000 of those species (Van Wyk et al., 1997). Fewer have been rigorously examined for therapeutic properties and only a small number have been tested for anti-DM related activities. However, it is encouraging that of the eight species (*A. ferox, A. afra, D. anomala, M. balsamina, O. ficus-indica, P. prunelloides, L. frutescens* subsp. *frutescens*, and *E. punctulatus*) that were the most frequently mentioned in Table 2 (traditional use), only two (*P. prunelloides* subsp. *frutescens* and *E. punctulatus*) have been neglected in follow-up validation studies. As far as the many other species used traditionally, much more research is required in this field to validate the traditional usage and to evaluate the mechanisms by which these plants work. Species selection for therapeutic screening is difficult as the ethnobotanical literature usually describes the usage of a plant species to lessen specific symptoms, rather than to treat a complex disease like DM. For example, many plants are recorded as being useful to decrease urinary output (a symptom of DM). However, increased urinary frequency and volume may also be a symptom of multiple other diseases including some urinary tract infections (UTIs) and prostatic hyperplasia (Upton 2013). Thus, it may not be possible to discern whether a plant was used specifically to treat DM or one of these pathologies. Where there was any doubt, the plant was excluded from our study. However, these other species may have anti-DM related activities and future studies should not neglect them. Another aspect worth noting is that when reviewing the ethnobotanical uses, the doses used were absent in almost all cases making correlation to toxicity difficult. Dosage is vitally important and future ethnobotanical reviews should include this during the survey process.

In this study, 137 plant species used traditionally for the treatment of diabetes were identified by a thorough literature search. Most of these plants are yet to be rigorously examined to validate their traditional use. Mechanistic detail has been determined for far fewer species. When efficacy studies were conducted, they have largely used the rat or rabbit model systems and (with some notable exceptions) the efficacy has not been established in humans. These *in vivo* models are convenient for the screening of new potential anti-DM therapies and they are relatively inexpensive and reproducible. However, they are often not the most relevant model to evaluate potential new DM therapies. To evaluate a potential DM therapy in these experimental animals, DM is induced with a chemical inducer. Alloxan or streptozotocin are most frequently used for this purpose. Both of these compounds are relevant for examining type 1 DM only and are not relevant to study the effects in type 2 DM. Alloxan treatment induces pancreatic β-cell death (as also occurs in type 1 DM), resulting in a substantially lower levels of secreted insulin and a corresponding increase in blood glucose levels (Singh and Pathak, 2015; Karthrikeyan and Islam, 2016). Streptozotocin treatment also substantially reduces insulin secretion, resulting in hyperglycaemia. Both of these treatments therefore induce an insulin sensitive form of DM. It is estimated that the insulin sensitive form of the disease (type 1 DM) currently accounts for only approximately 10% of the cases of DM in Western countries (American Diabetes Association, 2010). Notably, type 1 DM may already be effectively treated with intravenous insulin therapy.

In contrast, the insulin insensitive form of DM (type 2 DM) has relatively few and less effective treatments available. Metformin and SGLT2 inhibitors are the most frequently used chemotherapeutic options for the maintenance of blood glucose levels in individuals with type 2 DM (Mudaliar and Henry, 2001; Klein et al., 2004; Chao and Henry, 2010). However, these drugs are only generally effective in the early stages of the disease and lose efficacy as the disease progresses (American Diabetes Association, 2010). Furthermore, both classes of drugs have considerable toxicity and are associated with unwanted side effects. New therapies targeting type 2 DM pathways are urgently required. Furthermore, the prevalence of type 2 DM is increasing more rapidly globally than all other forms of the disease combined (WHO, 2019). Some studies have induced insulin sensitivity in laboratory animals by mid to long-term dietary modification. Whilst, this is a substantially better model for testing the efficacy of potential new therapies against type 2 DM, it generally more closely corresponds with the pre-diabetic state than with full type 2 DM and more relevant test models are required.

Several studies have also directly tested extracts and pure compounds against cultured cells *in vitro*. These methods have the advantage of being higher throughput and substantially less expensive than *in vivo* studies. The usage of standardised cell lines also results in greater reproducibility when similar studies are performed by different groups and it therefore allows for better comparisons between studies. Furthermore, cell culture studies are more relevant to type 2 DM. By testing a potential therapy against non-pancreatic cells, the effects of the drug on pancreatic insulin secretion are effectively negated. Glucose uptake into the cell must be via other pathways. Additionally, cell line studies are more suitable for mechanistic evaluations of the test therapy. However, whilst cell line studies have considerable advantages compared with *in vivo* assays, they are best considered as an intermediate step in the discovery of new type 2 DM therapeutics. The pharmacodynamic and pharmacokinetic properties of the therapy must also be considered. Thus, when a drug candidate is highlighted by these assays, substantial further research is needed to test the rate of absorption through the gut lumen, the clearance rate, interaction with other systems etc.

To be useful in the treatment of DM, an extract (or purified compound) must have a relatively low toxicity. This is particularly true for DM as the treatment regimens comprises of ongoing therapy. Notably, few of the studies screening the South African traditional medicine to treat DM also evaluated the toxicity of the extracts. In many cases, the highlighted plant species have multiple therapeutic uses and their toxicity has been evaluated in other studies. However, it is imperative that toxicity be evaluated parallel with anti-DM studies to provide an indication of the therapeutic index. Even if a plant extract is a potent antihyperglycemic agent, its therapeutic potential may be limited if it is also toxic to the host. Variability in the preparation and composition of extracts between studies also makes it difficult to link toxicology and activity results across multiple studies. Furthermore, several different efficacy and toxicity methodologies may be used in different studies, making comparisons difficult.

Additionally, selecting the most appropriate extraction technique is also important in evaluating a potential new therapy. Decoctions and infusions are generally the most common preparation methods in traditional medicine. Aqueous extracts are limited to extracting relatively high polarity compounds and often lack mid-low polarity compounds. This is desirable under Lipinski's rules of 5 (Lipinski, 2004) as mid-highly polar compounds have greater bioavailability. However, limiting investigations to aqueous extracts may overlook promising lower polarity compounds.

7. Conclusion

In conclusion, the ethnobotanical records of the use of South African plants to treat DM are relatively well documented, yet the follow-up validation studies have been neglected. Approximately only 31% of the plant species mentioned as a traditional means to treat or control blood sugar (Table 2) have been scientifically validated (Table 3) and further mechanisms of action of many of the identified plant species remain poorly examined. Furthermore, examining plant compounds, could yield important leads for therapy. A recent innovative approach to exploring anti-DM compounds from African medicinal plants using a DIA-DB Inverse Virtual Screening Web Server yielded 28 compounds with favorable anti-DM properties and this could be further extrapolated in the South African context of medicinal plant use for diabetes (Pereira et al., 2019). It is important to note that diabetes is a lifestyle disease and treatment is usually lifelong. Finding a natural alternative is extremely favourable and the quest to find a non-toxic effective supplement may provide great value, given the increasing epidemiology statistics especially in South Africa.

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