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Title: **Some common antidiabetic plants of the Indian subcontinent**

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Running Title: Some common Indian antidiabetic plants

Abstract

Diabetes mellitus (DM), a clinical manifestation characterized by chronic hyperglycaemia, is often ascribed to either a defect in insulin secretion, insulin resistance or both. A*yurveda* (Indian Traditional Medicinal System) have shown promising results in the treatment of diabetes using various plants and herbs with negligible side effects and cost effective treatment. However, only limited number of these plants have been explored and scientifically validated for their hypoglycemic effect. This review highlights some of the plants being commonly used in India for their hypoglycaemic effects.

Key words: Diabetes, medicinal plants, hypoglycaemic effect, herbal remedies

Introduction

Diabetes mellitus (DM) has been defined as a hyperglycaemic clinical manifestation due to a dysfunction of metabolic systems (viz. carbohydrate, lipid and protein metabolism) and is one of the most common endocrine disorders. DM is generally attributed to the abnormal secretion of insulin (by pancreatic β-cells), inability of the insulin to stimulate the peripheral utilization (muscle and adiposities) and/or increased endogenous glucose production by the liver. [1] DM is classified as Type 1 or Type 2 diabetes. The cause of the Type 1 diabetes has been attributed to lower insulin level in the body possibly due to autoimmune destruction of the β-cells. Approximately 80-90 % of the diabetic population suffers from Type 2 diabetes [2], which is generally due to abnormally-reduced insulin secretion and/or insulin resistance. Genetic, societal and environmental factors (e.g., obesity, improper diet, sedentary lifestyles, etc.) all play important roles in its aetiopathogenesis. [3, 4]

The estimated number of individuals aged 20 years or more suffering from DM worldwide will be ~366 million in 2030.[5] The most common cause of mortality in Type 2 diabetes patients is cardiovascular disease (CVD), which accounts for more than 50% of deaths.[6] With ever-increasing diabetes-related morbidity and mortality, there is growing public health concern.[7,8]

In a recent document, the International Diabetes Federation identified diabetes as the fourth leading cause of global mortality.[2] Though the prevalence of diabetes is much higher in developed countries, the number of patients in developing countries is also increasing and its impact will be increasing felt in the near future. [9] The majority of people suffering from diabetes in developing countries are in the 45 to 64 years age

bracket while in developed countries, it is over 64 years. By the year 2030, the estimated number of people under the age of 64 years suffering from DM in developing countries will be 82 million, with 48 million in developed countries.[10] Diabetes may grow to epidemic proportions in India, given increasing lifespan, continued urbanization and the resulting changes in dietary and lifestyle patterns. [11] As a projected estimate from 1995 to 2025 there will be a 300 % increase in the number of patients suffering from DM in India and the world's highest numbers of diabetic patients will also be in India. [12]

Concurrent with advancements in technology, there has been a decrease in physical activity as well as an increase in mental stress in India, which increases the prevalence of the disease. Two independent studies, the Chennai Urban Population Study and the Chennai Urban Rural Epidemiological Study, found a marked increase in the prevalence of DM within a short span. The results of these studies highlighted the impact of urbanization in the prevalence of diabetes in India [13], with the authors reporting a two-fold higher prevalence in people with a higher socio-economic status. [13]

As mentioned previously, DM is a collection of closely-related diseases characterized by hyperglycaemia. Type 1 DM is a catabolic disorder due to an autoimmune response, which results in the destruction of the insulin-secreting cells, the *Islets of Langerhans*. The condition leads to the drastic reduction in circulating insulin levels which further leads to ketosis and hyperglycemia in addition to lipid and protein metabolic dysfunction. The patient has to be administered exogenous insulin to reverse the metabolic dysfunction. [14] Unlike Type 1 DM, Type 2 DM is due to the relative decrease in insulin levels, which is mainly attributed to resistance of insulin activity. DM, particularly the type 2 variety, is often associated with complications of micro vascular

(retinal, renal, neuropathic) and macro vascular (coronary, peripheral vascular) ailments. Treatment of Type 2 DM includes administration of an active agent that either increases the amount of insulin secreted by the pancreas, increases the sensitivity of target organs to insulin and/or decreases the rate at which glucose is absorbed by the gastrointestinal tract.

Diabetes increases the risk of myocardial infarction in addition to acceleration of atherosclerosis. Uncontrolled diabetes increases the probability of renal failure and is one of the major causes of end stage renal disease. The nerve cells and arteries are also affected in DM patients, making the patients susceptible to foot ulceration. If not taken care of, the ulcer may become infected leading to gangrene and subsequent amputation. Diabetes may lead to polyneuropathy, defined as a neurological disorder of the peripheral nerves that often affects distal extremities.

Tissues are also significantly affected by DM. The retina, a structure rich in nerve cells, is also affected and often goes unnoticed for several years. Though diabetic retinopathy can be easily diagnosed and treated, it has emerged as a major cause of visual loss in patients. [15] Diabetic dermopathy is a skin disorder resulting in pigmentation of the skins. The condition is characterized by the formation of light brown scaly patches, which may be oval or circular. The condition is mainly due to the changes in the anatomy of the blood vessels that supply the skin, resulting in the leaking of blood constituents (in minor quantities) into the skin. The exact cause of micro and macro vascular complications being unknown, United Kingdom Perspective Diabetes Study (UKPDS) had shown control of hyperglycaemia produced beneficial effects.

Based on the above discussions, it is necessary to control the blood glucose level (BGL) in a diabetic patient within specified limits, with a controlled and restricted diet and lifestyle changes as the earliest non-pharmacologic controlling steps. Particularly, in type 2 DM an essential condition of management is the reduction of overall calorie with a reduced intake of saturated fats and simple sugars. Under the supervision of their family physician, patients should adhere to a weight management program Bariatric surgery has also been found to be effective in most patients.[16] The literature also suggests that increased physical activity in both type 1 and type 2 DM can also help in BGL management. [17]

The use of pharmacologically-active agents has gained prominence in DM management. A patient with DM may be treated with either insulin or with insulin secretagogue agents. In general, antidiabetic drugs (ADD) help reduce glucose toxicity by lowering the level of glycaemia. Unlike insulin (Type 1 and Type 2 DM), exenatide (Type 1 DM), and pramlintide (Type1 and Type 2 DM) which are given subcutaneously, most therapeutic agents used in Type 2 DM are administered orally (oral hypoglycaemic agents). ADDs can be classified into several groups based on their chemical characteristics. The choice of a therapeutic agent for treatment depends on several factors, including the nature of the diabetes, age, and physical condition of the patient. The experience of the physician also plays an important role in the selection of the therapeutic agent. Different classes of hypoglycaemic agents, along with their route of administration and therapeutic actions are detailed in (Table 1)

Currently available therapies for the treatment of DM include insulin and oral antidiabetic agents such as sulfonylurea, biguanides and alpha-glucosidase inhibitors,

which are used solely or in combination to achieve better glycaemic regulation (Table 1). The use of combined therapies mainly depends on the experience of the physician and the socio-economic condition of the patient. The use of these active agents often results in various side effects (e.g., dizziness, mild drowsiness, heartburn, nausea, vomiting, frequent urination or increased urine output, etc.), which has prompted the search for more effective and safer hypoglycaemic agents.

The treatment of DM in India dates back to the 6th century BC, the period when *Charaka* and *Sushruta* were documented. Plants provide an excellent source of drugs and a large proportion of currently-available drugs have been either derived directly or indirectly from plant sources. A look into present literatures suggests the existence of more than 800 plants that may possess hypoglycemic activity. [21] Many traditional Indian medicinal plants have been reported to possess hypoglycaemic activity and have been successfully used for the management of DM (Table 2).

Globally, scientists are using a wide array of chemically-derived plant compounds for their possible use in the treatment of diabetes. Most of these active compounds are secondary metabolites, which include alkaloids, flavonoids, phenolics, glycosides, polysaccharides, steroids, carbohydrates, glycopeptides, terpenoids, amino acids and inorganic ions. *In-vivo* experimentation with many plant extracts (e.g., *Cassia auriculata, Cymbopogon citrates,* etc.) in animal and human subjects indicated hypolipidaemic effects in addition to hypoglycaemic effects. Often, extracts derived from natural sources provide excellent pharmacological actions and negligible or no adverse effects. Therapeutic uses of plants being traditionally used on being explored may lead to the development of efficacious and cost-effective antidiabetic therapies.

Prior to the detailed discussion of some medicinal plants and their role in the treatment of DM, protocols used to ascertain the antidiabetic effects of a given formulation are being described in this review. Although *in-vitro* studies provide some initial important details and are more convenient in execution and cost effectiveness, it is necessary to ascertain the efficacy of the formulation in suitable animal models before clinical trials.[57-59] The treatment of DM typically involves the use of a therapeutic agent that controls glucose metabolism, resulting in: i) a decreased amount of glucose production, ii) an increased amount of glycogen stores, and iii) an increased insulin secretion and/or reduced absorption of the glucose. Efforts are being made to isolate and/or develop newer kinds of secretagogues e.g. incretins (gastrointestinal hormone responsible for insulin secretion) [60], transcription factors e.g. KLF11 (TIEG2) and peroxisome proliferator-activated receptors. [61, 62]

In-vitro test methods include studies that use either isolated pancreatic islet cell lines (IPICLs) or insulin-secreting cell lines (ISCLs). IPICLs are generally used to study the activity of the ion channels of the pancreatic β-cell membranes, which play an important role in the secretion of insulin. The cell membranes are hyperpolarized due to the continuous efflux of K^+ ions and blocked Ca^{2+} ion channels (resulting in increased cytoplasmic Ca^{2+} concentration) when the glucose level in the blood is below a threshold concentration, which does not allow insulin secretion. With the increase in BGL, there is an increased production of adenosine triphosphate (ATP) leading to the rapid depletion of adenosine diphosphate (ADP) with a subsequent closure of K^+ channels and a consequent increase in the opening of the Ca^{2+} channels. As the amount of Ca^{2+} ions increases

intracellularly, there is an exocytosis of insulin leading to abnormal electrophysiological activity in the β-cells.

The activity of β-cells in the presence of various therapeutic agents has been observed. [63,64] Although these cells play an important role in DM research, their use has been limited due to their reduced availability, which has led to the development of alternative insulin-secreting cell lines e.g. RIN, HIT, beta TC, MIN6 and INS-1 cells. The main advantage of these cell lines is their capacity to secrete insulin, even though their physiologies differ from that of β-cells. [65] Insulin resistance studies using adipose tissues and muscles may help to understand glucose uptake by these tissues in the presence of various bioactive agents. [66, 67]

Prior to clinical trials, glucose-controlled formulations under study are validated in animal models. Animal models for DM can be prepared either by (a) administering bioactive agent(s) having selective toxicity for the pancreatic β-cells, e.g. streptozotocin and alloxan; (b) surgical removal of pancreas and/or (c) use of transgenic mice.[68- 75]

The most commonly-used DM model is based on the administration of streptozotocin (STZ) and alloxan either parenterally, intravenously, intraperitoneally or subcutaneously.[68] STZ is concentrated in the pancreatic β-cells by the GLUT2 glucose transporters, which induces alkylation of the deoxyribonucleic acid (DNA) in addition to the activation of the poly adenosine diphosphate ribosylation. This results in the release of nitric oxide, which causes necrosis of the pancreatic β-cells. [68] Alloxan and dialuric acid (metabolite of alloxan), unlike STZ, release superoxide radicals resulting in the formation of hydrogen peroxide that increases the cytosolic Ca^{2+}concentration resulting in the necrosis of the pancreatic β-cells.[69] Anterior hypophysis extract has also been

used for inducing DM in animals.[74] For the surgical induction of DM in animals, at least 90-95% of the pancreas is removed to reduce the chances of hypertrophy of the remaining *Islets of Langerhans* present in the pancreas. This may lead to the secretion of insulin in sufficient quantities required for proper metabolic response. [76]

Medicinal plants having antidiabetic effect

Ayurveda and *Unani*, which are traditional Indian medicine systems, are based on the use of plants for the treatment of disease. The following section reviews traditional Indian medicinal plants used in the treatment of DM.

Gum Arabic (Source: *Acacia arabica*; Family: *Mimosaseae*)

Gum arabic (GA) also known as *acacia* is locally known as *babul* in India [77] and is obtained as an exudate from the *acacia* tree, which is a moderate to large-sized tree. Gummosis, the process of sealing of wounds in the bark of the trees, results in the formation of GA naturally. The GA formed due to the gummosis generally appears as large nodules. The tree can naturally be found throughout the drier parts of India. [32] GA consists of mixture of low molecular weight polysaccharides and high molecular weight hydroxyproline-rich glycoprotein. [78] Wadood *et al.* [22] reported on the hypoglycaemic effect of GA administered in normal alloxan diabetic rabbits. The group also reported that the hypoglycaemic activity of GA was due to the initiation of the insulin release from pancreatic β-cells and was without significant adverse effects. The aqueous methanolic extract of the pods of the plant had also been documented for its hypoglycaemic activity in alloxan induced diabetic rabbits. [79]

Wood Apple (Source: *Aegle marmelos*; Family: *Rutaceae*)

Local wood apple is commonly known as *bael*, a medium-sized tree easily cultivated in the Indian sub-continent. *In-vivo* oral administration of the aqueous extracts of the root bark and leaves in rats had shown a hypoglycaemic effect. [23,80] In addition to the hypoglycaemic effect, the leaf extracts also resulted in a significant reduction in urea, body weight, liver glycogen and serum cholesterol levels in alloxan induced diabetic rats. [80] The aqueous leaf extract also had the capability to reduce malate dehydrogenase levels, which often associated with diabetes, normalize the histo-pathological conditions of pancreas and kidney in STZ (streptozotocin) induced diabetic rat models. [24, 81] A recent study indicated that the leaf extract could up regulate the total muscarinic and muscarinic M_{1s} receptors in STZ-induced diabetes rat models. The effect was found to be equivalent to the action of the insulin. [82]

Aloe (Source: *Aloe vera* or *Aloe barbadensis*; Family: *Lilliaceae*)

The plants of the genus *Aloe* are distributed over tropical regions and the Arabian Peninsula. In general, these plants are small, stem less, herbaceous perennials having shallow root systems. Only four species of *Aloe* are available in India, and of these only *Aloe vera* (*Aloe barbadensis*) is widely available. [83] For centuries, *aloe* has been used for the treatment of Type 2 DM and hyperlipidaemia. [84] In a clinical study where subjects were administered for 42 days with either *aloe* juice or glibenclamide or combination of two and compared with placebo, the BGL of the patients treated with either *aloe* juice, glibenclamide or a combination of the two showed a significant reduction compared to the control subjects. [85] A 9 month study indicated a reduction in

BGL compared to a placebo group, though the results were not statistically significant. [26] The leaf pulp (gel) from *aloe* had also showed hypoglycaemic activity in Type 2 diabetic rat models. [86, 87] This effect was attributed to the polyphenols present in the gel. [88]

In a recently-conducted study on STZ-induced diabetes rat models, in which the rats were fed with *aloe*, results indicated a reduction of BGL (to normal range) along with increase in the body weight. The histo-pathology of the pancreas, liver and epithelium of the small intestine after the therapy indicated normal anatomy compared with the start of the therapy.[89] Studies had also confirmed the beneficial effect of *Aloe vera* gel on membrane-bound phosphatases and lysosomal hydrolases, which being important in intracellular metabolism, and restoration of enzymatic activities to near normalcy. [90] Phytosterols isolated from AV (namely lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol and 24-methylene-cycloartanol) had shown hypoglycaemic effects and reduced BGL even when used separately. [27]

Aloe ferox (AF) had also been found to alleviate symptoms of DM as well as cardiovascular diseases, cancer and neurodegeneration. [91] Aloe carboxypeptidase (which inhibits acetic acid-related intraperitoneal vascular permeability) extracted from *Aloe arborescens* could inhibit the STZ-induced vascular permeability of pancreatic islets. [92]

Kalmegh (Source: *Andrographis paniculata*; Family: *Acanthaceae*)

Andrographis paniculata is locally known as *kalmegh* and is an annual herb found in the plains of India and other Asian countries. It is used in traditional Indian medicine as an antioxidant and hepatoprotective. [93] It had been shown that oral administration of

Kalmegh ethanolic extracts reduced BGL in STZ-induced diabetic rat models compared to a placebo group administered distilled water. However, it did not show any hypoglycaemic effect in normal rats. The hypoglycaemic effect of the extract was similar to Metformin and showed a dose-dependent response. As well, it helped to maintain leptin levels, reduced glucose-6-phosphatase and reduced serum triglyceride levels without any effect on serum cholesterol levels. [29] Husen *et al*. [94] reported that the freeze-dried extract showed enhanced activity. Zhang and Tan [29] reported the reduction of fasting serum glucose levels after the administration of the extract in the STZ-induced diabetic rat models. The hypoglycaemic activity had been correlated to the presence of andrographolide, which increased the utilization of the plasma glucose thereby lowering the plasma glucose in diabetic rats lacking insulin.[28] Reyes *et al.* [95] indicated that the hypoglycaemic effects of *kalmegh* could help to restore the oestrous cycle in alloxan-induced diabetic rat models.

Neem (Source: *Azadirachta indica*; Family: *Meliaceae*)

Neem is a medium to large-sized fast-growing tropical evergreen tree abundant in the Indian subcontinent. The administration of the hydro alcoholic extract of the plant to STZ-induced diabetic rat models had shown a hypoglycaemic effect.[30] This observation was attributed to the inhibition of the action of the epinephrine on glucose metabolism thereby increasing the utilization of peripheral glucose.[33] The aqueous extract of the plant was found to inhibit aldose reductase, responsible for sugar-induced cataracts in DM patients and of rat lenses under *in-vitro* conditions.[96] The oral administration of extracts from the kernel and husk of the seeds were able to prevent the oxidative stress in

the heart and erythrocytes of the STZ-induced diabetes rat models. This helped in the protection of the animal from cardiac damage, but the extracts did not prevent renal or hepatic toxicity. [97, 98] In a recent study, Waqar *et al.* [99] concluded that the extracts of the plant might play an important role in the therapy of the DM.

Ivy gourd (Source: *Coccinia indica*; Family: *Cucurbitaceae*)

Coccinia indica is locally known as *ivy gourd* and is widely distributed throughout India. It is a perennial tendril climber and it is used in traditional Indian medicine for various ailments varying from earache, eruptions to DM. [100] Studies revealed that the leaf of the plant helped in the management of DM when administered orally as a single dose. The beneficial effect was attributed either to the insulin secretagogue effect or to the change in the activity profile of enzymes engaged in glucose metabolism.[101] The oral administration of the ethanolic extract of the leaves to normal and STZ-induced diabetic male rats indicated a hypoglycaemic effect of the extract, which was attributed to the reduction of the glucose synthesis by inhibiting the glucose-6-phosphatase and fructose-1,6-bisphosphatase (gluconeogenic enzymes) and by activating glucose-6-phosphate dehydrogenase (responsible for glucose oxidation).[102] A similar finding had been reported by Venkateshwaran and Pari. [103] They further added that the consumption of the leaf extract could reverse biochemical complications associated with DM. [103] In two other studies, it was reported that the ethanolic extract of the leaves had antioxidant properties and prevented the fatty acid changes produced during diabetes. [103, 104]

The suppression of the enzyme glucose-6-phosphatase was also reported by Hossain *et al*. [36] A hydro alcoholic extract of *Musa paradisiaca, Tamarindus indica,*

Eugenia jambolana and *Coccinia indica* was reported for the possible therapy of testicular disorders associated with DM. [105] A recent study indicated that the management of DM was improved when the leaf extract of *Coccinia indica* was administered with the root extract of *Musa paradisiaca.* [106] Pectin isolated from the fruit, when administered orally, showed a significant hypoglycaemic effect in normal rats. The therapy resulted in a reduction of the blood glucose level with a corresponding increase in liver glycogen. The biochemical profile of the rats indicated an increased activity of glycogen synthetase and a decrease in phosphorylase activity. [34] Ethanolic extract of the roots had shown a hypoglycaemic effect after oral administration. [35]

Banyan tree (Source: *Ficus benghalensis*; Family: *Urticaceae*)

This is a big tree widely distributed throughout India that can grow to an enormous size. The ethanolic bark extract, when administered orally, had shown hypoglycaemic effect in STZ-induced diabetic rats that showed elevated serum insulin levels. [39] Bengalenoside, a glucoside present in the bark, was reported to have hypoglycaemic activity. [37] This author also reported the hypoglycaemic activity of leucopelarogonidin and dimethyl ether of leucocyanidin-3-O-beta-D-gallactosyl cellobioside.[107,108] Leucopelarogonidin showed hypoglycaemic activity in normal dogs and alloxan diabetic dogs while the dimethyl ether compound showed an additive response when used in conjunction with insulin in the treatment of alloxan diabetes. This combination also helped reduced serum cholesterol and triglyceride levels. Furthermore, the ether, when used in isolation, showed a hypoglycaemic effect in normal rats. Leucopelarogonidin was found to be more potent as a secretagogue agent when compared to leucocyanidin-3-O-beta-D-

gallactosyl cellobioside. 3-O-α-L-rhamnoside (also isolated from bark) showed hypoglycaemic action in normal rats. [38]

China rose/ Jasson (Source: *Hibiscus rosa- sinensis*; Family: *Malvaceae*)

Locally the plant is named as *gurhal/orhul* and is an evergreen shrub widely distributed in East Asia. It is also widely cultivated throughout India. Oral administration of the ethanolic extract of flower showed a hypoglycaemic effect in rat models comparable to that of Tolbutamide. The hypoglycaemic effect of the extract was attributed either to the secretagogue effect on the pancreatic β-cells or by increasing glyconeogenesis in the liver. [109]. Oral administration of ethanolic extracts of *Hibiscus sabdariffa* had also shown hypoglycaemic effect in alloxan-treated rats. The extract was also more effective at reducing cholesterol, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) cholesterol levels than lovastatin. [110]

Mango (Source: *Mangifera indica*; Family: *Anacardiaceae*)

Mangifera indica is locally known as *aam* (mango) and is common in India. The seeds and fruits of the plants have been used for centuries in traditional Indian medicine for the treatment of various clinical ailments. In a Brazilian study, the tea prepared from the leaves of the plant showed no hypoglycaemic effect on normal and STZ-treated rat models. [111] Similar effects were also found with the leaf extracts, however the extract showed hypoglycaemic effect when administered 60 min prior to or concurrently with glucose, which was attributed to the reduction in the intestinal absorption of glucose. [41] Mangiferin (xanthone glucoside), when administered to STZ-treated rat models either

intraperitoneally or orally showed significant hypoglycaemic, antihyperlipidaemic and antiatherogenic properties. [42] Administration of the aqueous extract of stem/bark to STZ-treated diabetic rat models showed antinflammatory, analgesic and hypoglycaemic effects. [112]The aqueous extract of the stems were found to reduce the serum oxidative stress in elderly patients. In DM, the oxidative stress was very high, hence it had been postulated that the administration of the stem extract could improve patient's prognosis. [113]

Bitter melon (Source: *Momordica charantia*; Family: *Cucurbitaceae*)

Bitter melon is locally known as *karela* and is regarded as an antidiabetic and antihyperglycaemic agent in most Asian Countries. [114- 116, 23] The oral administration of the fruit juice and the seed powder had been reported to show hypoglycaemic effect both in animal models and human subjects. [117] Oral administration of the fruit juice resulted in improved glucose tolerance in 73% patients while 27% failed to respond to the therapy. Similar responses were also obtained in rat models fed with the alcoholic extracts of the fruit pulp; the hypoglycaemic effects were due to increased glucose utilization. [118]Some authors had also proposed that the consumption of the fruit enhanced glucose uptake thereby promoting insulin release.[45] Others had reported that the hypoglycaemic effect of the fruit was due to the presence of oleanolic acid 3-o-glucurnide and memordin, which decreased glucose uptake from the intestine. [43, 44] McWhorter [44] attributed the hypoglycaemic activity was due to the presence of vicine (pyrmadine nucleoside), polypeptide-p and charantin containing mixed sterols. He reported that these sterols enhanced glucose uptake and glycogen synthesis by the muscle

and liver thereby reducing glucose synthesis. In a separate study, a group claimed that the fruit juice was not able to show any hypoglycaemic effect in response to an external glucose load. [119] Srivastava *et al.* [120] reported that the aqueous extract of the fruit was more effective in reducing blood glucose in alloxan diabetic rats than the dried powder of the fruit. They also reported that the aqueous extract delayed the appearance of cataracts and other secondary complications associated with DM. Shibib *et al.* [102] indicated that the ethanolic extract of the fruit was able to produce a hypoglycaemic effect in normal and STZ induced diabetic rats. These were attributed to the inhibition of glucose-6-phosphatase and fructose-1, 6 biphosphatase in the liver with a subsequent stimulation of red blood cells and hepatic glucose-6-phosphate dehydrogenase activity. A recent study concluded that administration of the ethanolic extract of bitter melon to alloxan induced diabetic albino rats resulted in a hypoglycaemic effect with lowered glucose levels and that remained constant for 15 days even after discontinuation of the therapy.[121]

The acetone extract of bitter melon produced regeneration of pancreatic β-cells. [122]Some authors also believed that the fruit juice caused renewal of β-cells in STZ-induced diabetic rats and might also take part in the recovery of the functions of the partially destroyed β-cells. A water-soluble peptide, MC2-1-5, from bitter melon had also shown hypoglycaemic property. [123] Researchers hypothesized that triterpenoids present in the plant had the capability to overcome cellular insulin resistance by activating AMP-activated protein kinase. [124, 125] The consumption of bitter melon might help in the protection of glycosaminoglycans (GAGs), which promoted proper functioning of the kidney by maintaining the glomerular filtration barrier, thereby delaying complications associated with diabetes.[126] Their beneficial effect had been

attributed to the high amount of dietary (both soluble and insoluble) fibre in the plant. [127] Studies on alloxan induced diabetic rats had indicated other benefits, such as restoration of the oestrous cycle, hepato-ranal protective and hypolipidemic effects.[95,127] Conversely, others had reported no beneficial effects of the bitter melon in the treatment of DM. [128]

Curry tree (Source: *Murraya koenigii*; Family: *Rutaceae*)

The tree is commonly known as sweet *neem* and locally as *kadipatta*. Leaves of *Murraya koenigii* are used as a flavouring agent in various Indian dishes. They are also consumed orally by DM patients in the southern parts of India. Iyer and Mani [129] examined the administration of the powdered leaves to non-insulin dependent DM patients. They observed that the treatment led to reduction of the fasting and postprandial blood sugar levels with no changes in other elements of their blood biochemistry profiles. Oral administration of the leaves to normal rats, mildly diabetic rats (alloxan-treated) and moderately diabetic rats (STZ-treated) had resulted in hypoglycaemic and anti-hyperglycaemic (for mild diabetic rats) effects. The groups attributed these results to the protection of pancreatic β-cells from the alloxan and STZ cytotoxic effects. [130] Khan *et al*. [42] showed that administration of the leaves resulted in increased hepatic glycogen content, which resulted in lowered blood glucose levels. Oral administration of the methanolic extract of the plant leaves to normal and alloxan-induced diabetic rats resulted in hypoglycaemic effects. This was attributed to the anti-oxidant properties of the extract, which partially reversed pathological changes in the glucose metabolism.[131] In addition, methanolic extracts also reduced blood cholesterol levels and might be used for the

management of Type 2 DM associated with high cholesterol levels. [131, 132] However, the methanolic extract was regarded as moderately toxic, affecting the liver and kidneys when administered at high doses and might lead to liver inflammation.[133] The aqueous extract of the leaves showed similar hypoglycaemic effects with an improvement of the glucose tolerance.[134, 135]

Holy Basil (Source: *Ocimum sanctum*; Family: *Lamiaceae*)

The herb is locally known as *tulasi* and can be found throughout India where it is used in traditional medicine for the management of various conditions viz. bronchitis, cancer, DM and inflammations. The ethanolic extract of the leaves was reported to have hypoglycaemic effect as early as in 1968. [136]The hypoglycaemic effect of the ethanolic extracts had been found to be 91.55% and 70.43% in normal and diabetic rats, respectively, when compared with Tolbutamide. A clinical study reported that the leaf extract resulted in a significant reduction of the fasting and postprandial blood glucose levels as well as a mild reduction in cholesterol levels, with the authors suggesting that basil leaves might be used as an adjunct therapy in mild to moderate non-insulin dependent DM. [137] Similar effects were also reported in normal and alloxan-induced diabetes rats [138]. In addition to the hypoglycaemic effects, the ethanolic extract had also shown partial correction of hexokinase, glucokinase and phosphofructokinase enzyme activity in STZ induced diabetic rats. [138]The hypoglycaemic effect was also reported with the administration of the leaf powder in diabetic rats. [139]

The aqueous extracts of the plant had been found to inhibit rat lens aldose reductase, which played an important role in inducing cataract in DM patients.[96] The

ethanolic extracts of the leaves stimulated insulin secretion from rat pancreas, suggesting that this might be a mechanism for its antidiabetic actions.[140] However, oral administration of the aqueous extract of the leaves to alloxan induced diabetic rats indicated a decreased opacity index resulting in the formation of the cataract, even though the extract showed a significant hypoglycaemic effect. [138] Aqueous extracts of the leaves could lead to the inhibition of plasma lipid peroxidation with a concurrent increase in the activity of the antioxidant enzyme activity alongside normalizing the glutathione levels in STZ-induced diabetic rats. The leaf extract had also been suggested for the regulation of corticosteroid-induced hyperglycaemia. [141, 142] Lastly, curry leaves had been found to have no effects on the fructose-induced hyperglycemia, hyperinsulinaemia and hypertriglyceridaemia. [143] However, another study contradicted this reporting that oral administrations of the aqueous extracts of the whole plant delayed the development of insulin resistance. [144]

Indian Gentian (Source: *Swertia chirayita*; Family: *Gentianaceae*)

Locally, the plant is known as *chirata* and is primarily found in the temperate zone of the Himalayas. The aqueous extract of the plant have been used throughout history for controlling DM in traditional Indian medicine. Oral administration of the ethanolic and hexane extracts of the plant showed hypoglycaemic effects without any influence on the hepatic glycogen level in normal, glucose-fed and STZ-treated rats. When the therapy was continued for a longer period, there was a significant reduction in the hepatic glycogen which was attributed mainly to increased secretion of insulin from pancreatic β-cells.[145]Hexane extracts consisting of swerchirin (1, 8-dihydroxy-3, 5-

dimethoxyxanthone), showed hypoglycaemic activity in fasted, glucose-loaded and Tolbutamide-pretreated albino rats. [146]The hypoglycaemic activity of the xanthone was attributed to glucose-mediated insulin secretion from pancreatic β-cells. [147]This group also reported that the xanthone's hypoglycaemic effect was more potent than Tolbutamide. [50]

Indian blackberry (Source: *Syzygium cumini*; Family: *Myrtaceae*)

Locally the fruits are known as *jamun* and the evergreen tree are being seen throughout India. The fruits are well known for antihyperglycaemic properties. The presence of antioxidants in the fruit and seed might synergistically help these properties [148]. The ethanolic extract of the seed kernel showed hypoglycaemic effect with corresponding increase in glucose tolerance and hepatic glycogen level in STZ-treated rat, and these effects were similar to that of glibenclamide. [49] Similar hypoglycaemic effects were reported by Sharma *et al*. [149] in sub-diabetic, moderately diabetic and severely diabetic rabbits. The ethanolic extract of the seeds had also shown a hypoglycaemic effect with a concurrent improvement in pancreas histopathology. Furthermore, blood glucose levels were not elevated even 15 days after discontinuation of the therapy. Mandal *et al*. [150] orally administered the ethereal fraction of the ethanolic extract to STZ-treated rats, which showed significant recovery of the β-cells of the pancreas. The ethanolic extract of the seed kernels had been found to inhibit α-glucosidase enzyme activity, which was the probable mechanism by which these extracts exerted antidiabetic activities.[151] However, there were various reports that did not support the antidiabetic potential of the

plant. [50, 152,153] A recent review reported that the seeds, seed kernels and fruit should be used at higher doses to obtain beneficial effects. [154]

Fenugreek (Source: *Trigonella foenum-graecum*; Family: *Leguminosae*)

Locally known as *methi*, this plant is available worldwide. Oral administration of the seed powder had led to reduced fasting blood glucose levels and improved glucose tolerance in human subjects. [155,156]This action was attributed to the increased activity of the gluconeogenic enzymes (e.g. phosphoenolpyruvate carboxykinase) in the liver and kidneys as well as glycolysis enzymes (e.g. liver pyruvate kinase) in the liver of alloxan-treated rats. [157, 158] The powdered seeds had also been shown to alter the levels of glutamate dehydrogenase and D-beta-hydroxybutyrate dehydrogenase, thereby providing protection to the liver and kidneys of diabetic rats.[159] The powdered seeds could also protect against degeneration of the sciatic nerve and the seeds were used in conjunction with sodium orthovanadate for the long-term care of diabetes in tissues such as the peripheral nerve.[160, 161] Fenugreek also helped in the prevention of diabetic retinopathy and other ocular diseases [162]. The alcoholic and aqueous extract of the seeds had been found to have antihyperglycaemic effects in alloxanized albino rat models. [51] The aqueous extract of the seeds was also able to exert an anti-cataract effect in alloxan induced diabetic rats.[156] The water soluble fraction of the fenugreek seeds exerted antidiabetic effect by inhibiting carbohydrate digestion and absorption with subsequent enhancement of peripheral insulin action. [163]

Raw and germinated fenugreek seeds had shown antidiabetic effects in human subjects while the boiled seeds failed to show any desirable effect. [164]The amino acid 4-

hydroxyisoleucine isolated from the seeds had been found to induce glucose-mediated insulin release which might be responsible for the seed's antidiabetic properties. [165] Presences of saponins combined with its high fiber content were thought to contribute to the antidiabetic effects of the seeds. Regular consumption of the seeds might help in the management of diabetes along with prevention of the atherosclerosis and coronary heart disease [166, 167] due to beneficial effects on dyslipidaemia and inhibition of platelet aggregation.[53] Consumption of the seeds showed an increase in the lipid peroxidation and circulating antioxidants in alloxan-treated rats. The consumption of powdered seeds had been found to increase the activity of numerous antioxidant enzymes, including superoxide dismutase, catalase, glutathione peroxidase and Na^+/K^+ ATPase. [167]The mucilage extracted from the seeds had also shown antidiabetic effects [168]. Oral administration of the seed extract on STZ induced diabetic rats showed improved hemorheological properties in addition to the reduction of the blood glucose and lipid levels.[169,170] Mitra *et al.* [55] reported that the fenugreek seed powder was effective in reducing fasting blood sugar on human volunteers in a dose dependent manner upto 75g/day. The seed powder also exhibited dose dependent effect in reducing triglyceride levels in blood given in a dose upto 100g/day.

Myrobalan (Source: *Terminalia chebula*; Family: Combretaceae)

Terminalia chebula, commonly known as *haritaki* is a plant native to India. It is a medium to large deciduous tree with widely spreading branches. It is one of the most universally used plants in the *ayurveda* having immense medicinal value.

The fruits of the species have been used as a traditional medicine due to its high tannin content (chebulic acid, chebulagic acid, corilagin and gallic acid). [171, 172] Kumar *et al.* [56] reported that an oral administration of ethanolic extract of the fruits of *Terminalia chebula* (200mg/kg body weight/rat/day) for 30 days significantly reduced the glycosylated hemoglobin in blood. It was also observed that there was a significant morphological change in the mitochondria and endoplasmic reticulum of beta cells of pancreas in the streptozotocin treated rats. The aqueous extract of the fruits of *Terminalia chebula* reduced the blood glucose level up to 43.2% in streptozotocin (STZ) induced mild diabetic rats when administered daily once for two months in a dose of 200 mg/kg body weight. [173]Additionally, it had also been found to reduce the increase in glycosylated hemoglobin significantly and controlled the elevated blood lipids and serum insulin levels. [173]

Future challenges and conclusions

Though many plants have shown promising results as antidiabetic agents, their efficacy varies from patient to patient. As a result, clinical studies must be carried out in large populations (phase III trials) before any plant-based product can be introduced into clinical practice. Studies shall be designed to identify and determine any undesirable side effects that result from their consumption. Furthermore, depending upon the cultivation conditions, the amount of secondary metabolites (which may possess additional pharmacological activity) will vary, leading to batch-to-batch variability in bioactivity. As a result, protocols for plant cultivation must be designed to minimize any variation in chemical composition.

Given that natural plant extracts are compositionally-complex, greater efforts towards the isolation, identification and purification of bioactive constituents must be undertaken. As shown in Table 2, though numerous antidiabetic effects have been shown, the nature of the compounds responsible for activity towards DM remains largely unknown. As a result, substantial efforts are required to better determine the antidiabetic mechanism of most plant extracts. Other than an improved understanding, such knowledge will help to better identify and potentially predict incompatibilities if being used in combination with synthetic drugs. Finally, the use of plant products as adjutant to, or replacements for, synthetic drugs may substantially help in reducing the costs associated with treatment of DM.

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