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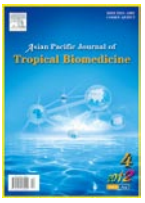

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An overview on antidiabetic medicinal plants having insulin mimetic property

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ABSTRACT

Diabetes mellitus is one of the common metabolic disorders acquiring around 2.8% of the world's population and is anticipated to cross 5.4% by the year 2025. Since long back herbal medicines have been the highly esteemed source of medicine therefore, they have become a growing part of modern, high-tech medicine. In view of the above aspects the present review provides profiles of plants (65 species) with hypoglycaemic properties, available through literature source from various database with proper categorization according to the parts used, mode of reduction in blood glucose (insulinomimetic or insulin secretagogues activity) and active phytoconstituents having insulin mimetics activity. From the review it was suggested that, plant showing hypoglycemic potential mainly belongs to the family Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae and Araliaceae. The most active plants are *Allium sativum, Gymnema sylvestre, Citrullus colocynthis, Trigonella foenum greacum, Momordica charantia* and *Ficus bengalensis*. The review describes some new bioactive drugs and isolated compounds from plants such as roseoside, epigallocatechin gallate, beta-pyrazol-1-ylalanine, cinchonain Ib, leucocyandin 3-O-beta-d-galactosyl cellobioside, leucopelargonidin-3- O-alpha-L rhamnoside, glycyrrhetinic acid, dehydrotrametenolic acid, strictinin, isostrictinin, pedunculagin, epicatechin and christinin-A showing significant insulinomimetic and antidiabetic activity with more efficacy than conventional hypoglycaemic agents. Thus, from the review majorly, the antidiabetic activity of medicinal plants is attributed to the presence of polyphenols, flavonoids, terpenoids, coumarins and other constituents which show reduction in blood glucose levels. The review also discusses the management aspect of diabetes mellitus using these plants and their active principles.

1. Introduction

Diabetes mellitus, one of the most common endocrine metabolic disorders has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications[1]. Human bodies possess enzymatic and non-enzymatic antioxidative mechanisms which minimize the generation of reactive oxygen species, responsible for many degenerative diseases including diabetes[2]. The disease is rapidly increasing worldwide and affecting all parts of the world. Due to deficiency of the insulin people suffering from diabetes have high blood glucose level[3]. Type 2 diabetes or non-insulin-dependent diabetes mellitus, is the most common form of the disease, accounting for 90%-95% of cases in which the body does not produce enough insulin or properly use it[4]. According to World Health Organization the diabetic population is likely to increase up to 300 million or more by the year 2025[5]. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides and glinides. Many of them have a number of serious adverse effects; therefore, the search for more effective and safer hypoglycemic agents is one of the important areas of investigation[6]. Aldose reductases, a key enzyme in the polyol pathway catalyze the reduction of glucose to sorbitol. Accumulation of sorbitol in the body causes various complications including cataract, neuropathy and nephropathy[7]. The hypoglycemic effect of several plants used as antidiabetic remedies has been confirmed, and the mechanisms of hypoglycemic activity of these plants are being studied. Natural products

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having antidiabetic potential which acts through either insulinomimetic or secretagogues properties are reviewed here. This review also focuses on the role of traditional therapeutic and natural medicines from traditional medicinal plants for diabetes. Traditional medicines from readily available medicinal plants offer great potential for the discovery of new antidiabetic drugs[8].

Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically in antidiabetic and antihyperlipidemic remedies. Antihyperglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, *etc.*, that are frequently implicated as having antidiabetic effect[9].

2. Medicinal plants used to treat diabetes

Plants have always been a very good source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The ethnobotanical information suggests that about 800 plants may possess anti-diabetic potential, among all of them *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum greacum* have been reported to be beneficial for treatment of type 2 diabetes[3,8]. Several such herbs have shown anti-diabetic activity when evaluated using different type of experimental techniques. Wide arrays of plant derived active principles representing different type of biological activity, among these alkaloids, glycosides, galactomannan gun, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids and inorganic ions have demonstrated activity including treatment of diabetes[10]. List of the medicinal plants having antidiabetic potential acording to the different part used and mode of action were presented in Table 1 and Table 2.

3. Pharmacologically screened insulinomimetic or insulin secretagogues plant material and phytoconstituents

The aim of this review is to collect the data available on plants material having hypoglycaemic activity through either increased secretion of the insuline from pancrease or similar action to the insulin reported in different source of literature. According to the search several plant species have been described as hypoglycaemic such as *Opuntia streptacantha, Trigonella foenum graecum, Momordica charantia, Ficus bengalensis, Polygala senega, Gymnema sylvestre, Allium sativum, Citrullus colocynthis* and *Aloe vera*[11]. The main focus of the present review is concerned about the experimental studies performed on hypoglycaemic activity of the plant material and the bioactive components related to the seceration of insulin or its action. Here all the plant materials which are listed were tested for their insulinomimetic or secretogogues activity in the different *in vivo* or *in vitro* model systems and represented according to alphabetical order. Moreover, phytoconstituents isolated from different plants which have shown insulinomimetic activty are also represented in the Table 3.

3.1. Acacia arabica (Leguminosae)

About 94% seed diet of *Acacia arabica* showed hypoglycemic effect in rats through release of insulin. However, powdered seeds of *Acacia arabica* at 2, 3 and 4 g/kg, p.o. exerted a significant hypoglycemic effect in normal rabbits by initiating the release of insulin from pancreatic beta cells[12].

3.2. Aegle marmelos (Rutaceae)

Aqueous leaf extract of *Aegle marmelos* showed antihyperglycemic activity in streptozotocin induced diabetic rats after 14 days treatment either by increasing utilization of glucose or by direct stimulation of glucose uptake through increased insulin secretion[13].

3.3. Agrimony eupatoria (Rosaceae)

Aqueous extract of *Agrimony eupatoria* evoked stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line *in vitro*. The effect of extract was found to be glucose-independent[11].

3.4. Alangium salvifolium (Alangiaceae)

Methanolic extract of *Alangium salvifolium* leaves possesses antihyperglycemic and antihyperlipidemic effects in dexamethasone induced insulin resistance in rats, which may be due to the antioxidant and insulinotropic effect of extract[14].

3.5. Allium sativum (Alliaceae)

Antihyperglycemic activity of ethyl ether extract at 0.25 mg/kg, p.o. was reported to be the most potent and active principle of *Allium sativum* (garlic) which was due to increased insulin like activity[13]. Oral administration of the ethanol extract, juice and oil of *Allium sativum* has remarkably blood sugar lowering effect in normal and alloxan-induced diabetic rats or a rabbit mediated through stimulation of insulin secretion from parital cells of pancreas[15]. Allicin, a sulfur-containing compound showed to have significant hypoglycemic activity due to increased hepatic metabolism, increased insulin release from pancreatic beta cells. S-allyl cystein sulfoxide (SACS), the precursor of allicin and garlic oil, stimulated *in vitro* insulin secretion from beta cells isolated from normal rats. The beneficial effects of SACS could be due to its antioxidant and secretagogues activity[11,16]. Daily oral feeding of garlic extracts at 100 mg/kg increased plasma insulin level with

Table 1
List of plants having antidiabetic activity[53].

S. No.	Plant part	Name of plants
1	Aerial parts	*Artemisia pallens, Bidens pilosa, Bixa orellana, Teramnus labialis*
2	Bark	*Cinnamomum zeylanicum, Croton cajucara*
3	Bulb	*Allium cepa, Allium sativum*
4	Flower	*Cassia auriculata, Gentiana olivier, Musa sapientum*
5	Fruit	*Carum carvi, Coriandrum sativum, Embellica officinalis, Juniperus communis, Momordica charantia, Xanthium strumarium*
6	Leaves	*Aloe barbadensis, Annona squamosa, Averrhoa bilimbi, Azadirachta indica, Beta vulgaris, Camellia sinensis, Cassia alata, Eclipta alba, Eucalyptus globulus , Euphrasia officinale, Ficus carica, Gymnema sylvestre, Gynura procumbens, Ipomoea aquatica, Mangifera indica, Myrtus communis, Memecylon umbellatum, Morus indica, Ocimum sanctum*
7	Rhizome	*Nelumbo nucifera*
8	Roots	*Clausena anisata, Glycerrhiza glabra, Helicteres isora, Pandanus odorus*
9	Seed	*Acacia arabica, Agrimony eupatoria, Lupinus albus, Luffa aegyptiaca, Lepidium sativum, Mucuna pruriens, Punica granatum*
10	Stem	*Amaranthus spinosus, Coscinium fenestratum*
11	Tubers	*Ipomoea batata*
12	Whole plant	*Abies pindrow, Achyranthus aspera, Ajauga iva, Aloe vera, Anacardium occidentale, Andrographis paniculata, Capsicum frutescens, Cryptolepis sanguinolenta, Enicostemma littorale, Ficus religiosa*

Table 2
List of plants having insulin mimetic or insulin secreatory activity[53].

S. No.	Plant botanical name	Common name	Family	Mechanism of action
1	*Abies pindrow*	Morinda	Pinaceae	Insulin secretagogue activity
2	*Acacia arabica*	Babool	Leguminosae	Release of insulin from pancrease
3	*Agrimony eupatoria*	Rosaceae	Leaves	Insulin releasing and insulin like activity
4	*Aloe barbadensis*	Gheequar	Liliaceae	Stimulating synthesis and release of insulin
5	*Annona squamosa*	Sharifa	Annonaceae	Increased plasma insulin level
6	*Averrhoa bilimbi*	Bilimbi	Oxalidaceae	Increase serum insulin level
7	*Bixa orellana*	Annotta	Bixaceae	Increase plasma insulin concentration and increase insulin binding on insulin receptor
8	*Boerhaavia diffusa*	Punamava	Nyctaginaceae	Increase plasma insulin concentration
9	*Camellia sinensis*	Green tea	Theaceae	Increase insulin secretion
10	*Capsicum frutescens*	Mirch	Solanaceae	Increase insulin secretion and reduction of insulin binding on the insulin receptor
11	*Cinnamomum zeylanicum*	Dalchini	Lauraceae	Elevation in plasma insulin level
12	*Clausena anisata*	–	Rutaceae	Stimulate secretion of insulin
13	*Eucalyptus globulus*	Eucalyptus	Myrtaceae	Increase insulin secretion from clonal pancreatic beta line (BRIN-BD 11)
14	*Ficus religiosa*	Peepal	Moraceae	Initiating release of insulin
15	*Hibiscus rosa*	Gudhal	Malvaceae	Stimulate insulin secretion from beta cells
16	*Helicteres isora*	Indian screw tree	Sterculiaceae	Decrease plasma triglyceride level and insulin sensitizing activity
17	*Ipomoea batata*	Shakarkand	Convolvulaceae	Reduce insulin resistance and blood glucose level
18	*Juniperus communis*	Hauber	Pinaceae	Increase peripheral glucose consumption and induce insulin secretion
19	*Olea europia*	Olive	Oleaceae	Increase insulin release and increase peripheral uptake of glucose
20	*Swertia chirayata*	Chirayata	Gentianaceae	Stimulates insulin release from islets
21	*Scoparia dulcis*	Mithi patti	Scrophulariaceae	Insulin-secretagogue activity
22	*Tinospora crispa*	Giloe	Menispermaceae	Anti-hyperglycemic, stimulates insulin release from islets
23	*Urtifca dioica*	Bichhu booti	Urticaceae	Increase insulin secretion
24	*Vinca rosea*	Sadabahar	Apocynaceae	Beta cell rejuvenation, regeneration and stimulation
25	*Zingiber officinale*	Adrak	Zingiberaceae	Increase insulin level and decrease fasting glucose level

concomitant decrease in plasma glucose levels[10]. Effect of aqueous garlic (10% v/v) extracts on isolated pancreas were shown to potentiate glucose-induced insulin secretion[17]. Effect of garlic on high-fat diet feed rats for 2 weeks suggests that garlic is insulinotropic rather than hypoglycemic[18].

3.6. Aloe vera (Liliaceae)

Hypoglycemic effect by bitter principle of *Aloe vera* in the rats is mediated through stimulation of synthesis or release of insulin from the beta-cells of Langerhans[12]. Effect of pseudoprototinosaponin AIII and prototinosaponins AIII on glucose uptake and insulin release suggested their hypoglycaemic effects are due to actions on hepatic gluconeogenesis or glycogenolysis[11]. Single as well as repeated doses of bitter principle of the *Aloe vera* showed hypoglycemic effect in diabetic rats, which was through stimulation of synthesis or release of insulin from pancreatic beta cells[16].

Table 3
List of plants phytoconstituents having insulin secretagogues or insulin mimetic activity.

S. No.	Plant botanical name	Family	Active constituents	References
1	*Aloe vera*	Liliaceae	Pseudoprototinosaponin AIII and prototinosaponins AIII	[11]
2	*Anemarrhena asphodeloides*	Liliaceae	Mangiferin and mangiferin-7-O- β -dglucoside	[8]
3	*Bauhinia variegata*	Caesalpiniaceae	Roseoside	[20]
4	*Camellia sinensis*	Theaceae	Epigallocatechin gallate	[13]
5	*Citrullus colocynthis*	Cucurbitaceae	Beta-pyrazol-1-ylalanine	[11]
6	*Ephedra distachya*	Ephedraceae	L-ephedrine	[15]
7	*Eriobotrya japonica*	Rosaceae	Cinchonain ib	[33]
8	*Eugenia jambolana*	Myrtaceae	Pandanus odorus (Toei-hom) a 4- hydroxybenzoic acid	[12]
9	*Ficus bengalensis*	Moraceae	Leucocyandin 3-O-beta-d-galactosyl cellobioside, leucopelargonidin-3-O-alpha-L rhamnoside	[11,13]
10	*Glycyrrhizae radix*	Fabaceae	Glycyrrhetinic acid, dihydroxy gymnemic triacetate	[36]
11	*Momordica charantia*	Cucurbitaceae	Momordicin, charantin, and galactose-binding lectin	[6]
12	*Panax ginseng*	Araliaceae	Polypeptides	[11]
13	*Prunella vulgaris*	Labiatae	Jiangtangsu	[15]
14	*Psidium guajava*	Myrtaceae	Strictinin, isostrictinin and pedunculagin	[15]
15	*Pterocarpus marsupium*	Fabaceae	Epicatechin	[6,16]
16	*Semen coicis*	Gramineae	Coixans	[15]
17	*Stevia rebaudiana*	Asteraceae	Stevioside, steviol	[41,42]
18	*Swertia chirayita*	Gentianaceae	Swerchirin	[10,11]
19	*Teucrium polium*	Lamiaceae	Apigenin	[45]
20	*Trigonella foenum-graecum*	Leguminosae	4-hydroxyleucine and hydroxyisoleucine	[10,16,48,49]
21	*Zizyphus spina-christi*	Rhamnaceae	Christinin-A	[50]

3.7. Annona muricata (Annonaceae)

Annona muricata played an important role in reduction of oxidative stress of pancreatic β-cells of streptozotocin induced diabetic rats, which was confirmed by the increased area of insulin immunoreactive β-cells and protection against degeneration of β-cells[9].

3.8. Annona squamosa (Annonaceae)

Annona squamosa commonly called custard apple plant possesses antidiabetic activity. It acts by promoting insulin release from the pancreatic islets, increasing utilization of glucose in muscle and inhibiting the glucose output from liver[9].

3.9. Asparagus racemosus (Liliaceae)

The ethanol extract, hexane, chloroform and ethyl acetate fractions of *Asparagus racemosus* root were shown to have dose-dependent insulin secretion in isolated perfused rat pancreas, isolated rat islet cells and clonal beta -cells. These findings reveal that constituents of *Asparagus racemosus* root extracts have insulinotropic activity[19].

3.10. Bauhinia variegata (Caesalpiniaceae)

Crude ethanolic extract of leaves of *Bauhinia variegata* and its major metabolite (6S,7E,9R)-9-hydroxymegastigma-4,7-dien-3-one-9-beta-glycopyraroside (roseoside) have insulinotropic activity in insulin-secreting cell line INS-1 and it was found to be dose-dependent[20].

3.11. Berberine

Berberine promoted glucose-stimulated insulin secretion rather than basal insulin secretion in dose-dependent manner in rat's pancreatic islets. Berberine can enhance glucose-stimulated insulin secretion in rat islets, and probably exerts the insulinotropic effect *via* a pathway involving hepatic nuclear factor 4 alpha (HNF4) alpha and glucokinase, which is distinct from sulphonylureas[21]. Significant insulin sensitizing activity was observed in 3T3-L1 adipocytes which were given 50 μM berberine plus 0.2 nM insulin to reach a glucose uptake level increased by 10 nM of insulin alone. This was associated with increased glucose transporter-4 translocation into the plasma membrane *via* enhancing insulin signalling pathways and the insulin receptor substrate-1-phosphoinositide 3 Kinase-Akt. Berberine also increased glucose-stimulated insulin secretion and proliferation in Min6 cells *via* an enhanced insulin/insulin-like growth factor-1 signalling cascade. Data suggested that berberine can act as an effective insulin sensitizing and insulinotropic agent[22].

3.12. Biophytum sensitivum (Oxalidaceae)

Leaf extract of the *Biophytum sensitivum* stimulates pancreatic beta cells to release insulin in diabetic male rabbits and exerts hypoglycemic activity[13]. Administration of the *Biophytum sensitivum* extract in 16-h fasted non-diabetic rabbits showed a significant rise in the serum insulin levels, which suggested a pancreatic mode of action of *Biophytum sensitivum*. The hypoglycaemic response of *Biophytum sensitivum* may be mediated through stimulating the synthesis/release of insulin from the beta cells of

Langerhans[23].

3.13. Boerhaavia diffusa (Nyctaginaceae)

Chloroform extracts of leaves of *Boerhaavia diffusa* showed antidiabetic activity in streptozotocin induced diabetic rats which mainly act by reducing blood glucose level and increasing insulin sensitivity[9]. Hypoglycemic and antihyperglycemic activity of aqueous leaf extract at 200 mg/kg p.o. for 4 weeks in normal and alloxan induced diabetic rats showed to increase plasma insulin levels and improve glucose tolerance[13].

3.14. Bougainvillea spectabilis (Nyctaginaceae)

The blood glucose lowering potential of ethanolic leaf extract of *Bougainvillea spectabilis* in streptozotocin-induced type I diabetic albino rats was probably due to increased glucose uptake by enhanced glycogenesis in the liver and also due to increased insulin sensitivity[9].

3.15. Brassica nigra (Cruciferae)

Oral administration of aqueous extract of *Brassica nigra* for two months decreased serum glucose level, which was due to the release of insulin from pancreas[24].

3.16. Cinnamon zeylaniucm (Lauraceae)

In vitro incubation of pancreatic islets with cinnamaldehyde isolated from *Cinnamon zeylaniucm* resulted in enhanced insulin release. The insulinotropic effect of cinnamaldehyde was due to increase in the glucose uptake through glucose transporter (GLUT4) translocation in peripheral tissues[25].

3.17. Caesalpinia bonducella (Cesalpinaceae)

Hypoglycemic activity of aqueous and ethanolic extracts of *Caesalpinia bonducella* in chronic type II diabetic model, showed an increase secretion of insulin in isolated islets[13].

3.18. Caffeine

Treatment with 0.01% caffeine solution in 90% pancreatectomized diabetic rats for 12-week reduced body weight, fats, and decreased insulin resistance. At the same time caffeine also enhanced glucose-stimulated first- and second-phase insulin secretion and beta-cell hyperplasia[26].

3.19. Camellia sinensis (Theaceae)

Epigallocatechin gallate, present in *Camellia sinensis* increases insulin activity and prevents oxidative damages in streptozotocin induced diabetic rats[13]. Lower dose of *Camellia sinensis* on SD rats fed with high fat diet for 2 weeks showed insulinotropic effect in experimental condition[27].

3.20. Capsicum frutescens (Solanaceae)

Capsicum frutescens increased serum insulin concentration in a high-fat (HF) diet-fed streptozotocin induced type 2 diabetes rats after 4 weeks treatment. The data of this study suggest that 2% dietary *Capsicum frutescens* is insulinotropic rather than hypoglycemic in the experimental methods[18].

3.21. Catharanthus roseus (Apocyaceae)

Dichloromethane-methanol extract of leaves and twigs of *Catharanthus roseus* in carbohydrate metabolism, showed to enhance secretion of insulin. The extract was also found to be helpful in prevention of damage caused by oxygen free radicals[9].

3.22. Citrullus colocynthis (Cucurbitaceae)

Citrullus colocynthis pulp extract at 300 mg/kg, p.o. was found to significantly increase insulin and decrease plasma glucose levels in alloxan induced diabetic rats. Immunohistochemistry procedure showed that the amount of insulin in beta-cells of the islets of Langerhans is greater in *Citrullus colocynthis* treated-diabetic rats in comparison to the control group[28]. Administration of the ethanol extract of the dried seedless pulp of *Citrullus colocynthis* at 300 mg/kg, p.o had insulinotropic actions in alloxan-induced diabetic rats[29]. Aqueous extract of *Citrullus colocynthis* showed dose-dependent increase in insulin release from isolated islets[12]. Different extracts such as crude extract, aqueous, alcoholic, purified extract and beta-pyrazol-1-ylalanine, the major free amino acid derivative present in the seeds significantly induced insulin secretion *in vitro* in the isolated rat pancreas and isolated rat islets[11].

3.23. Coccinia indica (Cucurbitaceae)

Oral administration of dried extract of *Coccinia indica* at 500 mg/kg, p.o. for 6 weeks significantly increased insulin concentration in a clinical study. The plant extract showed to exert beneficial hypoglycemic effect in experimental animals and human diabetic subject possibly through an insulin secreting effect or through influence of enzymes involved in glucose metabolism[12].

3.24. Cornus officinalis (Cornaceae)

Alcoholic extract of *Cornus officinalis* can increase GLUT4 mRNA and its protein expression in NIDDM rats by promoting proliferation of pancreatic islets and by increasing postprandial secretion of insulin and therefore accelerating the glucose transport[15]. Methanol extract and its fractions had potent insulin mimic activity on phosphoenolpyruvate carboxykinase expression. The ability of fractions to protect beta-cell against toxic challenge, and to enhance insulin secretion strengthens the role of *Cornus officinalis* in diabetes therapy[30].

3.25. Elephantopus scaber (Asteraceae)

The acetone extract of *Elephantopus scaber* showed a significant decrease in blood glucose level by improving insulin sensitivity, augmenting glucose dependent insulin secretion and stimulating the regeneration of islets of Langerhans in pancreas of STZ-induced diabetic rats[31].

3.26. *Enicostemma littorale (Gentianaceae)*

Aqueous extract of *Enicostemma littorale* induced serum insulin levels in alloxan-induced diabetic rats at 8 h was associated with potentiation of glucose-induced insulin release through K^+-ATP channel dependent pathway[32].

3.27. *Ephedra distachya (Ephedraceae)*

The alkaloids of *Ephedra distachya* herbs and l-ephedrine have shown antihyperglycemic effect in diabetic mice due to regeneration and restoration of atrophied pancreatic islets that induces the secretion of insulin[15].

3.28. *Eriobotrya japonica (Rosaceae)*

Aqueous extract of *Eriobotrya japonica* and the compounds cinchonain Ib, procyanidin B-2, chlorogenic acid and epicatechin, were tested for insulin secretory activity in INS-1 cells, showed significantl increase of insulin secretion from INS-1 cells in dose-dependent manner[33].

3.29. *Euccalyptus globulus (Myrtaceae)*

Aqueous extract of *Euccalyptus globulus* (0.5 g/L of solution) increased peripheral glucose utilization in the mouse abdominal muscle and increased insulin secretion from the clonal pancreatic beta cell line[12].

3.30. *Eugenia jambolana (Myrtaceae)*

Effect of *Eugenia jambolana* seeds extract in isolated pancreatic islet cells of normal and diabetic animals was investigated and found that it enhances insulin secretion from cells. *Eugenia jambolana* extract also inhibited insulinase activity from liver and kidney[11,12,16].

3.31. *Ficus bengalensis (Moraceae)*

The oral administration of the extract of *Ficus bengalensis* caused enhanced serum insulin levels in normoglycaemic and diabetic rats. The increased insulin secretion is mainly due to inhibited insulinase activity from liver and kidney[11,12]. Blood sugar lowering activity of a dimethoxy derivative of leucocyandin 3-O-beta-d-galactosyl cellobioside at a dosage of 250 mg/kg, p.o. isolated from the bark of *Ficus bengalensis* in normal and moderately diabetic rats was mainly due to insulinomimetic activity[13]. Glycoside of leucopelargonidin isolated from the bark of *Ficus bengalensis* demonstrated significant hypoglycaemic, hypolipidemic and serum insulin raising effects in moderately diabetic rats. Dimethoxy ether of leucopelargonidin-3- O-alpha-L rhamnoside at a dose of 100 mg/kg, p.o. showed significant hypoglycaemic and insulinomimetic activity in healthy and alloxan induced-diabetic dogs during a period of 2 hour[11].

3.32. *Fermented unsalted soybeans*

Effect of fermented unsalted soybeans in 90% pancreatectomized diabetic Px rats for 8-week enhanced insulin secretion. In addition, Chungkookjang potentiated insulin/IGF-1 signaling in islets *via* the induction of insulin receptor substrate-2 expression, leading to increased pancreatic duodenal homeobox-1, insulin promoter transcription factor. In parallel with the enhancement of the signaling, Chungkookjang elevated pancreatic beta-cell hyperplasia by increasing its proliferation and decreasing apoptosis[34].

3.33. *Genistein*

Genistein increases insulin secretion in both insulin-secreting cell lines (INS-1 and MIN6) and mouse pancreatic islets. It was found that genistein directly acts on pancreatic beta-cells, leading to activation of the cAMP/PKA signalling cascade to exert an insulinotropic effect[35].

3.34. *Ginkgo biloba (Ginkgoaceae)*

Effect of *Ginkgo biloba* extract in humans and healthy rats shows that *Ginkgo biloba* significantly increased the insulin concentration[11].

3.35. *Radix glycyrrhizae (Fabaceae)*

Radix glycyrrhizae and glycyrrhetinic acid enhanced glucose-stimulated insulin secretion in isolated islets. In addition, they induced mRNA levels of insulin receptor substrate-2, pancreas duodenum homeobox-1, and glucokinase in the islets, which contributed to improve beta-cell viability[36].

3.36. *Gymnema sylvestre (Asclepiadaceae)*

Alcoholic extract of *Gymnema sylvestre* stimulated insulin secretion from the rat islets of Langerhans and several pancreatic beta cell lines. In another study, oral administration of a water-soluble leaves extract of *Gymnema sylvestre* at 400 mg/day, p.o. to 27 IDDM patients on insulin therapy lowered fasting blood glucose and insulin requirements[10]. Pancreatic beta cells may be regenerated or repaired in type II diabetic patients on *Gymnema sylvestre* supplementation; this is supported by the raised insulin levels in the serum of patients after supplementation[11]. Gymnemic acid molecules dihydroxy gymnemic triacetate had the ability to release the insulin by the stimulation of a regeneration process and revitalization of the remaining beta cells. Aqueous extract of *Gymnema sylvestre* leaves stimulated insulin secretion from mouse cells and isolated human islets *in vitro*, without compromising cell viability[31].

Oral administration of *Gymnema sylvestre* to diabetic rats increased the number of pancreatic islet and beta cells, as well as insulin levels, suggesting a possible repair or regeneration of the endocrine pancreas[37]. Water-soluble extracts of *Gymnema sylvestre* leaves release insulin probably by causing regeneration of pancreatic beta cells both *in vivo* and *in vitro*[6].

3.37. Helicteres isora (Sterculiaceae)

Antihyperglycemic activity of butanol extracts of root of *Helicteres isora* at 250 mg/kg, p.o. in glucose loaded rats acts through insulin-sensitizing activity[13].

3.38. Hibiscus rosa sinensis (Malvaceae)

Oral administration of ethanol extract of *Hibiscus rosa sinesis* at 250 mg/kg, p.o. showed mild but significant hypoglycemia which was mainly due to insulin release by stimulation of pancreatic beta cells[10].

3.39. Hordeum vulgare (Gramineae)

The germinant fruits of *Hordeum vulgare* showed hypoglycemic and hyperinsulinemic effects in NIDDM subjects, due to mobilization of insulin in NIDDM, which makes it a suitable cereal for diabetes mellitus[15].

3.40. Lepechinia caulescens (Lamiaceae)

Lepechinia caulescens significantly decreased glucose tolerance suggesting that *Lepechinia caulescens* has insulinomimetic activity[11].

3.41. Medicago sativa (Fabaceae)

Aqueous extract of *Medicago sativa* evoked stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line *in vitro*. In another study it was found that insulin releasing activity of the methanol and water fractions is mainly due to the cumulative effect of its constituent present in it[11].

3.42. Momordica charantia (Cucurbitaceae)

Significant reduction of blood glucose level and increased concentration of plasma insulin have been observed in diabetic rats that were treated with fruit juice of *Momordica charantia*. The observed effect was due to an increase in the number of beta cells in treated animals compared to untreated one. The phytochemical momordicin, charantin, and a few compounds such as galactose-binding lectin and insulin-like protein isolated from various parts of this plant have been shown to have insulin mimetic activity[6,37]. Aqueous extract of unripe fruits of *Momordica charantia* has also been shown to partially stimulate insulin release from isolated beta-cell of obese-hyperglycemic mice suggesting that the insulin-releasing action is the result of perturbations of membrane functions[10]. *Momordica charantia* increases the renewal of partial cells in the pancreas or may permit the recovery of partially destroyed cells and stimulates pancreatic insulin secretion[15].

3.43. Mucuna pruriens (Leguminosae)

Blood glucose lowering activity of powdered seeds of *Mucuna pruriens* was observed at 0.5, 1 and 2 g/kg, p.o. in normal rabbits as well as 1 and 2 g/kg, p.o. in alloxan-diabetic rabbits. It possibly acts through stimulation of the release of insulin or by a direct insulin-like action due to the presence of trace elements like manganese, zinc, *etc*[10,13].

3.44. Nigella sativa oil (Ranunculaceae)

Significant decreases in blood glucose level, and increase in serum insulin level were observed on treatment with *Nigella sativa* oil for 4 weeks. Immunohistochemical staining of pancreas from *Nigella sativa* oil-treated group showed large areas with positive immunoreactivity for the presence of insulin[38].

3.45. Panax ginseng (Araliaceae)

Ginseng polypeptides isolated from the root of *Panax ginseng*, when injected subcutaneously at daily doses of 50 and 100 mg/kg for 7 successive days in mice resulted in decreased blood glucose, increased liver glycogen level and stimulated insulin secretion[11]. The aqueous ethanolic extract of Korean red ginseng significantly evoked a insulin release in a glucose-independent manner[39].

3.46. Pandanus odorus (Pandanaceae)

4-Hydroxybenzoic acid from *Pandanus odorus* at 5 mg/kg increased serum insulin levels and liver glycogen content in healthy rats[11].

3.47. Parinari excelsa (Chrysobalanaceae)

Flavonoid of *Parinari excelsa* showed hypoglycemic effect due to the ability of insulin secretory activity in the diabetic animal models[31].

3.48. Prunella vulgaris (Labiatae)

Jiangtangsu had been isolated from *Prunella vulgaris* and confirmed to have a remarkable blood sugar lowering effect in diabetic mice. The possible mechanism of Jiangtangsu is to repair cells of pancreatic islet to release insulin[15].

3.49. Psidium guajava (Myrtaceae)

Flavonoid glycosides such as strictinin, isostrictinin and pedunculagin are the effective constituents of *Psidium guajava*, which have been used in clinical treatment of diabetes due to improved sensitivity of insulin[15].

3.50. Pterocarpus marsupium (Fabaceae)

Flavonoid fraction from *Pterocarpus marsupium* has been shown to cause pancreatic beta cell regranulation. Epicatechin, its active principle, has been found to be insulinogenic thus enhancing insulin release and conversion of proinsulin to insulin *in vitro*[16]. An active principle-epicatechin isolated from the bark of *Pterocarpus marsupium* has been found to have protective and restorative effects on beta cells in diabetic subjects. Possibly, epicatechin acts by regenerating the beta cells and may produce actions similar to that of insulin[6].

3.51. Radix rehmanniae (Scrophulariaceae)

The pectin type polysaccharide, obtained from the rhizome of *Radix rehmanniae* exhibited hypoglycemic activity in normal and streptozotocins induced diabetic mice by stimulating the secretion of insulin and reducing the glycogen content in the mice[15].

3.52. Rehmania glutinosa (Scrophulariacea)

Intraperitoneal administration of the ethanol precipitate fraction obtained from the hot water extract from the rhizome of *Rehmania glutinosa* stimulated the secretion of insulin and reduced the glycogen content in the livers of healthy mice[11].

3.53. Ricinus communis (Euphorbiaceae)

Administration of ethanolic extract of *Ricinus communis* to the diabetic rats at 500 mg/kg, p.o. for 20 days, significantly increased the insulin levels and caused improvement in lipid profile and body weight of the diabetic animals[31].

3.54. Syzygium cumini (Rutaceae)

Oral administration of pulp extract of the fruit of *Syzygium cumini* to normoglycemic and STZ induced diabetic rats showed hypoglycemic activity in 30 min possibly mediated by insulin secretion and inhibited insulinase activity[10].

3.55. Salvia lavandifolia (Lamiacea)

Hypoglycaemic effect of *Salvia lavandifolia* may be due to potentiation of insulin release induced by glucose and hyperplasia of the pancreatic islet beta cells along with some other mechanisms[11]. The antidiabetic activity of the extract of *Salvia lavandifolia* at 10 mg/kg induced an increase in the size and number of cells in the islets of Langerhans with increase in pancreatic insulin content[11].

3.56. Sarcopoterium spinosum (Rosaceae)

The aqueous extract of *Sarcopoterium spinosum* exhibited an insulin-like effect on glucose uptake in hepatocytes by inducing increase in glucose uptake. It also increased insulin secretion *in vitro*[31].

3.57. Selaginella tamariscina (Selaginellaceae)

Intraperitoneal administration of *Selaginella tamariscina* at 25 g/kg for 12 days produced a decrease in blood glucose and serum lipid peroxide, as well as an increase in the concentration of serum insulin. Histological observations showed that this plant could repair the structure of pancreatic islet beta cells injured by alloxan[11].

3.58. Semen coicis (Gramineae)

Coixans isolated and purified from the dried Semen *coicis seeds*, decreased blood glucose in normal rats with increased serum insulin level. The anti-diabetic mechanism of coixans may be due to prevention of pancreatic beta-cells injury, induced by alloxan[15].

3.59. Smallanthus sonchifolius (Asteraceae)

Administration of 2% *Smallanthus sonchifolius* to diabetic rats for 30-day increased levels of circulating insulin, which may be due to increased synthesis and secretion of insulin[40].

3.60. Stevia rebaudiana (Asteraceae)

Effect of stevioside in isolated mouse islets and the clonal beta cell line INS-1 was investigated and found that glycoside stevioside exerts antihyperglycaemic, insulinotropic, and glucagonostatic actions in the type 2 diabetic GK rat[41]. In another study it was concluded that stevioside and steviol stimulate insulin secretion *via* a direct action on beta cells[42]. The natural sweetener stevioside, which is found in the plant *Stevia rebaudiana* acts through stimulating insulin secretion *via* direct action on the β-cells of pancreatic islets[8].

3.61. Swertia chirayita (Gentianaceae)

Hexane fraction of *Swertia chirayita* at 250 mg/kg, p.o. to normal rats significantly reduced blood sugar and increased plasma insulin without influencing hepatic glycogen content. However, when administered for 28 days, it significantly increased hepatic glycogen content in conjunction with other effects probably by releasing insulin[11]. Single oral administration of swerchirin (50 mg/ kg) to rats caused fall in blood glucose with marked depletion of aldehyde-fuchsin stained beta-granules and immunostained insulin in the pancreatic islets. Swerchirin at 100, 10 and 1 mM concentration greatly enhanced glucose stimulated insulin release from isolated islets[10].

3.62. Swertia punicea (Gentianaceae)

Ethanol extracts and ethyl acetate soluble fraction of *Swertia punicea* showed hypoglycemic effects in STZ-induced type-2 diabetic mice and may be beneficial to improve insulin resistance[31].

3.63. Tabernanthe iboga (Apocynaceae)

The effect of an aqueous extract of *Tabernanthe iboga* augmented glucose-stimulated insulin secretion in a dose-dependent manner. *Tabernanthe iboga* contains water soluble insulinotropic compounds. The insulin secretary effect of *Tabernanthe iboga* might involve the closure of K^+-ATP and the intensification of calcium influx through voltage-sensitive Ca^{2+} channels[43].

3.64. Teucrium polium (Lamiaceae)

Aqueous extract of *Teucrium polium* crude extract is able to enhance insulin secretion through enhancing insulin secretion by the pancreas[44]. The insulinotropic properties of *Teucrium polium* extracts can be attributed to the presence of apigenin existing only in methanol fraction but not in aqueoue fractions[45]. Crude extract of *Teucrium polium* is capable of enhancing insulin secretion at high glucose concentration and plant extract seems to be capable of regenerating the islets of Langerhans in the treated diabetic rats compared to the untreated diabetic rats[46].

3.65. Tinospora crispa (Menispermaceae)

Antihyperglycaemic effect of *Tinospora crispa* extract is probably due to the stimulation of insulin release *via* modulation of beta-cell Ca^{2+} concentration[11,47].

3.66. Tribuluks terrestris (Zygophyllaceae)

The extract of *Tribuluks terrestris* significantly decreases blood glucose level in normal and alloxan-induced diabetic mice, mainly due to the increased serum insulin level[15].

3.67. Trigonella foenum-graecum (Leguminosae)

4-Hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in rats, mice and humans[10,16,48,49]. *Trigonella foenum-graecum* has been observed to cause glucose-induced insulin release *in vitro* and *in vivo*[6]. A specific amino acid, hydroxyisoleucine, which represents 80% of the free amino acids in *Trigonella foenum-graecum* seeds, may possess insulin-stimulating properties[37]. The *Trigonella foenum-graecum* seeds may help to improve insulin sensitivity, which is presumed to be due to the effects of fiber, which slows carbohydrate metabolism resulting in reduced insulin levels and lowered blood glucose[37]. Anti-hyperglycemic effect of the extracts, powder and gum of *Trigonella foenum-graecum* seeds and leaves have been linked to delayed gastric emptying caused by the high fiber content, inhibition of carbohydrate digestive enzymes and stimulation of insulin secretion[15].

3.68. Zizyphus spina-christi (Rhamnaceae)

The effect of the butanol extract of *Zizyphus spina-christi* leaves and its major saponin glycoside, christinin-A, on the serum glucose and insulin levels showed that christinin-A potentiated glucose-induced insulin release in non-diabetic control rats[50]. Serum insulin and pancreatic cAMP levels showed significant increase in diabetic rats treated for a period of 4 weeks with the butanol extract of *Zizyphus spina-christi*[11].

4. Discussion

Diabetes is a disorder of carbohydrate, fat and protein metabolism caused due to insufficient production of insulin or due to its inhibitory action, which can be considered as a major cause of high economic loss which can in turn impede the development of nations[51]. Before there were drugs from drug companies, natural cures were used and they can still be used today. There are many herbs with strong anti-diabetic properties. Herbal treatments for diabetes have been used in patients with insulin dependent and non-insulin dependent diabetes, diabetic retinopathy, diabetic neuropathy *etc*. The families of plants with the most potent hypoglycaemic effects include Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae and Araliaceae. The most commonly studied species are: *Opuntia streptacantha*, *Trigonella foenum graecum*, *Momordica charantia*, *Ficus bengalensis*, *Polygala senega* and *Gymnema sylvestre*. In the experiments, oral glucose tolerance test, streptozotocin and alloxan-induced diabetic mouse or rat were most commonly used model for the screening of antidiabetic drugs. Numerous mechanisms of actions have been proposed for plant extracts. Some hypothesis relates to their effects on the activity of pancreatic beta cells, increase in the inhibitory effect against insulinase enzyme, increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may also be involved such as increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen or decrease of glycogenolysis, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates and reduction of the effect of glutathione[11].

In this review, natural products classified into terpenoids, alkaloids, flavonoids, phenolics, and some other categories have shown antidiabetic potential through the insulinomimetic activity of the plant extract. Roseoside, epigallocatechin gallate, beta-pyrazol-1-ylalanine, cinchonain Ib, leucocyandin 3-O-beta-d-galactosyl cellobioside, leucopelargonidin-3-O-alpha-L rhamnoside, glycyrrhetinic acid, dehydrotrametenolic acid, strictinin, isostrictinin and pedunculagin, epicatechin and christinin-A isolated from the plant material have shown significant insulinomimetic activity along with significant antidiabetic potential. Additionally, some flavonoids and polyphenols, as well as sugar derivatives, are found to be effective due to some other extrapancreatic mechanisms. In this review so many number of plants are included which have shown antidiabetic action through relese of insulin and some extra pancreatic mechanisms[8]. Plants such as *Allium cepa*, *Clerodendron phlomoides*, *Cinnamomum tamala*, *Coccinia*

indica, *Enicostemma littorale*, *Ficus bengalensis*, *Gymnema sylvestre* leaves, *Momordica charantia*, *Pterocarpus marsupium* and *Syzygium cumini* have a great antidiabetic potential, which have already been subjected to the clinical trial are included in the list, whereas some marketed herbal formulations (diasulin, pancreatic tonic 180 cp, chakrapani, diabecon, bitter gourd powder, dia-car, diabetes-daily care, gurmar powder, epinsulin, diabecure, syndrex, diabetawhich) which have been proved for its antidiabetic activity are also listed in the database[16,52]. Although all these plants have shown varying degree of hypoglycemic and anti-hyperglycemic activity not all were effective in severe experimental diabetes and its related complications. A novel anti-hyperglycemic amino acid has been extracted and purified from fenugreek seeds (4-hydroxyleucine) which reportedly increases glucose-induced insulin release[10].

In conclusion, this paper has presented a list of anti-diabetic plants used in the treatment of diabetes mellitus. It showed that these plants have hypoglycaemic effects and can be used to treat various type of secondary complications of diabetes mellitus. Plants have been a good source of medicine for the treatment of various type of disease, still many plants and active compounds obtained from plants have not been well characterized. More investigations must be carried out to evaluate the exact mechanism of action of medicinal plants with antidiabetic and insulino mimetic activity. It is always believed that plant is safe, but so many plant materials are not safe for the human being, that's why toxicity study of these plants should also be elucidated before consumption of these plant materials.

Conflict of interest statement

We declare that we have no conflict of interest.

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