Chapter 6

Antidiabetic Botanicals and their Potential Benefits in the Management of Diabetes Mellitus

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1. Introduction

1.1. Diabetes: Definition, aetiology and classification

The term "diabetes", when used alone, generally refers to diabetes mellitus (DM) and not a rare, unrelated disease called diabetes insipidus. DM is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism [1,2]. The magnitude of the challenge that diabetes presents to health services is enormous [3].

DM was traditionally classified based on whether or not the patient is insulin dependent or independent [4]. However, there has been a paradigm shift in the classification of DM from one based on the need for insulin therapy to maintain glycaemic control and prevent ketosis to that based on the underlying aetiopathogenetic mechanisms [5]. The current classes of DM and their aetiopathogenetic mechanisms are (i) Type 1A (auto-immune), (ii) Type 1B (non-auto immune or idiopathic) [6], (iii) Type 2 (insulin resistance), (iv) Gestational (diagnosed for the first time in pregnancy but usually characterized by insulin resistance) and (v) other specific aetiologies (secondary to other diseases and identified gene mutations) [5]. Once considered a disease of acute onset, it is now generally accepted that the 1A subtype is a genetically determined chronic immune-mediated disorder that leads to selective loss of pancreatic insulin-secreting β-cells [6]. The classic point of view regarding type I diabetes mellitus (T1DM) pathogenesis was that, in genetically predisposed individuals, some environmental factors may trigger an autoimmune process that leads to β-cell destruction; but despite considerable progress over recent years, the autoimmune process underlying T1DM is still poorly understood [6].

The high blood glucose level (hyperglycaemia) that accompanies T1DM and type 2 diabetes mellitus (T2DM) can cause serious health complications including ketoacidosis, kidney failure, heart disease, stroke, and blindness. Patients are often diagnosed with diabetes when they see a physician for clinical signs such as excessive thirst, urination, and hunger [7]. The direct symptoms of type-2 diabetes can be mild and may cause minimal interruption to activities of daily living. However, it is the complications of the disease which lead to damage to vital organs, and consequently, to substantial morbidity and mortality.

Diabetes in the young is often categorized as Type 1 and this comprises the auto-immune Type 1A and non-auto immune Type 1B. T2DM which is mainly diagnosed in adults is increasingly being reported in young people. The increased prevalence of T2DM in young people is associated with the increasing rates of obesity in young people. Type 2 diabetes accounts for 90% to 95% of all cases of diabetes [8-10].

2. Prevalence, global burden and increasing incidence of diabetes

Several statistics from various scientific studies on the incidence, prevalence and global burden of diabetes mellitus are available. While there might be minor discrepancies in these statistics, the consensus is that they are ominous and call for urgent and definitive action on this disease [11,12].

DM is estimated to affect 2.8% of the world's population at present and projected to cross 5.4% mark by 2025 [13]. Over the last decades, the prevalence of diabetes mellitus has reached epidemic proportions in Western societies, and is even higher in some developing countries [14 -16]. According to Shaw *et al.* [17], the world's prevalence of diabetes among adults (aged 20–79 years) will be 6.4%, affecting 285 million adults, in 2010, and will increase to 7.7%, and 439 million adults by 2030 and, between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries. More recently, the International Diabetes Federation (IDF) estimated that in 2011 there were 366 million people with diabetes and this was expected to rise to 552 million by 2030 [18]. The International Diabetes Federation (IDF) reported that 151 million people had diabetes in the 172 IDF member countries with a forecast that 334 million people will have the disease in 2025 [19]. The human cost of diabetes has been put at one death every 10 seconds [20].

Zhang *et al.*[21] estimated that global health expenditures to prevent and treat diabetes and its complications would be at US dollar (USD) 376 billion in 2010 and that by 2030, this number will exceed USD490 billion. In addition, diabetes leads to loss in productivity and economic growth. The American Diabetes Association estimated that the US economy lost USD58 billion, equivalent to about an half of the direct health care expenditure on diabetes in 2007, as a result of lost earnings due to lost work days, restricted activity days, lower productivity at work, mortality and permanent disability caused by diabetes [21]. Diabetes and its complications place huge burdens upon individuals, their careers and families and have crippling effects upon national health services [20].

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3. Pathological complications of diabetes mellitus

Persistent hyperglycaemia and the development of diabetes-specific microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (heart attack, stroke and peripheral arterial disease) complications are the main characteristics of all forms of diabetes mellitus. The importance of protecting the body against persistent elevation of blood glucose cannot be overemphasized because its direct and indirect effects on the human vascular system are the major cause of morbidity and mortality in both T1DM and T2DM [22]. Hospitalisations for complications account for more than half of the healthcare costs of T2DM and three-quarters of people with diabetes die from cardiovascular disease. Research has shown that the risk of development of both microvascular and macrovascular complications associated with elevated blood glucose increases with the length of time blood glucose is uncontrolled [23,24].

As a result of the association of diabetes with accelerated atherosclerotic macrovascular disease affecting arteries that supply the heart, brain and lower extremities, patients with diabetes have a much higher risk of myocardial infarction, stroke and limb amputation [25]. Lower limb amputations are at least 10 times more common in people with diabetes than in non-diabetic individuals in developed countries; more than half of all non-traumatic lower limb amputations are due to diabetes [26].

Diabetes is one of the leading causes of visual impairment and blindness in developed countries [27]. Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with T2DM [28]. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy [22]. According to Massin *et al* [29] lens opacification leading to cataract is a frequent comorbidity of diabetes, as adults with T2DM are five times more often affected than the general population. They also reported that while juvenile diabetic cataract is rare, adult-onset, mostly cortical cataract in T2DM patients is similar to age-related cataract in the general population, except for an earlier onset and greater prevalence [29,30]. Major risk factors for cataract in T2DM include hyperglycaemia, diabetes duration and the presence of diabetic retinopathy, although specific risk factors or markers may differ according to cataract subtype. Smoking, for example, is associated with nuclear opacities, whereas ultraviolet radiation increases the risk for cortical opacities, and high blood pressure and corticosteroids raise the odds for subcapsular cataract [31]. Various pathophysiological mechanisms are involved in cataract formation, including osmosis-driven lens overhydration triggered by the polyol pathway (mostly ascribed to juvenile cataract), lens protein glycation and an excess of free radicals, with the latter being particularly associated with the nuclear subset of age-related cataract [32,33].

Studies have shown an increased incidence of erectile dysfunction (ED) in diabetes patients. In addition, ED appears to arise about 10 years earlier in diabetic patients than in the general population [34] and is more severe, decreasing health-related quality of life. ED is most often a forewarning of cardiovascular disease; thus, the treatment of ED among diabetics is a priority. Diabetic ED is multifactorial in aetiology and more resistant to treatment compared with non-diabetic ED [35]

Diabetic neuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes [36]. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy [37].

Diabetic nephropathy has been defined by proteinuria > 500 mg in 24 hours in the setting of diabetes, which is however preceeded by lower degrees of proteinuria, or "microalbuminuria." Microalbuminuria is defined as albumin excretion of 30–299 mg/24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy [22]. This progression occurs in both type1 and type 2 diabetes. As many as 7% of patients with type 2 diabetes may already have microalbuminuria at the time they are diagnosed with diabetes [38]. In the European Diabetes Prospective Complications Study, the cumulative incidence of microalbuminuria in patients with type 1 diabetes was ~ 12% during a period of 7 years. In the U.K. Prospective Diabetes Study (UKPDS), the incidence of microalbuminuria was 2% per year in patients with type 2 diabetes, and the 10-year prevalence after diagnosis was 25% [38-40]. Diabetic nephropathy can progress to end-stage renal disease. Diabetes is the leading cause of renal failure in the United States accounting for nearly 44 percent of new cases [40].

Diabetes increases the risk that an individual will develop cardiovascular disease (CVD) [22]. Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound. CVD is the primary cause of death in people with either type 1 or type 2 diabetes and accounts for the greatest component of health care expenditures in people with diabetes [41,42]. Among macrovascular diabetes complications, coronary heart disease has been associated with diabetes in numerous studies beginning with the Framingham study [43]. More recent studies have shown that the risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in non-diabetic patients with a history of previous MI [44]. These discoveries have led to new recommendations by the American Diabetes Association (ADA) and American Heart Association (AHA) that diabetes be considered a coronary artery disease risk equivalent rather than a risk factor. Patients with type 1 diabetes bear a disproportionate burden of coronary heart disease. Studies have shown that these patients have a higher mortality from ischemic heart disease at all ages compared to the general population [45].

Diabetes is also a strong independent predictor of risk of stroke [46]. Patients with type 2 diabetes have a much higher risk of stroke, with an increased risk of 150–400%. Risk of stroke-related dementia and recurrence, as well as stroke-related mortality, is elevated in patients with diabetes [47]. In addition, the risk of tuberculosis is three times higher among people with diabetes [48].

Insulin resistance and glucose intolerance are components of metabolic syndrome, a group of metabolic risk factors that predisposes people to diseases related to fatty buildups in artery walls such as coronary heart disease, which can lead to heart attack, stroke and peripheral vascular disease [49]. People with this syndrome are also more likely to develop type 2 diabetes. Other components of metabolic syndrome are abdominal obesity, atherogenic dyslipidemia, raised blood pressure, proinflammatory state and prothrombotic state [49]. The

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term pre-diabetes has been used to describe the condition of individuals with a high risk of developing diabetes in the future and already showing a glycaemic abnormality [50,51].

People with diabetes require at least two to three times the health-care resources compared to people who do not have diabetes, and diabetes care may account for up to 15% of national health care budgets [52].

Many authors agreed that hyperglycaemia causes tissue damage through the following clearly defined mechanisms [25, 53]: increased flux of glucose and other sugars through the polyol pathway, increased intracellular formation of advanced glycation end products (AGEs), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase (PK) C isoforms, and overactivity of the hexosamine pathway.

3.1. Increased polyol pathway flux

Aldose reductase (alditol:NAD(P)$^+$ 1-oxidoreductase, EC 1.1.1.21) is the first enzyme in the polyol pathway. It is a cytosolic, monomeric oxidoreductase that catalyses the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction of a wide variety of carbonyl compounds, including glucose [54]. At the normal glucose concentrations found in non-diabetics, metabolism of glucose by this pathway is a very small percentage of total glucose use. But in a hyperglycaemic environment, increased intracellular glucose results in its increased enzymatic conversion to the polyalcohol sorbitol, with concomitant decreases in NADPH [25,55,56]. In the polyol pathway, sorbitol is oxidized to fructose by the enzyme sorbitol dehydrogenase, with NAD$^+$ reduced to NADH. Flux through this pathway during hyperglycaemia varies from 33% of total glucose use in the rabbit lens to 11% in human erythrocytes [25]. Thus, the contribution of this pathway to diabetic complications may be very much species, site and tissue dependent [25]. It has also been proposed that reduction of glucose to sorbitol by NADPH consumes NADPH [25]. As NADPH is required for regenerating reduced glutathione (GSH), this could induce or exacerbate intracellular oxidative stress. Decreased levels of GSH have in fact been found in the lenses of transgenic mice that overexpress aldose reductase, and this is the most likely mechanism by which increased flux through the polyol pathway has deleterious consequences [57]. This conclusion is further supported by recent experiments with homozygous knockout mice deficient in aldose reductase, which showed that, in contrast to wild-type mice, diabetes neither decreased the GSH content of sciatic nerve nor reduced motor nerve conduction velocity [25].

3.2. Increased intracellular formation of advanced glycation end-products

AGEs are found in increased amounts in diabetic retinal vessels and renal glomeruli and intracellular hyperglycaemia appears to be the primary initiating event in the formation of both intracellular and extracellular AGEs [23]. AGEs contribute to diabetic complications via three principal mechanisms: the modification of intracellular proteins including, most importantly, proteins involved in the regulation of gene transcription [58,59]; diffusion of these AGE precursors out of the cell and their modification of extracellular matrix molecules nearby, which changes signaling between the matrix and the cell and causes cellular dysfunction [60,

61]; and diffusion of AGE precursors out of the cell and their modification of circulating proteins in the blood, such as albumin, which can then bind to AGE receptors and activate them thereby causing the production of inflammatory cytokines and growth factors, which in turn cause vascular pathology [62-65].

3.3. Activation of protein kinase C (PKC)

PKCs are a family of at least 11 isoforms that are widely distributed in mammalian tissues. The enzyme phosphorylates various target proteins. The activity of the classic isoforms is dependent on both Ca^{2+} ions and phosphatidylserine and is greatly enhanced by diacylglycerol (DAG) [53]. Intracellular hyperglycaemia increases the *de novo* synthesis of DAG from the glycolytic intermediate dihydroxyacetone phosphate by reducing it to glycerol-3-phosphate and stepwise acylation [66]. Hyperglycaemia may also activate PKC isoforms indirectly through both ligation of AGE receptors[67] and increased activity of the polyol pathway [68], presumably by increasing reactive oxygen species. One significant effect of PKC activation is seen in the decrease in the vasodilator producing endothelial nitric oxide (NO) synthase (eNOS), while the vasoconstrictor endothelin-1 is increased. Transforming growth factor- β and plasminogen activator inhibitor-1 are also increased [69].Abnormal activation of PKC has been implicated in the decreased glomerular production of nitric oxide induced by experimental diabetes [70], and in the decreased production of nitric oxide in smooth muscle cells that is induced by hyperglycaemia [71]. Activation of PKC also contributes to increased microvascular matrix protein accumulation by inducing expression of TGF-b1, fibronectin and type IV collagen both in cultured mesangial cells [72] and in glomeruli of diabetic rats [66].

3.4. Increased flux through the hexosamine pathway

Glucose is one of the most largely used energy substrate in living cells. A fraction (2–3%) of the glucose entering the cell is converted into UDP–N-Acetyl Glucosamine (UDP-GlcNAc), through the hexosamine biosynthetic pathway (HBP). The level of UDPGlcNAc in the cell thus reflects the flux of glucose through this pathway [73]. In this pathway, fructose-6-phosphate is diverted from glycolysis to provide substrates for reactions that require UDP-*N* acetylglucosamine, such as proteoglycan synthesis and the formation of *O*-linked glycoproteins [23]. O-GlcNAcylation may affect the phosphorylation status of a protein, by regulating the phosphorylation of adjacent residues or by competing for the same serine or threonine residue (the so-called Yin-Yang mechanism), in which modification of a serine or threonine residue by either phosphorylation or O-GlcNAcylation differently affects the protein's function [73]. O-GlcNAcylations also regulate insulin signaling and seem to play an important part in the development of diabetes and its complications [74,75]. Inhibition of the rate-limiting enzyme in the conversion of glucose to glucosamine, glutamine:fructose-6-phosphate amidotransferase (GFAT), blocks hyperglycaemia-induced increases in the transcription of TGF-α, TGF-β1. This pathway has been shown to play a role both in hyperglycaemia-induced abnormalities of glomerular cell gene expression and in hyperglycemia-induced cardiomyocyte dysfunction in cell culture [25,76].

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4. Management of diabetes mellitus

Diabetes mellitus is a syndrome implying that efforts targeted at its management should be multifaceted. Adequate consideration should be given to all the accompanying comorbidities and all symptomatic and asymptomatic features. Efforts should be geared towards the attainment of normal or near normal glucose levels. The general objective of diabetes management include to (i) relieve symptoms (ii) correct associated health problems and reduce morbidity, mortality and economic costs of diabetes (iii) prevent as much as possible acute and long-term complications (iv) monitor the development of such complications and provide timely intervention and, (v) improve the quality of life and productivity of the individual with diabetes [77]. The orthodox approach to the management of diabetes mellitus has always included lifestyle modification and dietary therapy, administration of oral antidiabetic drugs, and insulin therapy.

4.1. Diet and lifestyle modification

Weight reduction and an increase in daily energy expenditure decrease insulin resistance and increase glucose tolerance [78]. Advice on diet and exercise are an important part of the treatment of T2DM and overweight patients are normally advised to restrict calorie intake, consume food with low total (especially saturated) fat content and high (predominately unrefined) carbohydrate content.

Dietary and lifestyle modifications are regarded as the mainstay of treatment and management for T2DM. The majority of people with T2DM are overweight and usually have other metabolic disorders of the insulin resistance syndrome. Therefore, the major aims of dietary and lifestyle changes are to reduce weight, improve glycaemic control and reduce the risk of coronary heart disease (CHD), which accounts for 70- 80% of deaths among those with diabetes [79]. Even modest weight reduction is associated with a reduction in insulin resistance, a reduction in hepatic glucose production, and perhaps, an improved islet β-cell function [80,81]. Several studies have demonstrated the effectiveness of diet and exercise in reducing the progression of diabetes [82-85].

Fat is the most energy-rich of all nutrients and reduction of fat intake helps to reduce total energy intake, which is important for many people with type 2 diabetes and some with type 1 diabetes. Results from several research studies suggest that populations consuming a low saturated fat diet have lower incidence and mortality from CHD compared with those living in countries with a high intake of saturated fat and that reduced saturated fat intake is associated with reduced levels of low-density lipoprotein (LDL) – cholesterol [86,87].

4.2. Oral antidiabetic drugs

Oral antidiabetic drugs (OADs) are normally introduced when lifestyle modifications fail to adequately control glycaemia. They are very useful for managing hyperglycaemia, especially in the early stages of disease. However, there are several limitations that prevent OADs from reaching their potentials [88]. Sulfonylureas cause hypoglycaemia by stimulating insulin

release from pancreatic β -cells. They bind to sulfonylurea (SUR) receptors on the β -cell plasma membrane, causing closure of adenosine triphosphate (ATP)-sensitive potassium channels, leading to depolarization of the cell membrane. This in turn opens voltage-gated channels, allowing influx of calcium ions and subsequent secretion of preformed insulin granules [89]. Acute administration of sulfonylureas T2DM patients increases insulin release from the pancreas and also may further increase insulin levels by reducing hepatic clearance of the hormone. Initial studies showed that a functional pancreas was necessary for the hypoglycaemic actions of sulfonylureas [90]. With chronic administration, circulating insulin levels decline to those that existed before treatment. But, despite this reduction in insulin levels, reduced plasma glucose levels are maintained [89].

Metformin, the popular antidiabetic drug has its origin in the plant *Galega officinalis.* It is one of the major success stories of the reward of prospecting for drugs from botanical sources. Metformin is antihyperglycaemic, not hypoglycaemic [91]. Clarke *et al.*reported that metformin does not cause insulin release from the pancreas and does not cause hypoglycaemia, even in large doses [92]. Metformin has been shown to increase peripheral uptake of glucose and to reduce hepatic glucose output by approximately 20-30% when given orally but not intravenously [93,94]. Impaired absorption of glucose from the gut has also been suggested as a mechanism of action, but has not been shown to have clinical relevance. Metformin has also been shown to decrease serum triglycerides and fatty acid concentrations and slows the rate of lipid oxidation. These actions indirectly inhibit gluconeogenesis [95].

The meglitinide analogues act on β-cell receptors to stimulate insulin secretion by binding to the sulfonylurea receptor subunit and closing the K^+ ATP channel but probably at a site distinct from that of the sulfonylurea receptor [96,97]. Closure of the potassium channel leads to depolarization of β-cell plasma membrane, which promotes influx of calcium ions through voltage-gated calcium channels, resulting in exocytosis of insulin granules [89]. α-Glucosidase inhibitors competitively block small intestine brush border enzymes that are necessary to hydrolyze oligo and polysaccharides to monosaccharides [98]. Inhibition of this enzyme slows the absorption of carbohydrates and the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects [99].

4.3. Insulin

Insulin has proven to be the therapy with the highest potential to achieve glycaemic target in diabetics. It is typically prescribed after OADs have failed, and often later than is ideal [88]. The physiological plasma insulin profile in healthy individuals displays low but constant insulin levels in fasting conditions, with sharp prandial peaks shortly (within 30 minutes) after meals followed by a slow return to basal levels when increased insulin secretion is no longer necessary. In order to avoid glycaemic excursions, exogenously administered insulin would ideally closely mimic the healthy physiological pharmacokinetic insulin profile [88].

Although all patients with T2DM become relatively insulinopenic late in the course of their disease, some patients with T2DM may have insufficient insulin secretion early in the course of the disease. This difference arises from the heterogeneity in the metabolic expression of the diabetic state and the difference in the extent to which different abnormalities contribute to

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the hyperglycaemic state. In lean patients with T2DM, impaired insulin secretion is a common defect, and insulin resistance tends to be less severe than in obese patients with T2DM [100].

5. Limitations of orthodox approaches in the treatment of diabetes mellitus

Despite the significant improvements recorded from the administration of the currently available therapies in the treatment of diabetes, several undesirable side effects have been observed in the course of treatment using these therapies. Reports have shown that the success of OADs is limited by their mechanisms of action, which often address the symptoms of diabetes rather than its underlying pathophysiology. For instance, up to 2.5% and 17.5% of sulfonylurea (SU)-treated patients experience major and minor hypoglycaemia, respectively, while gastrointestinal (GI) problems affect up to 63% of metformin, and 30% of acarbose-treated patients. These side effects can have a negative impact on patient adherence to treatment, resulting in higher HbA1c levels and increased risk for all-cause hospitalization and all-cause mortality [101].

Another limitation that hinders the efficacy of OADs is the tendency of health professionals to delay initiation and intensification of therapy. OADs are frequently initiated too late in the progression of the disease and intensification is delayed and thus exposes the patient to hyperglycemia [88]. According to the recent American Association of Clinical Endocrinologists (AACE) road map guidelines, combination therapy is to be initiated when continous titration of OAD monotherapy fails to achieve target HbA1c levels (ie, ≤ 6.5%) [102].

Although insulin is the most effective antihyperglycemic agent, its initiation is also delayed to an excessive degree. Brown *et al.* estimated that the average patient accumulated HbA1c- which contribute to excess glyacemic burden (HbA1c > 8%) from diagnosis until insulin initiation, thereby increasing the prevalence of complications [103]. The economic burden of managing diabetes is also a limitation to the use of oral antidiabetic drugs especially in less developed countries where the people can scarcely afford orthodox treatment. There is therefore the need to investigate the antidiabetic effects of indigenous plants and their continuous role in the management of diabetes mellitus with a view to developing new and more effective drugs to stem the tide of the ravaging epidemic of diabetes.

6. Therapeutic and chemoprophylactic potentials of botanicals

Terrestrial plants have been used as medicines in Egypt, China, India and Greece from ancient time and an impressive number of modern drugs have been developed from them [104]. According to the World Health Organization (WHO), a medicinal plant is any plant which, in one or more of its organs contains substances that can be used for therapeutic purposes, or which are precursors for chemo-pharmaceutical semi synthesis. Such a plant will have its parts including leaves, roots, rhizomes, stems, barks, flowers, fruits, grains or seeds, employed in the control or treatment of a disease condition and therefore contains chemical components

that are medically active. These non-nutrient plant chemical compounds or bioactive components are often referred to as phytochemicals ('phyto-' from Greek - *phyto* meaning 'plant') or phytoconstituents.

Phytochemicals have been isolated and characterized from fruits such as grapes and apples, vegetables such as broccoli and onion, spices such as turmeric, beverages such as green tea and red wine, as well as many other sources [105]. The WHO estimates that approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care [106].

7. Botanicals and their antidiabetic property

Many medicinal plants have ethnomedical claims of usefulness in the treatment of diabetes worldwide and have been employed empirically in antidiabetic and antihyperlipidemic remedies. Hundreds of plants with antidiabetic and hypoglycaemic activities have also been reported in literature. Despite this, studies on plants with these activities are still necessary. This is because a large percentage of plants are yet to be explored for their medicinal properties. Also, successful antidiabetic drug development from investigated plants is still largely absent although numerous dietary supplements have been formulated. Plants contain glycosides, alkaloids, terpenoids, anthocyanins, tocopherols, flavonoids, carotenoids, polyphenols, peptidoglycans, steroids, coumarins and other constituents that are frequently implicated as having antidiabetic activities [107]. The antidiabetic activities could be obtained from several parts of the plants - aerial parts, bark, flower, root, seeds, leaves, bulb, tubers and/or whole plant [108].

Many studies have confirmed the benefits of medicinal plants with hypoglycaemic effects in the management of diabetes mellitus. The plant families most studied for their hypoglycaemic effects include: Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae and Araliaceae [109]. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. During the past few years, efforts at the study of antidiabetic medicinal plants have culminated in the isolation and characterization of single bioactive compounds and the preparation of herbal extracts and multiherbal products. Interestingly, some of these extracts and herbal preparations have shown significant insulinomimetic and antidiabetic activities with more efficacy than conventional hypoglycemic agents [13]. For this paper, we shall briefly consider the antidiabetic potential of few of these botanicals.

7.1. Fenugreek

Leaves, seeds or the entire plant of *Trigonella foenum-graecum* L. (fenugreek) are used for the treatment of diabetes in many countries of the world and several human studies have confirmed the efficacy of the plant. The beneficial effect of the plant has been partly attributed to the high fibre content. The proposed mechanism of action was related to the inhibition of diffusion or transport of glucose independent of hormonal mechanisms [110].

7.2. *Gymnema sylvestre*

Extracts of *G. syvestre* have been reported to demonstrate antidiabetic activity possibly via reduction in insulin requirement by enhancing endogenous insulin availability, improving vitiated blood glucose homeostasis, better control of hyperlipidemia associated with diabetes, reduction in amylase activity in serum and, increase in β-cell function as shown by higher levels of serum C peptide. Extract of the leaves of the plant produced a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins, with a decrease in conventional drug dosages. Some patients were able to discontinue conventional drugs and even maintain their blood glucose homeostasis with extracts alone in T2DM patients [111,112].

7.3. *Morinda lucida*

Alcoholic and aqueous extracts of roots and leaves of *Morinda lucida* Benth (Rubiaceae) have been reported to possess remarkable antidiabetic property in alloxan- and streptozotocin (STZ)-induced diabetic rats. Suggested mechanisms of action include the stimulation of beta cells to release insulin [113, 114].

7.4. *C. chinensis* Franch, *Astragalus membranaceus*, and *Lonicera japonica*

Using scientifically validated animal models in a study, a multicomponent berberine-containing remedy comprising *C. chinensis* Franch, *Astragalus membranaceus*, and *Lonicera japonica* was used to treat male Zucker diabetic fatty rats. The three-herb medicine showed sustained glucose-lowering effects for 1 week after a single-dose treatment. Two-week treatment attenuated insulin resistance and fatty degeneration, with hepatocyte regeneration lasting for 1 month posttreatment. The beneficial effects were found to have persisted for 1 year after 1-month treatment and were associated with activation of AMPK, Akt, and insulin-like growth factor-binding protein (IGFBP)1 pathways, with downregulation of miR29-b and expression of a gene network implicated in cell cycle, intermediary, and NADPH metabolism with normalization of CYP7a1 and IGFBP1 expression. Authors concluded that the pluripotent effects of the medicine in altering gene expression, in part through changes in miRNA, explained its sustained beneficial effects on glucose metabolism, fatty liver, and cellular repair [115].

7.5. *Pterocarpus marsupium*

A crude extract (water decoction) of *P. marsupium* was reported to have protective and restorative effect on β-cells in alloxan-induced diabetic rats. The results were substantiated by histological observations. Various active principles responsible for the antidiabetic activity have been isolated [116,117].

7.6. Kolaviron

Kolaviron, a biflavonoid complex isolated from *Garcinia kola* possesses multiple biological activities. Kolaviron demonstrated significant hypoglycaemic effect when administered to alloxan diabetic rabbits. The blood sugar was lowered from 506 mg/100 mL to 285 mg/100 mL at 12 h after the administration of 100 mg/kg kolaviron. Kolaviron also inhibited rat lens aldose reductase (RLAR) activity, with an IC_{50} value of 5.4×10^{-6} [118]. Adaramoye and Adeyemi reported that fractions obtained from kolaviron reduced blood sugar levels in STZ-diabetic rats within 4 h of oral administration and showed favourable effect on the plasma lipid profile of diabetic animals [119]. In addition to its antidiabetic property, kolaviron showed remarkable protective effects on cardiac, renal and hepatic tissues of STZ-diabetic rats. Many antidiabetic drugs do not offer significant tissue-protective effect in diabetic animals [120].

7.7. *Aloe barbadensis*

Aloe barbadensis (*Aloe vera*), the acclaimed "miracle plant" has been documented to ameliorate the diabetic condition in human subjects and experimental animals and to probably prevent the onset of hyperglycemia in alloxan intoxicated rabbits [121]. Reports of studies on the effect of aloe vera in experimental and clinical diabetes are available. In general, these reports agreed on the antidiabetic efficacy of *Aloe vera*. Oral administration of *Aloe vera* gel extract at a dose of 300 mg/kg bodyweight per day to STZ-induced diabetic rats for a period of 21 days resulted in a significant reduction in fasting blood glucose, hepatic transaminases (aspartate aminotransferase and alanine aminotransferase), plasma and tissue (liver and kidney) cholesterol, triglycerides, free fatty acids and phospholipids and a significant improvement in plasma insulin [122]. Can *et al*. concluded from their study that Aloe gel extract has a protective effect comparable to glibenclamide against hepatotoxicity produced by diabetes if used in the treatment of T2DM [123]. Another research finding showed that orally ingested aloe sterols altered the expressions of genes related to glucose and lipid metabolism, and ameliorated obesity- and diabetes-associated disorders in rats [124].

7.8. *Vernonia amygdalina*

Alcohol extract of *V. amygdalina* was found to significantly improve glucose tolerance in STZ-diabetic rats, decrease fasting blood glucose, show protective effect over pancreatic β-cells and cause a slight increase in insulin level in STZ-induced diabetic rats [125]. The same authors found that *V. amygdalina* increased the expression of GLUT 4 in rat skeletal muscle and its translocation to plasma membrane as well. *V. amygdalina* was also found to significantly inhibit the key hepatic gluconeogenic enzyme, glucose-6-phosphatase. Investigation of the synergistic antidiabetic effect of *V. amygdalina* and other medicinal plants yielded positive results. A study on the synergistic antidiabetic activity of *V. amygdalina* and *Azadirachta indica* [126] showed that compared with single extracts, the combined extract of *V. amygdalina* and *A. indica* promptly lowered blood glucose and maintained a relatively steady level over the study period, in tandem with insulin. The features of diabetic pathology, indicated in the histology of the liver and pancreas, were reversed. The extent of recovery was partial with *V. amygdalina*, better with *A. indica*, and distinct and total with *V. amygdalina* and *A. indica* combined. The

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beneficial synergistic effect was postulated to be exerted via oxidative stress attenuation, insulin mimetic action and β-cell regeneration. The synergistic postprandial blood glucose modulatory properties of *V. amygdalina*, *Gongronema latifolium* and *Occimum gratissimum* aqueous decoctions has also been reported [127]. It was concluded from the study that the decoction containing the three vegetables was superior in activity to any one or blends of only two, of the three decoctions.

7.9. *Moringa oleifera*

Moringa oleifera is a popular food plant with multiple medicinal uses including treatment of diabetes [128]. Various parts of the plant have been shown to have antidiabetic potential in several studies. In severely diabetic animals, 200 mg/kg aqueous leaf extract of *M. oleifera* reduced fasting blood sugar by 69.2% after 21 days of treatment and also significantly reduced urine sugar [129]. The progression of diabetes was significantly reduced in STZ-diabetic rats treated with methanol extract *M. oleifera* pods for 21 days with treated animals showing a significant reduction in serum glucose and nitric oxide, with concomitant increases in serum insulin and protein levels [130]. It has also been shown that extracts of the bark of the plant prevented dexamethasone-induced insulin resistance in peripheral tissues [131].

7.10. Pinitol (3-O-methyl-D-chiro-inositol)

In a study which assessed the effects of pinitol supplementation on glucose tolerance and insulin sensitivity, investigators found that a single dose of pinitol, from a naturally-occurring food ingredient, administered acutely influences indices of whole-body glucose tolerance and insulin sensitivity in healthy subjects. The study showed that consumption of a pinitol-enriched beverage, containing a dose of 6.0 g, reduced the increase in glycaemia and insulinaemia provoked by oral carbohydrate over-load when compared with a placebo. They remarked that this dietary intervention would be an effective first-step strategy for treating hyperglycaemia and related insulin resistance states, although future research is warranted to evaluate whether chronic doses of pinitol are effective in subjects with altered glucose metabolism [132]. Inositol phosphoglycans (IPG) have been reported to be important post-receptor mediators of insulin action [133,134] and it was suggested that by acting as insulin's second messenger, pinitol could increase insulin sensitivity.

8. Mechanisms of action of antidiabetic botanicals

Antidiabetic botanicals have been reported to foster protection via several mechanisms. These include amelioration of oxidative stress, anti-inflammatory and antiatherogenic effects; control of metabolic fluxes among various organs and energy metabolism within individual tissues and cells leading to the maintenance of glucose and lipid homeostasis and stable levels of energy stores; cytoprotection of pancreatic β-cells; inhibition of aldose reductase; improvement of endothelial dysfunction; inhibition of angiogenesis and the regulation of the expression of

genes relevant for the development of T2DM A number of candidate genes have been identified in humans and many phytochemicals/extracts from traditional medicinal plants that can target diabetogenic genes have also been identified [135,136].

Medicinal plants can delay or inhibit glucose absorption, facilitate the entry of glucose into cells such as muscle cells, or stimulate insulin secretion by the pancreas. It was reported that oral administration of the ethanolic extract of *Allium sativum* showed significant antidiabetic effect in normal and alloxan-induced diabetic rats and that this effect was probably mediated through the stimulation of insulin secretion from the pancreas [137]. Oral administration of *Gymnena sylvestre* to diabetic rats was reported to increase the number of pancreatic islet cells as well as insulin levels suggesting a possible repair or regeneration of the pancreas [138]. *In vitro* and *in vivo* studies showed that water soluble extracts of *Gymnena sylvestre* released insulin probably due to the regeneration of pancreatic beta cells [139].

Aqueous extract of unripe fruit of *Momordica charantia* showed partial stimulation of insulin release from isolated beta cells of obese hyperglycaemic mice which is an indication of its insulin releasing action as a result of perturbations of membrane functions [140]. *Parinari excelsa* showed hypoglycaemic effects due to its insulin secretory activity in diabetic animal models [141]. Epicatechin which is the active principle isolated from the bark of *Pterocarpus maruspium* showed protective and restorative effect on beta cells of diabetic subjects. This may be due to its ability to regenerate beta cells [139].

Aqueous extract of *Citrullus colocynths* showed a dose dependent increase in insulin released from isolated islets [142]. Immunohistochemistry studies [143] showed that the amount of insulin in beta cells of the islet of Langerhans is greater in *Citrullus colocynthis* treated rats when compared with the control group.

A report on *in vitro* assays on some medicinal plants showed that they possess inhibitory activity on alpha glucosidase enzyme. In a study, thirty seven of forty-five samples examined showed IC_{50} values of between 2.33 μg/mL and 112.02 μg/mL, which were lower than that of acarbose (117.20 μg/mL) [144]. Also, 80% ethanol extract from *Garcinia daedalanthera* Pierre. leaves (Clusiaceae), *Antidesma celebicum* leaves (Euphorbiaceae), *Amaracarpus pubescens*, (Rubiaceae), and *Willughbeia tenuiflora* leaves (Apocynaceae) had the highest α-glucosidase inhibiting activity with IC_{50} of 2.33 μg/mL, 2.34 μg/mL, 3.64 μg/mL, and 8,16 μg/mL respectively. Meanwhile, types of enzyme inhibition mechanism from *Garcinia kydia* leaves (Clusiaceae), *Antidesma celebicum* leaves (Euphorbiaceae), and *Amaracarpus pubescens* leaves (Rubiaceae) were non-competitive inhibitor, competitive inhibitor, and mixed inhibitor respectively.

12. Conclusion

Diabetes mellitus and all its comorbidities constitute major causes of high economic loss which can in turn pose significant challenges to the economic development of developing

nations [145]. Despite efforts aimed at containing the disease, no definite cure has been found. Although the current available therapies have yielded appreciable improvements in the quality of life of diabetics, several reports have indicated that such improvements are not without the associated side effects. Studies have confirmed the benefits of medicinal plants with hypoglycaemic effects in the management of diabetes mellitus and many phytomedical preparations and compounds have been touted as candidates for antidiabetic drug development. However, the rate of developing these drugs is very slow, with only one clinical drug being reported to have gone from plant to pharmacy [110]. Therefore, there should be a focus on developing effective drugs from potent antidiabetic botanicals already identified while further research continues with new plants for the discovery of novel candidates for antidiabetic drugs. Also, potent herbal extracts should be standardized and made commercially available as many of these extracts often lack the drawbacks associated with single compounds.

Antidiabetic plants do not always have the same mechanism of actions because activities relate to their effects on the pancreatic β cells, the protective/inhibitory effect against insulinase and the increase of insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may involve improved glucose homeostasis, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates. The mechanisms of action of antidiabetic botanicals need to be properly delineated so that different cases of diabetes can be specifically addressed.

Further research studies on the antidabetic potentials of botanicals, especially in developing countries, are suggested. The aims of such studies should be to find the botanicals with the most effective antidiabetic activities and to examine the possibilities of developing these active ingredients into antidiabetic drugs for the effective management and treatment of diabetes.

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