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# MEDICINAL PLANTS POTENTIAL AGAINST DIABETES MELLITUS: REVIEW ARTICLE

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**ABSTRACT:** Diabetes mellitus (DM), both type I and type II, is a common metabolic disorder worldwide. It is characterized by hyperglycemia, lipid, and protein metabolism abnormalities, and accompanied by several clinical complications including retinopathy, neuropathy, and nephropathy. Many traditional herbs have been used for the treatment of DM. In the present review, we showed a list of these herbs describing their growth area, anti-diabetic properties, their active constituent, and mechanism of action. From the review, the anti-diabetic activity of herbs is largely attributed to the presence of polyphenols, flavonoids, terpenoids, and coumarins. Also, this review strongly suggests these herbs as a natural and safe alternative treatment to the regularly used chemical anti-diabetic therapies.

**INTRODUCTION:** Diabetes mellitus (DM) is a common metabolic disorder affecting many people worldwide. According to the World Health Organization (WHO), the diabetic population is likely to increase up to 300 million or more by the year 2025. About 10% of deaths are related to DM. Thus, it is characterized by chronic hyperglycemia usually lead to neuropathy, retinopathy, nephropathy, and cardiovascular diseases. These are the leading causes of morbidity and mortality in diabetic patients [1, 2, 3]. DM is caused by either inadequate secretion of the hormone insulin, inadequate response of target cells to insulin, or a combination of these factors. It is known to have a strong genetic component.

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DM is characterized by resistance to insulin associated with excess glucose production in the liver and impaired or decreased glucose utilization peripherally, particularly in muscles [4, 5]. There is no cure from DM and prevention of its long-term complications represents a mainstay global problem [4, 5, 6]. The currently available synthetic therapies for diabetes include insulin and various oral hypoglycemic agents such as sulfonylureas, biguanides, and glinides. However, these modalities have some serious adverse effects; therefore, finding out a reliable and safe treatment is important area of research.

The traditional medicines demonstrated a bright future in the treatment of many diseases including diabetes. The ethnobotanical information revealed that about 800 plants may have anti-diabetic potential and showed beneficial effects in either treatment or prevention of diabetes complications. Anti-diabetic activity of medicinal plants is mainly due to their ability to restore the function of pancreatic cells by causing an increase in insulin

secretion or by inhibition of intestinal absorption of glucose. The main active constituents of the plants are polyphenols, flavonoids, terpenoids, carotenoids, and coumarins.

This article reviews and emphasize the importance of some medicinal plants in the treatment of diabetes-associated complications.

**Medicinal Herbs Used in Treatment of Diabetes:** Plants have always been an excellent source of drugs, and many of the currently available drugs have been derived from them. The ethnobotanical surveys suggest that about 800 plants may possess anti-diabetic potential [7]. Some of these herbs might reduce blood glucose levels or might be useful for management of the disease complications [8]. Several reports explored the anti-diabetic activity as herbs contain different types of biological components. Among these alkaloids, glycosides, galactomannan gum, polysaccharides, peptidoglycans, hypoglycin, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids, and inorganic ions have demonstrated activity including treatment of diabetes [9, 10, 11].

**Botanical Components for Diabetes Treatment:** The aim of the present review is to collect the data available on anti-diabetic plants and show the phytoconstituents having insulin mimetic or secretagogue activities.

***Acacia arabica* (Leguminosae):** About 94% seed diet of *Acacia arabica* showed a hypoglycemic effect in rats through the 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].

***Aegle marmelos* (Rutaceae):** Aqueous leaf extract of *Aegle marmelos* showed anti-hyperglycemic 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].

***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 the extract was found to be glucose independent [14].

***Alangium salvifolium* (Alangiaceae):** Methanolic extract of *Alangium salvifolium* leaves possesses anti-hyperglycemic and anti-hyperlipidemic effects in dexamethasone-induced insulin resistance in rats, which may be due to the antioxidant and insulinotropic effect of extract [15].

***Annona muricata* (Annonaceae):** *A. muricata* played an important role in the reduction of oxidative stress of pancreatic $\beta$-cells of streptozotocin-induced diabetic rats, which was confirmed by the increased area of insulin immunoreactive $\beta$-cells and protection against degeneration of $\beta$-cells [16].

***Annona squamosa* (Annonaceae):** *Annona squamosa* commonly called custard apple plant possesses anti-diabetic activity. It acts by promoting insulin release from the pancreatic islets, increasing utilization of glucose in muscle and inhibiting the glucose output from liver [16].

***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 [17].

***Anacardium occidentale* Linn. (Anacardiaceae):** Herb originated from Brazil, it is used as folk medicine in African countries, mainly in Cameroon, for the treatment of diabetes mellitus. Hypo-glycemic and the protective role of *A. occidentale* were reported [6, 18]. The anti-hyperglycemic and renal protective activities of leaves of this herb were reported in streptozotocin-induced diabetic rats. It reduces diabetes-induced functional & histological alterations in the kidneys. It was shown that the histopathological study of *Anacardium occidentale* significantly reduced accumulation of mucopolysaccharides in the kidneys of diabetic animal [19].

***Annona squamosa* L. (Annonaceae):** Commonly called custard apple in English and Sharifa in Hindi. It is cultivated throughout India. The pharmacologically active ingredients are present in seeds, leaves and aerial parts of the plant [20]. The research reveals that the plant possesses both

hypoglycemic and anti-diabetic activity. It acts by enhancing insulin level from the pancreatic islets, increases utilization of glucose in muscle and inhibits the glucose output from the liver. Its margin of safety is high. The extract obtained from leaves of this plant is useful in maintaining healthy blood sugar and cholesterol levels [21].

***Annona muricata* L. (Annonaceae):** Commonly called soursop. It is a small evergreen tree growing 5 to 6 meters in height. Young branches are rusty-hairy, the malodorous leaves, and the plant is evergreen. *Annona muricata* is indigenous to most of the warmest tropical areas in South and North America, including the Amazon. The researchers revealed the immuno-histochemical and biochemical effects of aqueous extract of leaves on pancreatic $\beta$ cells of STZ (streptozotocin) treated diabetic rats. *A. muricata* Linn. leaf extract played an important role in the reduction of oxidative stress on pancreatic $\beta$ cells of streptozotocin-treated diabetic rats. The treatment increased the area of insulin immunoreactive $\beta$-cells and partially prevents degeneration of $\beta$-cells [22].

***Allium sativum* (Liliaceae):** Found in many kitchens - *Allium sativum* (garlic) - has also been used for medicinal purposes around the world. A majority of contemporary medical use and research for garlic has focused on the treatment of cardiovascular-related diseases. In clinical trials, garlic supplementation among patients with dyslipidemia produced a modest reduction in total cholesterol with no significant changes in LDL or HDL cholesterol levels [23, 24].

Pooled data from clinical trials of patients with hypertension have shown significant decreases in systolic (8.4 ± 2.8 mmHg) and diastolic (7.3 ± 1.5 mmHg) blood pressure levels in patients using garlic treatment compared to control groups. Less research has been conducted among patients with diabetes. Limited animal studies have suggested that the chemical components of garlic may increase insulin secretion or decrease degradation [23, 24]. Clinical trials of oral garlic in patients with type II diabetes have not demonstrated significant changes in blood glucose or insulin levels [25, 26].

***Aloe vera* (Liliaceae):** This desert plant is the source of the common gel used topically for dermatological conditions. In the Arabian peninsula, parts of the aloe plant have been used orally as a traditional treatment for diabetes. The gel derived from the meaty pulp of the leaf, taken orally, may produce hypoglycemic effects through $\beta$-cell stimulation [27, 28]. Two controlled, non-randomized trials in patients with type II diabetes who were given aloe gel juice reported decreases in fasting blood glucose during 6 weeks [28, 29]. However, these studies lacked sufficient details in reporting, including study design and results, leading to inconclusive evidence. In contrast to the gel, aloe latex from the inner lining of the leaf contains a harsh anthroquinone laxative that may be unsafe [30].

***Boerhaavia diffusa* Linn. (Nyctaginaceae):** Distributed widely all over in India, is a small perennial creeping herb, commonly known as Red hogweed. The root and the whole plant are used as an Ayurvedic medicine in India and Unani medicine for the treatment of diabetes, stress, dyspepsia, abdominal pain, inflammation, jaundice, enlargement of spleen, congestive heart failure and bacterial infections [16, 31]. Aqueous leaf extract of the plant has been studied for its anti-diabetic effect in alloxan-induced diabetic rats [32]. The anti-diabetic activity of the chloroform extract of the plant leaves on the chronic treatment of streptozotocin-induced NIDDM (non-insulin dependent diabetes mellitus) model diabetic rats was evaluated, and the herb possesses anti-diabetic activity. The herb mainly acts by reducing blood glucose level and increasing insulin sensitivity [33].

***Bougainvillea spectabilis* Linn. (Nyctaginaceae):** Is a very familiar ornamental plant commonly grown in Indian gardens. Bougainvillea is a genus of flowering plants native to South America from Brazil west to Peru and south to southern Argentina. The traditional plant has anti-diabetic potential.

The blood glucose lowering potential of *Bougainvillea spectabilis* wild leaf extract in streptozotocin-induced type I diabetic albino rats was reported. The ethanolic extract of the leaves has anti-hyperglycemic activity probably due to increased uptake of glucose by enhanced glycogenesis in the liver and also due to an increase in insulin sensitivity [34].

***Bridelia ndellensis* Beille. (Euphorbiaceae):** A medicinal plant used in Cameroon against diabetes. The water and methanol extract of leaf of allied species *B. ferruginea* has been proved as an active hypoglycemic agent in alloxan-induced diabetic rats [16].

The study of the glucose lowering of the ethanol extract and fractions of *B. ndellensis* stem bark in STZ (streptozotocin) type I and II diabetes rats at different prandial states was performed and significant lowering in blood glucose level was observed. The extract act by stimulation of islets cells and requires functional *β*-cells for its action [35].

***Bauhinia variegata* (Caesalpiniaceae):** Crude ethanolic extract of leaves of *Bauhinia variegata* and its major metabolite (6S, 7E, 9R)-9-hydroxy megastigma 4,7-dien-3-one-9-beta-glycopyranoside (rose side) have insulinotropic activity in insulin-secreting cell line INS-1, and it was found to be dose-dependent [36].

**Berberine:** Berberine glucose-stimulated insulin secretion rather promoted than basal insulin secretion in a 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 [37].

***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 hypoglycemic response of *Biophytum sensitivum* may be mediated through stimulating the synthesis/ release of insulin.

***Boerhaavia diffusa* (Nyctaginaceae):** Chloroform extracts *Boerhaavia diffusa* leaves showed anti-diabetic activity in streptozotocin-induced diabetic rats which mainly act by reducing blood glucose level and increasing insulin sensitivity [16]. Hypoglycemic and anti-hyperglycemic 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].

***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 [16].

***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 [38].

***Canavalia ensiformis* DC. (Leguminaceae):** Known as horse bean, the native of Central America and West Indices has been widely cultivated in humid tropics of Africa and Asia. The seeds have been reported to possess anti-hypercholesterolemic [39], and hypoglycemic activities [40]. The oral administration of aqueous extract of *C. ensiformis* seeds reduce urinary and blood glucose levels, and also elevated levels of triacylglycerol, ketone bodies and cholesterol associated with diabetes mellitus [16].

***Casearia esculenta* Roxb. (Flacourtiaceae):** Is a plant with medicinal properties known as wild cowrie fruit in English. The plant is in the form of shrub distributed in South India. *C. esculenta* has been a remedy which is popular for diabetes mellitus [41, 42, 43]. It has been reported that the plant contains hypoglycemic effect [44]. *C. esculenta* root extract contain hypoglycemic factors, which reduced blood sugar level in experimental animals. *C. esculenta* root extract has an influence on protein metabolism and marker enzymes in streptozotocin-induced diabetic rats. The study revealed that *C. esculenta* root extract has the anti-hyperglycemic effect and it may elevate liver and renal damage associated with streptozotocin-induced diabetes in rats [45].

***Cassia kleinii* Wight & Arn. (Caesalpiniaceae):** Is the medical remedy for the folk diabetic practitioners in South India. The traditional systems like Ayurveda and Siddha systems do not use this plant. The alcoholic extracts of leaves seem to show promising results for the development of

phytomedicines by exhibiting the anti-hyperglycemic activity on glucose feed hyperglycemic and alloxan-induced diabetic rats.

The leaf extract of *Cassia kleinii* may not act by potentiation of insulin but it could be used in insulin-independent diabetes because drug exhibited anti-hyperglycemic effect but not hypoglycemic effect in fasted rats. The action of drug may be mimicking some or all of the action of insulin on the metabolism of glucose [45].

***Catharanthus roseus* Linn. (Apocynaceae):** Commonly used as an anticancer agent, but the hot water decoction of the leaves and or the whole plant is used for the treatment of diabetes in subtropical and tropical areas of the world [46]. The reports indicate blood glucose lowering activity in the alcoholic extract of the leaves of *C. roseus*. The herb has prophylactic activity against the necrotic actions of alloxan monohydrate [47, 48, 49].

Anti-diabetic activity of a dichloromethane-methanol extract of the leaves and twigs was evaluated and its effect on enzymes of carbohydrate metabolism was studied. The mechanism may be due to enhanced secretion of insulin. The other researchers revealed that extract may be helpful in the prevention of damage caused by oxygen free radicals and increase in glucose utilization [50].

***Coccinia indica* Wight & Arn. (Cucurbitaceae):** Widely used in traditional treatment of diabetes mellitus in sub-Saharan Africa and Southeast Asia. Pectin isolated from the fruits of *C. indica* has hypoglycemic activity [51]. Alcoholic extract of the plant was found to be active in reducing blood glucose level, then this extract was subjected to further fractionation to evaluate its biochemical parameters affecting diabetes and results suggested toluene as an active fraction. The exact action of these principles may be due to their *β*-cell restorative properties against alloxan-induced damage [52].

***Cocculus hirsutus* Linn. (Menispermaceae):** Roots are bitter, acrid, laxative, demulcent and antiperiodic in fever, tonic, and diuretic, also known as patal garudi. The plant grows all over India, especially in dry regions. It is a straggling shrub, with softly villous young parts and resembles the plant path. Badole *et al*., have demonstrated the anti-hyperglycemic activity of aqueous extract of leaves of *Cocculus hirsutus* (L.) Diels in alloxan-induced diabetic mice. The antihyperglycemic potential of aqueous extract of *C. hirsutus* may be due to the lowering of serum glucose level in diabetic mice and increased glucose tolerance. Additionally, the extract prevents loss of body weight [53].

***C. fenestratum* Colebr. (Menispermaceae):** Commonly known as a tree in Western Ghats (India) and Sri Lanka. The plant has been mainly used for diabetes mellitus in the traditional, Ayurvedic and Siddha systems of medicine. Alcoholic stem extract of this plant regulates metabolism and improves antioxidant status in streptozotocin, nicotinamide-induced diabetic rats. The alcoholic extract regulates glucose homeostasis and decreased gluconeogenesis by *Coscinium fenestratum*. The drug also has a protective action on cellular antioxidant defense [54].

***Coccinia indica* (Cucurbitaceae):** Ayurveda is a traditional medical system from the Indian subcontinent that often uses herbs for treatment. The creeper plant *Coccinia indica* (ivy gourd) is prescribed in Ayurveda for the treatment of diabetes. *Coccinia* may produce hypoglycemia in a mechanism similar to insulin [55].

Two randomized, controlled trials (RCTs) [56, 57], and one controlled, nonrandomized trial [57] have suggested decreases in fasting blood glucose without adverse effects among type II diabetes patients after administration of *Coccinia*.

***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 an increase in the glucose uptake through glucose transporter (GLUT4) translocation in peripheral tissues [58].

***Caesalpinia bonducella* (Caesalpiniaceae):** Hypo-glycemic activity of aqueous and ethanolic extracts of *Caesalpinia bonducella* in chronic type II diabetic model, showed an increased secretion of insulin in isolated islets [13].

**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 [59].

***Camellia sinensis* (Theaceae):** Epigallocatechin gallate, present in *Camellia sinensis* increases insulin activity and prevents oxidative damages in streptozotocin-induced diabetic rats. The lower dose of *Camellia sinensis* on SD rats fed with high-fat diet for 2 weeks showed an insulinotropic effect in experimental condition [60].

***Capsicum frutescens* (Solanaceae):** *Capsicum frutescens* increased serum insulin concentration in a high-fat (HF) diet-fed streptozotocin-induced type II diabetes rats after 4 weeks of treatment. The data of this study suggested that 2% of dietary *Capsicum frutescens* is insulinotropic rather than hypoglycemic in the experimental methods [61].

***Catharanthus roseus* (Apocynaceae):** Dichloro-methane-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 the prevention of damage caused by oxygen free radicals [16].

***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 more significant in *Citrullus colocynthis* treated-diabetic rats in comparison to the control group [62]. 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 [63].

***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 a beneficial hypoglycemic effect in experimental animals and human diabetic subject possibly through an insulin-secreting effect or through the influence of enzymes involved in glucose metabolism [12].

***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 [64]. 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 [65].

***Dioscorea dumetorum* Pax. (Dioscoreaceae):** Used in the treatment of diabetes in traditional medicine, possesses hypoglycemic effect. *D. dumetorum* Pax. is commonly known as bitter yam. It occurs in Africa. An alkaloid present in an extract, dioscoretine, has been reported to possess hypoglycemic effect [66]. It has been reported that aqueous extract of *D. dumetorum* tuber control hyperlipidemia, hypercholesterolemia, and hyper-ketonemia. The herb mainly acts as an active hypoglycemic agent and works on the complications of diabetes [67].

***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 the pancreas of STZ-induced diabetic rats [68].

***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 [69].

***Ephedra distachya* (Ephedraceae):** The alkaloids of *Ephedra distachya* herbs and l-ephedrine have shown an anti-hyperglycemic effect in diabetic mice due to regeneration and restoration of atrophied pancreatic islets that induces the secretion of insulin [64].

***Eriobotrya japonica* (Rosaceae):** Aqueous extract of *Eriobotrya japonica* and the compounds cinchona in Ib, procyanidin B-2, chlorogenic acid, and epicatechin, were tested for insulin secretory

activity in INS-1 cells, showed a significant increase of insulin secretion from INS-1 cells in dose-dependent manner [64.]

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

***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 [12].

***Ficus hispida* Linn. (Moraceae):** Also known as Daduri for the treatment of diabetes. This small tree may be found throughout India. Different workers have reported for the hypoglycemic effects of different compounds obtained from *F. bengalensis* [16]. The hypoglycemic activity of *Ficus hispida* Linn. (bark) in normal and diabetic albino rats concluded that the water-soluble fraction of the alcoholic extract of *Ficus hispida* significantly decreases fasting blood glucose levels in normal and alloxan-induced diabetic rats. The extract has direct peripheral action on *β* cells but drug interaction can occur between *Ficus hispida* bark extract and insulin if given together [70].

***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 [12].

**Fermented Unsalted Soybeans:** Effect of fermented unsalted soybeans in 90% pancreatectomized diabetic 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 [71].

***Gymnema sylvestre* (Asclepiadaceae):** This botanical has also been used for two centuries in Ayurveda for the treatment of diabetes. Traditionally, the leaves of the plant are chewed, which can suppress the sweet taste sensation, giving rise to its Hindi name gurmar, or "sugar destroyer." In addition to affecting taste, the herb has demonstrated hypoglycemic effects in animal and human studies, perhaps functioning as an insulin secretagogue [72, 73]. An extract of *Gymnema* leaf, called GS4, has been studied as an adjuvant therapy to conventional care in two controlled, nonrandomized trials of patients with type I and type II diabetes, respectively [74, 75].

Both studies reported significant before-to-after improvements in fasting blood glucose and A1C levels among patients receiving GS4. No significant before-to-after changes were reported in the control groups. These studies lacked between-group comparisons and randomization, precluding definitive evidence for *Gymnema* for the treatment of diabetes.

**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 signaling cascade to exert an insulinotropic effect [76].

***Ginkgo biloba* (Ginkgoaceae):** Effect of Ginkgo biloba extract in humans, and healthy rats show that *Ginkgo biloba* significantly increased the insulin concentration [14].

***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. Pancreatic beta cells may be regenerated or repaired in type II diabetic patients on *Gymnema sylvestre* supplementation; the raised insulin levels support this in the serum of patients after supplementation [14].

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. Water-soluble extracts of *Gymnema sylvestre* leaves release insulin probably by causing regeneration of pancreatic beta cells both *in-vivo* and *in-vitro* [77].

***H. isora* (Sterculiaceae):** Anti-hyperglycemic activity of butanol extracts of root of *Helicteres isora* at 250 mg/kg, p.o. in glucose-loaded rats act through insulin-sensitizing activity [13].

***Hibiscus rosa sinensis* (Malvaceae):** Oral administration of ethanol extract of *Hibiscus rosa sinensis* at 250 mg/kg, p.o. Showed mild but significant hypoglycemia which was mainly due to insulin release by stimulation of pancreatic *β*-cells [11].

***Hordeum vulgare* (Gramineae):** The germinant fruits of *Hordeum vulgare* showed hypoglycemic and hyperinsulinemic effects in NIDDM subjects, due to the mobilization of insulin in NIDDM, which makes it a suitable cereal for diabetes mellitus [64].

***H. hemerocallidea* Fisch. Mey. (Hypoxidaceae):** It is a tuberous perennial plant which was previously known as *H. rooperi*. It is called the wonder plant in South Africa and has been reported to be an effective remedy for the adult onset diabetes mellitus [78]. The methanolic extract of *Hypoxis hemerocallidea* was reported for its hypoglycemic effect in normoglycaemic and in streptozotocin-induced diabetic rats, the herb can be used as a hypoglycemic agent, and it has property to cure the adult onset diabetes mellitus [79]. The action of the herbal plant material is not yet clear.

***Lepechinia caulescens* (Lamiaceae):** *Lepechinia caulescens* significantly decreased glucose tolerance suggesting that *Lepechinia caulescens* has insulinomimetic activity [14].

***Murraya koenigii* Linn. (Rutaceae):** Is commonly known as Curry patta and is widely used condiment and spice in India. In normal and alloxan diabetes the aqueous extract of the leaves of *M. koenigii* produced hypoglycemic effect [80]. Oral feeding of this plant for 60 days diet to normal rats showed an increase in the concentration of hepatic glycogen due to hypoglycemic activity [81]. It has been reported that feeding different doses of *M. koenigii* leaves to diabetic rats play a role in the control of mild diabetic rats to moderate, severe and type I diabetes [82]. It suppressed the blood glucose level and was found to have a beneficial effect on carbohydrate metabolism [83].

***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 [14].

***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 [77].

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. *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 [64].

***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*. [13]

***Nigella sativa* oil (Ranunculaceae):** Significant decreases in blood glucose level an increase in

serum insulin level were observed on treatment with *Nigella sativa* oil for 4 weeks. Immunohistochemical staining of the pancreas from *Nigella sativa* oil-treated group showed large areas with positive immunoreactivity for the presence of insulin [84].

***Opuntia streptacantha* (prickly pear cactus, nopal):** Found in desert regions of North America, nopal is used in Mexican cuisine and indigenous medicine. Mexican - American patients with diabetes have reported using nopal for glucose control [85]. Few studies of nopal have been published in English, and these have explored acute metabolic effects rather than clinical outcomes [86, 87].

***Panax ginseng* L. (Asian ginseng, Araliaceae):** Root has been used clinically in the treatment of type II diabetes throughout Asian countries. Historical records revealed that *P. ginseng* had been used clinically to treat type II diabetes. *In-vitro* and *in-vivo* animal studies and clinical trials support the claim that the roots of this plant possess anti-hyperglycemic activity. The ginsenoside plays important role in anti-hyperglycemic action and other constituents have a distinct pharmacological effect on energy metabolism [88].

***Panax quiquefolius* (Araliaceae):** The *Panax* genus contains multiple species described as ginseng, with two varieties most frequently used and studied: *Panax ginseng* (Asian ginseng, Chinese ginseng, Korean ginseng) and *Panax quinquefolius* (American ginseng). The root of this herb traditionally has been used in Asia and is one of the most popular botanicals in the United States. Ginseng has many proposed health benefits, including improved general well-being, increased concentration, and treatment of cardiovascular disease and diabetes (*Panax* is cognate to panacea). Ginseng can cause hypoglycemia, perhaps through activity similar to insulin or by altering hepatic glucose metabolism [89].

Buettner *et al*., in a systematic review [90], found conflicting clinical data of ginseng's effect on blood glucose in diabetic and non-diabetic populations. Variations in response may reflect chemical heterogeneity of different ginseng batches used in studies [91, 92].

***Pandanus odors* (Pandanaceae):** 4-Hydroxy benzoic acid from *Pandanus odors* at 5 mg/kg increased serum insulin levels and liver glycogen content in healthy rats [14].

***Parinari excelsa* (Chrysobalanaceae):** Flavonoid of *Parinari excelsa* showed hypoglycemic effect due to the ability of insulin secretory activity in the diabetic animal models [68].

***Prunella vulgaris* (Labiatae):** Jiangtangsu had been isolated from *Prunella vulgaris* and confirmed to have remarkable blood sugar lowering effect in diabetic mice. The possible mechanism of Jiangtangsu is to repair cells of pancreatic islet to release insulin [64].

***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 [64].

***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* [93].

***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 improving beta-cell viability [94].

***Radix rehmanniae* (Scrophulariaceae):** The pectin type polysaccharide, obtained from the rhizome of *R. rehmanniae* exhibited hypoglycemic activity in normal and streptozotocin-induced diabetic mice by stimulating the secretion of insulin and reducing the glycogen content in the mice [64].

***Rehmania glutinosa* (Scrophulariaceae):** Intra-peritoneal 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 [14].

***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 [68].

***Syzygium cumini* (Rutaceae):** Oral administration of pulp extract of the fruit of *Syzygium cumini* to normoglycaemic and STZ induced diabetic rats showed hypoglycemic activity in 30 min possibly mediated by insulin secretion and inhibited insulinase activity [11].

***Salvia lavandifolia* (Lamiaceae):** Hypoglycemic 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. The anti-diabetic 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 the increase in pancreatic insulin content [11].

***Sarcopoterium spinosum* (Rosaceae):** The aqueous extract of *Sarcopoterium spinosum* exhibited an insulin-like effect on glucose uptake in hepatocytes by inducing the increase in glucose uptake. It also increased insulin secretion *in-vitro* [68].

***Selaginella tamariscina* (Selaginellaceae):** Intra-peritoneal administration of *S. 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 [14].

***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 the prevention of pancreatic beta-cells injury, induced by alloxan [64].

***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 [95].

***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 anti-hyperglycemic, insulinotropic, and glucagonostatic actions in the type II diabetic GK rat [96].

***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. Single oral administration of swerchirin (50 mg/ kg) to rats caused a 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 [11].

***Swertia punicea* (Gentianaceae):** Ethanol extracts and ethyl acetate soluble fraction of *Swertia punicea* showed hypoglycemic effects in STZ induced type II diabetic mice and may be beneficial to improve insulin resistance [68].

***Syzyguim cumini* Linn. (Formerly *Eugenia jambolana*, Myrtaceae):** With putative anti-hyperglycemic effects. Many parts of the plant, like fruit, seeds, bark, and tea prepared from the leaves, have been used in the treatment of diabetes throughout Asian countries [97]. The anti-hyperglycemic effect has been reported in leaves [98], seeds [99], fruits [100], and bark [101], but researchers failed to identify any blood glucose lowering effect with extracts or tea prepared from leaves of the plant in normal rats and rats with STZ-induced diabetes mellitus, and normal volunteers. Tea prepared from leaves of *S. cumini* has no hypoglycemic effect but, as its mechanism of action could depend on specific abnormalities with the disease, the effect in diabetes is still possible [102].

***Terminalia chebula* Retz. (Combretaceae):** Has been widely used in diabetes in Ayurveda and is widely distributed in India. An herbal formulation containing *T. chebula* named Triphala is traditional medicine for the treatment of diabetes. Anti-

diabetic and renoprotective effects of the chloroform extract of *T. chebula* Retz seeds in streptozotocin-induced diabetic rats was proved. It has potent renoprotective action [103].

***Terminalia catappa* Linn. (Combretaceae):** Is found throughout the warmer parts of India and called an Indian almond. The anti-diabetic potential of petroleum ether, methanol and aqueous extract of *T. catappa* fruits on fasting blood sugar levels and serum biochemical analysis in alloxan-induced diabetic rats was performed. All the three extracts produced a significant anti-diabetic activity at dose levels of 1/5 of their lethal doses. The extract may act by *β*-cells regeneration. The effect may be due to *β*-carotine in reducing diabetic complications like glycosylation in alloxan-induced diabetic rats [104].

***Trigonella foenum graecum* (Leguminosae):** Fenugreek is grown in North America and Asia and often flavors Indian food. It has been used as medicine for diabetes in India and China. Mechanisms proposed for fenugreek in diabetes are decreased carbohydrate absorption and increased insulin secretion. Several clinical trials among patients with type I or type II diabetes suggest a potential effect, but studies thus far have lacked sufficient quality [105, 106].

***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 secretory effect of *Tabernanthe iboga* might involve the closure of $K^+$-ATP and the intensification of calcium influx through voltage-sensitive $Ca^{2+}$ channels in rat pancreatic islets of Langerhans [107].

**DISCUSSION:** Diabetes, a pathological condition characterized by loss of glucose homeostasis, is carbohydrate, fat, and protein metabolism disorder result by insulin insufficiency or due to its resistance [108]. The incidence of the disease is increasing all over the world as the disease poses many challenges not only to the physician but also to the researcher. The World Health Organization estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000. It is estimated that the number will increase to over 366 million by 2030 and that large increases will occur in developing countries, especially in people aged between 45 and 64 years [109]. In spite of the presence of known anti-diabetic medicine in the pharmaceutical market, remedies from medicinal plants are used with success to treat this disease.

Previous studies have reported that medicinal plants might be used in the treatment of insulin-dependent and -independent diabetes. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic ones. Medicinal plant families with the most potent hypoglycemic effects include Leguminaceae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae & Araliaceae. The most commonly studied species are: *Opuntia streptacantha*, *Trigonella foenum graecum*, *Momordica charantia*, *Ficus bengalensis*, *Polygala senega* and *Gymnema sylvestre*.

The hypoglycemic effect of medicinal plants is attributed to numerous mechanisms. These include their effects on the activity of pancreatic beta cells, increase in the inhibitory effect against insulinase enzyme, the 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, an 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 [14]. In this review, plant extracts containing terpenoids, alkaloids, flavonoids, or phenolic compounds have shown antidiabetic potential through the insulinomimetic activity. Roseoside, epigallocatechin gallate, beta-pyrazole-1- ylalanine, cinchonain Ib, leucocyandin 3-O-beta-d- galactosyl cellobioside, leucopelargonidin-3-O-alpha-L rhamnoside, glycyrrhetinic acid, dehydro-trametenolic acid, strictinin, isostrictinin and pedunculagin, epicatechin and christinin-A isolated from the plant material have shown significant insulinomimetic activity along with significant anti-diabetic potential [110].

**CONCLUSION:** In conclusion, this review has presented a list of anti-diabetic plants used in the treatment of diabetes mellitus. It showed that these

plants have hypoglycemic effects and can be used to treat various types of secondary complications of diabetes mellitus.

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