

Phytochemicals for Diabetes Management

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Abstract: Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Diabetes mellitus affects most of the people in both developed and developing countries. The treatment of diabetes with synthetic drugs is costly and chances of side effects are high. Phytomedicine has been used since ancient times in various parts of the world where access to modern medicine is limited. Medicinal plants and phytoconstituents play an important role in the management of diabetes mellitus especially in developing countries where resources are meagre. Phytochemicals identified from medicinal plants present an exciting opportunity for the development of new types of therapeutics for diabetes mellitus. Most prevalent among phytochemical groups are the alkaloids, glycosides, polysaccharides, and phenolics such as flavonoids, terpenoids and steroids. Despite considerable progress in the development of synthetic drugs, the discovery of phytomedicine as an alternative therapy is progressing. This article aims to provide a comprehensive review on various plant species from globe and their constituents, which have been shown to display potent hypoglycemic activity.

Keywords: Antidiabetic, diabetes management, diabetes mellitus, hyperglycemia, hypoglycemia, insulin, phytochemicals.

INTRODUCTION

The World Health Organization (WHO) defined diabetes mellitus as “a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both” [1]. Diabetes is a disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or mounting resistance to its action. Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin that it produces. Insulin is a hormone that regulates blood sugar. The increased production and ineffective scavenging of reactive oxygen species may play a critical role in diabetes mellitus. The disturbance of antioxidants defence system in diabetes is mainly because of alteration in antioxidant enzymes, impaired glutathione metabolism, and decreased ascorbic acid levels. It is becoming the third “killer” of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases [2]. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over the time leads to serious damages to many of the body's systems, especially the nerves and blood vessels. Over the time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. Diabetes increases the risk of heart disease and stroke. 50% of people with diabetes die of cardiovascular disease. Combined with reduced blood flow, neuropathy (nerve damage) in the feet increases the chance of foot ulcers, infection and eventual need for limb amputation.

Diabetic retinopathy is an important cause of blindness, and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. One percent of global blindness can be attributed to diabetes. Diabetes is among the leading causes of kidney failure [3]. With increasing rates of childhood and adult obesity, diabetes is likely to become even more prevalent over the coming decades. The drugs which lower the blood sugar level or treat the symptoms of diabetes mellitus are known as hypoglycemic drugs. It can be categorized into insulin and insulin preparations, which are employed only parenterally, and oral hypoglycemic drug which can be administered orally [4].

Plants have always been a good source of drugs. The ethnobotanical information reports about 800 plants that may possess anti-diabetic potential. The beneficial uses of medicinal plants in traditional system of medicine of many cultures are extensively documented. Several plants have been used as dietary adjuvant and in treating the number of diseases even without any knowledge on their proper functions and constituents. This practice may be attributed to the uncompromised cost and side effects of synthetic hypoglycemic agent. Although numerous synthetic drugs were developed for the treatment of diabetes mellitus but the safe and effective treatment paradigm is yet to be achieved [5].

WHO has recommended the evaluation of traditional plant treatments for diabetes as they are effective, non-toxic, with less or no side effects and are considered to be excellent aspirants for oral therapy [6]. A scientific validation of several plant species has proved the efficiency of the botanicals in reducing the sugar level. From the reports on their potential effectiveness against diabetes, it is assumed that the phytochemicals have a major role in the management of diabetes, which needs further exploration for the necessary development of drugs and nutraceuticals from natural resources.

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Herbal treatments for diabetes have been used in patients with insulin-dependent and non-insulin-dependent diabetes, diabetic retinopathy, diabetic peripheral neuropathy, etc however many herbal remedies used today have not undergone careful scientific evaluation and some have the potential to cause serious toxic effects and major drug-to-drug interaction. Compounds with different structure but with the same therapeutic activity isolated from different plant species act as active moieties for the treatment of various diseases. The use of these plants and phytoconstituents may delay the development of diabetic complications and may regulate the metabolic abnormalities through a variety of mechanisms [7]. Moreover, during the past few years many phytochemicals responsible for anti-diabetic effects have been isolated from the plants. Several phytoconstituents such as alkaloids, glycosides, flavonoids, saponins, dietary fibres, polysaccharides, glycolipids, peptidoglycans, amino acids and others obtained from various plant sources that have been reported as potent hypoglycemic agents have been further discussed (Fig. 1, Table 1) in the following segment.

PHYTOCHEMICALS IN THE MANAGEMENT OF DIABETES MELLITUS

Alkaloids

Different alkaloids have been isolated from several medicinal plants and investigated for their possible antidiabetic activity in different animal models. Alkaloids exert a wide range of antidiabetic activities through different mechanisms. Below are some important class of alkaloids reported with their mechanism of hypoglycemic or hyperglycemic activity.

Berberine, an isoquinoline alkaloid is obtained from the roots and stem bark of *Berberis* L. (Berberidaceae). This compound is mostly isolated from the roots of *B. aristata* DC. (5% in roots and 4.2% in stem-bark), *B. asiatica* Roxb. ex DC., *B. aquifolium* Pursh, *B. petiolaris* Wall. ex G. Don, *B. thunbergii* DC. (0.43%), and *B. vulgaris* [8-10]. Other species reported to contain berberine are *Coptis teeta* Wall. (rhizome 8-9%) and *Hydrastis Canadensis* L. [11]. Among Chinese herbs, the primary sources are *B. sargentiana* C.K. Schneid., *Phellodendron amurense* Rupr. and *Coptis chinensis* Franch.. *Coptis chinensis* rhizomes (Ranunculaceae) and related species used as its substitutes have about 4–8% berberine, while *P. amurense* bark has about 2–4% berberine. Singh *et al.* reported that berberine is isolated from the stems and roots of *Tinospora cordifolia* (Willd.) Miers (Menispermaceae) is known to have potent hypoglycemic activity [12]. Berberine acts as antihyperglycemic agent by inhibiting the activity of disaccharidases in Caco-2 cells. It decreases sucrase activity after preincubation with Caco-2 cells for 72 h. No significant effects on gluconeogenesis and glucose consumption of Caco-2 cells were observed, suggesting that the antihyperglycemic activity of berberine is due to its ability to inhibit alpha-glucosidase and decrease glucose transport through the intestinal epithelium [13].

Three alkaloids, boschniakine, 5, β -hydroxyskitanthine and tecomine were isolated from the *Tecoma stans* L. (Bignoniaceae). It was reported that tecomine exerted a potent stimulating effect on the basal glucose uptake rate in rat adipocytes from normoglycemic rats, whereas the other two

alkaloids boschniakine and 5, β -hydroxyskitanthine were inactive up to 100 μ M [14]

Casuarine 6-O- α -glucoside isolated from the methanol extract of the bark of *Syzygium malaccense* L. (Myrtaceae) was found to inhibit α -glucosidase activity [15].

Alkaloids like catharanthine, vindoline and vindolinine obtained from *Catharanthus roseus* (L.) G. Don (Apocynaceae) also lowered blood sugar levels when tested in normal and streptozotocin-induced diabetic rat models. Leurosine, vindoline, vindolinine and catharanthine, reduces blood glucose in normal and alloxan diabetic rabbits [16]. Vincristine and vinblastine, dimeric alkaloids obtained from the leaves and stems of *C. Roseus* are used traditionally in various regions of the world including India, West Indies as well as Nigeria to control diabetes [17].

Griffiths reported a new class of nortropane polyhydroxylated alkaloids of a calystegine which was isolated from the fruits of *Nicandra physalodes* L. (Solanaceae), and the structure was determined as 3-O-D-glucopyranosyl-calystegine B1. Although calystegine B1 showed no inhibitory activity towards the enzyme Calystegine B2 which is a potent inhibitor of α -glucosidases and R-galactosidases. This glucoside was a potent inhibitor of rice R-glucosidase. The introduction of the R-glucosyl residue to calystegine B1 and of the glucosyl or galactosyl residue to calystegine B2 is resulted in a significant decrease of glycosidase inhibitory activity. 4-O-R-D-Galactopyranosyl-calystegine B2 showed similar result. R-Glucosidase inhibitors have a potential for the treatment of diabetes because they reduce diet-induced hyperglycemia and endogenous insulin secretion by inhibiting intestinal R-glucosidases [18, 19].

Cryptolepine is an indoloquinolone alkaloid isolated from *Cryptolepis sanguinolenta* (Lindl.) Schltr. (Apocynaceae). The Antihyperglycemic activity of cryptolepine was measured *in vitro* and in a Non-insulin-dependent diabetes mellitus (NIDDM) mouse model to study initial structure and bioactivity of the cryptolepine nucleus. Cryptolepine significantly lowers glucose levels when orally given to diabetic mice. The antihyperglycaemic effect of cryptolepine leads to a significant decline in blood glucose concentration, associated with evidence of an enhancement in insulin-mediated glucose disposal. Cryptolepine increased glucose uptake by 3T3-L1 cells. After this successful attempt, a series of substituted and heterosubstituted cryptolepine analogs have been synthesised [20].

Harmane and norharmane, imidazoline alkaloids obtained from *Tribulus terrestris* L. (Zygophyllaceae) have a stimulatory action on insulin secretion by the activation of imidazoline I (3) binding sites in the pancreatic β cell. It was reported that Harmane, norharmane and pinoline (β carbolines) were found to increase insulin secretion 2-3 fold from isolated human islets of Langerhans [21, 22]. Harmane stimulates insulin secretion in a glucose-dependent manner [23].

Syzygium cumini (L.) Skeels (Myrtaceae), also known as *Eugenia jambolana* Lam., is an important plant mentioned in Ayurveda for the treatment of diabetes. The seeds, fruits and bark of the plant were claimed to contain an alkaloid jambosine which halts the distatic conservation of starch [24].

Table 1. List of important phytoconstituents used in the treatment of Diabetes mellitus.

Phytoconstituents	Plant Name	Part used	References [†]
Alkaloids			
Berberine	<i>Berberis</i> spp. <i>Tinospora cordifolia</i>	Roots, stem-bark	[8-13]
Casuarine 6-o- α -glucoside	<i>Syzygium malaccense</i>	Bark	[15]
Catharanthine, vindoline and vindolinine	<i>Catharanthus roseus</i>	Leaves, stems	[16]
Calystegine B2	<i>Nicandra physalodes</i>	Fruits	[18]
Cryptolepine	<i>Cryptolepis sanguinolenta</i>		[20]
Harmaine, norharmaine,	<i>Tribulus terrestris</i>		[21, 22]
Jambosine	<i>Syzygium cumini</i>	Seeds, fruits, bark	[24]
Jatrorrhizine, magnoflorine, palmatine	<i>Tinospora cordifolia</i>		[25]
Javaberine A, javaberine A hexaacetate, javaberine B hexaacetate,	<i>Talinum paniculatum</i>	Roots	[27]
Lepidine and semilepidine	<i>Lepidium sativum</i>	Seeds	[28]
Lupanine	<i>Lupinus perennis</i>		[29]
Mahanimbine	<i>Murraya koenigii</i>	Leaves	[32]
Piperumbellactam A	<i>Piper umbellatum</i>	Branches	[33]
Radicamines A and B	<i>Lobelia chinensis</i>		[34]
Swerchirin	<i>Swertia chirayita</i>		[36]
Tecomine	<i>Tecoma stans</i>		[14, 37]
Trigonelline	<i>Trigonella foenum-graecum</i>	Seeds	[39]
1-deoxynojirimycin	<i>Morus alba</i>	Leaves, bark	[41,42]
Glycosides			
Kalopanax	<i>Kalopanax pictus</i>	Stem bark	[44]
Jamboline or antimellin	<i>Syzygium cumini</i>	Seeds	[46]
Myrciacitrins I and II and myrciaphenones A and B	<i>Myrcia multiflora</i>	Leaves	[48]
Neomyrtillin	<i>Vaccinium myrtillus</i>	Leaves	[51]
Perlargonidin 3-o- α -1 rhamnoside	<i>Ficus bengalensis</i>	Bark	[52-54]
Pseudoprotinosaponin AIII & protinosaponin AIII	<i>Anemarrhena asphodeloides</i>	Rhizome	[57]
Vitexin, isovitexin and isorhamnetin 3-O- β -D-rutinoside	<i>Microcos paniculata</i>	Leaves	[58]
Flavonoids			
Bengalenoside	<i>Ficus benghalensis</i>	Stem bark	[30,41]
Cyanidin-3-galactoside,			[65]
Epigallocatechin gallate	<i>Camellia sinensis</i>	Leaves	[66, 70]
(-)-3-O-galloyl catechin, (-)-3-O-galloyl catechin	<i>Bergenia ciliata</i>		[71]
Genistein	<i>Glycine</i> spp.	Soya beans	[72]
Hesperidin, naringin	<i>Citrus</i> spp.		[73]
Prunin	<i>Amygdalus davidiana</i> var. <i>davidiana</i>	Stems	[75]
Kaempferitrin	<i>Bauhinia forficata</i>	Leaves	[76]

(Table 1) contd...

Phytoconstituents	Plant Name	Part used	References †
Flavonoids			
Kaempferol	<i>Jindai soybean</i>	Leaves	[77]
Kolaviron	<i>Garcinia kola</i>		[79]
Leucodelphinidin	<i>Ficus bengalensis</i>	Bark	[80]
Mangiferin	<i>Anemarrhena asphodeloides</i>	Rhizomes	[82]
Marsupin, pterostilbene	<i>Pterocarpus marsupium</i>	Heartwood	[83]
Quercetin	<i>Chamaecostus cuspidatus</i>	-	[86,93]
Rutin			[87]
Shamimin	<i>Bombax ceiba</i>	Leaves	[90]
Terpenoids and steroids			
α -amyrin acetate	<i>Ficus racemosa</i>	Fruits	[97]
Andrographolide	<i>Andrographis paniculata</i>	Leaves	[99]
3 β -acetoxy-16 β -hydroxybetulinic acid	<i>Zanthoxylum gillettii</i>	Stem bark	[100]
Bassic acid	<i>Bumelia sartorum</i>	Root bark	[101]
Charantin	<i>Momordica charantia</i>	Seeds, fruits	[102]
Christinin A	<i>Zizyphus spina-christi</i>	Leaves	[103]
Colosolic acid, maslinic acid	<i>Lagerstroemia speciosa</i>	Leaves	[104-107]
Corosolic acid	<i>Vitex</i> spp.	Leaves	[108]
Elatosides E	<i>Aralia elata</i>	Root cortex	[109]
Escins-IIA and IIB	<i>Aesculus hippocastanum</i>	Seeds	[110]
Forskolin	<i>Coleus forskohlii</i>	-	[111]
Ginsenosides	<i>Panax species</i>	Rhizomes	[113-121]
Gymnemic acid IV	<i>Gymnema sylvestre</i>	Leaves	[122-124]
Momordin ic	<i>Kochia scoparia</i>	Fruit	[128]
β -sitosterol	<i>Azadirachta indica</i>		[130]
Senegin derivatives	<i>Polygala senega</i>		[132]
Polysaccharides			
Aconitans A-D	<i>Aconitum carmichaeli</i>	Roots	[134]
Atractans A	<i>Atractylodes japonica</i>	Rhizomes	[136]
Ganoderans A and B.	<i>Ganoderma lucidum</i>	Fruit bodies	[138]
Galactomannan gum	<i>Cyamopsis tetragonolobus</i> <i>Amorphophallus konjac</i>	Seeds Tubers	[140,141]
Miscellaneous			
Allicin	<i>Allium sativum</i> <i>Allium cepa</i>	Bulbs	[150]
Bellidifolin	<i>Swertia japonica</i>		[151]
Bakuchiol	<i>Otholobium pubescens</i>	-	[154]
Curcuminoids	<i>Curcuma longa</i>	Rhizomes	[155]
Ellagitannins	<i>Terminalia chebula</i>	Fruits	[156]

(Table 1) contd...

Phytoconstituents	Plant Name	Part used	References †
Miscellaneous			
Ferulic acid	<i>Curcuma longa</i>	Leaves seeds	[158]
Ginseng polypeptides	<i>Panax ginseng</i>	Roots	[113]
4-hydroxyisoleucine	<i>Trigonella foenum-graecum</i>	Seeds	[159]
Kotalanol	<i>Salacia reticulate</i>		[163]
Masoprocol	<i>Larrea tridentate</i>		[164]
Paeoniflorin, 8-debenzoylpaeoniflorin	<i>Paeonia lactiflora</i>	Root	[169]

†Refer the numbered reference in the text.

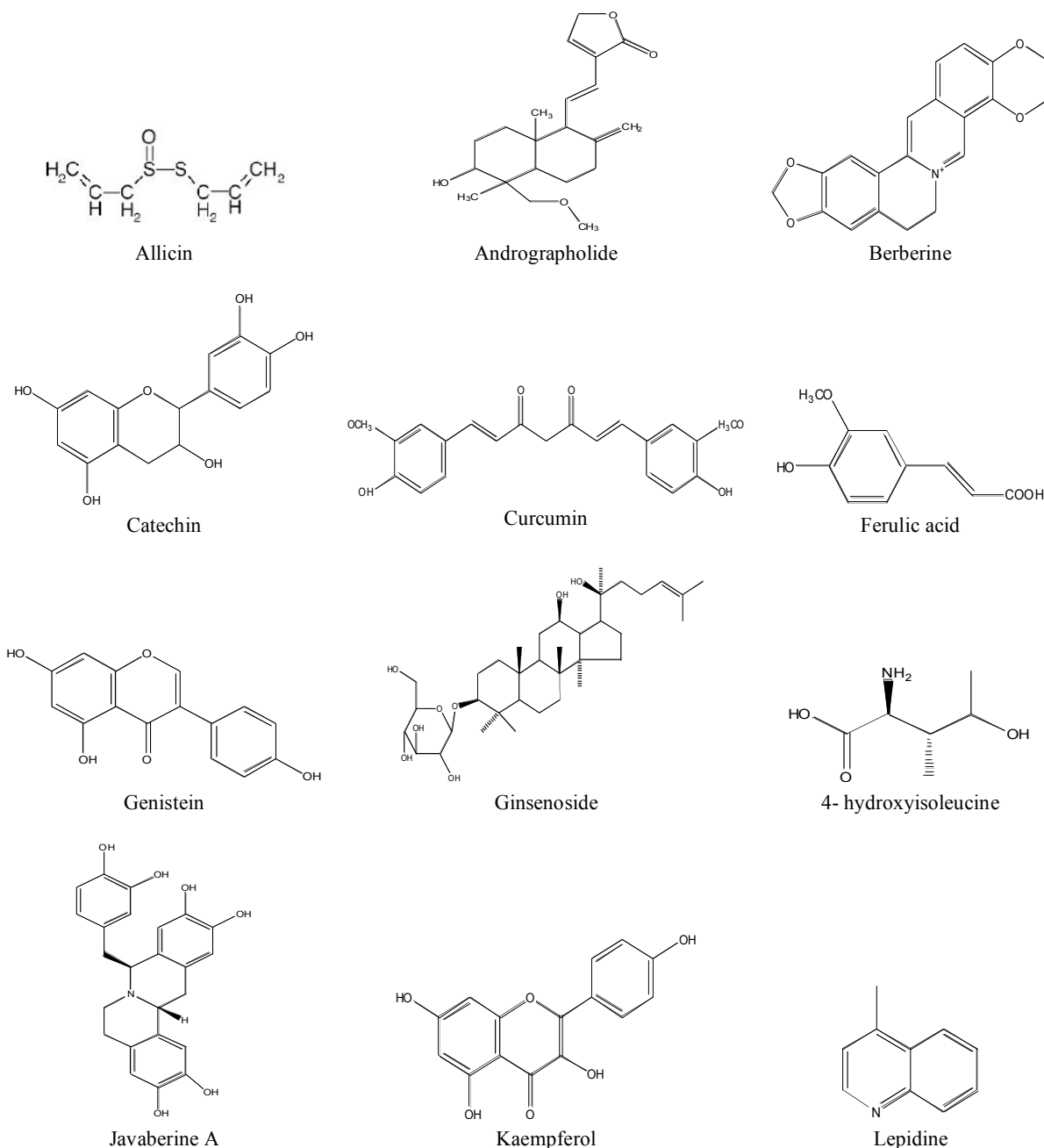


Fig. (1) contd....

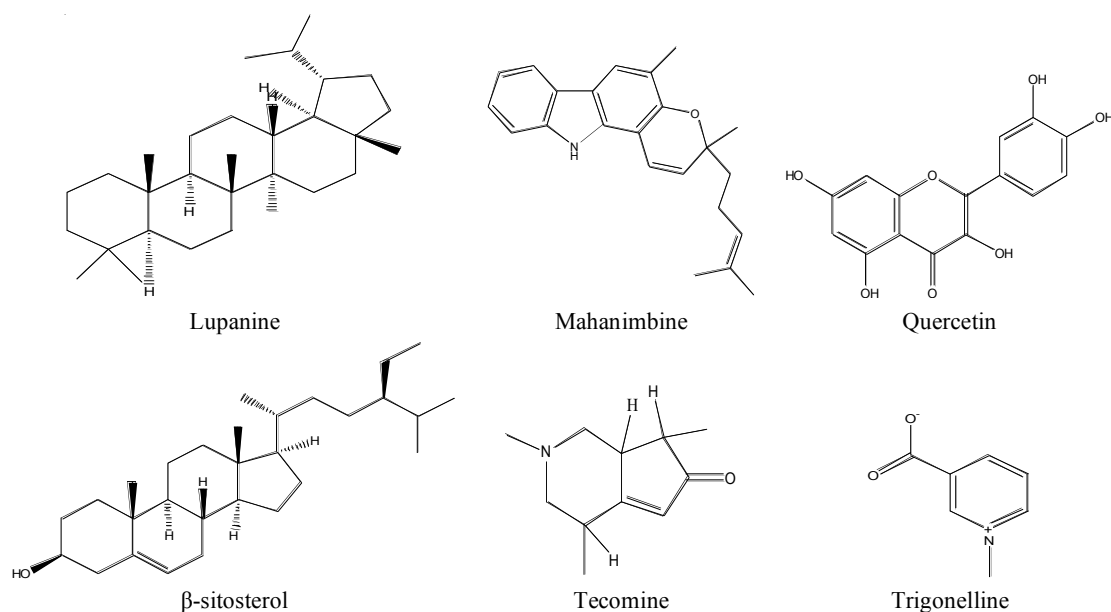


Fig. (1). Important phytochemicals for diabetes management.

Three major alkaloids, jatrorrhizine, magnoflorine, and palmatine of *Tinospora cordifolia* (Willd.) Miers (Menispermaceae) stimulated insulin secretion from the RINm5F cell line [25].

Three quinolizidine alkaloids javaberine A, javaberine A hexaacetate, and javaberine B hexaacetate were isolated from the roots of *Talinum paniculatum* Gaertner (Portulacaceae). These alkaloids are the inhibitors of TNF- α production by macrophages and fat cells. It has also been reported that *T. paniculatum* is useful as a dietary supplement and for the prevention of diabetes [26, 27].

Lepidine and semilepidine, a rare group of imidazole alkaloid are isolated from seeds of *Lepidium sativum* L. (Cruciferae) having an active moiety 2-benzylimidazole or imidazoline. The hypoglycemic activity of these compounds was assessed on alloxan induced diabetic rats for 21 days treatment. Results revealed that these constituents showed potent hypoglycemic activity. This effect may be through reducing oxidative damage and modulating antioxidant enzymes. The possible mechanism is that it may exert its anti-hyperglycaemic action by potentiating pancreatic secretion of insulin from the remaining islet β cells [28].

Lopez *et al.* isolated three quinolizidine alkaloids, namely lupanine, 13- α -OH lupanine and 17-oxo-lupanine, from *Lupinus perennis* L. (Fabaceae). The effect of these alkaloids was analysed based upon insulin secretion. Result shows that these alkaloids enhanced glucose-induced insulin release from isolated rat islet cells. However, their effect on insulin secretion was dependent on the glucose concentration in the incubation media. Lupanine increased it only at the two higher concentrations of glucose, whereas 13- α -OH lupanine and 17-oxo-lupanine increased insulin secretion only at the highest glucose concentration tested [29].

Seeds of *Lupinus termis* Forssk. (Fabaceae) have been reported to yield a fraction rich in quinolizidine alkaloids lupin, which exerted a glucose-lowering effect in alloxan-

induced diabetic rats but not in healthy rats [30]. Baldeon and co-workers have reported that *L. mutabilis* Sweet, legumes rich in proteins decrease blood glucose and improve insulin sensitivity in animals and humans. They reported the results of a phase II clinical trial conducted to assess the role of cooked *L. mutabilis* and its purified alkaloids on blood glucose and insulin in volunteers with diabetes. Results indicate that consumption of cooked *L. mutabilis* or its purified alkaloids decreased blood glucose and insulin levels [31].

Mahanimbine is a carbazole alkaloid isolated from *Murraya koenigii* (L.) Spreng. (Rutaceae) leaves tested for antidiabetic activity in streptozotocin-induced diabetic rats. Mahanimbine (i.p.) showed anti-diabetic effects after administration of 50 mg/kg and 100 mg/kg of mahanimbine for 30 days once a week [32].

Tabopda reported the isolation of three alkaloids named piperumbellactam A, piperumbellactam B and piperumbellactam C from the branches of *Piper umbellatum* L. (Piperaceae) and these compounds were tested for α -glucosidase enzyme inhibition. All these three alkaloids showed moderate inhibition of α -glucosidase enzyme [33].

Shibano and co-workers have reported two new pyrrolidine alkaloids, radicamines A and B from *Lobelia chinensis* Lour (Campanulaceae). The inhibitory activities of radicamines A and B were assessed with respect to α -glucosidase. These two new compounds, both polyhydroxy alkaloids having an aromatic ring, have been shown to exhibit very appealing biological activities, similar to that of 1-deoxyynojirimycin (α -glucosidase inhibitor) [34].

Three new isoquinoline alkaloids, schulzeines A, B and C were isolated from the marine sponge *Penares schulzei*. These alkaloids encompass two amino acids and a C28 fatty acid, the last of which was sulfated and inhibits α -glucosidase [35].

Xanthone was isolated from the n-hexane fraction of *Swertia chirayita* Bush (Gentianaceae) and identified as 1,8-

dihydroxy-3,5-dimethoxyxanthone (swerchirin). It has shown a very significant blood sugar lowering effect in fasted, fed and glucose loaded albino rats [36].

Traditional use of leaves from *Tecoma stans* (L.) Juss. ex Kunth (Bignoniaceae) for the treatment of NIDDM patients has been supported by the isolation of two hypoglycemic alkaloids, tecomine and tecostanine. These alkaloids exerted a rapid hypoglycemic effect when administered intravenously to healthy and alloxan-induced diabetic rabbits but were ineffective in pancreatectomized rabbits. The alkaloids showed poor stability and were required in sufficiently large doses to question their clinical potential [19, 37].

Trigonella foenum-graecum L. (Fabaceae) is one of the most important drug used to treat diabetes specially recommended for NIDDM patients [19]. Seeds exert a modest and transient hypoglycemic effect in healthy and mildly diabetic animals but were not effective in severely diabetic animals. The hypoglycemic activity has been attributed to an uncharacterized alkaloid known as trigonelline, although other possible hypoglycemic agents such as nicotinic acid have been isolated from the seeds [38, 39].

New polyhydroxylated alkaloid, (2R, 3R, 4R)-2-hydroxymethyl-3, 4-dihydroxy-pyrrolidine-N-propionamide was isolated by column chromatography using a variety of ion-exchange resins from the root bark of *Morus alba* L. (Moraceae). 3, 6 - dihydroxynortropane, 4-O-R-D-galactopyranosyl-calystegine B2 and known 1,4-dideoxy-1,4-imino-D-arabinitol were isolated from the fruits *Morus alba* showing no inhibitory activity against any glycosidases tested. 1, 4-Dideoxy-1,4-imino-D-arabinitol is a potent inhibitor of yeast R-glucosidase and mammalian isomaltase, mammalian R mannosidase and porcine kidney trehalase. Its N propionamide derivative significantly decreased its inhibition against all glycosidases [40, 41]

1-deoxynojirimycin, a polyhydroxylated piperidine alkaloid present in both leaves and bark of *M. alba*, is known to be one of the most potent α -glycosidase inhibitors [41, 42].

Six sugar-mimic alkaloids, (a) 1-deoxymannojirimycin, (b) 1,4-dideoxy-1,4-imino-D-ribitol (c), 2,5-Imino-1,2,5-trideoxy-L-glucitol (d), 2,5-dideoxy-2,5-imino-D-fucitol (e), β -homofuconojirimycin and (f) 1,4-dideoxy-1,4-imino-(hydroxyethyliminiumyl)-D-arabinitol were isolated from the pod extract of *Angylocalyx pynaertii* De Wild. (Fabaceae) inhibiting various α -L fucosidases activities. Among these alkaloids, (h) and (i) were found to be potent inhibitors of bovine epididymis α -L-fucosidase. Although 2, 5-imino-1,2,5-trideoxy-D-mannitol has been reported to be a weak inhibitor of snail -mannosidase, 1,4-dideoxy-1,4-imino-D-ribitol (b) was a better inhibitor of lysosomal -mannosidase than 2,5-imino-1,2,5-trideoxy-D-mannitol. The isomers of 2,5-imino-1,2,5-trideoxy-D-mannitol, (c) and (d), were very specific inhibitors of R-L-fucosidase with no significant inhibitory activity towards other glycosidases. 1,4-dideoxy-1,4-imino-D-arabinitol is known to be a potent inhibitor of yeast R-glucosidase and mammalian isomaltase. Recently, 1,4-dideoxy-1,4-imino-D-arabinitol has been found to be a potent inhibitor of glycogen phosphorylase both *in vitro* and *in vivo*. The N methyl derivative of 1,4-dideoxy-1,4-imino-D-arabinitol was isolated from the bark, while N-hydroxyethyl-DAB (f) was found in the pods. The N-

hydroxyethyl derivative of 1-deoxynojirimycin (DNJ), miglitol, is commercially available for the treatment of diabetes in several countries [19, 43].

Glycosides

Seven kinds of chemical constituents including hederagenin glycosides and phenolic glycosides were isolated from the stem bark of *Kalopanax pictus* Nakai (Araliaceae). The antidiabetic evaluation of these isolated compounds in streptozotocin-induced diabetic rats showed that kalopanax (saponin A) has a potent antidiabetic activity in contrast to a mild activity of hederagenin [44].

Jamboline (antimellin), a glycoside present in the seeds of *Syzygium cumini* (*Eugenia jambolana*), possesses antidiabetic properties [9]. Jamboline exerts hypoglycemic action by preventing conversion of starch into sugar and also diminishes quantity of sugar in urine and reduces thirst [45, 46].

A new flavanone glucosides (myrciacitrins I and II) and new acetophenone glucosides (myrciaphenones A and B) were identified from the leaves of *Myrcia multiflora* DC. (Myrtaceae). These compounds showed an inhibitory action on aldose reductase and alpha-glucosidase. The plant also inhibited increased serum glucose level in sucrose-loaded rats and in alloxan-induced diabetic mice [47]. Following the characterization of myrciacitrins I and II and myrciaphenones A and B, three new flavanone glucosides, myrciacitrins III, IV, and V, were isolated from the leaves of *M. multiflora*. The structures of new myrciacitrins were elucidated on the basis of physicochemical and chemical evidences. Myrciacitrins were found to show potent inhibitory activity on aldose reductase [48].

Leaves of *Vaccinium myrtillus* L. (Ericaceae) were widely used as a treatment for diabetes before the availability of insulin. Allen has extracted an active glycoside principle, neomyrtillin from the leaves of *V. myrtillus* [49]. The compound was found to be effective in reducing glycosuria and postprandial hyperglycemia in most adult-onset diabetic patients but was rarely effective in juvenile-onset patients. The extract was found to enhance the hypoglycemic action of exogenous insulin and reduced insulin requirements. From the above findings, it can be concluded that the compound might facilitate insulin action. Allen believes "that myrtillin plays some accessory part in carbohydrate metabolism and that, if used properly, it will prove valuable as an accessory factor in diabetic treatment" [49-51].

The antidiabetic effect of a dimethoxy derivative of perlargonidin 3-O- α -L rhamnoside isolated from the bark of *Ficus bengalensis* L. (Moraceae) has been compared with that of glibenclamide in moderately diabetic rats. *In vitro* studies showed that insulin secretion by β -cells was greater in the presence of the perlargonidin derivative than in the presence of a leucocyanidin derivative, reported to be a good antidiabetic agent. Glycoside of leucoplargonidin (p.o) isolated from the bark of *F. bengalensis* demonstrated significant hypoglycaemic, hypolipidemic and serum insulin raising effects in moderately diabetic rats. The compound showed significant hypoglycemic and serum insulin raising actions in healthy and alloxan induced-diabetic dogs during a

period of 2 h. This compound appears to stimulate insulin secretion [52-54].

Kato *et al.* reported two steroidal glycosides, PO-1 and PO-2, were isolated from rhizomes of *Polygonatum* sp. (Liliaceae). These compounds were tested as a new hypoglycemic agent in mice. PO-2 showed remarkable hypoglycemic activity in normal mice (i.p) whereas PO-1 slightly lowered the blood glucose in normal mice. Furthermore, PO-1 and PO-2 exhibited significant hypoglycemic effects in streptozotocin-induced diabetic mice. However, diosgenin did not affect the blood glucose level in either normal or streptozotocin-induced diabetic mice. From these findings, it can be concluded that glycoside region is important to exert hypoglycemic activity indicating that the branching glucose units are essential for the biological activity [55].

Pseudoprotinosaponin AIII & protinosaponin AIII were isolated from the rhizomes of *Anemarrhena asphodeloides* Bunge (Asparagaceae). Both glycosides affect glucose uptake and insulin release suggesting their hypoglycemic effects are due to the actions on hepatic gluconeogenesis or on glycogenolysis when tested in KK-Ay mice [56, 57].

Three flavonoid glycosides isolated from the leaves of *Microcos paniculata* L. (Tiliaceae), were investigated for their α -glucosidase inhibitory effects. All the three flavonoids *viz.* vitexin, isovitexin, and isorhamnetin 3-O- β -D-rutinoside revealed satisfactory inhibitory effects [58].

Flavonoids

Flavonoids represent a beneficial group of naturally occurring compounds with hypoglycemic potentials. These are widely distributed in plant kingdom and exhibit characteristic pharmacological properties. Over 400 traditional plant treatments for diabetes have been reported, though only a small number of these have received scientific and medical evaluation to assess their efficacy. The flavonoids can be widely classified into different categories like Anthocyanins, catechins, flavanols, flavones, flavanones etc. Some flavonoids have hypoglycemic properties. They may improve altered glucose and oxidative metabolisms of diabetic states. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes mellitus (T2DM) [59]. Some of the important phytoconstituents from the classes of flavonoid have been discussed below,

Anthocyanins, a significant group of polyphenols in bilberries and other berries, may also prevent T2DM and obesity. Anthocyanins from different sources have been shown to affect glucose absorption and insulin level, secretion, action and lipid metabolism by *in vitro* and *in vivo* methods [60, 61]. Many *in vitro* studies suggest that the anthocyanins may decrease the intestinal absorption of glucose by retarding the release of glucose during digestion [62, 63].

Ajgaonkar isolated a flavonoid glycoside, bengalenside, from an aqueous extract of stem bark of *Ficus benghalensis* [30]. This produced a mild hypoglycemic effect in healthy and alloxan-induced diabetic rodents [41].

Cyanidin-3-galactoside, a natural anthocyanin, was investigated for its α -glucosidase inhibitory activity against intestinal sucrase. A low dose of cyanidin-3-galactoside

showed a synergistic inhibition on intestinal α -glucosidase (maltase and sucrase) when combined with acarbose. This study shows that cyanidin markedly inhibits intestinal α -glucosidase and pancreatic α -amylase, which is one of the therapeutic approaches for the treatment of diabetes mellitus [64, 65].

Findings of Waltner-Law suggest that epigallocatechin gallate is an important hypoglycemic agent. Plants containing flavonoids are used to treat diabetes and the green tea flavonoid, epigallocatechin gallate is reported to have glucose-lowering effects in animals. It was found to decrease hepatic glucose production and increased tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1) like insulin. It also reduces phosphoenolpyruvate carboxykinase gene expression in a phosphoinositide 3-kinase-dependent manner and mimics insulin by increasing phosphoinositide 3-kinase, mitogen-activated protein kinase, and p70 (s6k) activity [66].

Another flavonoid molecule, (-) epicatechin, has been reported to possess insulin-like activity. Chakravarthy *et al.* suggested that (-) epicatechin protected the experimental albino rats against the diabetogenic actions of alloxan [67]. It mimics insulin effect on erythrocyte membrane acetylcholinesterase (AChE) and has a pronounced insulin-like effect on erythrocyte membrane bound AChE in type II diabetic patients [68, 69]. Epigallocatechin gallate, present in *Camellia sinensis* Kuntze (Theaceae) increases insulin activity and prevents oxidative damages, responsible for the hypoglycemic activity when tested in streptozotocin (STZ)-diabetic rats [70].

The extraction and fractionation of 50% aqueous methanol extract of *Bergenia ciliata* (Haw.) Sternb. (Saxifragaceae) led to the isolation of two active compounds, namely, (-)-3-O-galloylepicatechin and (-)-3-O-galloylcatechin. These isolated compounds demonstrated significant dose dependent enzyme inhibitory activities against rat intestinal α -glucosidase [71].

The soy isoflavones genistein was investigated for its possible hypoglycemic activity in Type II diabetes in male and female obese Zucker rats. The results indicated that the isoflavones significantly improved lipid and glucose metabolism by acting as a hypoglycemic peroxisome proliferator activated receptor (PPAR) agonist [72].

Effect of citrus bioflavonoids, hesperidin and naringin on blood glucose level, hepatic glucose-regulating enzymes activities, hepatic glycogen concentration, and plasma insulin levels were investigated in male C57BL/KsJ-db/db mice in an animal model for Type II diabetes. Supplementary diet contains citrus flavonoids (0.2 g/kg diet) that significantly reduced the blood glucose level as well as increased hepatic glucokinase activity and glycogen concentration in diabetic rats. Jung *et al.* suggested that hesperidin and naringin play an important role in preventing the progression of hyperglycemia, partly by increasing hepatic glycolysis and glycogen concentration or by lowering hepatic gluconeogenesis. Naringin also lowered the activity of hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. The plasma insulin, C-peptide and leptin levels in the diabetic mice were significantly increased as a result of supplementation [73].

Individual polyphenols, such as catechin, epicatechin, epigallocatechin, epicatechin gallate and isoflavones from soya beans also decrease S- Glut-1 mediated intestinal transport of glucose [74]. Methanol extract of *Amygdalus davidiana* var. *davidiana* (Carrière) de Vos ex Henry (*Prunus davidiana* (Carrière) Franch) (Rosaceae) stems and its main component, naringenin 7-O-beta-D-glucoside (prunin), produced a significant hypoglycemic effect after i.p administration. It was suggested that prunin can significantly reduce the level of blood glucose and total lipids in streptozotocin-induced diabetic rats [75].

Jorge and workers isolated flavonoid glycoside, kaempferol-3, 7-O- α -l-dirhamnoside (Kaempferitrin) from *Bauhinia forficata* Link (Fabaceae) leaves. The long term effect of kaempferitrin on glycaemia in diabetic rats as well as the *in vitro* effect of this compound on 14C-D-glucose uptake and 14C-leucine incorporation into protein in normal rat soleus muscle was studied. Kaempferitrin was found to have an acute lowering effect on blood glucose in diabetic rats and stimulate glucose uptake, as efficiently as insulin in muscle from normal rats. It suggests that blood glucose lowering activity of the compound attributed to altered intrinsic activity of the glucose transporter. [76].

Kaempferol glycoside-rich fraction was prepared from the leaves of unripe Jindai soybean (edamame) (*Lycine max* (L.) Merr., Fabaceae). The anti-diabetic effects of a kaempferol glycoside-rich fraction and kaempferol were determined in genetically type 2 diabetic KK-A(y) mice. The area under the curve in the oral glucose tolerance test (OGTT) tended to be decreased by feeding kaempferol glycoside-rich fraction and kaempferol. The liver triglyceride level and fatty acid synthase activity were both decreased in the mice fed with kaempferol glycoside-rich fraction and kaempferol when compared to those parameters in the control mice. Results suggest that kaempferol glycoside-rich fraction and kaempferol would be useful to improve the diabetes condition. The major flavonoids in kaempferol glycoside-rich fraction were identified as kaempferol 3-O- β -D-glucopyranosyl(1 \rightarrow 2)-O-[α -L-rhamnopyranosyl(1 \rightarrow 6)]- β -D galactopyranoside, kaempferol 3-O- β -D-glucopyranosyl(1 \rightarrow 2)-O-[α -L-rhamno-pyranosyl(1 \rightarrow 6)]- β -D-glucopyranoside, kaempferol 3-O- β -D-(2-O- β -D-glucopyranosyl) galactopyranoside and kaempferol 3-O- β -D-(2,6-di-O- α -L-rhamnopyranosyl) galactopyranoside, suggesting that these compounds or some of them may be concerned with the mitigation of diabetes [77].

A single oral administration of a water extract of aerial parts of *Equisetum myriochaetum* (Equisetaceae) at doses of 7 and 13 mg/kg and a butanol extract at a dose of 8 and 16 mg/kg reduced glycaemia in streptozotocin-induced diabetic rats 3 h after its administration. One caffeoyl glucoside and three kaempferol glucosides were isolated from the plant. So it can be concluded that these compounds may contribute to the antidiabetic effect in animal models [78].

Kolaviron, a mixture of C-3 and C-8 linked biflavonoids obtained from *Garcinia kola* Heckel (Guttifere) produced significant hypoglycemic effects (i.p.) in healthy and alloxan diabetic rabbits. Kolaviron inhibited rat lens aldose reductase activity with an IC₅₀ value of 5.4×10^{-6} M [79].

A leucodelphinidin derivative isolated from the bark of *Ficus bengalensis* showed hypoglycemic action at a dosage of 250 mg/kg when given to both healthy and alloxan diabetic rats. Its action was similar to that of an effective dose of glibenclamide (2 mg/kg) tested under the same conditions [80].

The rhizomes of *Anemarrhena asphodeloides* have been used as an oriental traditional medicine to treat diabetes. It contains the xanthone compound, mangiferin [81]. The effect of mangiferin, a plant natural polyphenol of C-glycosylxanthone structure, on blood lipids was studied with exercise in KK-Ay mice, an animal model of type 2 diabetes. Mangiferin reduced the blood cholesterol and triglyceride level of KK-Ay mice with exercise 2 weeks after oral administration when compared with the control group. Mangiferin has showed the dose-dependence antidiabetic activity in animal models [82].

The hypoglycemic effect of flavonoids (marsupin, pterosupin and pterostilbene) isolated from the heartwood of *Pterocarpus marsupium* Roxb. (Fabaceae) was investigated in diabetic rats (i. p.). Marsupin and pterostilbene significantly lowered the glycaemia of diabetic rats, and the effect was comparable to that of metformin [83].

Grape seed-derived procyanidins administered (p.o.) to streptozotocin-induced diabetic rats produced significant antihyperglycemic activity possibly by its insulinomimetic activity. Proanthocyanidins, flavonoids with an oligomeric structure, were found to improve the pathological oxidative state of a diabetic situation. They also stimulated glucose uptake in insulin sensitive cells *in vitro* [84].

Quercetin is an important flavonoid known to possess an enormous array of pharmacological activities. The administration of quercetin (i.p.) to normal as well as streptozotocin-induced diabetic rats resulted in marked reduction in plasma glucose level of diabetic animals while the glucose level of the normoglycemic rats remained unaltered. Quercetin also suppressed the glucose level in diabetic rats in a glucose tolerance tests, reduced plasma cholesterol and triglycerides significantly and increased their hepatic glucokinase activity probably by enhancing the insulin release from pancreatic islets of the diabetic rats [85].

Hii and Howell reported that some flavonoids like chrysin, naringenin and quercetin significantly improved the insulin release from isolated rat islets of langerhans in the presence of 20 mmol glucose/l. Quercetin exerted its stimulatory effect on insulin release partly by changing Ca²⁺ metabolism [86].

Sattanathan and others demonstrated the beneficial effect of flavonoid rutin supplementation tablets in 500 mg caplets (RUTIN 500 mg, natural bioflavonoid, manufactured by Nutraceutical Corp., USA for 60 days to be taken once a day. Supplementation of rutin tablets significantly reduced glucose levels of 30 patients. Rutin is a polyphenolic flavonoid, which could prompt the intact functional β cells to produce insulin and protect the functional β cells from further deterioration, which is necessary for them to remain active and to produce insulin. Rutin showed adjuvant effect with oral hypoglycemic agents and glycemic control and lipid profile in T2DM patients [87].

The plant *Psidium guajava* L. (Myrtaceae) contains flavonoid glycosides such as strictinin, isostrictinin and pedunculagin which have been used in the clinical treatment of diabetes due to improved sensitivity of insulin [2, 88].

Recently, Ganugapati reported that flavonoids isolated from banana flowers have the potential to activate the insulin receptor tyrosine kinase, and may represent an alternative choice for treatment of T2DM patients with insulin resistance [89].

Shamimin, a C-flavonol glucoside from the leaves of *Bombax ceiba* (Malvaceae) showed significant potency as a hypoglycaemic agent in Sprague-Dawley rats [90].

The pharmacological screening of extract of *Satureja hortensis* L. (Lamiaceae) leaves was carried out on normal animals and animals with experimental alloxan induced diabetes. The study revealed that the extract exhibits hypoglycemic activity by reducing blood sugar levels and is safe for long term. Flavonoids such as apigenin, luteolin, cinaroside, luteolin glucuronide, luteolin rutinoside, isoroifolin and phenylcarbonic acids, chlorogenic acid, and rosmarinic acid were isolated from the leaves of *S. hortensis* and drug dosage form named saturin - capsules containing 0.33 g of dried aqueous extract of leaves has been developed. Clinical trials of saturin capsules confirmed their efficacy in diabetes mellitus type 2 [91].

Quercetin was isolated as active principle from methanol extract of *Chamaecostus cuspidatus* (Nees & Mart.) C. Specht & D.W. Stev. (*Costus igneus* N.E. Br.) (Costaceae) rhizome. It may contribute to the reduction in blood glucose level and also lipid profile [92]. It has been investigated that quercetin in doses of 10 and 50 mg/kg promotes normalization of the level of glycemia and blood coagulation, increases liver glycogen content, reduces high blood serum concentrations of cholesterol and low density lipoproteins, seen in diabetes. This correlates with the previous report of Nuraliev & Avezov [93].

Activity-guided fractionation and chemical analysis led to the isolation of 5, 7, 3'-trihydroxy-3, 6, 4'-trimethoxyflavone from the leaves of *Brickellia veronicaefolia* (Kunth) A. Gray (Asteraceae). This flavone produced a significant hyperglycaemic action when tested in normoglycaemic and alloxan-induced diabetic mice (CD 1 mice) [94].

Terpenoids and Steroids

There are at least 4000 known triterpenes, which are derived from mevalonic acid pathway. Triterpenes are precursors to steroids in both plants and animals. Many terpenes and sterols occur free, but others occur as glycosides or in special combined forms. Triterpenoid and steroidal glycosides, referred to collectively as saponins. These are bioactive compounds present naturally in many plants and known to possess potent hypoglycemic activity [95]. A literature claims that terpenoids can reduce hyperglycemia. Few of such phytoconstituents have been isolated and identified by many scientists which are listed below,

Bioactivity guided isolation work on the fruits of *Ficus racemosa* L. (Moraceae) led to the identification of α -Amyrin acetate. α -Amyrin acetate lowered the blood glucose

levels in sucrose challenged streptozotocin induced diabetic rats (STZ-S) model. So, the findings suggest that α -amyrin acetate is an important antidiabetic active principle [96, 97].

Andrographolide, a diterpenoid lactone, obtained from the leaves of *Andrographis paniculata* Nees (Acanthaceae.) was found to possess significant hypoglycemic activity [98]. After this successful report of andrographolide as hypoglycemic agent, it was further investigated for the mechanism of glucose lowering action in streptozotocin-induced diabetic rats (STZ-diabetic rats) [99]. They observed that andrographolide lowered plasma glucose concentrations in a dose-dependent manner and increased plasma beta-endorphin like immunoreactivity (BER) dose-dependently in diabetic rats. Results suggest that andrographolide may activate alpha-ARs to enhance the secretion of beta-endorphin which can stimulate the opioid micro-receptors to reduce hepatic gluconeogenesis and to enhance the glucose uptake in soleus muscle, resulting in a decrease of plasma glucose in STZ-diabetic rats [98, 99].

Two pentacyclic triterpene acetates namely 3 β -Acetoxy-16 β -hydroxybetulinic acid and 3 β , 16 β -diacetoxybetulinic acid were isolated from the stem bark of *Zanthoxylum gillettii* (De Wild.) P.G. Waterman (*Fagara tessmannii* Engl.) (Rutaceae). Out of these two compounds, 3 β -Acetoxy-16 β -hydroxybetulinic acid was found to be a potent α -glucosidase inhibitor [100].

Bassic acid, an unsaturated triterpene acid isolated from the root bark of *Bumelia sartorum* Mart. (Sapotaceae) produced a significant hypoglycemic effect in alloxan-induced diabetic rats. Basic acid acts by increasing glucose uptake and glycogen synthesis in isolated rat diaphragm and plasma insulin levels. It appears that this effect was mediated by an insulin secretagogue effect in pancreatic β cells [101].

Charantin (mixture β -sitosterol-D-glucoside and stigmadin glucoside), a steroidal saponin, obtained from *Momordica charantia* L. (Cucurbitaceae) seeds is known to have an insulin-like activity, responsible for its hypoglycemic effect [102]. Charantin stimulates the release of insulin and blocks the formation of glucose in the blood stream, which may be helpful in the treatment of diabetes, particularly in noninsulin-dependent diabetes.

A Butanol extract of *Zizyphus spina-christi* L. (Rhamnaceae) leaves as well as christinin-A, (its principal saponin glycoside) was studied for its hypoglycemic effects. However, in streptozotocin-induced diabetic rats, both treatments significantly reduced serum glucose levels, liver phosphorylase and glucose-6-phosphatase activities, and significantly increased the serum pyruvate level and liver glycogen content after 4 weeks of treatment. There was also a marked improvement in glucose utilization in diabetic rats for both cases [103].

Lagerstroemia speciosa (L.) Pers. (Lythraceae) is a very important medicinal plant having antidiabetic activity. Colosolic acid and maslinic acid are the two terpenoids isolated from the leaves of the plant. Colosolic acid was found to be a glucose transport activator. The hypoglycemic effects of *L. speciosa* were studied using hereditary diabetic mice (Type II, KK-Ay/Ta Jcl). A treatment of 5 week duration with different extracts from banaba leaves showed beneficial

effects on the level of plasma glucose in non-insulin dependent diabetes mellitus [104, 105]. Corosolic acid, a triterpenoid compound present in *L. speciosa* and in other plants was found to possess antidiabetic activity [106, 107].

Corosolic acid isolated from the *Vitex leucoxylon* L.f. (Lamiaceae) extract was found to be effective in treating diabetic and inflammatory conditions. Iridoid glucoside is a monoterpenes with a glucose molecule isolated from the leaves of *V. negundo* L. and evaluates its effects on the derangement in plasma and tissue glycoprotein components in streptozotocin-induced diabetic rats were evaluated. The levels of blood glucose, plasma and tissues glycoproteins such as hexose, hexosamine, fucose and sialic acid were significantly increased whereas plasma insulin levels were significantly decreased in diabetic rats. On oral administration of iridoid glucoside at a concentration of 50 mg/kg b.w. once daily to diabetic rats for the period of 30 days reversed the above mentioned hyperglycemia induced biochemical changes to near normal levels. The anti-hyperglycemic effect of iridoid glucoside was comparable with glibenclamide, a known hypoglycemic drug. Based on the results obtained from this study, it may be concluded that iridoid glucoside possesses significant productive effect on glycoprotein metabolism in addition to its antidiabetic effects [108].

Elatosides E isolated from the root cortex of *Aralia elata* Seem. (Araliaceae) was shown to affect the elevation of plasma glucose levels in an oral sugar tolerance test in rats. Five new saponins named elatosides G, H, I, J, and K were isolated from the young root shoot of the plant. Elatosides G, H, and I were found to exhibit potent hypoglycemic activity in the oral glucose tolerance test in rats [109].

Five triterpene oligoglycosides named escins-Ia, Ib, IIa, IIb and IIIa were isolated from the seeds of *Aesculus hippocastanum* L. (Sapindaceae). These compounds were tested for their effects on ethanol absorption and hypoglycemic activity on oral glucose tolerance test in rats. Escins-Ia, Ib, IIa, and IIb were found to exhibit inhibitory effect on ethanol absorption and hypoglycemic activity on oral glucose tolerance test in rats. Among them, escins-IIa and IIb showed the higher activities for both bioassays [110].

Forskolin, a diterpene is isolated from *Coleus forskohlii* (Willd.) Briq. (Lamiaceae). The effects of forskolin on cyclic AMP content and insulin release have been studied in rat pancreatic islets. It was observed that forskolin stimulates glucose-induced insulin secretion *in vitro* [111]. This appears to reflect a general stimulatory influence of forskolin on adenylate cyclase activity, obviating its specific suitability as an antidiabetic treatment [112].

Ginsenosides, a diverse group of steroidal saponins are the principal bioactive constituents isolated from ginseng (*Panax* spp.) (Araliaceae). Some ginsenosides have demonstrated hypoglycemic properties [113]. Complex components in the carbohydrate fraction of ginseng root extract, including different panaxans A, B, C, D, E, panaxans I, J, K, L, and panaxans Q, R, S, T, U also demonstrated hypoglycemic properties in normal and alloxan-induced hyperglycemic mice [114,115]. Similar to Asian ginseng, three constituents obtained from the water extracts of American ginseng root, viz. quinquefolans A, B, and C displayed hypoglycemic actions in normal and hyperglycemic mice [116]. Subsequent

studies performed by Chung *et al.* showed that ginseng has distinct anti-diabetic properties [117, 118]. Experts stated that ginseng might exert its anti-diabetic actions through an array of mechanisms including actions on the insulin secreting pancreatic β -cells and the target tissues that take up glucose. Ginseng treatment increased insulin release from pancreatic β -cells, which is most likely caused by increased β -cell stimulation and augmented insulin synthesis [119-121].

Sugihara *et al.* isolated gymnemic acid IV, a pentacyclic triterpenoid from the leaves of *Gymnema sylvestris* R. Br. (Asclepiadaceae). The hypoglycemic potential of gymnemic acid IV was studied in experimental animal models of diabetes. Gymnemic acid IV inhibits the glucose absorption (glycosidase inhibition), increases glucose uptake in striated muscles, lowers blood glucose and increases the insulin secretion in pancreatic β -cells. The leaves of *Gymnema sylvestris* are reported to contain gymnemic acid (I). An oral administration of alcoholic extract of leaves of *G. sylvestris* showed significant hypoglycemic effect on blood glucose level in normal fasted rats [122-124]. So we can say that gymnemic acids are very important phytoconstituents in the treatment of diabetes mellitus [125].

Hou and coworkers isolated three novel sesquiterpenes lactone lactucain A, B, and C and new furofuran lignin lactucaside from *Lactuca indica* L. (Asteraceae). Among these compounds, lactucain A and lactucaside were found to produce significant hypoglycemic activity in animal models [126].

A new cardenolide, (-)-14-methoxyhyrcanoside and five new dihydrobenzofuran derivatives (securigran I to V) were isolated from an aqueous extract of the seeds of *Securigera securidacea* L. (Fabaceae). Kaempferol and astragalins were also isolated from the aqueous extract of the flowers of the plant. The total aqueous extract of these seeds showed hypoglycemic effect in animal models so it can be concluded that the hypoglycemic effect may be attributed to the above mentioned compounds [127].

Momordin Ic and 2'-O-beta-D-glucopyranoside are the principal saponin constituents isolated from the methanol extract of fruit of *Kochia scoparia* L. (Chenopodiaceae). These active constituents have shown to inhibit glucose and ethanol absorption in rats [128].

Two novel terpenoid-quinones, pycnanthuquinone A and pycnanthuquinone B were isolated from the ethanol extract of leaves and stems of *Pycnanthus angolensis* (Welw.) Warb. (Myristicaceae). Both compounds showed significant antihyperglycemic activity in a diabetic mouse model [129].

Mukherjee *et al.* reported that β -sitosterol, a steroid obtained from *Azadirachta indica* A. Juss. (Meliaceae) may be responsible for its hypoglycemic property [7]. Probable mechanism of β -sitosterol in type 2 diabetics is that it may assist in normalizing the insulin levels and the blood sugar levels. β -Sitosterol does this by inducing the secretion of insulin even in the absence of any stimulatory glucose concentration. This secretion therefore inhibits glucose-6-phosphatase enzyme [130].

A new triterpenoid saponins, segetalic acid 28-O- α -l-arabinopyranosyl-(1 \rightarrow 4)- α -l-arabinopyranosyl-(1 \rightarrow 3)- β -d-xylopyranosyl-(1 \rightarrow 4)- α -l-rhamnopyranosyl-(1 \rightarrow 2)- β -d-

fucopyranosyl ester have been isolated from the roots of *Gypsophila oldhamiana* Miq. (Caryophyllaceae). This compound has shown potent α -glucosidase inhibition activity [131].

Senegin-II, a triterpene glycosides is the main component of *Polygala senega* L (Polygalaceae) var, when given to healthy mice (i.p.), it reduced blood glucose levels. It also significantly lowered blood glucose level in KK-Ay mice. E-senegasaponins a, b and c were isolated from the roots of *Senega radix*. Their Z isomers were also isolated and named as Z-senegasaponins a, b, and c. The E and Z-senegasaponins a and b were found to be hypoglycemic in the oral D-glucose tolerance test in rats. Other bioactive saponins, named E-senegasaponin c and Z-senegasaponin c, were isolated from the roots of *Polygala senega* together with Z-senegins II, III and IV. The E and Z-senegasaponins c and E and Z-senegins II, III, and IV were also found to exhibit hypoglycemic activity in the oral D-glucose tolerance test. E and Z-senegins II also showed an inhibitory effect on alcohol absorption in rats. The effect of four triterpenoid glycosides isolated from the rhizomes of *P. senega*, senegins II-IV (1-3) and desmethoxysenegin II (4) were tested in healthy and KK-Ay mice. Compounds 1 and 2 reduced the blood glucose of healthy mice for 4 h after intraperitoneal administration and also significantly lowered the glucose level of KK-Ay mice under similar conditions. Compounds 3 and 4, as well as senegose A (5), an oligosaccharide ester, were inactive when tested in healthy mice [132].

Farias and coworkers isolated Trans-dehydrocrotonin (t-DCTN), a 19-nor-clerodane diterpene from the bark of *Croton cajucara* Benth (Euphorbiaceae) showing a significant hypoglycemic activity in alloxan-induced diabetic rats [133].

Polysaccharides

Various plants like *Aloe vera* (L.) Burm. f. (Xanthorrhoeaceae), *Ocimum sanctum* L. (Lamiaceae), and *Alpinia galanga* (L.) Willd. (Zingiberaceae) have been found to contain polysaccharides. Polysaccharide acts by various mechanisms such as by increasing the levels of serum insulin, reduces the blood glucose levels and improves glucose tolerance. Many polysaccharides have been proven beneficial for the treatment of hypoglycaemia. Few polysaccharides and their mechanisms for antidiabetic action are listed below,

Activity-guided fractionation of an aqueous methanol and aqueous extract of *Aconitum carmichaeli* Debeaux (Ranunculaceae) roots led to isolate four glycans, aconitans A, B, C and D. These glycans exhibited prominent hypoglycemic effects in normal and alloxan-produced hyperglycemic mice and markedly reduced the blood sugar level [134].

Takahashi and co-workers isolated anemarrans A, B, C and D, glycans from rhizomes of *Anemarrhena asphodeloides*. These constituents displayed significant hypoglycemic effects in normal and alloxan-induced hyperglycemic mice [135].

Atractans A, B and C, glycans were isolated from the rhizomes of *Atractylodes japonica* Koidz. ex Kitam. (Asteraceae). Hypoglycemic effects of these polysaccharides were studied in diabetic mice. Significant hypoglycemic effect was observed after the treatment of attractans A [136].

Administration of an aqueous methanol and water extract of *Ephedra distachya* L. (Ephedraceae) herbs caused transient hyperglycemia followed by long lasting hypoglycemia in mice. Activity-guided fractionation of the extract led to isolation of five glycans, ephedrins A, B, C, D and E, which exhibited significant hypoglycemic effects in normal and alloxan-induced hyperglycemic mice [137].

A water extract of the fruit bodies of *Ganoderma lucidum* (Curtis) P. Karst. (Ganodermataceae), significantly decreased plasma sugar level in mice. Fractionation of the extract led to isolate two glycans, ganoderans A and B. These glycans elicited remarkable hypoglycemic actions in normal and alloxan-induced hyperglycemic mice [138].

Seeds of *Cyamopsis tetragonolobus* (L.) Taub. (Fabaceae) are well known in Asian folklore as a useful aid for the diabetic treatment. In addition to the guar seeds, the pods are also believed to contain an antidiabetic principle [139]. Seeds of this plant are the source of galactomannan gum which is used as a bulking agent in pharmaceutical industries. The viscosity effect of guar is exploited as a dietary adjunct to delay the rate of glucose absorption and thereby helps to reduce postprandial hyperglycemia [140].

Polysaccharide glucomannan isolated from the tubers of *Amorphophallus konjac* (Araceae) was found to be closely related and similarly effective to guar gum in the treatment of diabetes [141].

Konno isolated lithospermans A, B and C and oryazarans A, B, C, and D from the roots of *Lithospermum erythrorhizon* Sieb. & Zucc. (Boraginaceae) and *Oryza sativa* L. (Poaceae) respectively. All these glycans proved to be efficient hypoglycemic agents [142].

Activity-guided fractionation of a non-sucrose portion of the juice from the stalks of *Saccharum officinarum* (Poaceae) yielded six glycans, saccharans A, B, C, D, E and F. These glycans exerted remarkable hypoglycemic actions in normal and alloxan-induced hyperglycemic mice which prominently reduced blood sugar level in mice [143, 144].

Dietary Fibers

The role of dietary fibers in diabetes has been studied by several scientists. It is proven that dietary fibres regulate blood sugar, which may reduce glucose and insulin levels in diabetic patients and may lower the risk of diabetes.

Nandini and coworkers stated that long term dietary treatment with increased amounts of fiber-rich low-glycaemia index natural foods improves blood glucose levels and reduces the number of hypoglycemic events in type I diabetic patients. An effect of soluble (5% guar gum) and insoluble (10 % wheat bran) dietary fibre supplementation on glycaemic control and nephropathy was investigated in streptozotocin treated diabetic rats. The results indicated that both soluble and insoluble dietary fibers ameliorated a significant increase in the activity of glutamine fructose-6-phosphate amidotransferase (GFAT) and decrease in the renal content of heparin sulfate in diabetic animals was observed [145].

Chau and coworkers obtained insoluble fiber-rich fractions including insoluble dietary fiber, alcohol insoluble

solid, and water-insoluble solid, from the peel of *Citrus sinensis* L. (Rutaceae). They showed that the fiber rich fraction effectively adsorbed glucose, retarded glucose diffusion and inhibited the activity of α -amylase to different level. It may be responsible for decreasing the rate of glucose absorption and concentration of postprandial serum glucose which ultimately exerts hypoglycemic action [146].

A high insoluble-fiber diet containing 15% cellulose in dry matter, high soluble-fiber diet containing 15% pectin in dry matter and low-fiber diet was tested for the effect on glycemic control in six dogs with alloxan-induced insulin-dependent diabetes mellitus. High insoluble-fiber and soluble-fiber diet fed animals showed significant reduced levels of plasma glucose concentration in the mean postprandial when compared to the levels dogs fed with low fiber diet [147].

The hypoglycemic and anti hyperglycaemic actions of fenugreek have been attributed to gastrointestinal effects of local dietary fibre. The high fiber content of the seeds (50-60%) might also contribute to a beneficial effect in diabetic patients [148].

A study investigated the effect of dietary carbohydrate and fiber on mucosal insulin receptors. It revealed that insulin binding was significantly affected by the consumption of dietary fiber [149].

Miscellaneous

Allium sativum L. (Liliaceae) contains higher amount of S-allyl cysteine sulphoxide, (allicin), a sulphur containing amino acid. It is efficient to reduce the diabetic condition in rats. It has shown effect as equivalent to the standard diabetic drug glibenclamide and insulin [150].

Ethyl acetate soluble fraction of *Swertia japonica* Makino (Gentianaceae) leads to the isolation of five known xanthenes and two triterpenoids. Among the xanthenes, bellidifolin (i.p. and p.o.) showed a potent and dose dependent hypoglycemic activity in streptozotocin-induced diabetic rats. Bellidifolin significantly lowered glucose concentrations and blood triglyceride levels in normal and streptozotocin-induced diabetic rats by both the route. It also stimulated glucose uptake activity in rat 1-fibroblasts expressing human insulin receptors [151].

A new tetrahydropyrane was isolated from the methanolic extract of roots of *Acrocomia mexicana* Karw (Palmae). Extract showed a significant blood sugar lowering effect on normal and alloxan-diabetic mice [152]. Betavulgarosides I-IV oleanolic acid oligoglycosides were isolated together with betavulgarosides VI, VII, VIII from the roots of *Beta vulgaris* L. (Chenopodiaceae). Betavulgarosides II, III and IV produced significant hypoglycemic effects in rats when demonstrated by an oral glucose tolerance test [153].

Oral administration of bakuchiol, meroterpene (a chemical compound having a partial terpenoid structure isolated from an extract of *Otholobium pubescens* (Poir.) J.W. Grimes (Fabaceae) reduced glycaemia in db/db mice in a dose-dependent manner [154].

Curcuminoids such as curcumin, demethoxycurcumin and bisdemethoxycurcumin isolated from *Curcuma longa* L.

(Zingiberaceae) were evaluated *in vitro* for the α -glucosidase inhibitory activity. The results of the study indicated that natural curcuminoid compound bisdemethoxycurcumin showed a remarkable inhibitory effect [155].

Bioassay-guided separation of methanol extract of dried fruits of *Terminalia chebula* Retz. (Combretaceae) lead to isolate three active ellagitannins, identified as chebulanin, chebulagic acid, and chebulinic acid. Isolated compounds were tested for mammalian α -glucosidase inhibitory activity and all the compounds have shown to possess potent intestinal maltase inhibitory activity [156].

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) found in the leaves and seeds of *Curcuma longa*. Ferulic acid at low dose (p.o) produced significant hypoglycemic activity in both types of diabetes as evident from a study on streptozotocin-induced diabetic mice and KK-Ay mice. The study suggested potent antioxidant activity of the compound in addition to its blood glucose lowering activity in experimental hyperglycemia in animals [157]. An *in vitro* study utilizing rat pancreatic RIN-5F cell suggested that amide compounds, derived from ferulic acid have stimulatory effects on insulin secretion [158].

Ginseng polypeptides (GPP) isolated from the roots of *Panax ginseng* C.A. Mey. decreased the level of blood sugar and liver glycogen in rats (i.v) at doses of 50-200 mg/kg without affecting total blood lipid concentrations. GPP was also found to decrease blood glucose and liver glycogen and stimulate the release of insulin when mice were injected subcutaneously with doses of 50 and 100 mg/kg for 7 successive days. In addition, GPP was found to decrease hyperglycaemia which was induced experimentally by injection of adrenaline, glucose and alloxan [113].

4-hydroxyisoleucine an unusual amino acid isolated from the seeds of *Trigonella foenum-graecum*, was found to be an effective antihyperglycemic agent [159].

The unripe fruits of *Blighia sapida* K.D. Koenig (Sapindaceae) are used in traditional treatment of diabetes in Central America and Africa. The hypoglycins (aminopropylpropionic acid) derivatives are isolated from the fruits [160, 161]. When Hypoglycins were studied scientifically it was observed that, they are effective in healthy and diabetic animals and humans, which promotes glucose use and inhibits gluconeogenesis [161,162].

A potent natural alpha-glucosidase inhibitor, kotalanol was isolated from aqueous extract of *Salacia reticulata* Wight (Celastraceae). An aqueous extract rich in this constituent decreased plasma glucose levels so it can be concluded that hypoglycemic effect of the extract was attributed to the presence of kotalanol which was found to show more potent inhibitory activity against sucrase than salacinol and acarbose [163].

Masoprocol (nordihydroguaiaretic acid, a lipoxygenase inhibitor) is a pure compound isolated from *Larrea tridentata* (Sessé & Moc. ex DC.) Coville (Zygophyllaceae). The oral administration of masoprocol dropped the plasma glucose concentrations in db/db mice models of type 2 diabetes, without any change in plasma insulin concentrations. The ability of insulin to lower plasma glucose concentrations was improved in masoprocol-treated db/db mice [164].

Leaves of *Medicago sativa* L. (Fabaceae) also known as alfalfa, are a rich source of the high manganese content [164]. Manganese chloride has been shown to exert a hypoglycemic action in an IDDM patient, and manganese is now recognized as a necessary cofactor for ATP phosphorylation of the 3-subunit of the insulin receptor [165, 166]. An anti-diabetic effect of alfalfa, which has been substantiated in streptozocin-induced diabetic mice, might also be associated with the high concentration of vitamin K [167].

Kumari *et al.* studied the hypoglycemic action of *Allium cepa* L. (Liliaceae) in alloxan induced diabetic rats. An oral administration of S-methyl cysteine sulphoxide (SMCS) isolated from *A. cepa* to alloxan diabetic rats controlled the blood glucose and lipids in serum and tissues and altered the activities of liver hexokinase, glucose 6-phosphatase and 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase towards normal values. These effects of SMCS were comparable to those of glibenclamide and insulin [150].

Leaves of *Morus insignis* Bureau (Moraceae) containing mulberrofuran U and moracin (M-3-O-β-D- glucopyranoside) showed hypoglycemic activity in streptozotocin-diabetic rats [168].

Paeoniflorin and 8-debenzoylpaeoniflorin, isolated from the dried roots of *Paeonia lactiflora* Pall (Ranunculaceae) produced a significant blood sugar lowering effect in streptozotocin-treated rats. This hypoglycemic action was also observed in normoglycemic rats [169].

CONCLUSION

Diabetes is possibly the world's fastest growing metabolic disease, and as knowledge of the heterogeneity of this disorder increases, so does the need for more appropriate therapies. Traditional plant medicines are used throughout the world for the management of diabetes because it is easily and cheaply available. The scientific validation of several plant species has proved the efficacy of the botanicals in management of diabetes acting through various mechanisms. However, many herbal remedies used today have not undergone careful scientific assessment and few of them have the potential to cause serious toxic effects and major drug-to-drug interaction. Therefore, there is a tapping need to search and develop new herbal formulations and nutraceuticals from natural resources especially with pure phytochemicals for the treatment of diabetes and to avoid serious diabetic complications. A systematic research and development in the form of drug delivery systems are necessary to explicate the pharmacological activities of herbal remedies being used nowadays to treat diabetes mellitus. The study of such medicines might offer a natural key to unlock a diabetologist's pharmacy for the future.

ABBREVIATIONS

AChE	=	Acetylcholinesterase
BER	=	Beta-endorphin like immunoreactivity
DNJ	=	Deoxyynojirimycin
GFAT	=	Glutamine fructose-6-phosphate amidotransferase
HMG -CoA	=	3-hydroxy-3-methylglutaryl-coenzyme A

NIDDM	=	Non-insulin-dependent diabetes mellitus
OGTT	=	Oral glucose tolerance test
SMCS	=	S-methyl cysteine sulphoxide
STZ	=	Streptozotocin
STZ-S	=	Streptozotocin induced diabetic rats
T2DM	=	Type 2 diabetes mellitus
t-DCTN	=	Trans-dehydrocrotonin
WHO	=	The World Health Organization

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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