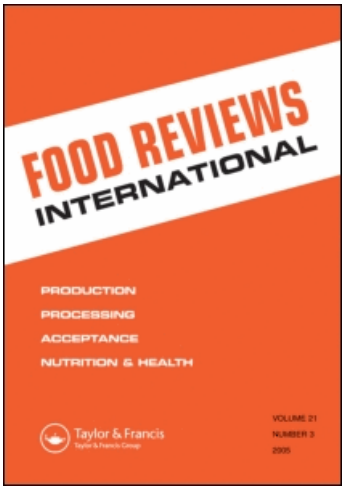

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Some Common Antidiabetic Plants of the Indian Subcontinent

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Diabetes mellitus (DM), a clinical manifestation characterized by chronic hyperglycaemia, is often ascribed to either a defect in insulin secretion, insulin resistance or both. Ayurveda (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 a 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.

Keywords Diabetes, medicinal plants, hypoglycaemic effect, herbal remedies

Introduction

Diabetes mellitus (DM) is 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), the 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 Type 1 diabetes has been attributed to lower insulin levels 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)

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In a recent document, the International Diabetes Federation identified diabetes as the fourth leading cause of global mortality.[2] Though the prevalence of the disease is much higher in developed countries, its incidence in developing countries is also on the rise, and its impact will be increasingly 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] In particular, DM may grow to epidemic proportions in India, given increasing lifespan, continued urbanization and the resulting changes in dietary and lifestyle patterns.[11] With a projected 300 % increase in the number of patients suffering from DM from 1995 to 2025, India will eventually have the world's highest numbers of diabetic patients.[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, both found a marked increase in the incidence of DM in the country. These studies highlighted the impact of urbanization, 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 this 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. Nerve cells and arteries are also affected in DM patients, making the patients susceptible to foot ulceration, and potentially gangrene and subsequent amputation if infection sets in. 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 in the skin. Though the exact cause of micro- and macro- vascular complications remains unknown, the United Kingdom Perspective Diabetes Study (UKPDS) showed that control of hyperglycaemia produced beneficial effects.

Based on the above discussions, it is necessary to control the blood glucose level (BGL) in diabetic patients within specified limits, with a controlled and restricted diet and lifestyle changes as the first non-pharmacologic treatments. In particular, in Type 2 DM, an essential condition of management is the reduction of overall caloric intake, with reduced ingestion 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 (Type 1 and Type 2 DM), which are given subcutaneously, most therapeutic agents used in Type 2 DM are administered orally. 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.

Table 1
Different classes of antidiabetic drugs with their mode of action

Group	Route of administration	Therapeutic action	Drug(s)	References
Insulin	Subcutaneous	Reduces blood glucose level	Insulin	[17]
Sulfonylurea	Oral	Insulin secretagogue	Tolbutamide, Glimeperide	[17]
Biguanides	Oral	Reduce hepatic glucose output and increase peripheral glucose uptake	Metformin, Phenformin	[17]
Meglitinides	Oral	Insulin sensitizers & secretogogue	Rosiglitazone	[17]
Thiazolidinediones	Oral	Bind to peroxisome proliferator activated receptor gamma (PPAR-γ) help in more production of insulin dependent enzymes	Rapaglamide, Miglitol	[18]
Alpha glucosidase inhibitor	Oral	Effect on glucose absorption from GI tract	Acarbose	[19]
Peptide analogue	Oral	Stimulates insulin release	Experimental	[20]

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 derived either directly or indirectly from plant sources. A look into the current literature suggests the existence of > 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 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, and 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 has indicated hypolipidaemic effects in addition to hypoglycaemic effects. Often, extracts derived from natural sources provide excellent pharmacological actions and negligible or no adverse effects. The therapeutic application of plants currently used in a more a traditional setting may lead to the development of widespread efficacious and cost-effective antidiabetic therapies.

Prior to the description of some medicinal plants and their role in the treatment of DM, protocols used to ascertain the antidiabetic effects of a given formulation will be reviewed. Although *in-vitro* studies can provide initial results and are more convenient in execution and cost-effectiveness, it is necessary to ascertain the efficacy of therapeutics in suitable animal models before proceeding to 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 an 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 insulin exocytosis leading to abnormal electrophysiological activity in the β-cells.

Table 2
Summary of reviewed plant species and their antidiabetic effect

Scientific name (common name)	Parts used	Active constituent	Animal model	Mechanism of action	References
Acacia arabica (Babul)	Seed	Not known	Alloxan-rabbit	↑Insulin release	(22)
Aegle marmelos (Bael)	Root, bark, Leaves	Not known	STZ-rat Alloxan rat	↓Malate dehydrogenase level, ↑Glycogen	(23–25)
Aloe vera (Aloe)	Dried sap	Lophenol, cycloartanol 24-methyl-lophenol	STZ-rat	↓Blood glucose level	(26, 27)
Andrographis paniculata (Kalmegh)	Leaves	Andrographolide	STZ-rat	↓Plasma glucose	(28, 29)
Azadirachta indica (Neem)	Leaves	Nimbidin, beta-sitosterol	STZ-rat	↑Peripheral glucose utilization	(30–33)
Coccinia indica (Ivy gourd)	Leaves, root Fruit	Alkaloid	STZ-rat	↓Glucose synthesis, ↑glycogen	(34–36)
Ficus benghalensis (Banyan tree)	Bark	Leucopelarogonidin, pelargonidin, leucocyanidin, Leucodelphinidine	STZ rat	↑Serum insulin, ↑Glycogen	(37–39)
Hibiscus rosa-sinensis (Jasson)	Leaves	Not known	Alloxan-rat	↑Glycogen	(40)
Mangifera indica (Mango)	Leaves	Mangiferin	STZ-rat	↓Glucose	(41, 42)
Momordica charantia (Bitter melon)	Seed, leaves, Fruit	Vicine, memordin polypeptide-p, charantin	STZ-rat, Alloxan -rat STZ-mice	↑Glucose tolerance ↑Insulin release	(43–45)
Murraya koenigii (Kadi patta)	Leaves	Not known	STZ- rat, DM-human subject	↑Glycogen ↑postprandial glucose	(46)
Ocimum sanctum (Tulasi)	Leaves	Eugenol (phenolic)	Alloxan-rat, STZ-rat	↓Blood glucose level	(47)
Swertia chirayita (Chirata)	Bark	Ophelic acid, chiratin, swerchirin	STZ rat	↑Insulin release	(48)
Syzygium cumini (Jamun)	Seed, leaves	Flavonoids, gallic acid, ellagic acid, tannins	STZ rat	↑Glucose tolerance	(49, 50)
Trigonella foenum graecum (Methi)	Seeds	Soluble dietary fibre, 4-hydroxyisoleucine	DM-human subject Alloxan-rat	↑Glucose tolerance, ↓Blood glucose level	(51–55)
Terminalia chebula	Seeds, fruit	Not known	STZ-rat	↓ Glucose	(56)

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 the 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 polyadenosine 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 an 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 *Accacia* 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 glycoproteins.[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, 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 are often associated with diabetes, and normalize the histo-pathological conditions of the pancreas and kidney in STZ (streptozotocin)-induced diabetic rat models.[24,81] A recent study indicated that the leaf extract could upregulate 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 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, stemless, 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 treated for 42 days with either *aloe* juice, glibenclamide, or a combination of the two, and compared with a placebo, the BGL of the patients significantly diminished with all treatments, as 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 with STZ-induced diabetes rat models, in which the rats were fed with *aloe*, results indicated a reduction of BGL to normal values, along with an increase in body weight. The histopathology 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 are 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.[27]

Aloe ferox (AF) had also been found to alleviate symptoms of DM as well as cardiovascular disease, cancer and neurodegeneration.[91] Aloe carboxypeptidase (which inhibits acetic acid-related intraperitoneal vascular permeability) extracted from *Aloe arborescens* were found to inhibit 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 agent.[93] It had been shown that oral administration of an *Kalmegh* ethanolic extract 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 compared to the extract. 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. Its hypoglycaemic activity has been correlated to the presence of andrographolide, which increases 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 alcoholic extract of the plant to STZ-induced diabetic rat models has 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 oxidative stress in the heart and erythrocytes of STZ-induced diabetes rat models. However, the extracts did not prevent renal or hepatic toxicity.[97,98] In a recent study, Waqar *et al.*[99] suggested that the extracts of the plant could play an important role in DM therapy.

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 used in traditional Indian medicine for various ailments, including ear aches, eruptions and DM.[100] Studies have revealed that the leaf of the plant can help in the management of DM when administered orally as a single dose, with its beneficial effect attributed to either an insulin secretagogue effect or to the change in the activity profile of enzymes engaged in glucose metabolism.[101] 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 was 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 fatty acid changes associated with DM.[103,104]

The suppression of the enzyme glucose-6-phosphatase was also reported by Hossain *et al.*[36] An 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 BGL reduction 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] The 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 with 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 to reduce 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 activity 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 the flower has shown 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 gluconeogenesis in the liver.[109] Oral administration of ethanolic extracts of *Hibiscus sabdariffa* has 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 anti–inflammatory, analgesic and hypoglycaemic effects.[112] The aqueous extract of the stems were found to reduce serum oxidative stress in elderly patients.[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 enhances glucose uptake thereby promoting insulin release.[45] Others have 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] Shane–McWhorter[44] attributed the hypoglycaemic activity 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 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 believe that the fruit juice causes 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 from bitter melon, MC2-1-5, has 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 promote proper functioning of the kidney by maintaining the glomerular filtration barrier, thereby delaying complications associated with diabetes.[126] Their beneficial effect has been attributed to the high amount of dietary (both soluble and insoluble) fibre in the plant.[127] Studies on alloxan-induced diabetic rats have indicated other benefits, such as restoration of the oestrous cycle, as well as hepato-renal protective and hypolipidemic effects.[95,127] Conversely, others have 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) resulted in hypoglycaemic and anti-hyperglycaemic (for mild

diabetic rats) effects. The groups attributed these results to the protection of pancreatic β-cells from 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 glucose metabolism.[131] In addition, methanolic extracts also reduced blood cholesterol levels, suggesting their use 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 effects as early as 1968.[136] The hypoglycaemic effect of the ethanolic extracts was 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 BGLs 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 has also shown partial correction of hexokinase, glucokinase and phosphofructokinase enzyme activity in STZ-induced diabetic rats.[138] A hypoglycaemic effect was also reported with the administration of the leaf powder to diabetic rats.[139]

The aqueous extracts of the plant has been found to inhibit rat lens aldose reductase, which played an important role in inducing cataracts.[96] The ethanolic extract of the leaves stimulated insulin secretion from the rat pancreas, suggesting that this might be a mechanism for its antidiabetic action.[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 cataracts, even though the extract showed a significant hypoglycaemic effect.[138] The leaf extract has also been suggested for the regulation of corticosteroid-induced hyperglycaemia.[141,142] Lastly, basil leaves have been found to have no effects on the fructose-induced hyperglycemia, hyperinsulinaemia and hypertriglyceridaemia.[143] However, another study contradicted this report, stating that oral administration of the aqueous extracts of the whole plant delayed 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 seen throughout India. The fruits are well known for their antihyperglycaemic properties. The presence of antioxidants in the fruit and seed might synergistically help these properties.[148] The ethanolic extract of the seed kernel has shown a hypoglycaemic effect with a corresponding increase in glucose tolerance and hepatic glycogen levels in STZ-treated rats, 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 also showed a hypoglycaemic effect with a concurrent improvement in pancreas histopathology. Mandal *et al*.[150] orally administered the ethereal fraction of the ethanolic extract to STZ-treated rats, which showed significant recovery of the pancreatic β-cells. The ethanolic extract of the seed kernels was found to inhibit α-glucosidase enzyme activity, which was the probable mechanism by which these extracts exerted their antidiabetic activity.[151] However, various reports do not support the antidiabetic potential of the plant.[50,152,153] A recent review reports 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. Numerous studies on the effects of fenugreek are based on its activity in powdered form, alcohol/aqueous extracts and germinated seeds. Oral administration of the seed powder had led to reduced fasting BGLs 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] Mitra *et al*.[55] reported that fenugreek seed powder was effective in reducing fasting blood sugar on human volunteers in a dose dependent manner up to 75 g/day. The seed powder also exhibited a dose-dependent effect in reducing triglyceride levels in blood given in doses up to 100g/day. The powdered seeds have 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 may also protect against degeneration of the sciatic nerve and, in conjunction with sodium orthovanadate, have been used for the long-term care of tissues such as the peripheral nerve.[160,161] Powdered fenugreek also helps in the prevention of diabetic retinopathy and other ocular diseases.[162]

The alcoholic and aqueous extracts of the seeds have been found to be antihyperglycaemic 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 is thought to exert an antidiabetic effect by inhibiting carbohydrate digestion and absorption with subsequent enhancement of insulin action.[163]

Raw and germinated fenugreek seeds have 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 has been found to induce glucose-mediated insulin release, which might be responsible for the seed's antidiabetic properties.[165] The presence of saponins and its high fibre content are thought to contribute to the antidiabetic effects of fenugreek. 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 its beneficial effects on dyslipidaemia and inhibition of platelet aggregation.[53] Consumption of the seeds has shown an increase in the lipid peroxidation and circulating antioxidants in alloxan-treated rats. The consumption of powdered seeds had been shown to increase the activity of numerous antioxidant enzymes, including superoxide dismutase, catalase, glutathione peroxidise, 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 blood glucose and lipid levels.[169,170]

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*, as it is thought to have an 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 the ethanolic extract of the fruits of the plant (200 mg/kg body weight/rat/day) for 30 days significantly reduced glycosylated hemoglobin in the blood. There were significant morphological changes in the mitochondria and endoplasmic reticulum of pancreatic β-cells in streptozotocin-treated rats. The aqueous extract of the fruits also reduced the blood glucose level up to 43.2% in streptozotocin-induced mild diabetic rats when administered daily once for two months at a dose of 200 mg/kg body weight.[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 should be designed to identify and determine any undesirable side effect(s) that results 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 these are used in combination with

synthetic drugs. Finally, the use of plant products as adjuvants or replacements for synthetic drugs may substantially help in reducing costs associated with treatment of DM.

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