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Medicinal plants: A promising source of anti-diabetic agents in sub-Saharan Africa

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ABSTRACT

The rising burden of Diabetes mellitus (DM) globally and particularly in sub-Saharan Africa calls for alternative treatment solutions. This is because the currently available drugs for its management are limited due to undesirable adverse effects and high cost. Thus, this review explores diabetes and summarizes its treatment options, focusing mainly on medicinal plants therapy. Information on twenty-five selected medicinal plants from sub-Saharan Africa having hypoglycemic and anti-diabetic potentials was obtained via electronic search of major databases, such as Pubmed/Medline, Scopus, Google Scholar and web of science. Predominant bioactive compounds found in these plants include tannins, carpaine, terpenoids, hexadecenoic acid, luteolin, saponins, glycosides, rutin, quercetin, vindoline and kaempferol. Robust evidence indicates that these medicinal plants and their bioactive components exert their antidiabetic potentials via different mechanisms, including: regeneration of pancreatic β -cell and insulin secretion; inhibition of α -amylase, inhibition of intestinal glucose absorption and liver glucose production; antioxidative stress; limitation of glycogen degradation and gluconeogenesis; anti-inflammatory, immunoregulatory. DM imposes a tremendous burden in the region, and its prevalence is not abating; thus the rich flora of the region with known hypoglycemic and antidiabetic efficacy could be explored as a complementary therapy in its management.

INTRODUCTION

Diabetes is among the too many non-communicable diseases (NCDs) in sub-Saharan Africa that pose a serious health challenge. The upsurge in these NCDs is multifactorial, ranging from unhealthy lifestyles to aging population [1]. There is a rising increase in the incidence of chronic disorders such as diabetes mellitus (DM) in sub-Saharan Africa, with dire consequences both in terms of human and economic capital [2,3]. DM is an ailment characterized by high blood sugar level (fasting blood glucose greater than 7.0 mmol/L) or plasma blood glucose higher than 11.1 mmol/L two hours after a meal due to deficit or diminution in the efficacy of circulating insulin with dire consequences [4]. Globally,

in 2017, it was estimated that 425 million people suffers from DM, including 16 million in Africa [5].

The continuous and rapid increase in the prevalence and impact of DM globally, with a special interest in Sub-Saharan Africa, calls for urgent attention. The devastating impact of diabetes in sub-Saharan Africa is one with both health care and an economic dimension. The steady rise in complications and mortality figures attributed to DM in the sub-Saharan region has ranked it one of the leading causes of mortality associated with non-communicable diseases [6-8]. In sub-Saharan Africa, the inability to combat this incessant health concern has been tailored towards poor funding, fund diversion by regional politicians, inability to access proper diagnosis and effective treatment, poor regional study guidelines, implementation and documentation challenges, urbanization and inequality among private

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and public health sector with respect to the quality of health-care services rendered. These factors have greatly been attributed to the increased morbidity and mortality rates of the disease in the region as against other regions globally [7].

Literature had reported that type 1 DM (T1DM) accounts for 5-10% of all diabetic cases while type 2 DM (T2DM) accounts for 90-95% pan-nationally [9,10]. T2DM is more prevalent than T1DM in Africa [10]. In a study conducted in South Africa, the rise in prevalence of T2DM was attributed to the standard of living and lifestyles that intimately imitate that of Western Countries [11]. The acceleration of T2DM has been associated with obesity and unhealthy dietary habits [12,13].

As a result of the serious complications associated with DM, such as cardiovascular linked ailment and chronic kidney disease, it is becoming one of the major causes of death throughout the world. DM is regarded as a threat to public health owing to the inaccessibility of adequate drugs for its management, particularly in developing countries such as in Africa. The high morbidity and mortality associated with this disease stem from a lack of proper management and treatment. Due to the poor socio-economic status of Africa, it is quite difficult to monitor and manage DM properly. Worldwide, conventional drugs for the management of DM have been linked with adverse side effects and are mostly expensive, making them unaffordable in some developing countries, especially in Africa. Thus, this necessitates the need to investigate cheap and readily available medicinal plants [14].

Humans consume different plant species both for nutritional and/or medicinal purposes. It has been reported that 80% of the global population employs traditional medicine and medicinal plants for health care in different manifestations [15]. Africa is blessed with diverse forms of these plants, some of which are employed in the management of DM. The use of medicinal plants in treating diseases has become part and parcel of the health care system in many African countries. Robust evidence showed that many indigenous populations have patronized traditional health practitioners or taken self-medication using herbs before orthodox health medication [2]. Globally, positive results have been obtained by several researchers on the hypoglycemic potentials of several medicinal plants, thus accentuating the argument that these plants could be employed in the discovery of new compounds to treat a good number of ailments, including DM [2]. Due to the high cost and negative side effects of conventional drugs, these medicinal plants could be harnessed and optimized for the management of DM [3].

Thus, there is a need for proper documentation of these diverse medicinal plants with therapeutic efficacy in the management of DM in sub-Saharan Africa, and doing so will provide valuable information in the scientific investigation of the potency/efficacy of these plants in the direction of DM. However, any and every form of positive change geared towards effective diabetes care for most sub-Saharan Africa populace must begin with a robust evaluation of policy framework devoid of corruption, as well as with the application of proper healthcare protocols, adequate availability of diagnostic tools and consistent treatment plans.

Hence, this article documented some plants recommended or used for the management of DM in sub-Saharan Africa in vitro and or in vivo, the parts used, extract type, bioactive components and the mechanism of actions of the phytochemicals responsible for their antidiabetic potentials; likewise, it provides recommendation for future research.

MATERIALS AND METHODS

Information on medicinal plants from sub-Saharan Africa having hypoglycemic and anti-diabetic potentials was obtained from August 2021 to February 2022 in published article from 2008 to 2021 via electronic search of major databases, such as Pubmed/Medline, Scopus, Google Scholar and web of science using search terms: diabetes mellitus, medicinal plants, sub-Saharan Africa, traditional medicine and other related words. The validation of the scientific names and authorities of the plant were carried out using “www. theplantlist.org” database.

Ethical information

This review work does not require ethical information or approval as animals, human subjects and informed consent were not involved in the study.

Prevalence and Pathophysiology of diabetes mellitus in sub-Saharan Africa

Recently, the diabetes prevalence in sub-Saharan Africa as against other regions globally is alarming. This rise in regional diabetes incidence if not checkmated has been predicted to attain the highest percentage increase in diabetes incidence than any region worldwide [6]. The International Diabetes Federation (IDF) estimated that incidences of diabetes among people of sub-Saharan Africa as at 2015 was 14.2 million, with a likely estimated increase in the figure to 34.2 million, 25 years after (2040). According to IDF reports [6], the diabetes prevalence ranges from a low 0.6% to a high 18.2% in Benin and Réunion off the coast of Madagascar, respectively. This indicates a high variance in prevalence not only between countries, but also among urban versus rural areas, with the highest-burden on the urban areas. The huge gap in diabetes prevalence is partly attributed to body mass index (BMI) and followed lifestyle in different regions and differences in study methods and locations where these prevalence estimates are generated [16]. An accurate estimation of diabetes prevalence in the sub-Saharan Africa region has greatly been impaired by wide urban-rural variations, resulting in limited comprehensive surveys. In this region, current and extensive knowledge of diabetes should primarily be based on epidemiological data collation in periodic and convenience-based community testing initiatives and diabetes complication data of patients obtained from hospitals [16]. That this is crucial is evidenced in earlier studies that have reported that T2DM remains predominant as against other forms of the disease, with an estimated 85%-90% of cases in sub-Saharan Africa [17].

Similarly, type 1 diabetes and other variants of diabetes (ketosis-prone and malnutrition-related diabetes) account for 5%-15% of cases in sub-Saharan Africa [16,18]. Ignorance, urbanization and lack of access to quality healthcare

contribute to the increasing cases of diabetes [6,18]. Peculiar cultural practices and microvascular complications occasioned by infectious diseases, such as tuberculosis and HIV, are also important considerations in diabetes of African descent [19-23].

The pathophysiology of the two major types (1 and 2) of diabetes in sub-Saharan Africa, especially type 2 and its subtypes, differs significantly from that obtained globally (Figure 1). In type 1 diabetes, hypoglycaemia, hyperosmolar non-ketotic coma and diabetic ketoacidosis (DKA) are common diagnostic products of clinical evaluation presented by sub-Saharan Africa patients in their 20 to 40 years of age [24]. Non clinical presentation such as autoimmune responses (autoinsulin antibodies, islet cell antibodies, and glutamic acid decarboxylase enzyme antibodies) observed in type 1 diabetes of patients in HICs of sub-Saharan Africa is quite low compared to what is obtained and documented from their Western counterparts. Similarly, HLA DR3/4 which are known genetic markers that confer type 1 diabetes susceptibility in Western (Caucasian) patients, does not influence the prevalence of diabetes type 1 in sub-Saharan Africa patients [24].

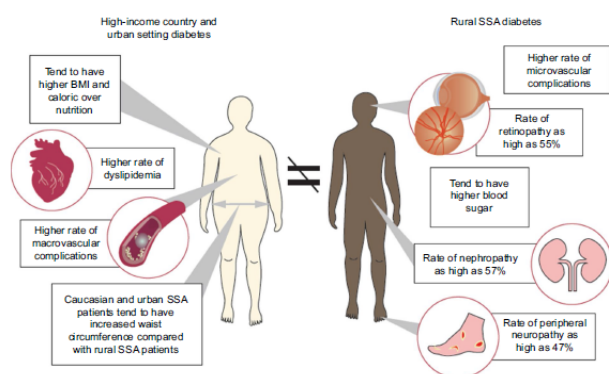


Figure 1. Pathological presentation of differences in diabetes incidence of high-income countries (HICs) and urban centres compared with low and middle-income countries (LMICs) and rural areas of sub-Saharan Africa (SSA) [7]

Unlike previous studies, in a recent genetic variations study of diabetes, high risk of type 2 diabetes was identified among the sub-Saharan Africa population, compared to other global regions [25]. In this study, 12 risk alleles were identified and validated to boost the risk of T2D in 5 or more separate subpopulations. The pattern of these risk alleles are congruous and are in decreasing frequencies in the human genomes from Sub-Saharan Africa and via Europe to East Asia regions. In comparison with European frequency-matched control genomic and risk alleles for other ailments, the differential frequencies were statistically significant. The T2D risk alleles differential frequencies bring about remarkable differentiation of genetic risks of T2D with higher risk in the African in comparison to the Asian populations [25]. The rapid and steady drift by sub-Saharan Africa population towards urbanization and its lifestyle highlights the rationale for the migration-related genetic polymorphism of type 2 diabetes in patients compared to regional global figures (Figure 2).

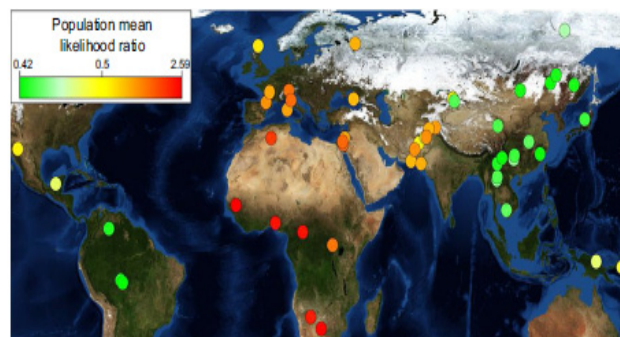


Figure 2. Genetic polymorphism and the likelihood of type 2 diabetes development [26].

The rationale for the steady drop in beta-cell function and rapid incidence of diabetes in sub-Saharan Africa patients remains inconclusive. Factors such as variations in genetic composition, genetic predisposition to less functional beta-cells, differences in the distribution of fat and fat islets, environmental factors (toxins and infection), intrauterine growth retardation consequences, and economic vices (malnutrition) observed among sub-Saharan Africa patients are hypothesis attributed to the increased diabetes condition in the region [27].

Irrespective of links between obesity and diabetes, a great percentage of patients in sub-Saharan Africa do not fall within the established depiction of type 2 diabetes seen in Western settings such as sedentary lifestyle, abnormal anthropometric and biochemical parameters, metabolic syndrome and reduced beta-cell function [16,18]. The unique form of type 2 diabetes manifested by most rural sub-Saharan Africa patients is malnutrition-related diabetes with BMI ≤ 25 , resulting in pancreatic calcification due to prolonged malnutrition. Unlike their counterparts in Western settings, patients with such conditions present clinical symptoms of non-ketone-related severe hyperglycemia.

For sub-Saharan Africa to tackle diabetes and its unique features, substantial and adequate research towards appreciating the dynamics and discrete nature of the disease progression and the characteristics of the various associated genotype and phenotype must be developed. This review therefore focuses on medicinal plants as promising sources of anti-diabetic agents vis-a-viz their mechanisms of action.

Management of diabetes

The approach deployed in the management of diabetes depends on several factors, including their etiology. T1DM is caused by the autoimmune destruction of beta cells in the pancreas, leading to absolute absence of insulin secretion, while type 2 diabetes is caused by insulin resistance and beta cell dysfunction which diminishes insulin secretion. The major goal in treating type 1 diabetes (T1D) and type 2 diabetes (T2D) is to control blood sugar levels within the normal range with minimal variations. T2D is the commonest type of diabetes, with about 90% prevalence [28]. Early diagnosis and commencement of effective treatment are essential in proper management and prevention of the complications of diabetes. The blood glucose should be $<7\%$ (53 mmol/mol) or HbA1c of 8% (64 mmol/mol) [29].

Lifestyle modifications

Lifestyle changes are important in the management of diabetes. These changes must be holistic, ranging from diet to physical activities. For these lifestyle changes to be effectively implemented, education from diabetes educators is central [29]. The educators should emphasize the need to abide by the treatment regimen to gain the desired outcome. Proper dieting and physical activity aid in the utilization of glucose.

Use of oral hypoglycaemic agent

There are several oral hypoglycaemic agents. The ones recommended depend on several factors, including the patient phenotype. However, metformin is the generally recommended first line treatment (from 500 mg to 2000 mg daily). For simplicity, the oral agents are classified as shown in Table 1. These agents can be used as monotherapy or in combination, depending on the patient's plasma glucose baseline before commencement of treatment.

Table 1. Oral hypoglycaemic agents

Class	Mechanism of action	Common side effects	Contraindications	Drugs	References
Biguanide	Acts by decreasing hepatic gluconeogenesis; increased peripheral utilization of glucose in skeletal muscle and fat; inhibition of alimentary glucose absorption	Lactic acidosis, weight loss, gastrointestinal disturbances	Chronic kidney disease, liver failure	Metformin	[30]
Sulfonylureas	Increases the release of insulin through the stimulation of pancreatic beta cells	High risk of hypoglycemia and weight gain	Severe cardiovascular comorbidity and obesity	Glimepiride, Gliclazide, Glyburide, Chlorpropamide, Tolbutamide	[31]
GLP-1 agonists	Stimulation of glucose-dependent insulin release from the pancreatic islets	Nausea increased and risk of pancreatitis	Gastrointestinal disorders	Exenatide, Liraglutide, Semaglutide	[32]
Amylin analogs	Reduces glucagon release, reduces gastric emptying and increases satiety	Risk of hypoglycemia and nausea	Gastroparesis	Pramlintide	[33,34]
Meglitinides	Inhibits adenosine triphosphate-dependent K ⁺ channels in pancreatic β -cells to increase insulin secretion	Risk of hypoglycemia and weight gain	Severe renal or liver failure	Nateglinide Repaglinide	[35]
DPP-4 inhibitors	Increases incretin levels (GLP-1 and GIP), Inhibits GLP-1 degradation → promotes glucose-dependent insulin secretion	gastrointestinal disturbance pancreatitis and arthralgia	Liver failure, moderate to severe renal failure	Vildagliptin, Alogliptin, Linagliptin, Saxagliptin, Sitagliptin and Omarigliptin	[36]
SGLT-2 inhibitors	Reduces renal tubular glucose reabsorption which increases glucosuria	Genital yeast infections and urinary tract infections, polyuria and dehydration, diabetic ketoacidosis	Chronic kidney disease, recurrent urinary tract infections	Dapagliflozin, Canagliflozin, Empagliflozin and Ertugliflozin	[37]
Alpha-glucosidase inhibitors	Inhibits the absorption of carbohydrates from the small intestine	Gastrointestinal disturbances	Any preexisting intestinal conditions	Acarbose, Miglitol and Voglibose	[38]
Thiazolidinediones	Reduces insulin resistance through the stimulation of PPARs (peroxisome proliferator-activated receptors) and increases transcription of genes involved in glucose metabolism	Weight gain, edema and cardiac failure	Congestive heart failure and liver failure	Pioglitazone and Rosiglitazone (banned)	[39]

Insulin

This involves the use of exogenous insulin to complement the non-existent or little endogenous. This is the primary approach for type 1 diabetes (insulin-dependent diabetes). However, insulin use is also a viable option for management for type 2 diabetes that has deteriorated badly with massive loss of beta cells of the pancreas. The use of insulin is also recommended in T2D patients who are unstable, that is patients whose plasma glucose are severe and cannot swallow tablets [29]. Insulin can also be used in combination with other oral hypoglycaemic agents like metformin.

Cell/tissue transplantation

This is a procedure that involves the replacement of impaired or non-functional cells/tissues/organs. This approach is applied in the treatment of T1D, where there is a lack of insulin due to the destruction of the islet cells. A whole pancreas can be transplanted, or the islet cells producing the insulin are implanted in the patient [40]. The

transplantation of the whole pancreas is faced with organ rejection. The patients are given immunosuppressive agents to minimize organ transplant. In the case of islet cell transplantation, only the cells producing insulin are implanted. This gives the opportunity of transplanting only healthy cells [40].

Medicinal plants in the management diabetes mellitus

The use of medicinal plants in the treatment of DM dates back to medieval times. This form of therapy poses minimal side effects in comparison with Western drug counterparts, as orthodox drugs are laden with severe negative side effects [41,42]. The effectiveness/efficacy of these plants is attributed to the phytochemical composition, which acts individually or in synergy to bring about desired antidiabetic potentials [43]. The comprehension of the exact mechanisms of actions of these phytochemicals is crucial in developing remedies for DM. The molecular mechanisms of action are the hallmarks in the management of DM using phytochemicals. These phytochemical components of plants may facilitate the reversal or delay of the commencement and progression of T2DM through diverse molecular pathways. Accumulating evidence indicate that these medicinal plants and their bioactive components exert their hypoglycemic and antidiabetic

potentials via different mechanisms. These include: regeneration of pancreatic β -cell and insulin secretion, inhibition

of α -amylase, inhibition of intestinal glucose absorption and liver glucose production. Their other mechanisms of action are: antioxidative stress, limitation of glycogen degradation and gluconeogenesis, anti-inflammatory, immunoregulatory, anti-apoptosis, as well as modulation of intracellular signaling transduction pathways [44,45]. Unlike the Western drugs, the medicinal plants deploy several of the mechanisms listed above which are complementary or work in synergy in reducing plasma glucose level.

The causes of T2DM are multifactorial and thus, its management regimen involves multiple pathways. This principle is applicable in herbal medicine in which a cocktail of different herbal ingredients from diverse plant sources is taken as a remedy for DM [46]. DM can be managed using different methods such as diet modification, lifestyle alteration, use of glucose lowering drugs, injection of exogenous insulin, and herbal therapies. Literature review has shown that medicinal plants are used in the management of DM in different parts of the world. In these evidences, a substantial percentage of the global population was reported to be dependent on traditional medicine to manage diabetes. This was also in accord with the report of WHO factsheet (No,134) that estimated that about 80% of the population in African and Asian countries depend on herbal medicine for their primary healthcare [47]. Traditional medicine was also accepted in terms of accessibility, affordability and culturally accepted kind of health care regimen trusted by many people. This also stands out in managing the persistent increase in chronic non-communicable diseases in the midst of soaring health-care costs and nearly universal austerity [48]. Thus, in this review, twenty-six selected different medicinal plants used in DM management in sub-Saharan Africa were chosen. The most apparent phytochemicals responsible for their actions are presented in Table 2 and 3, respectively.

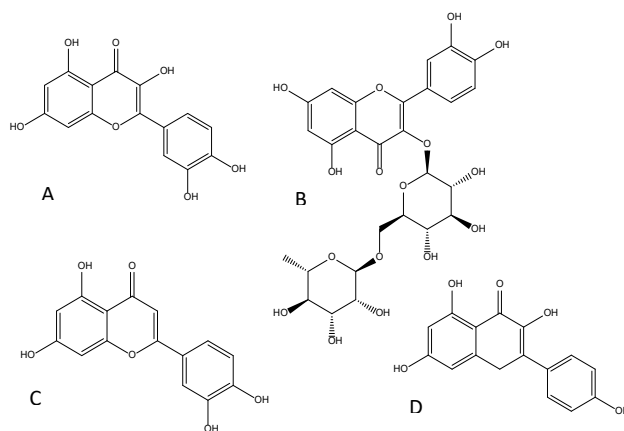
DISCUSSION AND CONCLUSION

DM is a metabolic and an endocrine disorder that affects both humans and animals with serious complications when left unchecked. Currently, there is no successful treatment/cure for DM, but it can be managed with insulin, modification of diet and administration of oral antidiabetic agents. Medicinal plants could serve as an alternative therapy in managing DM due to severe adverse effects, high cost, inaccessibility and unaffordability associated with conventional antidiabetic drugs [43].

Intensive research has been geared towards DM and its management using efficacious bioactive compounds isolated from natural origin. Several studies have been carried out in this regard using medicinal plants. Interestingly, results have shown that many of these plants possess antidiabetic effects and have demonstrated specific bioactive antidiabetic principles via various mechanisms of action [43]. The activities of these plants may be due to either a single compound or mixture of phytochemicals. These phytochemicals associated with antidiabetic action include but are not limited to alkaloids, phenolics, flavonoids, glycosides, saponins, polysaccharides, stilbenes, tannins, terpenes, and glycosides [43,108]. Mechanistically, some of the actions of these plants are mediated via upregulation of insulin secretion,

diminution in liver glucose output and modulation of certain enzymes associated with metabolism of carbohydrate like α -glucosidase inhibitors. Others are: regulation of PPAR γ , antioxidant potential, modulation of the effect of some glycolytic enzymes such as phosphoenolpyruvate carboxykinase, attenuation of glycosylated haemoglobin and enhancement of the expression of glucose transporters, etc.

In this review, flavonoid compounds were observed to be the most common bioactive phytochemical. Flavonoid antidiabetic potentials are partly ascribed to their antioxidant properties and partly due to their capacity in the modulation of cell signaling. Flavonoids are seen in diets such as fruits, vegetables, beverages, chocolates, herbs and plants [109]. The most popular flavonoids observed in this review which have been reported to have antidiabetic potentials and their structures are shown in Figure 3.



A=Quercetin; B=Rutin; C=Luteolin; D=Kaempferol

Figure 3. Structures of flavonoids

Kaempferol is a flavonol seen in Ginkgo biloba, tea, grapefruits, edible berry and vegetables [110-112]. Mechanistically, it exerts its action by inhibiting apoptosis, diminution in the activity of caspase-3 in beta cells, cAMP signalling improvement and facilitation of production of insulin and secretion [113]. In addition, it is also linked with improvement of antioxidant production and diminution of IL-1 β , TNF α , lipid peroxidation, nitrite and glycosylated haemoglobin [106,107].

Rutin is found in oranges, grapes, buckwheat, lemons, limes, berries and peaches [114,115]. Rutin exerts its action via improvement of insulin secretion, restoration of glycogen content, reduction of oxidative stress and inhibition of advanced glycation end products (AGEs) production. Other mechanism include: reduction of glycosylated haemoglobin and pro-inflammatory cytokines including IL-6 and TNF α and restoration of liver antioxidant status [102,103].

Luteolin activates insulin action and facilitates transcriptional activation of PPAR γ [99]. Moreover, it reduces inflammatory molecules, monocyte Chemotactic Protein-1 (MCP-1), resistin and upregulates adiponectin levels in obese mice [100]. It has equally been reported that luteolin brings about improvement in the secretion of insulin. Luteolin is seen in carrots, peppers, cabbage, apple, vegetables and fruits [116-118].

Quercetin is a flavonol found in onions, berries, apples, pepper and coriander [119]. Mechanistically, it exerts its

Table 2. Medicinal plants with anti-diabetic potentials from sub-Sahara Africa

S/N	Scientific name of plant	Family	Common/local names of plant	Local use	Plant part used in the study	Type of study/Model	Solvent used	Activity	Active compound(s)	Effective dose	References
1.	<i>Allium sativum</i> L.	Amaryllidaceae	Garlic; Ikonofile in IsiZulu, Eastern Cape in South Africa	Used in treatment of diabetes	Whole plant	<i>In vivo</i>	Old age gallic extract	Hypoglycemic, hypolipidemic; reduces proteinuria	Phenylpropanoid, Saponins, steroids, tannins, cardiac glycosides, propenyl cysteine and allyl cysteine Saponins	300 mg/kg	[49,50]
2.	<i>Aloe mesgalacantha</i> Baker	Aloaceae		Used in the treatment of diabetes, wounds, colon cleaner, malaria, urine retention, dandruff, and impotence in Ethiopian folk medicine	Leaf	<i>In vivo</i>	Leaf latex extract	Improvement in parameters such as oral glucose tolerance, body weight, lipid profile, and hypoglycemic and antioxidant activity	alkaloids, flavonoids, terpenoids, tannins, phenolic compounds, saponins, and anthraquinones	100, 200 and 400 mg/kg	[51]
3.	<i>Anacardium occidentale</i> Linn	Anacardiaceae	Cashew; Kaju, Sas-hu and Kanju in Yoruba, Igbo and Hausa, respectively, in Nigeria	Used for treatment of diabetes; high cholesterol, heart disease, stomach and intestinal (gastrointestinal) ailments, skin problems etc.	Leaf	<i>In vitro</i>	Ethanol, Water, methanol	Inhibition of α -amylase	Polyphenol, Flavonoid, glycosides, alkaloids, tannins, saponins, 2-hydroxy-6-pentadecylbenzamide, anacardic acid, pendacylsalicylic, cardol	Inhibition of α -amylase was best at a concentration of 240 μ g/mL	[52–54]
4.	<i>Artemisia annua</i> L	Asteraceae	sweet wormwood.	Used for the treatment of coughing, rhinitis, headache, dyspepsia, intestinal problems, malaria, diabetes, renal problems	Twig and leaf	<i>In vivo</i>	Water		Phenolic acid, flavonoids, terpenoids, deoxyartemisinin, artemisinic acid and luteolin, pentacyclic triterpenes, chlorogenic acid	5 g/L	[55,56]
5.	<i>Bauhinia reticulata</i> DC	Leguminosae	Camel's foot	Used for washing wounds, mouthwash, in the treatment of fever, colds, stomach-ache, indigestion, diabetes and diarrhoea	Root	<i>In vivo</i>	Ethanol	Decrease in Fasting Blood Glucose (FBG)/ anti-hyperglycaemic activity	Alkaloids, saponins, phenolics, triterpenes and phlobatins	200 mg/kg b.w	[57,58]
6.	<i>Biden pilosa</i> L.	Asteraceae	Black-jack, beggar-ticks, and Spanish needle	Used as foods and medicines. Used in treatment of snake bites, wounds and diabetes	Leaf	<i>In vivo</i>	Aqueous	hypoglycemic effects	Flavonoids, terpenoids, phenylpropanoids and porphyrins	200 mg/kg	[59,60]
7.	<i>Carica papaya</i> L	Caricaceae	Paw paw; Ibepe, Okworo-gbogbo and Gwanda in Yoruba, Igbo and Hausa, respectively, in Nigeria	Used for treatment of fever, diabetes mellitus, infections and to heal wounds.	Leaf	<i>In vitro</i>	Ethanol, methanol, and water	Inhibition of α -amylase	Terpenoids, alkaloids, flavonoids, glycosides, saponins and steroids, kaempferol, quercetin, 5, 7-dimethoxycoumarin, carpine and pseudocarpaine	Inhibition of α -amylase was best at a concentration of 240 μ g/mL	[53,54,61]
8.	<i>Cassia filiformis</i> Linn	Lauraceae	Woe vine	Treatment of headache, malaria, oedema, urinary problems, suppression of lactation	Leaf	<i>In vivo</i>	Ethanol	Decrease in FBG	Tannins, calcium carbonate, calcium oxalate crystals, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, hexadecanoic acid, methyl ester, hexadecanoic acid, ethyl ester, 7-octadecenoic acid, ethanol, 2-[9 octadecenyloxy]-, and 9,12,15-octadecatrienoic acid, ethyl ester		[62,63]
9.	<i>Catharanthus roseus</i> (Linn. G. Donn)	Apocynaceae	Madagascar periwinkle	Used for treatment of diabetes mellitus	leaf	<i>In vitro</i>	Aqueous	α amylase and α glucosidase inhibitor	Chlorogenic acid, quercetin, coumaric and rutin and vindoline n-hexadecanoic acid	50 g/mL	[64]
10.	<i>Copaifera salikounda</i> (Heckel)	Fabaceae	Ekuejula, Ovbialeke in Nigeria; Entedua in (Ghana)	Seed pod is used as a food ingredient and in treatment of rheumatoid arthritis and diabetes	Seed pods	<i>In vivo</i>	Ethanol	Stimulation of insulin release and α -glucosidase inhibition	7-octadecanoic acid methyl ester, 9-octadecenoic acid, Octadecanoic acid, Phenol, 2-methyl, 8- methyl -7-dodecen-1-ol acetate, Phthanic acid, Cyclopropaneundecanal, 2-Nonyl and 1,4-benzenediol, 2-methyl	200 mg/kg and 400 mg/kg	[65,66]
11.	<i>Cymbopogon Citrullus</i> (DC.) Stapf	Poaceae	Lemon grass; Mchachai in Tanzania	Used in treatment of diabetes, oral thrush, anti-tussive, anti-emetic, antiseptic, arthritis	Leaf and Stem	<i>In vivo</i> ethnomedical survey	Cold water	Improve glucose tolerance ability, insulin sensitivity, β -cell functions. anti-hyperglycaemic activity	Terpenes, alcohols, ketones, aldehyde, flavanoids, phenols and citral	0.5 g/mL	[67,68]

12.	<i>Daniella Olivera</i> (Rolle) Hutch. & Dalziel.	Fabaceae	Ilorin balsam (espoiva) or copalhu Africana, in Nigeria	Used in the treatment of diabetes, skin ailments, inflammation, and genito-urinary tract diseases. It also serves as an antiseptic, antibacterial, laxative, purgative, diuretic, and antihypertensive agent	Leaf	<i>In vivo</i>	Ethanol	Decrease in FBG	Alkaloids, phenol tannin, phylate, oxalate, saponin, steroid, β -Cubebene, Copaene, Cis-murola-4(14), 5-diene, aromadendrene, murolene, spathulenol, hexadecanoic acid, polyalthic acid	[69,70]
13.	<i>Ficus asperifolia</i> Linn.	Moraceae	Epim (sandpaper leaf)	Used for the treatment of diabetes, scabies, and infections	Leaf	<i>In vitro</i>	Ethanol, methanol, and water	Inhibition of α -amylase	Tannins, saponins, flavonoids, Alkaloids, glycosides, Phenols	[71,72]
14.	<i>Hagenia abyssinica</i> (Bruce) J. F. Gmel.	Rosaceae	African rosewood; Vepa in India	Used in treatment of diabetes, helminthic infections, typhoid fever, wound healing, epilepsy, sexually transmitted diseases, and symptomatic ailments (diarrhea, common cold, and cough)	Leaf	<i>In vivo</i>	Hydro methanol	It Regulates GLUT4 and reduces FBG. Inhibition of α glucosidase	Phenols, Saponins, flavonoids, triterpenoids, anthraquinones	[73]
15.	<i>Hibiscus sabdariffa</i> Linn	Malvaceae	Roselle, Zobo	Used to reduce high blood pressure, cholesterol levels, as well as blood sugar levels. Darken hair colour	Stem bark	<i>In vitro</i>	Ethanol, methanol, and water	Inhibition of α -amylase	Flavonoids, anthocyanins, terpenoids, steroids, alkaloids, sesquiterpene, quinones, and naphthalene, malic acid, α -tocopherol, linoleic acid, 5-(Hydroxymethyl) fufural, delphinidin-3-O-sambubioside	[74,75]
16.	<i>Ipomoea oblongata</i> E. Mey. ex Choisy	Convolvulaceae	E. Mey Ubhoqo in Mthokho, South Africa	Used for wound-healing, arthritis, reproductive ailments, diabetes, respiratory infections, lymphatic filariasis, inflammation, asthma, kidney failure and hypertension	Root	<i>In vitro</i>	Water and methanol	amelioration of persistent hyperglycemia, oxidative stress and modulation of various metabolic pathways involved in the pathogenesis of diabetic complication	glycosides, steroids, terpenoids, alkaloids, flavonoids, and tannins	[76,77]
17.	<i>Khaya senegalensis</i> Juss	Meliaceae	African mahogany	Used in treatment of Malaria, Headaches, Fever, epilepsy, diabetes mellitus	Leaf, stem, and bark	<i>In vitro</i>	Ethanol, methanol, and water	Inhibition of α -amylase	Saponins, tannins, triterpenes, flavonoids, alkaloids, 1, 2, 3-benzenetriol, n-Hexadecanoic acid, oleic acid, pentadecanoic acid, n-Hexadecanoic acid, 9, 12-Octadecadienoic acid, and 11-Octadecenoic acid	[78,79]
18.	<i>Momordica charantia</i> Linn	Cucurbitaceae	Bitter melon; Ejirinw, Alo-ose, Kakayi in Yoruba, Igbo and Hausa, respectively, in Nigeria; Karela in India	Used in treatment diabetes, viral and bacterial infections	Fresh fruit	<i>In vitro</i>	Fruit juice extract	Activation of β cells	saponins, triterpenes, vitamins, minerals, flavonoids, ascorbic acid, lecithin and steroids	[54,80]
19.	<i>Moringa oleifera</i> Lam	Moringaceae	Moringa; Drumstick tree; Mlonge in Tanzania; Eweigbale and Okweoyelbe in Yoruba and Igbo, respectively, in Nigeria	Used in treatment of hypertension, diabetes, and paralysis	Leaf	<i>In vivo</i>	Methanol	Enhance antioxidant status and reduce lipid peroxidation	Phenolic compounds such as kaempferol, quercetin, catechin, Gallic acid, caffeic acid, p-coumaric acid, vanillin, ferulic acid, protocatechuic acid, cinnamic acid and epicatechin.	[54,81]
20.	<i>Nauclea diderrichii</i> (De Wild.) Merr. (ND)	Rubiaceae	Badi in Gabon	Used for treatment of diabetes mellitus	Leaf & Bark	Pharmacological & Toxicological study	water	α -glucosidase inhibitor	Alkanols, Saponin, Flavonoid, methyl ester, Isophytol Steroids, pilocarpine, 13-heptadecyn-1-ol, 4-cyclopentene-1,3-dione, benzyloxy (butyl) dimethylsiane, catechol, heptadecane, hydroquinone, hexadecanoic acid, methyl ester, pentacosanoic acid, 16-octadecenoic acid,	[82,83]

21.	<i>Ocimum gratissimum</i> Linn	Lamiaceae	Scent Leaf; Efirin nla, Nchanwu and Dadoya in Yoruba, Igbo and Hausa, respectively, in Nigeria	Leaf	<i>In vitro</i>	Ethanol, methanol, and water	Inhibition of α -amylase	Polyphenols, flavonoids, fatty acids, oleic acid, n-Hexadecanoic acid, squalene, z-2-Octadecen-1-ol acetate, Terpeneol, cis- α , Alkaloids, tannins, saponins, flavonoids, steroids, glycosides, protocatechuic acid, gallic acid	Inhibition of α -amylase was best at a concentration of 240 μ g/mL	[53,84,85]
22.	<i>Parkia biglobosa</i> (Jacq.) G. Don	Fabaceae	African Locust bean tree	Stem bark	<i>In vitro</i>	Ethanol, methanol, and water	Inhibition of α -amylase	Alkaloids, tannins, saponins, flavonoids, steroids, glycosides, protocatechuic acid, gallic acid	Inhibition of α -amylase was best at a concentration of 240 μ g/mL	[86-88]
23.	<i>Rauwolfia vomitoria</i> Oliv. (Apocynaceae)	Apocynaceae	Asofejeje, Akanta and Wada in Yoruba, Igbo and Hausa, respectively, in Nigeria	Leaves	<i>In vivo</i>	Hydro methanolic extract	Hypoglycemic activity	2- Formyl-9-[D-d-ribofuranosyl]hypoxanthine, 5-Cyclopropylcarbonyloxy-pentadecane, 1,2,5-Oxadiazol-3-carboxamide-4,4'-azobis-2,2'-dioxide, 1-(5-Bicyclo[2.2.1]heptyl)ethylamine, 1-Adamantanemethylamine, a-methyl	500mg/kg	[89-91]
24.	<i>Sarcocephalus pobeguinii</i> Hua ex Pellegr. (SP)	Rubiaceae	Water kusia	Bark	Pharmacological & Toxicological study	Water	α -glucosidase selective inhibitor	Alkaloid, Saponin, Flavonoid, Steroids, Strictonamide	45% inhibition at 1 mg/mL concentration	[82,92]
25.	<i>Vernonia amygdalina</i> Del.	Asteraceae	Bitter leaf; Ewuro, Onugu and Shiwaka in Yoruba, Igbo and Hausa, respectively, in Nigeria	leaf	<i>In vivo</i>	Methanol	α -glucosidase inhibitor	vernolide and vernodol essential oil, tannins, alkaloid, saponins, glycosides, anthraquinones and flavonoids	400mg/kg	[54,93]

Table 3. Identified phytochemicals and their mechanism of action

S/N	Phytochemicals	Structural families	Mechanism of action	References
1.	Tannins	Polyphenol	Regeneration of pancreatic β cells and insulin secretion. Inhibits extracellular microbial enzymes through inhibition of oxidative phosphorylation in microbial growth	[94,95]
2.	Carpaine	Alkaloid	Facilitates glucose transport, carbohydrate digestion and absorption; possesses antithrombocytopenic activity	[96]
3.	Terpenoids	Terpene	Inhibition of α -amylase, promotes Glut4, GLP-1, and adiponectin. It also increases insulin levels	[97]
4.	Hexadecenoic Acid	Fatty acid	Regenerates the pancreatic- β cells and insulin secretion. Possesses anti-inflammatory activities, as it inhibits phospholipase A2	[95,98]
5.	Luteolin	Flavonoid	Potentiates insulin secretion and action, increases transcriptional activation of PPAR γ , decreases circulating levels of inflammatory molecules, Monocyte Chemoattractant Protein-1 (MCP-1), resistin and elevates adiponectin levels in obese mice	[99,100]
6.	Saponin	Glycoside	Induces insulin production and helps in amelioration of oxidative stress; helps to increase the activity of glucose-6- phosphate, alleviates hyperglycemia, and decreases lipid levels, increases GLUT and inhibits disaccharidase activity	[43,101]
7.	Glycosides	Glycoside	Decreases the serum α -amylase and lactate dehydrogenase activities, modulates oxidative stress parameters such as malondialdehyde, exhibits antidiabetic activities by increasing insulin secretion and decreasing glycosylated haemoglobin	[43]
8.	Rutin	Flavonoid	Improves insulin secretion, restores glycogen content, decreases the level of oxidative stress, inhibits advanced glycation end products (AGEs) formation, decreases glycosylated haemoglobin and pro-inflammatory cytokines such as IL-6 and TNF α and restores liver antioxidant status	[102,103]
9.	Quercetin	Flavonoid	Increases the activities of antioxidant enzymes, decreases lipid peroxidation, reduces intestinal glucose absorption by inhibiting GLUT2, blocks tyrosine kinase and the recovery of cell proliferation	[104,105]
10.	Vindoline	Alkaloid	Vindoline induced relatively high glucose uptake in pancreatic beta TC6 or myoblast C2C12 cells. It also inhibits protein tyrosinase phosphatase-1B (PTP-1B)	[43]
11.	Kaempferol	Flavonoid	promotes the inhibition of apoptosis, reduction of caspase-3 activity in beta cells, improves cAMP signaling and enhances insulin synthesis and secretion, promotes the enhancement of antioxidant production and reduction of IL-1 β , TNF α , lipid peroxidation, nitrite, and glycosylated haemoglobin	[106,107]

Glut4: glucose transporter 4; GLP-1: Glucagon-like peptide 1; PPARs: peroxisome proliferator-activated receptors; MCP-1: Monocyte Chemoattractant Protein-1; AGEs: advanced glycation end products; IL-6: interleukin-6; TNF α : tumor necrosis factor alpha; PTP-1B: protein tyrosinase phosphatase-1B; IL-1 β : interleukin 1 beta; GLUT2: glucose transporter 2

antidiabetic effect via improvement of antioxidant enzymes, reduction of lipid peroxidation, diminution in the absorption of glucose in the intestine by inhibiting GLUT2 [104,105]. It also causes blockage of tyrosine kinase and the recovery of cell proliferation.

The two common alkaloids observed in this review and their structures are depicted in Figure 4. Alkaloids have been linked as the active components in some medicinal plants with antidiabetic potentials. Robust evidence has shown the antidiabetic effect of an alkaloid from Capparis deciduas in diabetic mice [120]. It was shown that the antidiabetic potential was mediated by improvement of GLUT 4, glucokinase activity, peroxisome proliferator-activated receptor- γ (PPAR γ) and reduction in total cholesterol and triglycerides, mitigation of glucose-6- phosphatase activity and improvement in the

hepatic glycogen content. A compelling study also shows that carbazole alkaloids isolated from *Murraya koenigii* are responsible for the antidiabetic efficacy of the plant. It was reported that koenidine intake improved insulin sensitivity, and assisted in the uptake of glucose and translocation of GLUT 4 in L6-GLUT 4 myocytotubes [121]. The antidiabetic effect of *Catharanthus roseus* has also been reported, and four alkaloids – Vindoline I, Vindolidine II, Vindocine III and Vindolinine IV obtained from dichloromethane extract of *C. roseus* are responsible for this action. Accordingly, they induce the uptake of glucose in pancreatic beta TC6 or myoblast C2C12 cells [122].

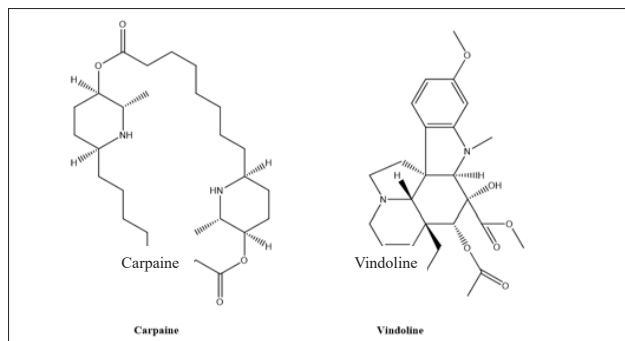


Figure 4. Structure of different alkaloids: Carpine, Vindoline

In this review, information was listed that indicated that tannins have also been implicated as among the bioactive components of the studied plants having antidiabetic activity. Studies have reported the antidiabetic and antioxidant properties of condensed tannins obtained from various food items such as cereals, legumes, oilseeds and vegetables [123]. Mechanistically, it was affirmed in this study that condensed tannins isolated from α -amaranth grain, finger millet, field bean, sunflower seed, drumstick and amaranth leaves showed their antidiabetic actions primarily via inhibition of the activation of α -amylase and α -glucosidase activities. Tannic acid has also been reported to promote the transportation of glucose and inhibition of differentiation in 3T3-L1 adipocytes [124]. Research has ascribed this action to the phosphorylation of insulin receptors and translocation of glucose transporter 4 (GLUT 4).

Furthermore, saponins have been revealed to have antidiabetic potential. Reports have shown that many medicinal plants exhibit their antidiabetic potential as a result of their saponins content. The saponin content of *Anabasis articulata* has been indicated to be responsible for its antidiabetic potential [125]. In *Astragalus membranaceus*, the saponin content has been demonstrated to attenuate oxidative stress and AGEs formation. Saponins isolated from *Enteda phaseoloides* have been reported to elevate serum insulin levels, mitigate hyperglycemia and lower lipid levels [126].

Africa is endowed with a rich diversity of medicinal plants, many of which are currently employed in the traditional management of DM. This review indicates that these plants have demonstrated *in vitro* and *in vivo* hypoglycemic and anti-diabetic potential and are useful agents in the management of DM and its complications. However, effective pharmacovigilance of herbal medicines is still urgently needed for safety and effective use in therapeutic management [127]. Hopefully, the therapeutic efficacy of

these medicinal plants can be explored towards a possible integration into the healthcare system.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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