

A pharmacological appraisal of medicinal plants with antidiabetic potential

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ABSTRACT

Diabetes mellitus is a complicated metabolic disorder that has gravely troubled the human health and quality of life. Conventional agents are being used to control diabetes along with lifestyle management. However, they are not entirely effective and no one has ever been reported to have fully recovered from diabetes. Numerous medicinal plants have been used for the management of diabetes mellitus in various traditional systems of medicine worldwide as they are a great source of biological constituents and many of them are known to be effective against diabetes. Medicinal plants with antihyperglycemic activities are being more desired, owing to lesser side-effects and low cost. This review focuses on the various plants that have been reported to be effective in diabetes. A record of various medicinal plants with their established antidiabetic and other health benefits has been reported. These include *Allium sativa*, *Eugenia jambolana*, *Panax ginseng*, *Gymnema sylvestre*, *Momrodica charantia*, *Ocimum sanctum*, *Phyllanthus amarus*, *Pterocarpus marsupium*, *Trigonella foenum graecum* and *Tinospora cordifolia*. All of them have shown a certain degree of antidiabetic activity by different mechanisms of action.

KEY WORDS: Antioxidant, diabetes mellitus, hypoglycemic, medicinal plants

Diabetes mellitus is a global health crisis, which has been persistently affecting the humanity, irrespective of the socioeconomic profile and geographic location of the population. According to an estimate, one person is detected with diabetes every 5 s somewhere in the world, while someone dies of it every 10 s.^[1] Diabetes mellitus has attained a pandemic form. Hence, it is very important to control diabetes and its complications to alleviate the human suffering. Scientists are desperately trying to manage this crippling disorder. Because plants are of enormous medicinal importance, they are being extensively explored for their use against diabetes. Herbal drugs can be quite acceptable as these drugs are known to cause less adverse effects.^[2] They are quite popular in developing countries.^[3] The increased admiration of herbal medicines for diabetes may be due to the side-effects associated with

the conventional antidiabetic drugs.^[4] The World Health Organization (WHO) has also substantiated the utilization of herbal remedies for the management of diabetes.^[5] Till date, numerous medicinal plants have been reported to be effective in diabetes, yet plenty of research is still needed to be done. This article focuses on the various plants that could be effective in the treatment of diabetes mellitus.

Prevalence of Diabetes Around the World

Diabetes is a metabolic disorder critically afflicting the population of both developed and developing countries. According to the Diabetes Atlas, the global prevalence of diabetes is estimated to be 4.6%, representing 151 million people, and is expected to go up to 333 million people by 2025. Recent reports have estimated an increase in these figures, with the global prevalence reaching up to 6.6%, representing 285 million people in 2010 and by 2030, it will rise up globally up to 7.8% (438 million people). Also, individual national prevalence rates from over 1% to almost 31% have been reported, severely affecting the developing countries and, more specifically, the lower socioeconomic groups. Diabetes is rapidly emerging as a major public health challenge. In 2010, diabetes will share 11.6% of the entire international healthcare expenses, much of which

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will comprise hospital admissions and medications. According to the International Diabetes Federation (IDF), the overall cost assessment for the global prevention and treatment of diabetes will run up to US\$490 billion by 2030.^[1] The occurrence of diabetes is higher in men than in women, but more women are reported to be suffering from diabetes than men. A notable increase in the proportion of people suffering from diabetes with >65 years of age is also reported.^[6] Studies have indicated a shocking rise in the prevalence of diabetes in India.^[2] According to the WHO, India had 31.7 million diabetic subjects in the year 2000, and this number would increase up to 79.4 million by the year 2030.^[6] Currently, India has the highest number of diabetic patients, and India is being called the diabetic capital of the world.^[7] Studies have shown a significant age-related prevalence in the urban population, largely among the people with sedentary life style.^[8]

Pathophysiology of Diabetes Mellitus

Diabetes mellitus is divided into two main types: type I (insulin -dependent diabetes mellitus or IDDM) and type II (non -insulin -dependent diabetes mellitus or NIDDM). IDDM occurs due to insulin insufficiency because the body does not generate any insulin and patients entirely depend on an exogenous supply of insulin. IDDM is more pronounced in children and young adults. It causes severe damage to the pancreatic β -cells. It is categorized as autoimmune (immune mediated) diabetes (type 1A) or idiopathic diabetes with β -cell destruction (type 1B), although the precise description of the later is still unknown.^[9] Patients suffering from NIDDM are unable to respond to insulin and can be treated with exercise, diet management and medication. Mostly, its onset is in adulthood, largely occurring in obese people over 40 years of age. NIDDM is the most widespread type. It indicates a condition with disturbed carbohydrate and fat metabolism. Hypertension, hyperlipidemia, hyperinsulinemia and atherosclerosis are often allied with diabetes. Both the types demonstrate some frequent symptoms like high blood sugar levels, unusual thirst, extreme hunger, frequent urination, extreme weakness, blurred vision etc. Although the pathophysiology of diabetes is not entirely understood, many studies indicate the participation of free radicals in the pathogenesis of diabetes^[10] and its complications.^[11-13] Free radicals are proficient enough of damaging cellular molecules, proteins, lipids and DNA, leading to alternation of cell functions. In fact, the abnormalities in lipids and proteins are one of the key reasons for the development of diabetic complications. During diabetes, free radicals oxidize the lipoproteins, and various irregularities of lipoprotein metabolism also occur in very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in diabetes.^[2] Different extracellular proteins are also modified into glycoprotein due to high blood glucose, which is associated with severe diabetic complications.^[14] Reactive oxygen species (ROS) are being reported to be formed in different tissues in diabetes^[15,16] by various sources such as the nonenzymatic glycosylation reaction,^[17] the electron transport chain in mitochondria^[18] and membrane -bound NADPH

oxidase.^[19,20] ROS are also involved in the progression of insulin resistance as well as pancreatic β -cell dysfunction.^[21] Also, advanced glycation end products (AGEs) are produced by non -enzymatic glycosylation of proteins, which tends to mount up on long -lived molecules in tissues creating abnormalities in cell and tissue functions.^[22,23] AGEs also play a role in improved vascular permeability in both micro- and macro-vascular structures by sticking to specific macrophage receptors, which leads to free radical production and endothelial dysfunction. AGEs, produced on nucleic acids, may also lead to altered gene expression and mutation. In diabetes, oxidative stress coexists along with decrease in the antioxidant status, which can lead to the detrimental effects due to free radicals.^[24] Vitamins C and E, the natural antioxidants, have been reported to decrease the oxidative stress in experimental diabetes.^[25] Numerous plant products have been reported to have a significant antioxidant activity, which may be of some benefit in diabetes.^[26,27]

Conventional Treatment

Diabetes is a multidimensional disorder and its management needs firm adherence to the prescribed treatment plan. The contemporary treatment of diabetes is focused on suppressing and controlling blood glucose to a normal level. The common agreement on management of type II diabetes is transformation in lifestyle along with appropriate diet and weight control. However, antidiabetic drugs are needed as these measures cannot provide satisfactory results. Antidiabetic drug therapy includes insulin injections and oral hypoglycemic drugs. These drugs act by various mechanisms to control the blood glucose level. However, many side-effects such as hypoglycemia, lactic acid intoxication and gastrointestinal upset, etc. have been reported in patients.^[28] Because the antidiabetic medication may sometimes involve prescribing more than one drug at the same time, which can augment the severity of these side-effects, efforts are being made to find a suitable antidiabetic and antioxidant therapy.

Medicinal Plants with Antidiabetic Activity and other Beneficial Effects

There are various herbal antidiabetic remedies used in various traditional systems of medicine prevailing around the world, although only some of them have been scientifically assessed for their efficacy. A list of the various medicinal plants with their antidiabetic and associated useful effects is given in Table 1.

Aegle marmelos (Bengal quince*, Bel[†]): Family - Rutaceae

The leaf extract of *Aegle marmelos* (*A. marmelos*), when given to alloxanized rats, has shown to reduce the blood sugar, urea, liver glycogen and serum cholesterol and also improve digestion. Along with this, it has also checked the peak rise in blood sugar in the oral glucose tolerance test (OGTT).^[150,174] Reduction in oxidative stress along with decreased blood glucose level has also been reported with the methanolic extract in alloxanized rats as apparent from the significant diminution in lipid peroxidation along with restored antioxidant enzyme

Table 1: Medicinal plants with antidiabetic and other medicinal properties

Plant name	Traditional/common name	Part used	Antidiabetic effect and other important effects	Reference
<i>Acacia arabica</i> (Leguminosae)	Guar gum*, Gum Arabic*	Seeds	Hypoglycemic, stimulate pancreatic β -cells for insulin release	[29]
<i>Acorus calamus</i> (Araceae)	Sweet flag* or Calamus*	Radix	Hypoglycemic, increased glucose consumption, decrease in triglyceride, free fatty acid, insulin sensitizer	[30,31]
<i>Aloe vera</i> (Liliaceae)	True or medicinal aloe*	Aloe gel, leaves	Hypoglycemic, hypolipidemic, antioxidant, increases glucose tolerance, stimulation of synthesis and/or release of insulin from pancreatic β -cells, enhanced insulin transport, anti-inflammatory	[32-37]
<i>Anethum graveolens</i> (Umbelliferae)	Dill*	Leaves	Hypoglycemic, antioxidant, decrease in serum insulin level	[38]
<i>Annona squamosa</i> (Annonaceae)	Sugar apple*	Leaves	Hypoglycemic, antihyperglycemic, antioxidant, increased plasma insulin level	[39-42]
<i>Areca catechu</i> (Palmae)	Betel nut*, supari†	Fruit	Hypoglycemic	[43]
<i>Astragalus membranaceus</i> (Leguminosae)	Yellow leader*	Root	Hypoglycemic, hypolipidemic, decrease in insulin resistance, potential insulin sensitizer, decreased expression of protein tyrosine phosphatase 1B (PTP1B)	[44-49]
<i>Averrhoa bilimbi</i> (Oxalidaceae)	Bilimbi†, cucumber tree* or tree sorrel*	Leaves	Hypoglycemic, hypolipidemic	[50, 51]
<i>Azadirachta indica</i> (Meliaceae)	Neem†	Leaves, seeds	Antihyperglycemic, antioxidant, antibacterial, antimalarial, antifertility, hepatoprotective	[52,53-56]
<i>Baccharis trimera</i> (Asteraceae)	-	Aerial parts of plant	Hypoglycemic	[57]
<i>Barleria lupulina</i> (Acanthaceae)	-	Aerial parts	Antihyperglycemic	[58,59]
<i>Bauhinia forficata</i> (Fabaceae)	Pata de Vaca†	Leaves	Hypoglycemic, antioxidant effect, useful in preventing diabetic complications	[60,61]
<i>Berberis aristata</i> (Berberidaceae)	Barberries* or pepperidge bushes*	Root	Antihyperglycemic, antioxidant	[62]
<i>Beta vulgaris</i> (Chenopodiaceae)	Chukkander†, beetroot* or garden beet*	Root	Increase in glucose tolerance	[63]
<i>Bixa orellana</i> (Bixaceae)	Achiote†, aploppas†	Leaves	Concentration-independent inhibition of human pancreatic α -amylase	[64]
<i>Brassica juncea</i> (Brassicaceae)	Mustard greens*, indian mustard*, chinese mustard* and leaf mustard*	Leaves	Hypoglycemic, antioxidant	[65,66]
<i>Butea monosperma</i> (Papilionaceae)	Palasa†, flame of the forest*	Bark, leaves, flower	Hypoglycemic, antihyperglycemic, antioxidant, thyroid inhibitory effect	[67-70]
<i>Camellia sinensis</i> (Theaceae)	Tea*	Leaves	Anti-hyperglycemic, antioxidant	[71,72]
<i>Capparis spinosa</i> (Capparaceae)	Caper bush*	Fruit	Antihyperglycemic, no change in basal insulin level	[73]
<i>Carum carvi</i> (Apiaceae)	Caraway*, meridian fennel*	Fruit	Antihyperglycemic, no change in basal insulin level	[73]
<i>Casearia esculenta</i> (Salicaceae)	-	Root	Antihyperglycemic, antihyperlipidemic, antioxidant	[74,75]
<i>Cassia auriculata</i> (Caesalpinaceae)	Ranawara† or avaram†, avaram senna*	Leaves, flowers	Antihyperglycemic and hypolipidemic activity, α -glucosidase inhibitory activity	[76,77]
<i>Cassia glauca</i> (Caesalpinaceae)	-	Leaves, bark	Antihyperglycemic, antihyperlipidemic	[78]
<i>Cinnamomum osmophloeum</i> (Lauraceae)	Pseudocinnamomum* or indigenous cinnamon*	Leaves	Enhanced adipopectin secretion and activation of insulin-signaling pathway	[79]
<i>Cinnamomum verum</i> (Lauraceae)	True cinnamon*, ceylon cinnamon*	Leaves	Concentration-dependant inhibition of human pancreatic α -amylase	[64]
<i>Citrullus vulgaris</i> (Cucurbitaceae)	Water melon*	Peel of fruit	Hypoglycemic, antihyperlipidemic, amelioration of thyroid dysfunction, inhibit lipid peroxidation	[80]
<i>Citrus sinensis</i> (Rutaceae)	Sweet orange*	Peel of fruit	Antihyperglycemic, antiperoxidative, antithyroid, insulin stimulating property, hypolipidemic, cardioprotective	[81-84]
<i>Citrus paradisi</i> (Rutaceae)	Grapefruit*	Seeds	Hypoglycemic, hypolipidemic, decrease in cardiovascular risk factors	[85]
<i>Cochlospermum vitifolium</i> (Cochlospermaceae)	-	Bark	Hypoglycemic, vasorelaxant and hepatoprotective properties	[86]
<i>Combretum micranthum</i> (Combretaceae)	Kinkeliba†	Leaves	Antihyperglycemic	[87]
<i>Coscinium fenestratum</i> (Menispermaceae)	-	Stem	Antidiabetic, hypolipidemic	[88]
<i>Costus igneus</i> (Costaceae)	Fiery costus* or spiral flag*	Leaves	Hypoglycemia	[89]

Table 1 (Contd...)

■ Khan, et al.: Review on anti-diabetic plants

Table 1 (Contd...)

Plant name	Traditional/common name	Part used	Antidiabetic effect and other important effects	Reference
<i>Costus speciosus</i> (Costaceae)	Crape ginger*	Root	Anti-hyperglycemic, antihyperlipemic and antioxidative effects	[90]
<i>Curcuma longa</i> (Zingiberaceae)	Turmeric*	Rhizome	Concentration-dependant inhibition of human pancreatic α -amylase	[64]
<i>Dendrobium chrysotoxum</i> (Orchidaceae)	Golden-bow dendrobium* or fried-egg orchid*	Stem	Antioxidant and anti -hyperglycemic	[91]
<i>Dioscorea polygonoides</i> (Dioscoreaceae)	Jamaican bitter yam*	Root	Hypoglycemic, hypolipidemic	[92]
<i>Embllica officinalis</i> (Euphorbiaceae)	Amla [†] , dhatriphala [†]	Fruit	Hypoglycemic, antioxidant, decrease in lipid peroxidation, antibacterial, antiulcerogenic, hepatoprotective, gastroprotective	[93,94-96]
<i>Ficus bengalensis</i> (Moraceae)	Bur [†] , banyan*	Aerial root, stem bark	Hypoglycemic, antioxidant, concentration dependant inhibition of human pancreatic α -amylase	[64,97,98]
<i>Ficus carica</i> (Moraceae)	Common fig*	Leaves	Hypoglycemic, hypolipidemic	[99-101]
<i>Ficus racemosa</i> (Moraceae)	Cluster fig tree* or goolar [†]	Bark	Strong hypoglycemic effect	[102]
<i>Globularia alypum</i> (Plantaginaceae)	-	Leaves	Antihyperglycemic, no effect on insulin secretion	[103]
<i>Gymnema montanum</i> (Asclepiadaceae)	-	Leaves	Antihyperglycemic, antihyperlipidemic, decrease in lipid peroxides, inhibition of apoptotic pathway	[104,105]
<i>Gynostemma pentaphyllum</i> (Cucurbitaceae)	Jiaogulan [†]	Leaves	Alternation of activities of glucose metabolic enzymes	[106]
<i>Hedychium spicatum</i> (Zingiberaceae)	Spiked ginger lily*, sandharlika [†]	Rhizome	Antihyperglycemic, inhibition of intestinal α -glucosidase activity	[107]
<i>Helichrysum plicatum</i> (Asteraceae)	-	Flower	Antihyperglycemic, antioxidant	[108]
<i>Helicteres isora</i> (Sterculiaceae)	-	Root, fruit, bark	Hypoglycemic, antihyperlipidemic, insulin sensitizer	[109-111]
<i>Hypophylla auriculata</i> (Acanthaceae)	Marsh barbel*	Aerial parts of plant	Hypoglycemic, antioxidant, decreased lipid peroxidation	[112]
<i>Hypoxis hemerocallidea</i> (Hypoxidaceae)	African star grass*, african potato*	Tuberous root	Anti-inflammatory, antineoplastic, antioxidant, antidiabetic and anti-infective properties, stimulate insulin release	[113-117]
<i>Indigofera mysorensis</i> (Fabaceae)	-	Whole plant	Antihyperglycemic, potential insulin sensitizer	[118]
<i>Juniperus chinensis</i> (Cupressaceae)	Chinese juniper*	Fruit	Antihyperglycemic, hypolipidemic	[119]
<i>Lagerstroemia speciosa</i> (Lythraceae)	Giant crape-myrtle*, queen's crape-myrtle*, banabá plant for philippines*, or pride of India*	Leaves	α -glucosidase inhibitor	[120]
<i>Linum usitatissimum</i> (Linaceae)	Flax* (also known as common flax* or linseed*)	Seeds	Inhibition of pancreatic amylase activity	[121]
<i>Liriope spicata</i> (Ruscaceae)	Creeping lilyturf*	Tuberous roots	Hypoglycemic and hypolipidemic	[122,123]
<i>Matricaria chamomilla</i> (Asteraceae)	German chamomile*	Aerial part of plant	Antihyperglycemic, antioxidant, protection of β -cells	[124]
<i>Momordica cymabalaria</i> (Cucurbitaceae)	Kadavanchi [†]	Fruit	Hypoglycemic, hypolipidemic	[125]
<i>Morus alba</i> (Moraceae)	Mulberry*, white mulberry*	Leaves	Inhibition of α -glucosidase, sucrose, maltase, inhibit porcine pancreatic α -amylase activity and reduced starch hydrolysis	[121,126]
<i>Morus indica</i> (Moraceae)	-	Leaves	Hypoglycemia	[89]
<i>Murraya koenigii</i> (Rutaceae)	Curry patta [†] , curry tree*	Leaves	Antihyperglycemic, enhances glycogenesis and reduce glycosylated Hb, gluconeogenesis, urea, uric acid, creatinine and glycogenolysis, concentration-independent inhibition of human pancreatic α -amylase	[64,127,128]
<i>Musa sapientum</i> (Musaceae)	Banana*	Flower	Antihyperglycemic, antioxidant	[129-131]
<i>Olea europaea</i> (Oleaceae)	Olive tree*	Leaves	Hypoglycemic, antioxidant, antihypertensive, anti -inflammatory, antiatherogenic, hypocholesterolemic	[132]
<i>Paeonia lactiflora</i> (Paeoniaceae)	Chinese peony*	Roots	Inhibition of PTP1B	[133]
<i>Paspalum scrobiculatum</i> (Poaceae)	Koda millet*, koda millet*	Grains	Antihyperglycemic, increase in serum insulin level, hypolipidemic	[134]
<i>Persea americana</i> (Lauraceae)	Avocado* or alligator pear*	Leaves	Hypoglycemic, hypocholesterolemic	[135]
<i>Phaseolus vulgaris</i> (Fabaceae)	Hulga [†] , white kidney bean*, common bean*	Seeds	Hypoglycemic, hypolipidemic, inhibition of α -amylase activity, alternation in level of insulin receptor and GLU -4 mRNA in skeletal muscle, enhanced production of adinopectin, decreased TNF- α level	[136,137-140]

Table 1 (Contd...)

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Plant name	Traditional/common name	Part used	Antidiabetic effect and other important effects	Reference
<i>Pistacia atlantica</i> (Anacardiaceae)	Mt. Atlas mastic tree* and as the Persian turpentine tree*	-	<i>In vitro</i> inhibition of α -amylase and α -glucosidase activity, acute postprandial antihyperglycemic	[141]
<i>Polygonatum odoratum</i> (Ruscaceae)	Angular solomon's -seal* or scented solomon's -seal*	Roots	Insulin sensitizers	[142]
<i>Punica granatum</i> (Lythraceae)	Anar [†]	Flowers, peel of fruit	Antioxidant, anti-hyperglycemic effect, inhibit TNF- α -stimulated free fatty acid release and attenuated TNF- α inhibition of adipopectin secretion, prevent diabetes via binding with PPAR- γ receptor, production of NO, inhibition of lipid peroxidation, inhibition of α -glucosidase activity	[81,136, 143-146]
<i>Raphanus sativus</i> (Brassicaceae)	Japanese radish*	Root, sprout	Hypoglycemic, improved lipid metabolism	[147-149]
<i>Retama raetam</i> (Fabaceae)	-	Fruit	Antihyperglycemic, inhibition of intestinal glucose absorption, stimulate pancreatic insulin release	[150,151]
<i>Rhodiola sachalinensis</i> (Crassulaceae)	-	Root	Hypoglycemic, hypolipidemic, antioxidant, increase in serum insulin level	[152,153]
<i>Rubus fruticosus</i> (Rosaceae)	-	-	Hypoglycemic, antihyperglycemic, no effect on insulin secretion	[103]
<i>Sclerocarya birrea</i> (Anacardiaceae)	Murula [†]	Stem bark	Hypoglycemic, increased plasma insulin level, prevented body weight loss, hypocholesterolemic, renoprotective, cardioprotective, antidiarrhoeal, antidiabetic, anti-inflammatory, antimicrobial, antiparasmodial, antihypertensive, anticonvulsant, antinociceptive and antioxidant properties	[154-157]
<i>Sutherlandia frutescens</i> (Fabaceae)	Cancer bush*, balloon pea*	Shoot	Hypoglycemic, anti -inflammatory, restores insulin levels and reduces intestinal glucose uptake	[158,159]
<i>Swietenia macrophylla</i> (Meliaceae)	Big leaf* Mahogany*, big-leaf mahogany*	Seeds	Hypoglycemic, hypolipidemic	[160]
<i>Swietenia mahagoni</i> (Meliaceae)	West Indian mahogany*	Bark	Antidiabetic, antioxidant	[161]
<i>Syagrus romanzoffiana</i> (Arecaceae)	Queen palm* or cocos palm*	Seed	Inhibition of α -glucosidase, reduce post-prandial blood glucose level	[162]
<i>Syzygium alternifolium</i> (Myrtaceae)	Shahajire [†]	Seeds	Hypoglycemic and antihyperglycemic	[163]
<i>Syzygium cumini</i> (Myrtaceae)	Jambul [†]	Seeds	Concentration-dependant inhibition of human pancreatic α -amylase	[64]
<i>Terminalia catappa</i> (Combretaceae)	-	Fruit	Hypoglycemia	[164]
<i>Tridax procumbens</i> (Asteraceae)	Dhaman grass*	Whole plant	Antihyperglycemic, hypoglycemic, correction in body weight	[165]
<i>Vaccinium angustifolium</i> (Ericaceae)	Canadian low bush blueberry*	Root, stem, leaf, fruit	Enhanced glucose transport, increase in glucose stimulated insulin release, reduced apoptosis, enhanced β -cells proliferation	[166]
<i>Vaccinium bracteatum</i> (Ericaceae)	-	Leaves	Potential hypoglycemic effect, body weight recovery	[167]
<i>Vaccinium vitis-idaea</i> (Ericaceae)	-	Berry	Potent antiglycating action, prevent insulin resistance and other metabolic diseases	[168,169]
<i>Vernonia amygdalina</i> (Asteraceae)	Bitter leaf*	-	Hypoglycemic and antihyperglycemic	[170,171]
<i>Withania somnifera</i> (Solanaceae)	Ashvagandha [†] , winter cherry*	Root	Hypoglycemic, diuretic and hypocholesterolemic, antioxidant, suppresses metformin-induced hypothyroidism	[172,173]

*English common name, [†]Regional name

levels.^[175] Treatment of streptozotocin-diabetic rats with the leaf extract of *A. marmelos* demonstrated superior functional state of pancreatic β -cells as it facilitates in the regeneration of damaged pancreas.^[176] Further investigation has revealed the presence of various important chemical constituents such as scopoletin and umbelliferone, which provides additional therapeutic benefits (in hyperthyroidism and collagen-mediated diabetic nephropathy).^[177,178]

Allium cepa (Onion*): Family - Amaryllidaceae

The ether extract of *Allium cepa* (*A. cepa*) has shown

antihyperglycemic activity in diabetic rabbits.^[179] Also, a 1 ml solution (0.4 g *A. cepa*/rat) when given to streptozotocin -diabetic rats causes an augmentation in fasting serum diabetic HDL levels, demonstrating alleviation of hyperglycemia along with considerable antioxidant activity.^[180] Moreover, when diabetic patients were administered a single oral dose of onion juice, it markedly controlled the post-prandial glucose levels.^[181] *A. cepa* is also reported to have a hypolipidemic effect. Administration of S-methyl cysteine sulfoxide (SCMS), a sulfur-containing amino acid from onion, significantly controlled the levels of blood glucose as well as lipids and

also normalized the activities of glucose 6 -phosphatase and 3 -hydroxy -3 -methylglutaryl coenzyme -A (HMG Co -A) reductase in alloxanized rats.^[182] A new compound, (S(S) R(C)) -S -(3 -pentenyl) -L -cysteine sulfoxide, which is obtained from the seed extract of *A. cepa* var. *tropeana* has also been reported to contain antioxidant properties.^[183]

Allium sativa (Garlic*): Family - Amaryllidaceae

When the aqueous extract of garlic [Figure 1] is given orally to sucrose-fed rabbits, it considerably improved hepatic glycogen and free amino acid content, reduced fasting blood glucose and triglyceride levels in serum.^[184] Also, garlic extract administered to streptozotocin-diabetic rats not only decreased the blood glucose level but also inhibited the lipid peroxidation and inhibited the superoxide formation. This study has also recommended its long-term use in preventing diabetic complications. However, the extrapolation of these results to humans needs further research.^[152] Most recent findings have also proposed that aged garlic extract inhibits the generation of glycation -derived free radicals and AGEs *in vitro*. S -allyl cysteine, [Figure 1] a chief ingredient of aged garlic, is a potent antioxidant that can inhibit AGEs synthesis and, thus, deserves more attention.^[185] Evidence also proposes that the antioxidative, anti -inflammatory and antiglycative properties of garlic are accountable for its role in preventing diabetes and its complications.^[186] Allicin, [Figure 1] a sulfur -containing compound isolated from garlic, is the reason for its pungent odor and also has considerable hypoglycemic action,^[187] which is thought to be due to the augmented hepatic metabolism, insulin release and/or insulin-sparing effect.^[188] Researchers have also reported that allicin contains considerable antioxidant^[189] and antimalarial activities.^[190] S -allyl cysteine sulfoxide (SACS), the precursor of allicin and garlic oils, is reported to control lipid peroxidation better than glibenclamide and insulin and also stimulated *in vitro* insulin release from the β -cells isolated from normal rats.^[191] Ajoene, [Figure 1] obtained from garlic, has been reported to show antithrombotic, anti -tumor, antifungal and antiparasitic properties,^[192] thus making garlic a useful plant.

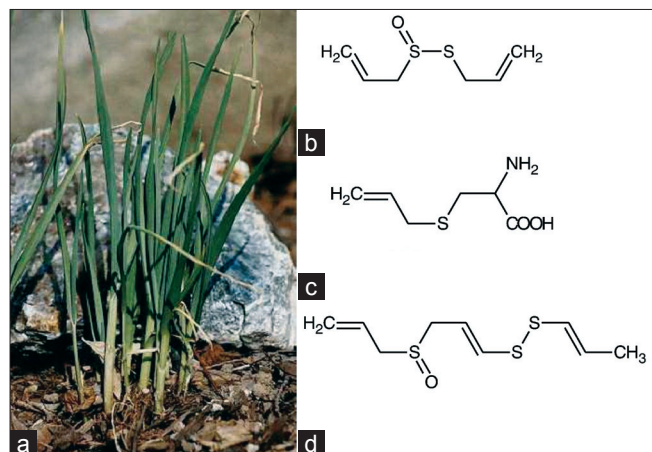


Figure 1: Garlic and its antidiabetic constituents. (a) *Allium sativa* (garlic), (b) allicin, (c) S-allyl cysteine, (d) ajoene

Caesalpinia bonducella (Gray Nicker*): Family - Fabaceae

The aqueous and ethanolic extracts of *Caesalpinia bonducella* (*C. bonducella*) demonstrated potent hypoglycemic activity in chronic type II diabetes. These extracts also improved glycogenesis, thereby escalating the liver glycogen content.^[193] Aqueous and 50% ethanolic extracts of *C. bonducella* seeds have also shown antihyperglycemic and hypolipidemic activities in streptozotocin -diabetic rats.^[194] Oral administration of seed extracts to alloxanized rats not only produced considerable lowering of the blood urea nitrogen levels but it also lowered the elevated cholesterol as well as LDL levels, confirming that the drug also has the potential to show antidiabetic as well as antihyperlipidemic effects. This antihyperglycemic action may be due to obstruction in absorption of glucose.^[195]

Capparis deciduas (Kerda[†], Kair[†], Karir[†]): Family - Capparaceae

Hypoglycemic effect was reported in alloxanized rats fed with the fruit powder of the *Capparis decidua* (*C. decidua*) plant. The powdered extract also significantly decreased the alloxan-induced lipid peroxidation in erythrocytes, kidney and heart. *C. decidua* is also reported to alter antioxidant enzyme levels and decreases oxidative stress.^[196] The antidiabetic potential may be due to the alkaloids present in it. When the alkaloid-rich fraction of *C. decidua* plant was given to streptozotocin -diabetic rats, it demonstrated promising results, establishing its claim for further purification and categorization of the individual alkaloids.^[197]

Coccinia indica (Ivy Gourd*, Little Gourd*): Family - Cucurbitaceae

The combined extract of *Coccinia indica* (*C. indica*) with *Musa paradisiaca* has shown a defensive effect against diabetes through β -cell regeneration in streptozotocin -diabetic albino rats.^[198] Also, an aqueous -methanol extract of *C. indica* along with *Musa paradisiaca*, *Tamarindus indica* and *Eugenia jambolana* provided considerable defense against testicular dysfunction along with lowering of blood glucose.^[199] In a study on diabetic patients, dried extracts of *C. indica*, when administered, helped to restore the normal activities of lipoprotein lipase, glucose -6 -phosphatase and lactate dehydrogenase,^[200] while in a double -blind, placebo -controlled, randomized trial on type 2 diabetic patients, the alcoholic extract of the herb significantly decreased the fasting and postprandial blood glucose levels in the experimental group as compared with the placebo group. However, no considerable alterations in the serum lipid levels were observed.^[201]

Eriobotrya japonica (Loquat[†]): Family - Rosaceae

Eriobotrya japonica (*E. japonica*) has been reported to show a distinct hypoglycemic action in normal and alloxanized rabbits and mice.^[202-204] Studies have revealed that 300 mg/kg of the leaf extract in streptozotocin-diabetic mice induced significant decrease in plasma glucose concentration, glycosylated serum

protein, total cholesterol, triglycerides and oxidative stress.^[205] The leaf extracts of *E. japonica* are also known to inhibit 11 β -hydroxy steroid dehydrogenase (HSD) type 1, preferentially over 11 β -HSD2, which might add to the antidiabetic effect of the plant.^[206] Further, studies demonstrated that sesquiterpene glycosides and polyhydroxylated triterpenoids are the active ingredients of *E. japonica* accountable for controlling diabetes mellitus.^[207] Also, the total triperpene acid fraction from the leaves demonstrated a high anti-diabetic potential beside hypolipidemic and antioxidant profile in alloxan and streptozotocin-diabetic mice.^[208]

Eugenia jambolana (Jambul[†]): Family - Myrtaceae

Decoction of *Eugenia jambolana* (*E. jambolana*) seed kernel is used as a domestic preparation for diabetes and it also forms a key ingredient of several antidiabetic herbal formulations. The pulp extract of *Eugenia* demonstrated hypoglycemic activity promptly than the seed extract in streptozotocin-diabetic mice. Increased serum insulin levels and inhibition of insulinase activity from liver and kidney was observed on oral administration of the extract in diabetic rats.^[209] Ethanolic extract of *Eugenia* seed kernel also established its antioxidant potential along with hypoglycemic effect in streptozotocin-diabetic rats.^[210] Combination treatment of lower dose of glimepiride together with ethanolic *Eugenia* seed extract showed potent hypoglycemic as well as antihyperglycemic activities without stern hypoglycemia in normal rats, concluding its possible use in considerable dose reduction of standard drugs.^[211] However, examination of the Brazilian *Eugenia* fruit has uncovered no beneficial effect of the plant extract in diabetic rats.^[212]

Ginseng species: - Family - Araliaceae

Ginseng root has been used since long because of its medicinal properties. Medicinally important ginseng species include *Panax ginseng* (Asian ginseng^{*}) [Figure 2] and *Panax quinquefolius* (American ginseng^{*}). The main chemical constituents of the entire ginseng species are ginsenosides, polysaccharides, peptides, polyacetylenic alcohol and fatty acids, with ginsenosides being the most important pharmacological constituent.^[213] Ginsenosides have been the object of countless researches as they are believed to be the key principles behind the efficacy and potential effects of ginseng. Therefore, it is also imperative to assess its worth using various analytical techniques.^[214] Animal study data indicate that both Asian ginseng^[215,216] and American ginseng^[217,218] have a prominent hypoglycemic effect, which may be due to ginsenoside Rb-2 [Figure 2] and, more specifically, because of panaxans I, J, K and L in type 1 diabetic models.^[219-222] American ginseng has also been reported to inhibit the tumor necrosis factor- α (TNF- α)-stimulated free fatty acid release and also attenuated the TNF α -inhibition of adiponectin secretion.^[136] Hypoglycemic activity of ginseng has also been established by clinical studies.^[223,224] However, a few adverse effects of ginseng have been observed, most common of which are nervousness and excitation, which are diminished with continued use or dosage

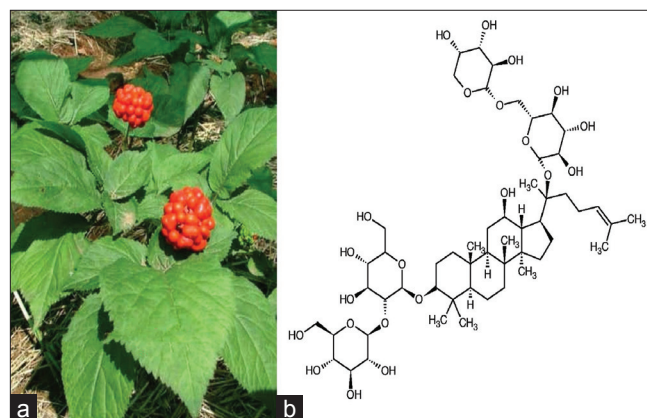


Figure 2: Ginseng and its antidiabetic constituent. (a) *Panax ginseng* (Asian ginseng), (b) Ginsenoside Rb2

reduction. Massive overdose of drug can lead to ginseng abuse syndrome.^[225] The suggested dosage is 1 - 3 g of the plant's crude root daily or 200 - 600 mg of standardized extract.^[226]

Gymnema sylvestre (Gymnema^{*}, Australian cow plant^{*}): Family - Asclepiadaceae

Gymnema sylvestre (*G. sylvestre*) has been used in the treatment of diabetes since ages. Assessment of the alcoholic extract of *G. sylvestre* on insulin secretion from the islets of langerhans and several pancreatic β -cell lines of rats has uncovered that the extract stimulated insulin release from several β -cells and islets, due to increased cell permeability.^[227] The ethanolic extract of *Gymnema* displayed hypoglycemic and antihyperglycemic activity in rats when given alone or in combination with any standard drug, and could be used for dose reduction of the standard drug.^[211] Recently, an active compound, dihydroxy gymnemic triacetate, has been isolated from its acetone extract. When it was given orally to streptozotocin-diabetic rats, it produced considerable hypoglycemia along with hypolipidemic effects.^[228] In a study on type 2 diabetic subjects, the *G. sylvestre* extract was given daily to 22 patients along with oral hypoglycemic drugs, which improved blood sugar control. Five patients were able to retain blood sugar control with *Gymnema* extract without the help of oral medication.^[229] One of its side-effects may be reduction/loss of taste sensation. The recommended dosage of *G. sylvestre* extract is 400 - 600 mg/day.^[230]

Mangifera indica (Mango^{*}): Family - Anacardiaceae

Although no change in blood glucose level was reported when the aqueous mango extract was given to streptozotocin-diabetic rats, antidiabetic activity was observed when the aqueous extract was given before/along with glucose, which could be due to decreased intestinal glucose absorption.^[231] Analysis of the peel extract of *Mangifera indica* (*M. indica*) [Figure 3] in rats revealed their potential to ameliorate diet-induced change in serum lipids, thyroid dysfunctions and hyperglycemia, which could be due to polyphenols and ascorbic acid present in the test peel extract.^[80] Lupeol,

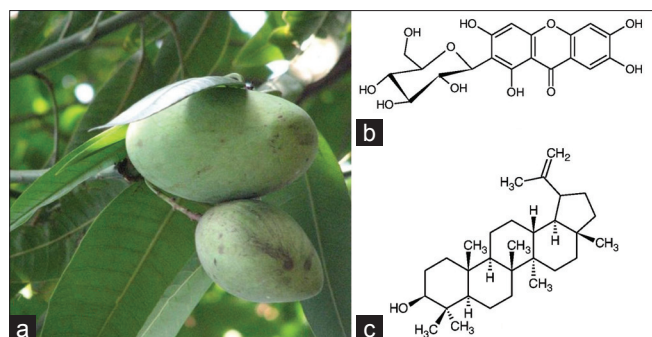


Figure 3: Mango and its antidiabetic constituents. (a) *Mangifera indica* (mango), (b) mangiferin, (c) lupeol

[Figure 3] a triterpene found in mango, is acknowledged to display antioxidant, antilithiatic and antidiabetic effects and is also established to be valuable in combating oxidative stress-induced cellular injury of mouse liver by modulating cell -growth regulators.^[232] Also, mangiferin, [Figure 3] a xanthone glucoside, isolated from mango leaves possesses considerable antidiabetic, antihyperlipidemic and antiatherogenic properties as obvious from lowering of fasting glucose level, decrease in total cholesterol, triglycerides and LDL -cholesterol along with elevation of the HDL -cholesterol level and diminution of atherogenic index in diabetic rats.^[233]

***Momordica charantia* (Bitter gourd*, Karela[†]): Family - Cucurbitaceae**

It is commonly used as an antidiabetic agent. Extracts from various parts of the plant have shown hypoglycemic activity in different animal models. Ethanolic extracts of *Momordica charantia* (*M. charantia*) showed hypoglycemic and antihyperglycemic effect in normal and streptozotocin-diabetic rats, which could be due to inhibition of glucose -6 -phosphatase and stimulation of hepatic glucose -6 -phosphate dehydrogenase activity.^[234] Studies concerning mechanism of bitter gourd in alloxanized rats suggested its potential antidiabetic, antihyperlipidemic and other valuable effects in amelioration of diabetic complications. Furthermore, it restores the altered histological architecture of the islets of Langerhans.^[235] The latest finding on high -fat -fed rats treated with bitter gourd extract showed better insulin sensitivity, glucose tolerance and insulin signaling. Detection of the possible mechanism of these effects may unlock novel therapeutic targets for the management of obesity/dyslipidemia -induced insulin resistance.^[236] Aqueous seed extract of *Momordica* also provides notable protection against lipid peroxidation in streptozotocin-diabetic rats due to its antioxidant activity.^[237,238] Antidiabetic screening of *Momordica* on differentiating 3T3 -L1 adipocytes has shown inhibition of TNF- α -stimulated free fatty acid release and attenuation of TNF- α -induced inhibition of adiponectin secretion.^[136] Animal studies have suggested many parallels between the actions of metformin and bitter gourd.^[239] Recent extensive screening has identified triterpenoids to be the hypoglycemic components present in *Momordica* that may be responsible for insulin resistance and in activation of AMP -activated protein kinase.^[240] Polypeptide p, isolated from

the fruit, seeds and tissues of *M. charantia* showed significant hypoglycemic effect in human.^[241] Because diet is one of the approaches in the management of diabetes mellitus, there is scope for exploiting the antidiabetic potency of *Momordica* to the maximum extent.^[242] However, there are insufficient evidences to recommend it for type 2 diabetes mellitus due to a lack of significant data on morbidity, expected expenditure, etc.^[243] Traditionally, it is used to cure numerous disorders. A number of studies have authenticated its use in diabetes and its complications as antibacterial, antiviral, anticancer, abortifacient, etc. However, only a few reports showing positive results on its clinical use are available.^[244]

***Ocimum sanctum* (Holy basil*, Tulsi[†]): Family - Lamiaceae**

Ocimum sanctum (*O. sanctum*) is known for its therapeutic benefits since ancient times. The aqueous extract of *O. sanctum* leaves demonstrated considerable decrease in blood sugar level in both normal and alloxanized rats.^[245] Marked fall in fasting blood glucose along with decrease in uronic acid, total cholesterol, triglyceride and total lipid level point toward its health-benefitting effects.^[246] Administration of the ethanolic leaf extract has been reported to lessen the plasma glucose level along with increase in the renal glycogen content, while skeletal muscle and hepatic glycogen levels are decreased in streptozotocin-diabetic rats.^[247] This plant is also known to possess antimicrobial, adaptogenic, hepatoprotective, anti-inflammatory, anti -carcinogenic, neuroprotective, cardio-protective, mosquito repellent and numerous other therapeutic activities.^[52,248]

***Phyllanthus amarus* (Stonebreaker*, Seed-Under-Leaf*): Family - Phyllanthaceae**

Traditionally, *Phyllanthus amarus* (*P. amarus*) is used in the treatment of diabetes. The methanolic extract of *P. amarus* was found to reduce the blood sugar in alloxanized diabetic rats along with potential antioxidant activity.^[249] Complete inhibition of TNF- α -stimulated free fatty acid release and attenuation of TNF- α -induced inhibition of adiponectin secretion was observed while screening its antidiabetic effects on 3T3 -L1 adipocytes.^[136] *P. amarus* is a potential diuretic and hypotensive drug for humans.^[250] Interestingly, other plants of the *Phyllanthus* species also possess medicinal properties.^[93,251-253]

***Psidium guajava* (Common guava*): Family - Myrtaceae**

Various studies revealed that various parts of *Psidium guajava* have antidiabetic property. The aqueous guava leaf extract showed hypoglycemic activity in alloxanized and streptozotocin-diabetic rats, which is attributed to the various tannins, flavonoids and other chemical constituents of the plant.^[254,255] In a different study, anti -hyperglycemic activity of the ethanol extract of stem bark of the plant was assessed on normal, alloxanized and normal glucose-loaded rats, and the results showed that the extract displayed considerable

hypoglycemic activity in all except normal and glucose-loaded rats.^[256] Antidiabetic property was also observed when the butanol-soluble fraction of the leaves was given to Lepr db/Lepr db mice.^[257] The leaf extract of guava was shown to inhibit the α -glucosidase activity in the small intestine of diabetic mice.^[258] Considerable hypolipidemic activity has also been reported when the aqueous extract of the raw fruit peel was given to streptozotocin-diabetic rats, besides hypoglycemic and antidiabetic activity.^[259]

***Pterocarpus marsupium* (Indian kino tree*): Family - Fabaceae**

Pterostilbene, obtained from *Pterocarpus marsupium* (*P. marsupium*) wood, showed hypoglycemic activity in dogs.^[260] Flavonoids obtained from *P. marsupium* have been reported to cause pancreatic β -cell regranulation.^[261] The flavanoid fraction has also showed antihyperlipidemic activity.^[262] Also, the aqueous extract of the latex of *P. marsupium* was found to possess marked α -glucosidase inhibitory activity.^[76] One of the active principles of *Pterocarpus*, (-) epicatechin, has insulinogenic action. It stimulates oxygen uptake in fat cells and tissue slices of different organs, and also enhances the glycogen content of the rat diaphragm in a dose-dependent manner.^[263]

***Trigonella foenum graecum* (Fenugreek*): Family - Fabaceae**

Fenugreek seeds are frequently used as a constituent of spices. Oral administration of the plant extract produced lowering of the blood glucose levels in both normal as well as diabetic rats.^[264] Administration of fenugreek seeds also enhanced glucose metabolism and stabilized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats.^[265] Fenugreek plant has also been reported to show antioxidant activity.^[266,267] Further, daily oral treatment of its steroids to diabetic rats demonstrated a significant decrease of blood glucose level and a substantial enhancement of the area of insulin -immunoreactive β -cells along with considerable reduction in sperm shape abnormality and improved sperm count.^[268] 4-hydroxyisoleucine, isolated from fenugreek seeds, exhibits marked potential as an anti-diabetic agent by suppressing progression of type II diabetes in the db/db mice model, as apparent from improvement of insulin sensitivity and glucose uptake in peripheral tissue.^[269] When fenugreek oil is given to alloxanized rats, notable reduction in renal toxicity besides improved hematological status and antidiabetic effect has also been accounted, which could be due to the immunomodulatory activity and insulin stimulation action of fenugreek.^[270] Fenugreek seeds are also known to possess a hypolipidemic effect^[271] and also offer antilithogenic potential due to its encouraging effect on cholesterol metabolism.^[272] Its seed has also been shown to be effective in the prevention of retinopathy and other diabetic complications when used alone or in combination with sodium orthovanadate.^[273,274] The seed extract also considerably repressed the 7, 12 -dimethylbenz (α) anthracene (DMBA) -induced mammary hyperplasia and reduced its incidence.^[275] It has shown no genotoxic effect, and has a wide safety margin. Also,

adding the fenugreek seed extract to foodstuffs for diabetic patients is predicted to be safe.^[276]

***Tinospora cordifolia* (Guduchi[†]): Family - Menispermaceae**

Tinospora cordifolia (*T. cordifolia*) is extensively employed for treating diabetes mellitus in the traditional system of medicine.^[277-279] Oral administration of the root extract of *T. cordifolia* led to a considerable decrease in blood and urine glucose and in lipids in alloxanized rats and also prevented reduction in body weight.^[280] Also, the aqueous root extract of the plant resulted in considerable decrease in blood glucose and brain lipids in alloxanized rats. Although the extract showed significant antihyperglycemic effect, its effect was comparable only to 1 unit/kg of insulin.^[281] It is also accounted that the daily administration of the aqueous or alcoholic extract of *T. cordifolia* reduces the blood glucose level and enhances glucose tolerance in rodents.^[282]

***Stevia rebaudina* (Sweet Leaf*, Sugar leaf*): Family - Asteraceae**

Stevioside, [Figure 4] a natural sweetener obtained from the plant *Stevia rebaudiana* (*S. rebaudiana*), [Figure 4] has been used in the treatment of diabetes since a long time. It stimulates secretion of insulin via a direct action on the pancreatic cells, and is thought to have significant antidiabetic potential.^[283,284] However, a comparative study between *S. rebaudiana* and stevioside has revealed that the hypoglycemia due to *S. rebaudiana* leaves was partially mediated by inhibition of hepatic gluconeogenesis and did not involve stevioside and peroxisome proliferator -activated receptor -gamma (PPAR - γ) receptors activation.^[285] Rebaudioside, [Figure 4] a new diterpene glycoside, also possesses insulinotropic effects and may provide support in the treatment in type 2 diabetes mellitus.^[286] A study of stevioside on insulin -sensitive lean (Fa/ -) and insulin -resistant obese (Fa/Fa) Zucker rats revealed the skeletal muscle glucose transport system to be one of its possible sites of action.^[287] Stevioside is also reported to exercise antihyperglycemic, insulinotropic, blood pressure lowering and glucagonostatic effects in type 2 diabetic Goto - kakizaki

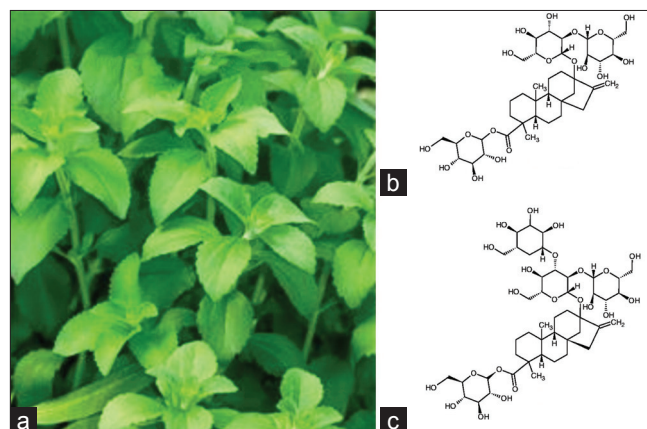


Figure 4: Stevia and its antidiabetic constituents. (a) *Stevia rebaudiana* (sweet leaf), (b) stevioside, (c) rebaudioside

rats, proving its worth in the treatment of type 2 diabetes and metabolic syndrome.^[284,288] Stevioside and steviol may have a potential as an antihyperglycemic agent. While investigating their effects on insulin release from normal mouse islets and the β -cell line INS -1, it came to appear that the insulinotropic effects of stevioside and steviol were significantly reliant on the prevailing glucose concentration, and that they also stimulate insulin secretion by acting on pancreatic β -cells.^[289]

Conclusion

The number of people suffering from diabetes mellitus has been increasing dramatically over the past few decades, and this demands special attention towards its management. The few conventional therapies available are either expensive or often related with adverse effects; therefore, various traditional therapies with antihyperglycemic effect are increasingly sought by patients. Medicinal plants provide better alternatives as they are generally less-toxic and affordable; yet, their safety and efficacy needs more evaluation by controlled clinical studies. Although herbs are less likely to have drawbacks of the conventional drugs used for diabetes, potential herb-drug interactions should be kept in mind for those receiving conventional antidiabetic medications. Taking all these details into account, further research is required to validate the antidiabetic effects of medicinal plants.

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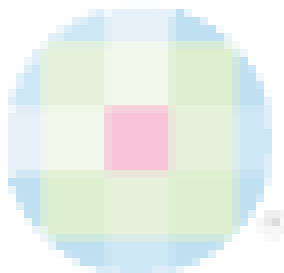
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