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Treatment of Diabetes with Indian Herbs and Herbal Medicines: A Review

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Abstract

Diabetes mellitus, one of the most common metabolic diseases, affects 2.8% of the global population and is expected to climb to 5.4% by 2025. Herbal remedies have long been known as a valuable source of medicine, and they are becoming an increasingly important aspect of modern, high-tech medicine. The current review presents profiles of plants with hypoglycemic properties found in literature from various databases, with proper categorization based on the parts used, mode of blood glucose reduction (insulinomimetic or insulin secretagogues activity), and active phytoconstituents with insulin mimetics activity. According to the review, plants with hypoglycemia potential primarily belong to the families Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, and Araliaceae. Allium sativum, Gymnema sylvestre, Citrullus colocynthis, Trigonella foenum greacum, Momordica charantia, and Ficus bengalensis are the most active plants. The review discusses various new bioactive pharmaceuticals and isolated plant components, including 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 displaying substantial insulinomimetic and antidiabetic activity with better efficacy than traditional hypoglycaemic medications. Thus, according to the review, the antidiabetic effect of medicinal plants is mostly ascribed to the presence of polyphenols, flavonoids, terpenoids, coumarins, and other substances that reduce blood glucose levels. The review also examines the management of diabetes mellitus using these plants and their active principles.

Key Words: Diabetes, Insulin secretagogues, Insulin mimetics, Phytoconstituents, Pancrease, Blood glucose, Insulin, Beta cell, Antidiabetic activity, Medicinal plant, Metabolic disorder, Herbal medicine, Diabetes mellitus, Hypoglycaemic activity

Introduction

Herbal medicine has grown exponentially in recent years, and these treatments are gaining favour in both developing and developed countries due to their natural origins and lack of negative effects. Many commonly used traditional remedies are derived from medicinal plants, minerals, and organic substances.[1] Herbal medicine, also known as botanical medicine or phytomedicine, is the medical use of any plant's seeds, berries, roots, leaves, bark, or flowers.

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Herbalism, which has long been used outside of conventional medicine, is becoming increasingly popular as new analyses and research demonstrate its efficacy in the treatment and prevention of disease. A number of medicinal herbs known as rasayana, which have been utilised for over 1000 years, are present in herbal formulations used in Indian traditional health care systems.[2] Most practitioners in Indian systems of medicine develop and deliver their own formulas.[3] The World Health Organisation (WHO) has compiled a list of 21,000 plants used for therapeutic purposes around the world. There are 2500 species in India, with 150 of them being used economically on a considerable basis.[3] India is the world's largest producer of medicinal herbs and is known as the botanical garden. The current research focuses on herbal medicinal formulations and plants used in the treatment of diabetes mellitus, a significant disabling disease that causes massive economic losses around the world.[4]

Diabetes and Significance

Diabetes is a chronic carbohydrate, lipid, and protein metabolic condition characterised by elevated fasting and postprandial blood sugar levels. The global diabetes prevalence is expected to rise from 4% in 1995 to 5.4% by 2025. According to WHO, poorer countries will bear the lion's share of the burden. Diabetes is not only prevalent in India, but it is also quickly expanding in the urban population, according to studies conducted in the last decade.[5] Diabetes affects around 33 million persons in India, according to estimates. This figure is expected to rise to 57.2 million by 2025.

Diabetes mellitus is a complex metabolic condition caused by insulin deficiency or malfunction. Diabetes type I (insulin-dependent) is characterised by insulin deficiency due to a lack of functioning beta cells. Those with this condition are thus completely reliant on an exogenous source of insulin, whereas those with Type II diabetes (insulin independent) are unable to respond to insulin and can be managed with dietary changes, exercise, and medication. Type II diabetes is the most common kind of diabetes, accounting for 90% of all diabetics. Both diabetes disorders can cause symptoms such as: (i) high blood sugar levels; (ii) unusual thirst; (iii) frequent urination; (iv) severe hunger and weight loss; (v) blurred vision; (vi) nausea and vomiting; (vii) extreme weakness and weariness; (viii) irritability, mood swings, and so on.

Though the biology of diabetes is not completely understood, experimental data suggests that free radicals have a role in the aetiology of diabetes [6] and, more crucially, in the development of diabetic complications [7-9]. Free radicals can damage biological molecules, DNA, proteins, and lipids, altering cellular activities. Many recent studies show that antioxidants capable of neutralising free radicals are helpful in both preventing experimentally induced diabetes in animal models [10-11] and lowering the severity of diabetic sequelae[9].

The key causative factors for the development of diabetes complications are lipid and protein imbalances. Extracellular and long-lived proteins such as elastin, laminin, and collagen are the primary targets of free radicals in diabetes patients. Hyperglycemia causes these proteins to be changed to produce glycoproteins. Diabetes problems such as cataracts, microangiopathy, atherosclerosis, and nephropathy have been linked to the alteration of these proteins found in tissues such as the lens, vascular wall, and basement membranes.[12] Lipoproteins are oxidised by free radicals during diabetes. Diabetes also causes numerous lipoprotein metabolism anomalies in very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). Diabetes causes increased oxidative stress, which increases lipid peroxidation. Aside from that, non-enzymatic glycosylation of proteins produces advanced glycation end products (AGEs). AGEs build up on long-lived molecules in tissues, causing defects in cell and tissue activities.[13-14] Furthermore, through binding to certain macrophage receptors, AGEs lead to enhanced vascular permeability in both micro and macrovascular tissues. As a result, free radicals develop and endothelial dysfunction occurs. AGEs can also be found on nucleic acids and histones, where they can cause mutations and changes in gene expression.

Diabetes is a complex disease that causes a variety of problems, necessitating a multifaceted therapy strategy. Diabetes patients either do not produce

enough insulin or their cells do not respond to insulin. Patients are given insulin injections if they are completely deficient in insulin. In the case of cells that do not respond to insulin, numerous different medications are produced to address potential carbohydrate-metabolism abnormalities. For example, glucosidase inhibitors such as acarbose, miglitol, and voglibose are used to treat post-prandial hyperglycemia at the gut level. These block carbohydrate breakdown, limiting glucose uptake by cells. A biguanide, such as metphormine, is used to increase glucose absorption by peripheral cells. Sulphonylureas, such as glibenclamide, are insulinotropic and act as a secretogogue in pancreatic cells. Although numerous treatments are available, there are certain limits due to high costs and side effects such as hypoglycemia, weight gain, gastrointestinal disturbances, liver toxicity, and so on.[15] Based on recent discoveries and the role of oxidative stress in the complications of diabetes mellitus, efforts are being made to find appropriate antidiabetic and antioxidant therapy.

Medicinal herbs are being researched for the treatment of diabetes once more. Many pharmaceuticals have been developed from prototypic compounds found in medicinal plants. Metformin is an example of an effective oral glucose-lowering medication. Its creation was inspired by the usage of Galega officinalis to treat diabetes. Guanidine, a hypoglycemic component, is abundant in Galega officinalis. Because guanidine is too toxic for therapeutic usage, the alkyl biguanides synthalin A and synthalin B were developed as oral anti-diabetic medicines in Europe in the 1920s but were phased out after insulin became widely available. However, metformin was developed as a result of experience with guanidine and biguanides. Over 400 traditional plant remedies for diabetes have been reported to date, but only a limited number of these have been scientifically and medically evaluated to determine their efficacy. Some herbal extracts have been shown to have a hypoglycemic impact in human and animal models of type 2 diabetes. The World Health Organization's Diabetes Expert Committee has suggested that traditional medicinal herbs be studied further.[16]

The absence of scientific and clinical data confirming the efficacy and safety of herbal medicine is a major barrier to its incorporation into current medical practises. Clinical research on herbal pharmaceuticals is required, as is the development of simple bioassays for biological standardisation, pharmacological and toxicological evaluation, and the development of numerous animal models for toxicity and safety evaluation. It is also critical to determine the active component(s) of these plant extracts.[17-18]

How do herbs work?

It is uncertain what specific ingredient most herbs contain that has a therapeutic effect. Whole herbs are made up of a variety of elements that are likely to work in concert to provide the intended medical effect. A plant's constituents will vary depending on the environment (temperature, pests, soil quality), how and when it was harvested, and how it was processed.

How are herbs used?

Herbalists favour using entire plants over removing their constituent parts for the reasons listed in the previous section. The components of whole plant extracts are numerous. Together, these elements provide therapeutic effects and reduce the likelihood of negative effects from any one element. Several herbs are frequently combined to increase effectiveness, promote synergistic effects, and lower toxicity.[19]

When prescribing herbs, herbalists must take numerous factors into consideration. For instance, the type and species of the plant, its habitat, the storage and processing methods, and the presence of pollutants.[20] What are the benefits of herbal medicine? Asthma, eczema, premenstrual syndrome, rheumatoid arthritis, migraine, menopausal symptoms, chronic fatigue, and irritable bowel syndrome are just a few of the many illnesses that herbalists treat. The best way to use herbal remedies is to follow a skilled professional's instructions. Before self-medicating, be careful to speak with your doctor or a herbalist. The uses of a few common herbs are detailed here. For thorough descriptions of usage as well as information on dangers, negative effects, and possible interactions, please refer to our monographs on each herb.

What is the future of herbal medicine?

The FDA still categorises herbs as dietary supplements and prevents producers from making

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claims that their products may treat or prevent particular diseases, despite the fact that herbal medicine is experiencing resurgence in the United States. However, plants are regarded as medications in several European nations and are subject to regulation. Their usefulness and safety are actively investigated by the German Commission E, an expert medical body.[20]

Indian Medicinal Plants with Antidiabetic and Related Benifits

Numerous herbal treatments are recommended for diabetes and its consequences. The primary components of these compositions are medicinal herbs. Table 1 [21] provides a list of medicinal plants with antidiabetic and related positive effects. In Table 2, a list of these formulations is provided. Many of the drugs that are currently on the market have either been directly or indirectly produced from plants, which have historically been a very good source of pharmaceuticals. About 800 plants, according to ethnobotanical data, may have anti-diabetic properties; among them, Momordica charantia, Pterocarpus marsupium, and Trigonella foenum greacum have all been shown to be effective in treating type 2 diabetes.[4, 9] Several of these plants have demonstrated anti-diabetic effects when tested using various experimental methodologies. Numerous plant-derived active ingredients have been shown to have biological effects, including the treatment of diabetes.[11] These include alkaloids, glycosides, galactomannan, polysaccharides, peptidoglycans, hypoglycans, guanidine, carbohydrates, glycopeptides, terpenoids, amino acids, and inorganic ions. Tables 3 and 4 contain a list of medicinal plants with anti-diabetic potential organised by the various parts employed and method of action.

6.1 *Acacia arabica*: (Babhul) (Leguminosae)

It is primarily found in untamed habitats in India. By acting as an insulin secretagouge, the plant extract counteracts diabetes. In control rats, it causes hypoglycemia, but not in alloxanized animals. When normal rabbits received 2, 3, and 4 g/kg of powdered *Acacia arabica* seeds, the release of insulin from the pancreatic beta cells resulted in a hypoglycemic effect.[22]

6.2 *Aegle marmelos*: (Bengal Quince, Bel or Bilva) (Rutaceae)

In comparison to control, giving alloxanized rats aqueous extract of the leaves improves digestion and lowers blood sugar, urea, and serum cholesterol. This extract not only showed hypoglycemic action but also reduced the peak rise in blood sugar at one hour in an oral glucose tolerance test.[23]

6.3 *Agrimony eupatoria* (Rosaceae)

The BRIN-BD11 pancreatic beta cell line's in vitro insulin production was stimulated by an aqueous extract of *Agrimony eupatoria*. Extract was shown to have no influence on glucose levels.[24]

6.4 *Alangium salvifolium* (Alangiaceae)

The antioxidant and insulinotropic activities of the *Alangium salvifolium* leaf methanolic extract may account for the antihyperglycemic and antihyperlipidemic benefits in dexamethasone-induced insulin resistance in rats.[25]

6.5 *Allium cepa*: (onion) (Alliaceae)

Different ether soluble fractions of dried onion powder as well as its insoluble fractions exhibit anti-hyperglycemic effect in diabetic rabbits. Additionally, the antioxidant and hypolipidemic properties of allium cepa are well documented. S-methyl cysteine sulphoxide (SMCS), an amino acid from the Allium cepa family that contains sulphur, was administered to alloxan-induced diabetic rats for 45 days at a dose of 200 mg/kg.[26] This treatment significantly reduced blood sugar levels, lipid levels in serum and tissues, and liver hexokinase, glucose 6-phosphatase, and HMG Co A reductase activity.[27] A single oral dose of 50 g of onion juice dramatically reduced post-meal glucose levels in diabetic patients.[28]

6.6 *Allium sativum*: (garlic) (Alliaceae)

This perennial herb is grown all over India. The sulfur-containing component allicin, which gives garlic its strong aroma, has been found to have considerable hypoglycemic action.[29] Increased hepatic metabolism, increased insulin release from pancreatic beta cells, and/or an insulin sparing effect are suggested to be the causes of this impact.[30] In comparison to sucrose controls, aqueous homogenate of garlic (10 ml/kg/day) significantly boosted hepatic glycogen and free amino acid content, lowered fasting blood

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glucose, and decreased triglyceride levels in serum in rabbits fed on sucrose (10 g/kg/day in water for two months).[31] S-allyl cystein sulfoxide (SACS), a sulfur-containing amino acid and the precursor to allicin and garlic oil, effectively regulated lipid peroxidation more effectively than glibenclamide and insulin. Additionally, it enhanced diabetic conditions. Additionally, beta cells derived from healthy rats were induced by SACS to secrete insulin in vitro.[32] In addition, *Allium sativum* has been shown to have antibacterial, anticancer, and cardioprotective properties.

6.7 *Aloe vera* and *Aloe barbadensis* (Liliaceae)

Popular indoor plant aloe has a long history of use as a variety of folk remedies. Gel and latex are the two fundamental compounds that can be extracted from the plant. Aloe latex, sometimes known as "aloe juice," is an exudate from the pericyclic tubules just below the outer epidermis of the leaves and is a bitter yellow liquid. *Aloe vera* gel is the leaf pulp or mucilage. In both normal and diabetic rats, aloe gum extracts efficiently enhance glucose tolerance.[33] Exudates from Aloe barbadensis leaves were used to treat chronic diabetes in rats that had been alloxanized, but not a single dosage. In diabetic rats, bitter principle from the same plant in both acute and chronic doses had a hypoglycemic effect. Through stimulation of insulin synthesis and/or release from pancreatic beta cells, *Aloe vera* and its bitter component exert this activity.[34] Additionally, this herb exhibits dose-dependent anti-inflammatory properties and speeds up wound healing in diabetic rats.[35]

6.8 *Annona muricata* (Annonaceae)

As evidenced by the increased area of insulin immunoreactive -cells and protection against β-cell degeneration, anona muricata was crucial in reducing the oxidative stress on pancreatic β-cells in streptozotocin-induced diabetic rats.[36]

6.9 *Annona squamosa* (Annonaceae)

The plant Annona squamosa, sometimes known as the custard apple plant, has antidiabetic properties. It works by enhancing muscle glucose uptake, encouraging insulin release from pancreatic islets, and reducing hepatic glucose output.[36]

6.10 *Asparagus racemosus* (Liliaceae)

Asparagus racemosus root extracts in ethanol, hexane, chloroform, and ethyl acetate were shown to exhibit dose-dependent insulin production in isolated rat islet cells, isolated rat pancreas, and clonal beta cells. These results demonstrate that Asparagus racemosus root extract components have insulinotropic action.[37]

6.11 *Azadirachta indica*: (Neem)

In streptozotocin-treated rats, hydroalcoholic extracts of this plant exhibited anti-hyperglycemic action, and this effect was attributed to an increase in glucose absorption and glycogen deposition in isolated rat hemidiaphragms [38-39]. This plant not only possesses anti-diabetic properties but also anti-bacterial, anti-malarial, anti-fertility, hepatoprotective, and antioxidant ones.[40]

6.11 *Bauhinia variegata* (Caesalpiniaceae)

Bauhinia variegata leaf crude ethanolic extract and its primary metabolite (6S,7E,9R)Roseoside, or α-9-hydroxymegastigma-4,7-dien-3-one-9-beta-glycopyraroside have been discovered to have dose-dependent insulinotropic action in the insulin-secreting cell line INS-1.[41]

6.12 *Berberine*

In rat pancreatic islets, berberine enhanced glucose-stimulated insulin secretion rather than baseline insulin production in a dose-dependent manner. In contrast to sulphonylureas, *berberine* can increase glucose-stimulated insulin production in rat islets and likely achieves its insulinotropic action through a route involving hepatic nuclear factor 4 alpha (HNF4 alpha) and glucokinase.[42] In 3T3-L1 adipocytes treated with 50 M *berberine* and 0.2 nM insulin to achieve a glucose uptake level enhanced by 10 nM of insulin alone, significant insulin sensitising action was seen. This was connected to enhanced insulin signalling pathways and the insulin receptor substrate-1-phosphoinositide 3 Kinase-Akt activity, which resulted in increased glucose transporter-4 translocation into the plasma membrane. Through a strengthened insulin/insulin-like growth factor-1 signalling cascade, berberine also promoted glucose-stimulated insulin production and proliferation in Min6 cells. Data revealed that *berberine* can function as a potent insulinotropic and insulin sensitising agent.[43]

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6.13 *Biophytum sensitivum* (Oxalidaceae)

In diabetic male rabbits, a leaf extract from the *Biophytum sensitivum* promotes the release of insulin from pancreatic beta cells and has hypoglycemic effects.[44] In 16-hour fasting, non-diabetic rabbits, administration of the *Biophytum sensitivum* extract caused a substantial increase in blood insulin levels, suggesting a pancreatic mechanism of action for the herb. It's possible that Biophytum sensitivum's hypoglycaemic response is caused by boosting the production and release of insulin from its beta cells.[45]

6.14 *Boerhaavia diffusa* (Nyctaginaceae)

In streptozotocin-induced diabetic rats, chloroform extracts of *Boerhaavia diffusa* leaves shown anti-diabetic action that primarily operates by lowering blood glucose levels and raising insulin sensitivity.[36] Aqueous leaf extract demonstrated hypoglycemic and antihyperglycemic action at 200 mg/kg p.o. for 4 weeks in normal and alloxan-induced diabetic rats, improving plasma insulin levels and glucose tolerance.[44]

6.15 *Bougainvillea spectabilis* (Nyctaginaceae)

The ability of an ethanolic leaf extract of *Bougainvillaea spectabilis* to reduce blood sugar levels in streptozotocin-induced type I diabetic albino rats was likely a result of both improved insulin sensitivity and greater glucose absorption through enhanced glycogenesis in the liver.[36]

6.16 *Brassica nigra* (Cruciferae)

Due to the release of insulin from the pancreas, oral treatment of *Brassica nigra* aqueous extract for two months reduced blood glucose levels.[46]

6.17 *Cinnamon zeylaniucm* (Lauraceae)

Increased insulin release was seen when pancreatic islets were incubated in vitro with cinnamaldehyde extracted from Cinnamon zeylaniucm. Cinnamaldehyde's insulinotropic impact was brought on by a rise in glucose absorption via GLUT4 translocation in peripheral tissues.[47]

6.18 *Caesalpinia bonducella* (Cesalpinaceae)

The Indian tribal people employ *Caesalpinia bonducella*, which is extensively dispersed throughout the country's coastline area, to regulate their blood sugar. In chronic type II diabetes animals, both the aqueous and the ethanolic extracts demonstrated strong hypoglycemic action. These extracts also boosted glycogenesis, which raised the amount of liver glycogen.[48] Insulin secretion from isolated islets may be increased by two fractions, BM 169 and BM 170 B. In streptozotocin (STZ)-diabetic rats, the aqueous and 50% ethanolic extracts of *Caesalpinia bonducella* seeds shown antihyperglycemic and hypolipidemic effects.[49] The inhibition of glucose absorption may be the cause of the seed extracts' antihyperglycemic effects. The medication may have both antidiabetic and antihyperlipidemic effects.[50]

6.19 *Caesalpinia bonducella* (Cesalpinaceae)

The hypoglycemic efficacy of *Caesalpinia bonducella* aqueous and ethanolic extracts in a chronic type II diabetes animal revealed an increase in insulin production in isolated islets.[44]

6.20 *Caffeine*

In 90% pancreatectomized diabetic rats treated with 0.01% caffeine solution for 12 weeks, body weight, fat, and insulin resistance were reduced. The production of first- and second-phase insulin in response to glucose as well as beta-cell hyperplasia were both facilitated by coffee at the same time.[51]

6.21 *Camellia sinensis* (Theaceae)

In streptozotocin-induced diabetic rats, epigallocatechin gallate, a component of *Camellia sinensis*, enhances insulin activity and reduces oxidative damage.[13] In experimental conditions, a lower dosage of Camellia sinensis on SD rats fed a high-fat diet for two weeks demonstrated an insulinotropic effect.[52]

6.22 *Capsicum frutescens* (Solanaceae)

After 4 weeks of therapy, capsicum frutescens enhanced the blood insulin concentration in type 2 diabetic rats fed a high-fat (HF) diet and streptozotocin-induced diabetes. According to this study's results, using experimental procedures, 2% dietary Capsicum frutescens is insulinotropic rather than hypoglycemic.[53]

6.23 *Catharanthus roseus* (Apocyaceae)

In studies on the metabolism of carbohydrates, a dichloromethane-methanol extract of *Catharanthus roseus* leaves and twigs was shown to increase insulin production. Additionally, the extract was discovered to be beneficial in preventing damage brought on by oxygen free radicals.[36]

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6.24 *Citrullus colocynthis* (Cucurbitaceae)

In alloxan-induced diabetic rats, a pulp extract of Citrullus colocynthis at 300 mg/kg, p.o., was found to dramatically raise insulin and lower plasma glucose levels. Diabetes-treated rats receiving Citrullus colocynthis had more insulin in their beta cells than the control group, according to an immunohistochemistry procedure.[54] In alloxan-induced diabetic rats, the 300 mg/kg, p.o. ethanol extract of the dried seedless pulp of Citrullus colocynthis demonstrated insulinotropic effects.[55] Insulin release from isolated islets increased in a dose-dependent manner when *Citrullus colocynthis* extract was used.[56] Beta-pyrazol-1-ylalanine, the main free amino acid derivative contained in the seeds, and various extracts, including crude, aqueous, alcoholic, and refined extracts, dramatically increased insulin production in the isolated rat pancreas and isolated rat islets in vitro.[24]

6.25 *Coccinia indica* (Cucurbitaceae)

In a clinical investigation, oral treatment of *Coccinia indica* dried extract at 500 mg/kg, p.o. for 6 weeks dramatically raised insulin concentration. The plant extract had a positive hypoglycemic impact in diabetic humans and experimental animals, which may have been caused by an effect on insulin secretion or by the influence of enzymes involved in glucose metabolism.[56]

6.26 *Cornus officinalis* (Cornaceae)

By encouraging the growth of pancreatic islets, boosting postprandial insulin production, and ultimately speeding the glucose transport, an alcoholic extract of Cornus officinalis can enhance GLUT4 mRNA and its protein expression in NIDDM rats.[57] Methanol extract and its components significantly increased the expression of phosphoenolpyruvate carboxykinase by acting as strong insulin mimics. The importance of *Cornus officinalis* in the treatment of diabetes is strengthened by the fractions' capacity to shield beta cells from toxic assault and to increase insulin output.[58]

6.27 *Capparis decidua*

This is prevalent across India, particularly in arid regions. After feeding alloxanized rats fruit powder containing 30% of the *Capparis decidua* (*C. decidua*) fruit extract for three weeks, hypoglycemic effects were seen. Additionally, in erythrocytes, kidney, and heart, this extract greatly decreased lipid peroxidation caused by alloxan. In order to lessen oxidative stress, *C. decidua* was also discovered to change the amounts of the enzymes catalase and superoxide dismutase.[59] Additionally, *C. decidua* had hypolipidemic activity.[60]

6.28 *Coccinia indica*

Patients with diabetes received dried extracts of *Coccinia indica* (*C. indica*) (500 mg/kg body weight) for six weeks. These extracts improved the lowered and elevated activities of glucose-6-phosphatase, lactate dehydrogenase, and lipoprotein lipase (LPL) in untreated diabetics.[61] The oral administration of 500 mg/kg of *C. indica* leaves resulted in enhanced glucose tolerance in both normal and diabetic dogs and substantial hypoglycemia in alloxanized diabetic dogs.

6.29 *Elephantopus scaber* (Asteraceae)

By increasing insulin sensitivity, enhancing glucose-dependent insulin secretion, and encouraging the regeneration of islets of Langerhans in the pancreas of STZ-induced diabetic rats, the acetone extract of *Elephantopus scaber* demonstrated a considerable drop in blood glucose level.[62]

6.30 *Enicostemma littorale* (Gentianaceae)

In alloxan-induced diabetic mice, aqueous extract of *Enicostemma littorale* increased blood insulin levels at 8 hours and was linked to a potentiation of glucose-induced insulin release via a K+-ATP channel-dependent route.[63]

6.31 *Ephedra distachya* (Ephedraceae)

Due to regeneration and repair of atrophied pancreatic islets that increase the release of insulin, the alkaloids of *Ephedra distachya* herbs and l-ephedrine have demonstrated antihyperglycemic action in diabetic rats.[57]

6.32 *Eriobotrya japonica* (Rosaceae)

When the insulin secretory activity of an aqueous extract of *Eriobotrya japonica* and the chemicals cinchonain Ib, procyanidin B-2, chlorogenic acid, and epicatechin were examined in INS-1 cells, the results revealed a substantial and dose-dependent increase in insulin secretion.[64]

6.33 *Euccalyptus globulus* (Myrtaceae)

Enhanced peripheral glucose uptake in the mouse abdominal muscle and enhanced insulin release

from a clonal pancreatic beta cell line were both seen in response to an aqueous extract of *Euccalyptus globulus* (0.5 g/L of solution).[56].

6.34 *Eugenia jambolana*: (Indian gooseberry, jamun) (Myrtaceae)

Eugenia jambolana kernel decoction is a common home treatment for diabetes in India. This also makes up a significant portion of several herbal diabetic medications. Blood glucose levels are reduced as a result of the antihyperglycemic effects of aqueous and alcoholic extracts as well as lyophilized powder. This fluctuates depending on the degree of diabetes. It is lowered by 73.51% in mild diabetes (plasma sugar >180 mg/dl), 55.62% in moderate diabetes (plasma sugar >280 mg/dl), and 17.72% in severe diabetes (plasma sugar >400 mg/dl), respectively. [29] Within 30 minutes of injection, the jamun pulp extract shown hypoglycemic action in streptozotocin-induced diabetic rats, however the jamun seed took 24 hours. In diabetic rats, oral treatment of the extract led to a rise in blood insulin levels. On incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic mice, it was shown that insulin production was boosted. Additionally, the liver and kidney's insulinase activity was decreased by these extracts.[65]

6.35 *Ficus bengalensis* (Moraceae)

In rats with diabetes and normoglycemia, oral treatment of the *Ficus bengalensis* extract increased blood insulin levels. Inhibited insulinase activity from the liver and kidney is the primary cause of the increased insulin secretion.[24, 56] The principal mechanism by which a dimethoxy derivative of leucocyandin 3-O-beta-d-galactosyl cellobioside, isolated from the bark of *Ficus bengalensis*, reduced blood sugar levels in normal and mildly diabetic rats was its insulinomimetic action.[44] In severely diabetic rats, the leucopelargonidin glycoside from the *Ficus bengalensis* bark significantly reduced blood sugar, reduced cholesterol, and raised serum insulin levels. In healthy and alloxan-induced-diabetic dogs, the dimethoxy ether of leucopelargonidin-3-O-alpha-L-rhamnoside demonstrated considerable hypoglycaemic and insulinomimetic action over the course of two hours.[24]

6.36 *Fermented unsalted soybeans*

In 90% pancreatectomized diabetic Px rats, the effect of fermented unsalted soybeans for 8 weeks increased insulin secretion. Additionally, Chungkookjang enhanced pancreatic duodenal homeobox-1, an insulin promoter transcription factor, and potentiated insulin/IGF-1 signalling in islets through the activation of insulin receptor substrate-2 expression. Chungkookjang increased pancreatic beta-cell proliferation and decreased apoptosis in order to boost pancreatic beta-cell hyperplasia concurrently with the signaling's improvement.[66]

6.37 *Genistein*

In insulin-secreting cell lines (INS-1 and MIN6) as well as mice pancreatic islets, *genistein* stimulates insulin production. It was discovered that genistein exerts an insulinotropic action by directly acting on pancreatic beta-cells and activating the cAMP/PKA signalling cascade.[64]

6.38 *Ginkgo biloba* (Ginkgoaceae)

Ginkgo biloba extract has been shown to considerably boost insulin levels in healthy individuals and rats.[24]

6.39 *Radix glycyrrhizae* (Fabaceae)

In isolated islets, Radix glycyrrhizae and glycyrrhetinic acid improved glucose-stimulated insulin production. Additionally, they increased the mRNA levels of glucokinase, pancreatic duodenum homeobox 1, and insulin receptor substrate-2 in the islets, which helped to increase beta-cell survival.[67]

6.40 *Gymnema sylvestre* (Asclepiadaceae)

The rat islets of Langerhans and various pancreatic beta cell lines were induced to secrete insulin by an alcohol-based preparation of *Gymnema sylvestre*. *Gymnema sylvestre* water-soluble leaf extract was given orally to 27 individuals with insulin-dependent diabetes in another trial, and it was found to reduce fasting blood glucose levels and insulin requirements.[1] *Gymnema sylvestre* nutrition may help type II diabetes patients renew or repair their pancreatic beta cells, as seen by the patients' higher blood insulin levels following treatment.[24] Gymnemic acid molecules, namely dihydroxy gymnemic triacetate, were able to release the insulin by causing the surviving beta cells to undergo a process of regeneration and renewal. Without affecting cell viability, an aqueous extract of

Gymnema sylvestre leaves enhanced insulin production from isolated human islets and mice cells in vitro.[62] *Gymnema sylvestre* was given orally to diabetic rats and boosted insulin levels as well as the number of pancreatic islet and beta cells, pointing to a potential repair or regeneration of the endocrine pancreas.[68] *Gymnema sylvestre* water-soluble extracts cause pancreatic beta cells to regenerate both in vivo and in vitro, which releases insulin.[69]

6.41 *Helicteres isora* (Sterculiaceae)

In glucose-loaded rats, butanol extracts of the root of *Helicteres isora* at a dose of 250 mg/kg, p.o. had antihyperglycemic effects.[44]

6.42 *Hibiscus rosa sinensis* (Malvaceae)

Hibiscus rosa sinesis ethanol extract given orally at a dose of 250 mg/kg p.o. caused moderate but detectable hypoglycemia, which was mostly brought on by the activation of pancreatic beta cells, which produce insulin.[1]

6.43 *Hordeum vulgare* (Gramineae)

Due to the mobilisation of insulin in NIDDM, the germinant fruits of *Hordeum vulgare* demonstrated hypoglycemic and hyperinsulinemic effects in NIDDM individuals, making it a potential cereal for diabetes mellitus.[57]

6.44 *Lepechinia caulescens* (Lamiaceae)

Significantly lowering glucose tolerance with Lepechinia caulescens may indicate that it possesses insulin-like action.[24]

6.45 *Medicago sativa* (Fabaceae)

The BRIN-BD11 pancreatic beta cell line's in vitro insulin production was stimulated by an aqueous extract of *Medicago sativa*. In a different investigation, it was discovered that the methanol and water fractions' ability to release insulin is mostly caused by the interaction of the individual parts that make them up.[24]

6.46 *Momordica charantia* (Cucurbitaceae)

Diabetic rats given *Momordica charantia* fruit juice showed a significant drop in blood glucose level and an increase in plasma insulin concentration. The difference between treated and untreated animals' beta cell counts is what caused the impact that was seen. Momordicin, charantin, and a few other phytochemicals that have been isolated from other portions of this plant, including galactose-binding lectin and insulin-like protein, have all been found to exhibit insulin-mimetic activity.[68-69] It has also been demonstrated that an aqueous extract of unripe *Momordica charantia* fruits may partially induce the release of insulin from isolated beta cells of obese, hyperglycemic rats, indicating that the insulin-releasing effect is caused by changes in membrane functions.[24] *Momordica charantia* promotes pancreatic insulin secretion and increases pancreatic partial cell renewal or may allow partial cell recovery.[57]

6.47 *Mucuna pruriens* (Leguminosae)

Powdered *Mucuna pruriens* seeds showed blood glucose-lowering action at doses of 0.5, 1, and 2 g/kg p.o. in healthy rabbits as well as 1 and 2 g/kg p.o. in alloxan-diabetic rabbits. Due to the inclusion of trace elements like manganese, zinc, etc., it may operate by stimulating the release of insulin or by having a direct insulin-like effect.[1, 44]

6.48 *Mangifera indica: (Mango)*

Despite the fact that an oral administration of the plant's aqueous extract had no effect on the blood glucose levels of normoglycemic or streptozotocin-induced diabetic rats, the leaves of this plant are employed as an anti-diabetic medication in Nigerian folk medicine. However, when the extract and glucose were given to the rats at the same time as well as when the extract was given to them 60 minutes before the glucose, antidiabetic effect was seen. The findings suggest that *Mangifera indica* aqueous extract has hypoglycemic action. This could be caused by a decrease in the intestinal absorption of glucose. [70].

6.49 *Momordica charantia*: (bitter gourd)

In India and other Asian nations, *Momordica charantia* is frequently used as an antihyperglycemic and antidiabetic medication. In several animal models, extracts of fruit pulp, seeds, leaves, and the entire plant were proven to exhibit hypoglycemic effects. When given subcutaneously to langurs and humans, polypeptide p, which was extracted from the fruit, seeds, and tissues of *M. charantia*, significantly reduced blood sugar levels.[71] In normal and STZ diabetic rats, ethanol extracts of *M. charantia* (200 mg/kg) had antihyperglycemic and hypoglycemic effects. This may be due to liver enzymes other than fructose-1,6-biphosphatase inhibiting glucose-6-phosphatase and activating glucose-6-phosphate dehydrogenase.[72]

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6.50 *Nigella sativa* oil (Ranunculaceae)

Four weeks of therapy with *Nigella sativa* oil resulted in appreciable reductions in blood sugar levels and a rise in serum insulin levels. Large regions with positive immunoreactivity for the presence of insulin were visible when the pancreas from the *Nigella sativa* oil-treated group was stained.[73]

6.51 *Ocimum sanctum*: (holy basil)

It is typically referred to as Tulsi. This plant has a long history of being valued for its healing abilities. Both normal and alloxan-induced diabetic rats significantly reduced their blood sugar levels when given an extract of *Ocimum sanctum* leaves in water.[74] Tulasi showed significant hypoglycemic and hypolipidemic effects in diabetic rats by reducing fasting blood glucose, uronic acid, total amino acids, total cholesterol, triglycerides, and total lipid.[75] On days 15 and 30 of the trial, oral treatment of plant extract (200 mg/kg) for 30 days caused a drop in plasma glucose of around 9.06 and 26.4%, respectively. In diabetic rats compared to controls, skeletal muscle and hepatic glycogen levels declined by 68 and 75%, respectively, but renal glycogen content rose by a factor of 10.[76] Additionally, this plant exhibited anti-asthmatic, anti-stress, antibacterial, antifungal, antiviral, anticancer, gastric antiulcer, antioxidant, antimutagenic, and immunostimulant properties.

6.52 *Panax ginseng* (Araliaceae)

When mice were subcutaneously injected with ginseng polypeptides taken from the root of *Panax ginseng* at daily dosages of 50 and 100 mg/kg for 7 consecutive days, the mice's blood glucose levels declined, their liver glycogen levels rose, and their insulin production was stimulated.[11] The Korean red ginseng aqueous ethanolic extract strongly induced an insulin release in a glucose-independent way.[24, 77]

6.53 *Pandanus odorus* (Pandanaceae)

In healthy rats, administration of 5 mg/kg of the 4-hydroxybenzoic acid from *Pandanus odorus* raised blood insulin levels and the amount of liver glycogen.[24]

6.54 *Parinari excelsa* (Chrysobalanaceae)

The *Parinari excelsa* flavonoid's capacity to induce insulin secretory activity in diabetic animal models led to a hypoglycemic effect.[62]

6.55 *Prunella vulgaris* (Labiatae)

Jiangtangsu was extracted from *Prunella vulgaris*, and research in diabetic mice shown that it has a great blood sugar reducing impact. Jiangtangsu's potential method involves repairing pancreatic islet cells so they can release insulin.[57]

6.56 *Psidium guajava* (Myrtaceae)

Due to enhanced insulin sensitivity, flavonoid glycosides such strictinin, isostrictinin, and pedunculagin are the active components of *Psidium guajava*, which have been utilised in clinical treatments for diabetes.[57]

6.57 *Phyllanthus amarus*: (bhuiawala)

It is a herb from the Euphorbiaceae family that may grow up to 60 cm tall. It is frequently referred to as Bhuiamala. It is dispersed over India's drier regions, namely the Deccan, Konkan, and south Indian states. It is traditionally employed in the treatment of diabetes. Strong antioxidant activity was reported in *Phyllanthus amarus* methanolic extract. In rats with diabetes that had been alloxanized, this extract also decreased blood sugar.[78] Additionally, the plant has anti-inflammation, anti-mutagenic, anti-carcinogenic, and anti-diarrheal properties.

6.58 *Pterocarpus marsupium*: (Fabaceae)

It is a deciduous tree that is often found in mountainous areas of India. Pterostilbene, a component produced from the wood of this plant, caused hypoglycemia in dogs [79-80], demonstrating that the tannates present in the extract are the source of the extract's hypoglycemic effect. It has been demonstrated that the flavonoid fraction from *Pterocarpus marsupium* induces pancreatic beta cell regranulation.[81] This plant's marsupin, pterosupin, and liquiritigenin all shown antihyperlipidemic action.[82] Its active ingredient, epicatechin, has been discovered to be insulinogenic, increasing insulin release and proinsulin conversion to insulin *in vitro*. (Epicatechin) raises the glycogen content of rat diaphragm in a dose-dependent way, stimulating oxygen absorption in fat cells and tissue slices of multiple organs similarly to insulin.[83]

6.59 *Radix rehmanniae* (Scrophulariaceae)

By promoting insulin secretion and lowering the mice's glycogen levels, the pectin-type polysaccharide from the rhizome of *Radix rehmanniae* showed hypoglycemic action in both

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normal and streptozotocin-induced diabetic mice.[57]

6.60 *Rehmania glutinosa* (Scrophulariacea)

Insulin secretion was enhanced and the amount of glycogen in the livers of healthy mice was decreased after intraperitoneal injection of the ethanol precipitate fraction made from the hot water extract from the rhizome of *Rehmania glutinosa*.[24]

6.61 *Ricinus communis* (Euphorbiaceae)

Diabetes-prone rats were given an ethanolic extract of *Ricinus communis* at 500 mg/kg, p.o. for 20 days. This treatment dramatically raised insulin levels and improved the lipid profile and body weight of the diabetic animals.[62]

6.62 *Syzygium cumini* (Rutaceae)

Syzygium cumini fruit pulp extract was administered orally to rats with normoglycemia and STZ-induced diabetes, and it produced hypoglycemic effects in 30 minutes that may have been caused by insulin secretion and reduced insulinase activity.[1]

6.63 *Salvia lavandifolia* (Lamiacea)

Salvia lavandifolia's ability to lower blood sugar levels may be attributed to a variety of processes, including hyperplasia of the pancreatic islet beta cells and potentiation of insulin release brought on by glucose.[24] With a rise in pancreatic insulin content, the extract of *Salvia lavandifolia*'s antidiabetic effect caused an increase in the size and number of cells in the islets of Langerhans at a dose of 10 mg/kg.[24]

6.64 *Sarcopoterium spinosum* (Rosaceae)

By causing an increase in glucose absorption, the aqueous extract of *Sarcopoterium spinosum* had a similar impact to insulin on glucose uptake in hepatocytes. Additionally, it enhanced in vitro insulin secretion.[62]

6.65 *Selaginella tamariscina* (Selaginellaceae)

Selaginella tamariscina 25 g/kg intraperitoneally injected for 12 days resulted in a decrease in blood glucose and serum lipid peroxide as well as an increase in serum insulin concentration. The plant was able to restore the structure of pancreatic islet beta cells damaged by alloxan, according to histological examinations.[24]

6.66 *Semen coicis* (Gramineae)

In normal rats, coixans, which were extracted and purified from the dried *Semen coicis* seeds, reduced blood sugar levels while raising serum insulin levels. Coixans' potential role in the treatment of diabetes may lie in their ability to stop pancreatic beta-cell damage brought on by alloxan.[57]

6.67 *Smallanthus sonchifolius* (Asteraceae)

The 30-day administration of 2% *Smallanthus sonchifolius* to diabetic rats raised the amount of circulating insulin, possibly as a result of improved insulin synthesis and secretion.[84]

6.68 *Stevia rebaudiana* (Asteraceae)

According to research on the effects of stevioside on isolated mouse islets and the clonal beta cell line INS-1, the type 2 diabetic GK rat exhibits antihyperglycemic, insulinotropic, and glucagonostatic responses to the glycoside stevioside.[85] According to the results of another investigation, stevioside and steviol directly affect beta cells to promote insulin secretion.[86] The natural sweetener stevioside, which is found in the plant *Stevia rebaudiana*, works by directly activating the -cells of pancreatic islets to secrete insulin.[87]

6.69 *Swertia chirayita* (Gentianaceae)

Normal rats given the 250 mg/kg p.o. hexane fraction of *Swertia chirayita* dramatically lowered blood sugar and boosted plasma insulin without changing the amount of hepatic glycogen. However, when given for 28 days, it greatly increased the amount of hepatic glycogen along with other effects, perhaps due to the release of insulin.[24] Swerchirin (50 mg/kg) was given to rats once orally, and this resulted in a significant decrease in blood sugar levels as well as the aldehyde-fuchsin and immunostained beta-granules and insulin in the pancreatic islets. Swerchirin significantly increased the amount of glucose-stimulated insulin released from isolated islets at concentrations of 100, 10 and 1 mM.[1]

6.70 *Swertia punicea* (Gentianaceae)

In STZ-induced type-2 diabetic mice, *Swertia punicea* ethanol extracts and the ethyl acetate soluble fraction had hypoglycemic effects and may help to reduce insulin resistance.[62]

6.71 *Trigonella foenum graecum*: (fenugreek)

Fenugreek seeds are widespread across India and are frequently used as one of the main ingredients in Indian spices. A new amino acid called 4-hydroxyleucine, found in fenugreek seeds, enhanced the release of insulin from isolated islet cells in both rats and humans.[88] Both normal

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and diabetic rats had dose-dependent decreases in blood glucose levels after oral administration of 2 and 8 g/kg of plant extract.[89] Fenugreek seed administration also enhanced glucose oxidation and restored normal creatinine kinase activity in the heart, skeletal muscle, and liver of diabetic rats. Additionally, it decreased the activity of fructose 1,6-bisphosphatase and glucose-6-phosphatase in the liver and kidneys.[90] Additionally, this plant has antioxidant action.[91-92]

6.72 *Tabemanthe iboga* (Apocynaceae)

A dose-dependent impact of *Tabernanthe iboga* aqueous extract enhanced glucose-stimulated insulin production. Insulinomimetic chemicals are found in *Tabernanthe iboga*. The closure of K+-ATP and the amplification of calcium influx through voltage-sensitive Ca2+ channels may be involved in Tabernanthe iboga's insulin secretory effect.[93]

6.73 *Teucrium polium* (Lamiaceae)

Teucrium polium crude extract in aqueous form can increase pancreatic insulin secretion, which in turn increases insulin secretion.[94] *Teucrium polium* extracts have insulinotropic effects, which can be linked to the presence of apigenin, which is only present in the methanol fraction and not the aqueous fraction.[95] *Teucrium polium* crude extract has the ability to increase insulin production at high glucose concentrations, and plant extract appears to be able to regenerate the islets of Langerhans in diabetic rats treated vs those not treated.[96]

6.74 *Tinospora cordifolia*: (Guduchi) (Menispermaceae)

It is a large, glabrous, ascending shrub of the Menispermaceae family. It is readily available across India and is sometimes called "Guduchi." In alloxan diabetic rats, oral treatment of the *Tinospora cordifolia* (T. cordifolia) root extract for six weeks led to a significantly lower level of blood and urine glucose as well as lipids in serum and tissues. Additionally, the extract stopped the body's weight from dropping.[97] For the treatment of diabetes mellitus, *T. cordifolia* is frequently utilised in Indian ayurvedic medicine.[98-100] Blood glucose and brain lipids were significantly reduced in alloxan diabetic rats after oral treatment of an aqueous *T. cordifolia* root extract. Although the aqueous extract could have a considerable anti-hyperglycemic impact in a variety of animal models at a dosage of 400 mg/kg, its efficacy was only comparable to one unit/kg of insulin.[101] It has been claimed that administering *T. cordifolia* extract on a regular basis lowers blood sugar levels and improves glucose tolerance in animals.[102]

6.74 *Tribuluks terrestris* (Zygophyllaceae)

Due mostly to the elevated serum insulin level, *Tribuluks terrestris* extract dramatically lowers blood glucose levels in both normal and alloxan-induced diabetic mice. [57]

6.75 *Trigonella foenum-graecum* (Leguminosae)

In rats, mice, and humans, 4-hydroxyleucine, a new amino acid from fenugreek seeds, raised glucose and promoted the release of insulin by isolated islet cells. [1,103-105]. *In vitro* and *in vivo* studies have shown *Trigonella foenum-graecum* can promote the release of insulin in response to glucose.[69] In *Trigonella foenum-graecum* seeds, hydroxyisoleucine, which makes up 80% of the free amino acids, may have the ability to stimulate the production of insulin [68] *Trigonella foenum-graecum* seeds may aid in enhancing insulin sensitivity, which is thought to be a result of fiber's effects on slowing carbohydrate metabolism, which lowers blood glucose and insulin levels.[68] *Trigonella foenum-graecum* seeds and leaves have an anti-hyperglycemic action, which has been connected to delayed stomach emptying brought on by the high fibre content, inhibition of carbohydrate digesting enzymes, and stimulation of insulin secretion.[57]

6.76 *Zizyphus spina-christi* (Rhamnaceae)

The butanol extract of *Zizyphus spina-christi* leaves, which contains the main saponin glycoside christinin-A, potentiated glucose-induced insulin release in non-diabetic control rats, according to research on the effects on blood glucose and insulin levels. In diabetic rats administered the butanol extract of *Zizyphus spina-christi* over a period of 4 weeks [24], serum insulin and pancreatic cAMP levels significantly increased.

Herbal Drug Formulations

On the recommendation of their doctors, diabetic patients employ a variety of formulations (see Table 2) that are readily available on the market.

The 'Himalaya' brand of diabetes medication is said to stimulate B-cell repair and regeneration,

boost c peptide level, increase hepatic and muscle glucagon contents, and increase peripheral glucose utilisation. It shields B-cells from oxidative damage and possesses antioxidant effects. By lowering the levels of glycated haemoglobin, bringing the microalbuminuria back to normal, and adjusting the lipid profile, it has an effect similar to insulin. Long-term diabetic problems are reduced.

The active ingredient in the epinsulin sold by Swastik formulations is epicatechin, a benzopyran. The islet's cAMP concentration is elevated by epicatechin, and this results in a rise in insulin release. It contributes to the process of turning proinsulin into insulin by boosting cathepsin activity. Additionally, it inhibits Na/K ATPase activity from the patient's erythrocytes and has an insulin-like impact on the osmotic fragility of human erythrocytes. It corrects neuropathy, retinopathy, and irregular glucose and lipid metabolism. It preserves the health of all the diseased organ systems. It is said to be an excellent adjuvant for insulin-dependent diabetic mellitus (IDDM) and a cure for non-insulin-dependent diabetes mellitus (NIDDM), reducing the quantity of insulin required. Along with current oral hypoglycemic medications, it is suggested. It has a reputation for reducing diabetes complications. Since it has a mild hypoglycemic effect, there is no danger of hypoglycemia.

Pancreatic Tonic is an ayurvedic herbal supplement that is now offered as a dietary supplement. It is a botanical blend of ancient Indian ayurvedic herbs.

Garry and Sun advertise bitter gourd powder. Low blood and urine sugar levels are a result. It cleanses blood and strengthens the body's defences against illnesses. Excellent medical benefits may be found in bitter gourd. It has medicinal properties and acts as a laxative, stomachic, antibilious, and antipyretic tonic. Additionally, local African and Asian therapies employ the bitter gourd. Particularly, the bitter gourd is employed as a traditional remedy for diabetes. Bitter glycosides, saponins, alkaloids, reducing sugars, phenolics, oils, free acids, polypeptides, sterols, 17-amino acids, including methionine, and a crystalline substance called p-insulin are among its constituents. In addition to being antihaemorrhoidal, astringent, stomachic, emmenagogue, hepatic stimulant, anthelmintic, and blood purifier, it is said to have hypoglycemic effect.

Admark Herbals Ltd.'s Dia-Care is marketed as having an 18-month cure rate for both Type 1 and Type 2 diabetes after 90 days of treatment. Insulin users will finally be freed from their reliance on it. The entire course of therapy is completed in six phases, each lasting 90 days. A little over 5 grammes of powder, or about 1 tea spoon, is combined with 1/2 glass of water, thoroughly stirred, and left overnight. The only thing that has to be consumed in the morning on an empty stomach is water, not sediment. Fresh water is poured to the remaining medication, which is then stored for the whole day and ingested 30 minutes prior to supper. The medication has an extremely bitter taste. It is a completely natural formula with no negative side effects.

Diabetes-Daily Care, made by Nature's Health Supply, is a special natural formula that improves sugar metabolism safely and efficiently. Diabetes Daily CareTM combines all of the natural components indicated in Table 2 in the dosage that is best for the body to use. It was created specifically for people with type 2 diabetes.

Gurmar powder, produced by Garry and Sun, is an anti-diabetic medication that blocks sacharides' intestinal absorption, preventing blood sugar swings. Additionally, it links the metabolic processes of the liver, kidney, and muscles. Gurmar has the ability to lower blood sugar levels and promote insulin production. When administered to the tongue in diabetes, it suppresses sweet taste receptors and eliminates glycosuria. It dulls the flavour of sweets and items that are bitter, such quinine (effects persist for one to two hours). Along with these qualities, it also regulates the metabolism of the liver, kidney, and muscles and acts as a diuretic and heart stimulant.

The Ayurvedic remedy DIABETA, which comes in capsule form, is an anti-diabetic with a mix of effective immunomodulators, antihyperlipidemics, anti-stress, and hepatoprotective of plant origin. The Diabeta formulation is based on historical ayurvedic references, which are further supported by contemporary research and clinical testing. In order to properly manage the variables and processes that result in diabetes mellitus, the

hormone beta operates on several locations in a variety of ways. It combats the numerous causes of diabetes and treats the degenerative consequences that arise as a result of the disease. As a single agent addition to synthetic anti-diabetic medications, Diabeta is secure and efficient in controlling Diabetes Mellitus. When administered as an adjuvant to cases of uncontrolled diabetes, diabetes aids in overcoming resistance to oral hypoglycemic medications. In addition to promoting symptomatic alleviation of problems including weakness, giddiness, leg pain, body discomfort, polyuria, and pruritis, diabetes gives patients a sense of well-being.

Fenugreek seed extracts are included in the Plethico Laboratory product Syndrex. Over a millennium, fenugreek has been a component of traditional remedies. Currently, animal models and cultured islet cells are being used to understand the mechanism of this anti-diabetic medication.

As a result, a wide variety of plants have been utilised singly or in combination with other ingredients to treat diabetes and its consequences. The lack of clearly specified active components in this herbal composition is one of its main issues. Knowing the active ingredient and how their molecules interact is crucial for analysing the product's therapeutic effectiveness and standardising it. The mechanism of action of several of these plants is now being studied using model systems.

Rasayana Therapy in Diabetes Mellitus

The Rasayana school of Ayurveda is significant. A higher quality of life and longer longevity are the primary objectives of Rasayana treatment. Rasayana incorporates a nutrition plan, code of behaviour, and medicine formulation. Many of the medications utilised in Rasayana treatment for diabetes mellitus, including as Phyllanthus emblica, Azadirachta indica, Ocium sanctum, and Tinospora cordifolia, have exceptional antioxidant qualities.(2006) Patel et al. Aeara Rasayana (antistress), Ajasrika Rasayana (dietary control), Osad Rasayana (preventive), and Naimittika Rasayana (hypoglycemic) are the four components of the Rasayana strategy to treating diabetes.

Pharmacologically screened insulinomimetic or insulin secretagogues plant materials and phytoconstituents

The purpose of this study is to compile information on plant material that exhibits hypoglycaemic activity, either by increasing pancreatic insulin production or by acting similarly to insulin as described in various literature sources. Numerous plant species, including *Opuntia streptacantha, Trigonella foenum graecum, Momordica charantia, Ficus bengalensis, Polygala senega, Gymnema sylvestre, Allium sativum, Citrullus colocynthis, and Aloe vera*, have been identified as hypoglycemic, according to the search.[24] The experimental research on the hypoglycaemic activity of plant material and the bioactive substances connected to the formation of insulin or its action are the primary focus of the current review. Here, every plant material that is included has been put in alphabetical order after being evaluated for their insulinomimetic or secretogogue activities in various in vivo or in vitro model systems. Additionally, Table 5 includes phytoconstituents derived from several plants that have demonstrated insulinomimetic activity.

Discussion

Diabetes, a condition of the metabolism of carbohydrates, fats, and proteins brought on by inadequate insulin production or by its inhibitory impact, is a significant contributor to significant economic loss and can obstruct national development.[17]

Natural remedies were employed before to the development of pharmaceuticals and can still be utilised now. Numerous plants have potent anti-diabetic effects. Patients with both insulin-dependent and non-insulin-dependent diabetes, diabetic retinopathy, diabetic neuropathy, etc. have employed herbal remedies for the disease. Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae, and Araliaceae are the plant families having the most hypoglycaemic effects. The species Opuntia streptacantha, Trigonella foenum graecum, Momordica charantia, Ficus bengalensis, Polygala senega, and Gymnema sylvestre are the most often investigated ones. The

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most frequently utilised models in the research for the screening of anti-diabetic medications were the oral glucose tolerance test, streptozotocin, and alloxan-induced diabetic mouse or rat. For plant extracts, a variety of mechanisms of action have been suggested. Some theories centre on how the plant extracts affect the function of pancreatic beta cells, the enzyme insulinase, insulin sensitivity, and insulin-like activity. There may be additional mechanisms at work as well, including an increase in peripheral glucose uptake, an increase in hepatic glycogen synthesis or a decrease in glycogenolysis, an inhibition of intestinal glucose absorption, a decrease in the glycaemic index of carbohydrates, and a diminution of the effect of glutathione.[24]

Through the insulinomimetic action of the plant extract, natural compounds categorised into terpenoids, alkaloids, flavonoids, phenolics, and some other categories have demonstrated antidiabetic promise in this study. 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, it has been shown that a few flavonoids, polyphenols, and sugar derivatives are efficacious thanks to a few different extrapancreatic processes. This study includes a large number of plants that have demonstrated antidiabetic effect via insulin release and some other pancreatic mechanisms.[87]

The list also includes plants with a high potential for treating diabetes, including Allium cepa, Clerodendron phlomoides, Cinnamomum tamala, Coccinia indica, Enicostemma littorale, Ficus bengalensis, Gymnema sylvestre leaves, Momordica charantia, Pterocarpus marsupium, and Syzygium cumini, While some commercialised herbal formulations that have been demonstrated to have antidiabetic activity are also listed in the database [103],[153] (e.g., Diasulin, Pancreatic Tonic 180 cp, Chakrapani, Diabecon, Bitter Gourd Powder, Dia-Car, Diabetes-Daily Care, Gurmar Powder). Not all of these plants were useful in treating severe experimental diabetes and associated consequences, despite the fact that they all shown varied degrees of hypoglycemic and anti-hyperglycemic action. Fenugreek seeds have been used to extract and purify a new amino acid (4-hydroxyleucine), which is said to boost glucose-induced insulin release.[1]

The list of anti-diabetic plants used to treat diabetes mellitus has been offered in this paper's conclusion. It demonstrated that these herbs have hypoglycaemic properties and may be utilised to treat different kinds of diabetes mellitus secondary problems. Although many plants and the medicinal chemicals extracted from them have not yet been thoroughly characterised, they have historically been a reliable source of medicine for the treatment of many different types of sickness. To determine the precise mechanism of action of medicinal plants with antidiabetic and insulinomimetic activities, more research must be done. It is a common misconception that plants are harmless, yet many plant products are poisonous to humans. As a result, toxicity studies of these plants should be clarified prior to their intake.

Table 1: Indian medicinal plants with antidiabetic and related beneficial properties

Plant Name	Ayurvedic/ common name/ herbal formulation	Antidiabetic and other beneficial effects in traditional medicine	References
Annona squamosa	Sugar apple	Increased plasma insulin level, hypoglycemic and antihyperglycemic effects of ethanolic leaf extract	[106-108]
Artemisia pallens	Davana	Hypoglycemic, increases the use of peripheral glucose, or prevents the absorption of glucose	[109]
Areca catechu	Supari	Hypoglycemic activity	[110]

Beta vulgaris	Chukkander	increases OGTT glucose tolerance	[111]
Boerhavia diffusa	punarnava	Enhancement of hexokinase activity, inhibition of fructose bisphosphatase and glucose-6-phosphatase, elevation of plasma insulin levels, and antioxidant	[112-114]
Bombax ceiba	Semul	Hypoglycemic activity	[115]
Butea monosperma	palasa	Antihyperglycemic activity	[116]
Camellia sinensis	Tea	Anti-hyperglycemic activity and antioxidant activity	[117-118]
Capparis decidua	Karir or Pinju	Hypoglycemic, antioxidant, hypolipidaemic activity	[60]
Caesalpinia bonducella	Sagarghota, Fevernut	Hypoglycemic, insulin secretagogue, hypolipidemic activity	[48-49],[119]
Coccinia indica	Bimb or Kanturi	Hypoglycemic activity	[61]
Emblica officinalis	Amla, Dhatriphala, a constituent of herbal formulation, "Triphala"	Decreases lipid peroxidation, antioxidant and hypoglycemic activity	[120-122]
Eugenia uniflora	Pitanga	Hypoglycemic activity, inhibits lipase activity	[123]
Enicostema littorale	krimihrita	Hexokinase activity should be elevated while glucose 6-phosphate and fructose 1,6-bisphosphatase activity should be decreased. Hypoglycemic action that is dose dependant	[124-125]
Ficus bengalenesis	Bur	Hypoglycemic, antioxidant activity	[126]
Gymnema sylvestre	Gudmar or Merasingi	Anti-hyperglycemic effect, hypolipidemic activity	[127-128]
Hemidesmus indicus	Anantamul	Anti snake venom activity, anti-inflammatory activity	[129]
Hibiscus rosa-sinesis	Gudhal or Jasson	Triggers the release of insulin from pancreatic beta cells	[130]
Ipomoea batatas	Sakkargand	improves insulin sensitivity	[131]
Momordica cymbalaria	Kadavanchi	Hypoglycemic, hypolipidemic activity	[132-133]
Murraya koenigii	Curry patta	Hypoglycemic, increases glycogenesis and decreases gluconeogenesis and glycogenolysis	[134]
Musa sapientum	Banana	Antihyperglycemic, antioxidant	[135-137]
Phaseolus vulgaris	Hulga, white kidney bean	Alpha amylase activity is inhibited by hypoglycemia, hypolipidemia, and antioxidants. GLUT-4 and insulin receptor mRNA levels in skeletal muscle are abnormal.	[138-140]
Punica granatum	Anar	Effects as antioxidants and on hyperglycemia	[141]

Salacia reticulata	Vairi	inhibition of -glucosidase and inhibitor of sucrase	[142]
Scoparia dulcis	*Sweet broomweed*	antioxidant, antihyperlipidemic, hypoglycemic, and insulin-secretagogue action	[143-145]
Swertia chirayita	Chirata	stimulates islet insulin release	[146]
Syzygium alternifolium	Shahajire	Hypoglycemic and antihyperglycemic activity	[147]
Terminalia belerica	Behada, a constituent of "Triphala"	Antibacterial, hypoglycemic activity	[148]
Terminalia chebula	Hirda	Antibacterial, hypoglycemic activity	[148]
Tinospora crispa		Anti-hyperglycemic activity, stimulates insulin release from islets	[149]
Vinca rosea	Sadabahar	Anti-hyperglycemic activity	[150]
Withania somnifera	Ashvagandha, winter cherry	Hypoglycemic activity, diuretic and hypocholesterolemic	[151]

Table 2: Formulated Herbal Drugs with antidiabetic properties

Drug	Company	Ingredients
Diabecon	Himalaya	*Gymnema sylvestre, Pterocarpus marsupium, Glycyrrhiza glabra, Casearia esculenta, Syzygium cumini, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, Tribulus terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera*, Triphala, *Commiphora wightii*, shilajeet, *Momordica charantia, Piper nigrum, Ocimum sanctum, Abutilon indicum, Curcuma longa, Rumex maritimus*
Diasulin		*Cassia auriculata, Coccinia indica, Curcuma longa, Emblica officinalis, Gymnema sylvestre, Momordica charantia, Scoparia dulcis, Syzygium cumini, Tinospora cordifolia, Trigonella foenum graecum*
Pancreatic tonic 180 cp	ayurvedic herbal supplement	*Pterocarpus marsupium, Gymnema sylvestre, Momordica charantia, Syzygium cumini, Trigonella foenum graceum, Azadirachta indica, Ficus racemosa, Aegle marmelos, Cinnamomum tamala*
Ayurveda alternative herbal formula to Diabetes:	Chakrapani Ayurveda	Gurmar (*Gymnema sylvestre*) Karela (*Momordica charantia*) Pushkarmool (*Inula racemosa*) Jamun Gutli (*Syzygium cumini*) Neem (*Azadirachta indica*) Methika (*Trigonella foenum gracecum*) Guduchi (*Tinospora cordifolia*)
Bitter gourd Powder	Garry and Sun natural Remedies	Bitter gourd (*Momordica charantia*)
Dia-care	Admark Herbals Limited	Sanjeevan Mool; Himej, Jambu beej, Kadu, Namejav, Neem chal.
Diabetes-Daily Care	Nature's Health Supply	Alpha Lipoic Acid, Cinnamon 4% Extract, Chromax, Vanadium, Fenugreek 50% extract, *Gymnema sylvestre* 25% extract Momordica 7% extract, Licorice Root 20% extract
Gurmar	Garry and Sun	Gurmar (*Gymnema sylvestre*)

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powder	natural Remedies	
Epinsulin	Swastik Formulations	Vijaysar (*Pterocarpus marsupium*)
Diabecure	Nature beaute sante	*Juglans regia, Berberis vulgaris, Erytherea centaurium,* Millefolium, Taraxacum
Diabeta	Ayurvedic cure Ayurvedic Herbal Health Products	*Gymnema sylvestre, Vinca rosea* (Periwinkle), *Curcuma longa* (Turmeric), *Azadirachta indica* (Neem), *Pterocarpus marsupium* (Kino Tree), *Momordica charan*tia (Bitter Gourd), *Syzygium cumini* (Black Plum), *Acacia arabica* (Black Babhul), *Tinospora cordifolia* , *Zingiber officinale* (Ginger)
Syndrex	Plethico Lab.	Germinated Fenugreek seed extract

Table 3: List of plants having antidiabetic activity [152].

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 4: List of plants having insulin mimetic or insulin secreatory activity [152].

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

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				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

Table 5: 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	[24]
2	*Anemarrhena asphodeloides*	Liliaceae	Mangiferin and mangiferin-7-O-β-dglucoside	[87]
3	*Bauhinia variegata*	Caesalpiniaceae	Roseoside	[41]
4	*Camellia sinensis*	Theaceae	Epigallocatechin gallate	[44]
5	*Citrullus colocynthis*	Cucurbitaceae	Beta-pyrazol-1-ylalanine	[24]
6	*Ephedra distachya*	Ephedraceae	L-ephedrine	[57]
7	*Eriobotrya japonica*	Rosaceae	Cinchonain ib	[154]
8	*Eugenia jambolana*	Myrtaceae	Pandanus odorus (Toei-hom) a 4-hydroxybenzoic acid	[56]
9	*Ficus bengalensis*	Moraceae	Leucocyandin 3-O-beta-d-galactosyl	[24],[44]

			cellobioside, leucopelargonidin-3- O-alpha-L rhamnoside	
10	*Glycyrrhizae radix*	Fabaceae	Glycyrrhetinic acid, dihydroxy gymnemic triacetate	[67]
11	*Momordica charantia*	Cucurbitaceae	Momordicin, charantin, and galactose-binding lectin	[146]
12	*Panax ginseng*	Araliaceae	Polypeptides	[24]
13	*Prunella vulgaris*	Labiatae	Jiangtangsu	[57]
14	*Psidium guajava*	Myrtaceae	Strictinin, isostrictinin and pedunculagin	[57]
15	*Pterocarpus marsupium*	Fabaceae	Epicatechin	[146],[103]
16	*Semen coicis*	Gramineae	Coixans	[57]
17	*Stevia rebaudiana*	Asteraceae	Stevioside, steviol	[85],[86]
18	*Swertia chirayita*	Gentianaceae	Swerchirin	[11],[24]
19	*Teucrium polium*	Lamiaceae	Apigenin	[95]
20	*Trigonella foenum-graecum*	Leguminosae	4-hydroxyleucine and hydroxyisoleucine	[11],[103],[104],[105]
21	*Zizyphus spina-christi*	Rhamnaceae	Christinin-A	[155]

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