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Review Article

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ANALYZING THE MECHANISMS INVOLVED IN THE ANTIDIABETIC ACTIVITY OF SOME NATIVE PLANTS

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ABSTRACT

Background: Research on diabetes treatment is advancing yearly, and it is estimated that 643 million adults worldwide will have diabetes by 2030. This is a comprehensive review of antidiabetic mechanisms in medicinal plants, aims to identify natural antidiabetic plants and provide details on their mechanisms of action, and rigorous testing techniques. **Methodology:** Information was gathered from offline and online sources to identify indigenous medicinal plants that lower blood glucose. Different databases were searched for ethnopharmacological literature using the following keywords: medicinal plants, diabetes, and India. Other sections about clinical trials, toxicological evaluations of certain plants, and preclinical trials have since been added. These sections were retrieved from Scopus using pertinent keywords. In this study, 117 species of medicinal plants from 55 families that are used to treat diabetes mellitus were listed. **Conclusion:** The variety of plants discussed in this review clearly demonstrated the importance of herbal plants in the treatment of diabetes. Result of the study shows Fabaceae, Rutaceae, and Combretaceae were the most prevalent plant families and species having antidiabetic properties among these plants. It also gives researchers information that they may use to develop future plans, like finding plants that may be effective in preventing diabetes and isolating bioactive molecules to help manage the disease. More research is necessary to completely comprehend these newly identified anti-diabetic drugs at the molecular, therapeutic, and physiological levels, nevertheless, in order to treat and manage diabetes mellitus globally.

INTRODUCTION

Diabetes is a severe medical condition that results in persistently elevated blood glucose levels because of a progressive dysregulation of carbohydrate metabolism brought on by either insulin resistance or insufficient insulin hormone. An estimated 537 million adults aged 20 to 79 are affected globally (10.5% of all adults in this age range). Worldwide, 643 million people will have diabetes by 2030, and by 2045, that number will rise to 783 million. The IDF 10th edition states that the prevalence of diabetes has increased in Southeast Asia (SEA) countries for at least 20 years and that current estimates have surpassed all earlier projections. Over 10% of adults worldwide were diagnosed with diabetes in 2021. In 2021, the prevalence of diabetes was 10.5% in the world, 8.8% in Southeast Asia, and

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9.6% in India. By 2045, these rates are expected to increase to 12.5%, 11.5%, and 10.9%, respectively [1].

Gene therapy, stem cell therapy, statin therapy, and other medications are examples of current treatments. Recent medical developments have also created new medications targeting these pathways. These include GLP-1 receptor agonists, SGLT2 inhibitors, and incretin mimetics, which have demonstrated encouraging outcomes in enhancing glycaemic control and lowering the risk of complications. However, these therapies can have serious side effects, are frequently costly, and are unavailable to patients in developing nations. Additionally, To tailor care for individuals with diabetes and modify treatments for complex presentations, the application of artificial intelligence (AI) in diabetes care is being investigated more and more. However, the quick development of AI also brings problems like possible biases, moral dilemmas, and implementation issues, which need to be addressed to ensure its use is fair. Guaranteeing ethical and inclusive advancements in AI technology can help individuals with diabetes and healthcare professionals manage their condition. Notwithstanding these developments, diabetes is still a serious health issue, and more study is required to create efficient cures and avoid its complications [2–3].

Since the time of Charaka and Sushruta, diabetes mellitus has been treated in India using traditional medicine. Many of the medications on the market today have direct or indirect plant origins, as plants have long been recognized as excellent sources of pharmaceuticals. According to ethnobotanical data, around 800 plants may have reported anti-diabetic properties. Several of these herbs have demonstrated anti-diabetic activity when evaluated using currently available experimental techniques. Many active principles derived from plants that represent a variety of chemical compounds have shown activity compatible with their potential application in the management of insulin-dependent diabetes mellitus. These include guanidine, glycopeptides, galactomannan gun, polysaccharides, peptidoglycans, alkaloids, terpenoids, and amino acids. *Galega officinalis* was the traditional method used to discover metformin, one of the commonly used hypoglycaemic medications. Therefore, plants may provide anti-diabetic medications (among others), but the scientific community needs to give this information more attention. The current study reviewed a few of the many medicinal plants that are used to treat diabetes [3]. Herbal therapy is a holistic approach to therapy that incorporates mental, emotional, and spiritual aspects. Mind, spirit, emotions, and lifestyle are all considered in any naturopathic approach. Usually, herbal remedies have no unfavorable side effects or drug effects. Finding the best course of action, of course, requires carrying out a clinical trial and understanding the effects of medicinal plants. It has been suggested that when using herbs, we should refer to them as indications and contraindications instead of side effects [4].

While herbal medicines often promote the body's natural healing process, scientific pathology has identified specific diseases whose symptoms are the focus of synthetic medications. Herbal remedies often work gently, supporting the systems and processes that have become impaired [3-4].

Methods for Managing Diabetes Mellitus

One of the most crippling lifestyle diseases is diabetes, which frequently occurs as a prelude to a wide range of other conditions, including obesity, cardiovascular disease, chronic eye illnesses, and more. Recently, there has been an increased interest in the pathophysiology of diabetes mellitus and the potential for managing it with the oral administration of hypoglycaemic agents. The goal of clinical diabetes treatment is to prevent the decline of pancreatic β-cell function and, more recently, insulin deficiency and resistance. Below is a quick summary of medications frequently prescribed in clinics to treat or manage diabetes mellitus [5-6].

The above figure depicts several antidiabetic medications' sites of action. Metformin acts on the skeletal muscle and liver. Thiazolidinediones (TZDs) indirectly increase insulin sensitivity, decrease hepatic glucose synthesis, and enhance glucose disposal by modifying adipocyte lipid metabolism. Pancreatic β-cells are the target of sulfonylureas, meglitinides (glinides), and GLP-1 receptor agonists, which increase secretion. GLP-1 agonists also slow stomach emptying and lessen pancreatic α-cells' excess glucagon secretion. The endogenous incretin hormones GLP-1 and GIP are broken down less and are present in higher amounts when DPP-4 inhibitors are used. α-glucosidase inhibitors reduce the pace at which the small intestine breaks down carbohydrates. In T2DM, SGLT-2 inhibitors decrease blood glucose and cause glucosuria. Analogues of amylin decrease postprandial glucagon secretion and slow stomach emptying. Recently, the USA approved the

use of the dopamine receptor agonist bromocriptine to treat hyperglycemia. It improves the diurnal hypothalamic control of glucose homeostasis. The bile sequestrant may also influence the secretion of incretin hormones [5-6].

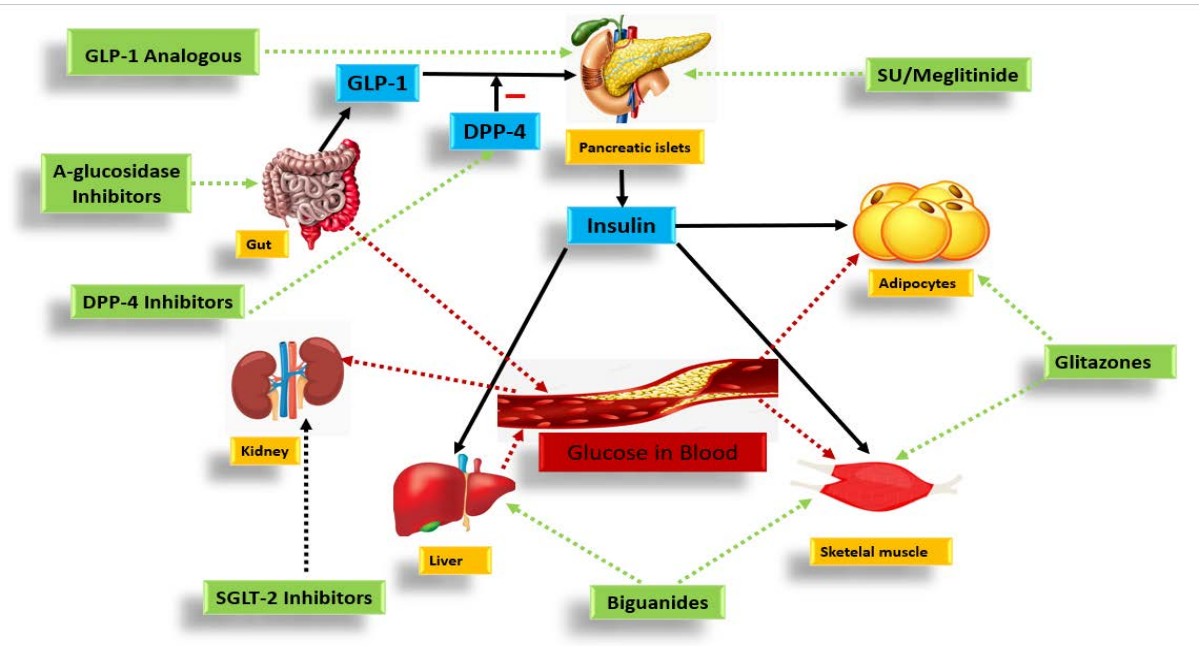

Figure 1: Site of action of antidiabetic agents

DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SU: sulfonylurea; SGLT-2: Sodium-glucose cotransport-2

Medicinal Plants for the Management of Diabetes Mellitus

This review attempts to discover natural antidiabetic plants and provide information on their origins, mechanisms of action, and rigorous testing methodologies and also some common antidiabetic mechanisms and their site of action, exerted by oral hypoglycaemics listed in figure 1. We have included indigenous herbs with hypoglycaemic effects in this study. Information was retrieved and arranged based on the experiment's type, mode of action, plant parts, and source.

***Caesalpinia digyna* (Fabaceae)**

Traditional Ayurvedic medicine uses *Caesalpinia digyna* (Family: Fabaceae) for several medical conditions, including diabetes treatment. The lipid profile improved upon bergenin (10 mg/kg) derived from *C. digyna* administration. Antioxidant enzymes like SOD and CAT had lower activity levels. Animals such as rats with diabetes had much higher levels of TBARS than control rats did. The TBARS level was lowered, and the SOD and CAT levels were significantly increased upon the administration of bergenin (10 mg/kg; p.o.), and this shows the antioxidant property of the plant. The BSLB results indicate that the extract from *C. digyna* leaves has strong cytotoxicity; therefore, additional safety testing is necessary, which should be the top priority when developing any medication [7].

***Syzygium cumini Linn.* (Myrtaceae)**

It is found from South India to the Himalayas. Because it lowers urine sugar levels and relieves extreme thirst, seed powder has been used to treat diabetes. The subacute study showed no antagonistic effects when administered at 750 mg/kg and 1500 mg/kg, while the acute toxicity results showed an LD50 of over 3000 mg/kg. Hematological, serum biochemical and histological analysis demonstrated that *Syzygium cumini* did not cause any adverse effects on the kidney, heart, liver, spleen, or paired lungs. The drug *S. cumini* may stimulate the body's insulin release, much like tolbutamide. It led to a significant drop in blood sugar (17.04%) in rats that had diabetes brought on by alloxan. Also, Using an in vitro model, the impact of an extract rich in polyphenols, both free and bound, from the leaves of *S. cumini* (Linn) Skeels was assessed regarding its effects on antioxidant, α-amylase, and α-glucosidase activities [8].

***Melia azedarach Linn*. (Meliaceae)**

The literature suggests that there have been a few reports regarding *M. azedarach's* antidiabetic effect. It has been discovered that *M. azedarach* helps blood sugar levels to drop. Seldom are fatal poisonings caused by *Melia azedarach* leaf extract documented. 400 g of bark, 30 to 40 seeds, or six to nine fruits are considered to be sufficient to cause *M. azedarach*

poisoning in humans, which can cause neurological, respiratory, cardiovascular, or gastrointestinal problems and, in extreme situations, death [9].

***Averrhoa bilimbi Linn* (Oxalidaceae)**

This tree, a member of the Oxalidaceae family, is small, reaching a maximum height of 15 meters and a maximum diameter of 30 centimeters. Plants have been shown to contain amino acids, citric acid, cyanidin-3-O-h-D-glucoside, phenolics, and potassium ions among their chemical constituents. When given intraperitoneally to Type I diabetic rats, ethanolic leaf extract of *Averrhoa bilimbi* and its semi-purified fractions have been shown by some researchers to have hypoglycaemic and hypolipidemic effects. *Averrhoa bilimbi* leaf ethanolic extract's semi-purified fractions, the aqueous and butanol fractions, significantly lower blood sugar and triglyceride levels in HFD-STZ-diabetic rats. Plants had no effect on LDL- or total cholesterol levels, but they dramatically lowered the level of kidney lipid peroxidation. However, because of its high oxalate content, which causes intratubular oxalate crystal deposition, fruit juice can cause acute renal failure due to acute tubular necrosis when used in high concentrations [10].

***Commelina communis L.* (Commelinaceae)**

The Asiatic dayflower, or *Commelina communis*, is an annual herbaceous plant from the dayflower family. The following ailments have been treated with leaf tea gargles: diuretics, acute tonsillitis, UTIs, obesity, diabetes mellitus, diarrhoea, and acute intestinal enteritis. In vitro, α-glucosidase activity was shown to be inhibited in a concentration-dependent manner by water-based extracts of leaves of the plant (CE-L) and entire plants (CE-W). CE-L inhibited α-glucosidase more successfully than CE-W did [11].

***Aerva lanata* (Amaranthaceae)**

The upright, hoary-tomentose herb *Aerva lanata* grows in tropical Africa, Java, the Philippines, Ceylon, and India. *A. lanata's* aqueous extract is relatively safe when taken orally, moderately toxic when taken intraperitoneally, and safe with antioxidant effects when taken over an extended period. Nevertheless, it exhibits the potential for harmful consequences like organ cellular damage, dyslipidemia, and decreased male reproductive potential. Therefore, caution must be used when using it over an extended period. According to folklore, the plant's hot water extract benefits people with diabetes mellitus. The obtained blood glucose data unambiguously demonstrate that in rats with alloxan-induced diabetes, the alcoholic extract from *A. lanata* produces significant and consistent hypoglycaemic effects. The blood glucose levels of the diabetic rats, but not the normal rats, significantly decreased after receiving continuous treatment with AAL for 15 days. Another possible mechanism of action of AAL could be the improvement of liver function and subsequent increase in blood glucose uptake and utilization due to terpenes and flavonoids in the extract, which are reportedly hepatoprotective agents [12].

***Picrorrhiza kurroa* (Scrophulariaceae)**

A tiny herb known as *Picrorrhiza kurroa* is found in the Himalayan region, ranging from Kashmir to Sikkim. The dried rhizomes of the plant are used in medicine. It has been demonstrated that the rhizome extract possesses antioxidant activity comparable to that of BHA and a-tocopherol. Preclinical studies showed that oral administration of *P. kurroa* extract at a dosage of 2000 mg/kg body weight did not cause any toxicological effects in Wistar rats. As a standardized formulation, its safety for use was verified. It has recently been noted that the *P. kurroa* extract can scavenge oxygen free radicals, including superoxidase and hydroxyl radicals, and that it can also prevent the lipid peroxidation in rat liver homogenate that is caused by the Fe2+ ascorbate system. Alloxan is known to primarily cause damage to the pancreas by generating oxygen-free radicals, which is why it causes diabetogenic activity. It was observed that *P. kurroa* extract lowered blood glucose levels in both alloxan-induced diabetic animals and normal, glucose-loaded animals [13].

***Chaenomeles sinensis* (Rosaceae)**

The ethyl acetate fraction of Koehne fruit has excellent antioxidant and antidiabetic properties. *Chaenomeles sinensis* is a member of the Rosaceae family. In streptozotocin-induced diabetic rats, the ethyl acetate fraction of *Chaenomeles sinensis* (Thouin) Koehne fruits exhibited anti-diabetic and anti-acetylcholinesterase properties [14].

***Coccina grandis* (Cucurbitaceae)**

The findings verify that the water-based leaf extract of *C. grandis* exhibits in vivo anti-diabetic properties using enhanced insulin biosynthesis, most likely due to β-cell regeneration in the pancreas of rats induced with streptozotocin. Furthermore, diabetic rats treated with the plant extract show

antihyperlipidemic effects. Patients with newly diagnosed type 2 diabetes who received treatment with a herbal medication of C. grandis (500 mg daily) for three months saw a significant improvement in their glycemic and specific lipid profile parameters with well-tolerated safety [15].

Biophytum sensitivum (*Oxalidaceae*)

It is a weed that grows in moist, shaded areas throughout the tropical regions of India. The plant was found to be beneficial only in mild to moderate cases of diabetes and not in severe cases; however, in alloxanized rabbits, its leaf extract was shown to have a significant anti-hyperglycaemic effect, possibly via stimulation of pancreatic β-cells [16].

***Curcuma longa* (Zingiberaceae)**

Curcumin improves the pathologic events in type 2 diabetes via a variety of molecular targets and distinct mechanisms, according to several studies. Curcumin specifically plays a role in controlling lipid metabolism. Curcumin inhibits the expression of transcription factors implicated in hepatic lipogenesis, including the carbohydrate response element-binding protein (ChREBP) and the sterol regulatory element-binding protein 1c (SREBP1c), which stimulates cholesterol synthesis. Curcumin also makes lipid mobilization enzymes such as acyl-CoA cholesterol acyltransferase (ACAT) and carnitine palmitoyltransferase-1 (CPT1) more active. Human studies revealed no harmful effects, and taking 6 g of curcumin daily for 4–7 weeks was safe. However, there could be some negative effects, like upset stomachs. Additionally, oral bioavailable curcumin formulations were safe for human use at 500 mg twice daily for 30 days [17].

***Rhazya stricta* (Apocynaceae)**

It was recently discovered that giving streptozotocin-diabetic rats leaf extract at doses of 0.5, 2, and 4 g/kg improved insulin levels and reduced plasma glucose levels. With an increase in GLP1 secretion, the majority of extract fractions demonstrated excellent results against diabetes by inhibiting the enzymes DPP-IV (up to 61%) and β-secretase (up to 83%) with IC50s of 979 μg/ml and 169 μg/ml, respectively. When comparing extract-treated mice to control, the outcomes of in vivo studies showed a significant drop in blood glucose and HbA1c levels and favorable effects on other parameters like lipid profiles, liver functions, and renal functions. However, several studies have shown that *R. stricta* extract is genotoxic and mutagenic in microorganism models and toxic in animal models [18].

Table 1: List of plants with the corresponding mechanism that exhibit antidiabetic activity

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
Fabaceae	*Acacia arabica*	Seed, Bark	Through peripheral glucose consumption and lipid peroxidation, the hypoglycaemic mechanism produces an effect similar to that of insulin.	Hot-water extract of *A.arabica* (HWAA) at a dose of 250 mg/5 mL/kg), 40 no of SD Rat, in-vivo	[19]
	Cassia auriculata	Flower	Decreases Serum TG, TC level	A dose of 50 mg/kg.b.wt and 200 mg/kg.b.wt) administered, in-vivo	[20]
	Glycine max	Seed	liver TG level and FAS activity were both decreased	A dose of 200 and 400 mg/kg of the formulation was administered to 24 no of rats, in-vivo	[21]
	Tamarindus indica	Bark	Glutamate pyruvate transaminase (GPT) and glutamate oxaloacetate transaminase (GOT) activities in the liver and kidney dramatically decline,	A dose of 80 mg/0.5 ml distilled water administered , in-vitro	[22]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
			Downregulation of TET-1 Gene Expression		
	Xanthocercis zambesiaca	Seed	The antihyperglycemic action may be partially attributed to potentiation of insulin release.	A dose of 2000 mg/kg administered to animals, in-vivo	[23]
	Retama raetam	Bark	Significantly inhibits glucose absorption by intestine, α-glucosidase inhibitor	A dose of RR extract at 500 mg/kg/day administered to animals, in-vivo	[24]
	Acacia farnesiana	bark	shielding effect on the capacity to scavenge radicals against DPPH+, ABTS+, and TBARS formation.	24 no of Wistar rats administered 25 mg/kg dose, in-vivo	[25]
	Acacia nilotica	Leaf, bark	Decreases Oxidative stress	24 no of Wistar Rats, 100–200 mg/kg dose , in-vivo	[26]
	Caesalpinia sappan	Stem	Decreases the peroxisome proliferator-activated receptor (PPARY)	30 no of SD rats, 5000 mg/kg dose , in-vivo	[27]
Rutaceae	*Aegle marmelos*	Leaf, Seed, Fruit	Alpha amylase inhibition	30 no of rats were administered 300 mg/kg/day dose, in-vivo	[28]
	Citrus reticulate	Fruit	Antioxidant activity on pancreatic β-cells	24 no of rats administered 100 mg/kg b.w./day dose, in-vivo	[29]
	Feronia elephantum	Fruit	Regulates adiponectin which promotes the reversal of insulin resistance and inhibit α-amylase and α-glucosidase.	30 no of mice administered 200 mg/kg dose, in-vivo	[30]
	Murraya koenigii	Leaf, Fruit	Antioxidant activity on pancreatic β-cells	100, 200 and 400 mg/kg dose body weight administered to 30 no of albino rats, in-vivo	[31]
	Limonia acidissima	Fruit	Antioxidant activity on pancreatic β-cells	400 mg/kg dose administered to 24 no of rats, in-vivo	[32]
Boraginaceae	*Cordia dichotoma*	Stem bark	Antioxidant activity on pancreatic β-cells	250 & 500 mg/kg dose per body weight administered to 24 no of rats, in- vivo	[33]
Alliaceae	*Allium cepa*	Bulb	Reduces blood sugar, serum lipids, oxidative stress, and lipid peroxidation while raising insulin secretion and antioxidant enzyme activity.	A dose of10 mL/kg of body weight administered to 30 no of rats, in-vivo	[34]
	Allium sativum	Root	Antioxidant activity on pancreatic β-cells	500 mg/kg garlic extract administered to 24 no of rats, in-vivo	[35]
Asphodelaceae	*Aloe barbadensis*	Leaf	Antioxidant activity on pancreatic β-cells	400 mg/kg dose administered to 24 no of rats, in-vivo	[36]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
Meliaceae	*Azadirachta indica*	Leaf, Seed, bark	Increases glucose uptake	400 mg/kg body weight administered to 24 no of rats, in-vivo	[37]
	Melia dubia	Fruit pulp	Antioxidant activity on pancreatic β-cells	300 mg/kg wt. administered 24 no of mice, in-vivo	[38]
Chenopodiaceae	*Beta vulgaris*	Whole Plant	Insulin-Sensitizing, Antioxidant Effects, and Upregulation of PPARα	500 mg/kg dose administered to 30 no of rats, in-vivo	[39]
Oxalidaceae	*Biophytum. Sensitivum*	Whole Plant	Increases the hexokinase activity and decreases glucose-6-phosphatase activity	200 mg/kg dose was administered to 24 diabetic rats, in-vivo	[40]
	Averrhoa bilimbi	Leaf	Antioxidant activity on pancreatic β-cells	A dose of 125 mg/kg body weight administered to 24 no of rats, in-vivo	[41]
Brassicaceae	*Brassica juncea*	Seed, Leaf	Depleting the serum glucose level	A dose of 450 mg/kg body weight administered to 24 no of Adult male Swiss albino rats, in-vivo	[42]
	Lepidium sativum	Leaf, seeds	*potent inhibition of renal glucose reabsorption*	Diabetic rats administered methanolic extract of the L. sativum seeds orally at a daily dose of 200 mg/kg, in-vivo	[43]
	Raphanus sativus	Whole plant	strengthen the antioxidant defense system, lower lipid peroxidation and oxidative stress, enhance hormonally induced glucose hemostasis, encourage energy metabolism and glucose uptake, and lessen intestinal glucose absorption.	A dose of 250mg/kg body weight administered to rats, in-vivo	[44]
Leguminosae	*Cajanus cajan*	Seed	Antioxidant, Increases insulin sensitivity	A dose of 200 and 400 mg/kg body weight to rats, in-vivo	[45]
Solanaceae	*Withania somnifera*	Leaf	Decreases Oxidative stress markers	A dose of 1000 mg/kg orally administered to animals, in-vivo	[46]
	Lycium barbarum	Fruit	improve insulin resistance and reduce inflammation levels	A dose of 200 mg/kg/day administered to 24 no of animals, in-vivo	[47]
	Withania coagulans	Fruit	encourages pancreatic β cells to secrete insulin	A dose of 300 mg/kg body weight administered to animals, in-vivo	[48]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
	Physalis alkekengi	Aerial parts and fruit	Antioxidant, improved insulin sensitivity by preventing the mRNA and protein expression of cytochrome P450-2E1 (CYP2E1).	Aerial parts in methanol and aqueous extracts at the dose of 200 and 400 mg/kg administered to the animals, in-vivo	[49]
	Capsicum frutescens	capsaicin	prevents the glycation cycle by acting as an anti-diabetic, protects the pancreatic β-cells	A dose of 2000 mg/kg dose was given to albino mice, in-vivo	[50]
Apocynaceae	*Catharanthus roseus*	Whole Plant	Boost insulin secretion from the Langerhans β-cells or via an extrapancreatic route.	A dose of 0.5 and 1 mL/kg body weight administered to animals, in-vivo	[51]
Lauraceae	*Cinnamomum zeylanicum*	Leaf, Bark	Reduces the activity of pancreatic α-amylase and α-glucosidase and enhances the uptake of glucose by cells via GLUT-4 membrane translocation.	A dose of 15 mg/kg body weight administered to 46 no of rats, in-vivo	[52]
Apiaceae	*Coriandrum sativum*	Leaf	Enhances glycogenesis and glycolysis	A dose of 40 mg/kg has shown antihyperglycemic activity in streptozotocin induced diabetic rats, in-vivo	[53]
	Cuminum cyminum	Seed	*Stimulation of insulin release*, β-cell protective action	An oral dose of 250 mg/Kg body weight administered to rats, in-vivo	[54]
Zingiberaceae	*Curcuma longa*	Root	Increases antioxidant enzyme activity such as paraoxonase-1, superoxide dismutase-1 (SOD1), catalase, and glutathione peroxidase	100 mg/kg body weight administered to 30 no of animals, in-vivo	[55]
	Zingiber officinale	Bulb	Increases Insulin Release and Sensitivity	A dose of 500 mg/kg/bw administered to rats, in-vivo	[56]
Myrtaceae	*Eucalyptus globules*	Leaf	Antioxidant activity on pancreatic β-cells	A dose of 150 mg/kg administered to 24 no of animals, in-vivo	[57]
	Psidium guajava	Leaf, Fruit	Reduces glycogen phosphorylase expression	400 mg/kg body weight administered to the animals, in-vivo	[58]
	Baccharis trimera	Leaf	*Activates macrophages, Antioxidant*	A dose of 2 g/kg administered in mouse, in-vivo	[59]
	Syzygium cordatum	Leaf	Antioxidant activity on pancreatic β-cells	A dose of 100–2000 mg/kg administered to the animals, in-vivo	[60]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
	Syzygium jambolanum	Fruit	Decreases the amount of sugar in the urine in diabetes mellitus	100 mg/kg dose administered to 24 no of rats, in-vivo	[61]
Moraceae	*Ficus bengalensis*	Stem bark	Reduces blood sugar level	250 mg/kg) oral dose administered to 24 alloxan diabetic rats, in-vivo	[62]
	Ficus carica	Stem bark	Induces insulin secretion, inhibits glucose absorption, increases glucose uptake and enhances insulin sensitivity	Ethanol extract at a dose of 200 mg/kg body weight administered to animals, in-vivo	[63-64]
	Egyptian Morus alba	Root bark	Antioxidant, Down regulation of lipid peroxidases	Daily dose of 250 mg/kg administered to 30 rats, in-vivo	[65]
	Artocarpus heterophyllus	Sapogenin	Antioxidant activity on pancreatic β-cells	A dose of 500 mg/kg of body weight administered to 30 no of rats	[66]
Asclepiadaceae	*Gymnema sylvestre*	Gymnemcacid, Gymnema, Saponin	Inhibits glucose absorption in the intestine	30 rabbits with a dose of 300 mg/kg body weight of the drug administered, in-vivo	[67]
Poaceae	*Hordeum vulgare*	Beta-glucan	Helps in lowering blood sugar	A dose of 100mg/kg and 200mg/kg body weight was administered to the rats, in-vivo	[67]
Acanthaceae	*Hygrophila auriculata*	Roots, seeds	*potent antioxidant*	A dose of 2 g/kg body weight administered to 36 no of mice, in-vivo	[68]
	Strobilanthes crispus	leaf	Improves in serum lipid profiles	30 no of mice at a dose of 100 or 200 mg/kg administered, in-vivo	[69]
Cucurbitaceae	*Ibervillea sonorae*	Monoglyceride Fatty acid	Uses a PI3K-independent mechanism to increase the uptake of glucose in human preadipocytes.	100, 200, and 400 mg/kg dose administered to animals, in-vivo	[70]
	Momordica charantia	Charantin, Momordicin,	Encourage the endocrine pancreas to secrete insulin and to cause the liver to absorb glucose.	400 mg/kg in dose administered to male mice, in-vivo	[71]
	Coccinia indica	B-amyrin, Lupeol	Stimulates insulin secretion	A dose of 400 mg kg^{-1} body weight of the MeOH extract administered to animals, in-vivo	[72]
	Momordica balsamina	Fruit	Decreases blood glucose concentration and improved erythropoietin secretion	A dose of 200 and 250mg/kg body weight administered to animals, in-vivo	[73]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
Euphorbiaceae	*Jatropha curcas*	Whole plant	Antioxidant activity on pancreatic β-cells	A dose of 150 and 250mg/Kg body weight administered to 24 rats, in-vivo	[74]
	Phyllanthus emblica	Fruit	Antioxidant activity on pancreatic β-cells	A dose of 10 mg/kg body weight administered to animals, in-vivo	[75]
	Emblica officinalis	Fruit	Antioxidant activity on pancreatic β-cells	A dose of 200 and 400 mg/kg body weight administered to animals, in-vivo	[76]
Anacardiaceae	*Mangifera indica*	Leaf, Stem Bark, Fruit	Inhibition of α-glucosidase and α-amylase enzymes, reduces serum glucose level	20 mg/kg administered to animals, in-vivo	[77]
	Rhus coriaria	Fruit	*prevent diabetes by inhibiting ROS*	Rats were dosed with 250, 500 or 1000 mg/kg of the extract, in-vivo	[78]
Lamiacea	*Mentha piperita*	Leaf	*decreases the plasma glucose concentration*	25- 400 µg/ml were tested in in-vitro biochemical assays.	[79]
	Ocimum sanctum	Leaf	Superoxide and hydroxyl free radical scavenging action	A dose of 400 mg/kg administered to alloxan induced diabetes mellitus in rats, in-vivo	[80]
	Leonotis leonurus	Leaf	Antioxidant activity on pancreatic β-cells	A dose of 125, 250 and 500 mg/kg induced to rats, in-vivo	[81]
	Salvia officinalis	Leaf	Antioxidant activity on pancreatic β-cells	Two different doses 10 and 30 mg/kg administered to animals, in-vivo	[82]
Musaceae	*Musa sapientum*	Flower	Antioxidant activity on pancreatic β-cells	50 mg/kg dose administered to diabetic animals, in-vivo	[83]
	Musa paradisiaca	Fruit	stimulation of insulin production and glucose utilization	A dose of 100 mg/kg administered to animals, in-vivo	[84]
Nymphaeaceae	*Nelumbo nucifera*	Flower	Antioxidant activity on pancreatic β-cells	A dose of 200 and 400 mg/kg body weight was administrated at a single dose per day to STZ induced diabetic rats, in-vivo	[85]
Ranunculaceae	*Nigella sativa*	Whole plant	Improves glucose tolerance, decreases hepatic gluconeogenesis, normalizes blood sugar and lipid imbalance, and stimulates insulin secretion	A dose of 0.5 ml, 1 ml, 1.5 ml administered to rat, in-vivo	[86]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
Turneraceae	*Turnera diffusa*	Leaf	Antioxidant activity on pancreatic β-cells	150 mg/kg of the hydroalcoholic extract of the aerial part of plant administered to animals, in-vivo	[87]
Utricaceae	*Urtica dioica*	Leaf	Stimulates insulin secretion, acts as insulin imitator	The administration of hydroalcoholic extract of Urtica dioica at doses of 50, 100, and 200 mg/kg/day to Wistar rats, in-vivo	[88]
Ericaceae	*Vaccinium myrtillus*	Leaf, Fruit	Antioxidant activity on pancreatic β-cells	A dose of 40 mg/kg. body weight administered to animals, in-vivo	[89]
Liliaceae	*Aloe vera*	Leaf	Increases insulin sensitivity	A pure extract of A. vera leaf was given orally at a doses of 100, 200, 400 mg/kg to animals, in-vivo	[90]
Amaranthaceae	*Amaranthus esculentus*	Whole plant	ameliorates oxidative stress	A dose of 400 mg/kg administered to animals, in-vivo	[91]
Annonaceae	*Annona squamosa*	Leaf, Fruit-Pulp	Antioxidant activity on pancreatic β-cells	Plant extracts at 100 mg/kg and 200 mg/kg administered to animals, in-vivo	[92]
	Malmea depressa	Root	*Improves glycemic control by blocking hepatic glucose production*	A dose of 120 mg/kg body weight administered to animals, in-vivo	[93]
Crassulaceae	*Bryophyllum pinnatum*	Leaf	Inhibits α-amylase and α-glucosidase	50 and 500 mg/kg administered to animals, in-vivo	[94]
Burseraceae	*Canarium schweinfurthi*	Stem bark	Antioxidant activity on pancreatic β-cells	38, 75 and 150 mg/kg administered to rats, in-vivo	[95]
Asteraceae	*Chamaemelum nobile*	Leaf	Antioxidant activity on pancreatic β-cells	A dose of 20mg/kg body weight administered to STZ diabetic rats, in-vivo	[95]
	Eugenia jambolana	Fruit pulp, Seed	Increases peripheral glucose utilization, increases insulin secretion, inhibits glucose absorption	A dose of 200 mg/kg/d administered to 36 no of rats, in-vivo	[96]
	Artemisia sphaerocephala	Fruit	Antioxidant activity on pancreatic β-cells	A dose of 200 mg/kg body weight administered to animal, in-vivo	[97]
	Taraxacum officinale	Fruit	Antioxidant activity on pancreatic β-cells	A single dose of 2 ml of 2000 mg/kg body weight of the test sample was administered via a	[98]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
				gavage needle to each of the rats, in-vivo	
Menispermaceae	*Coscinium fenestratum*	Stem bark	Antioxidant activity on pancreatic β-cells	A dosage of 60mg/kg body weight administered to 30 rats, in-vivo	[99]
Rubiaceae	*Hintonia standleyana*	Stem bark	Antioxidant activity on pancreatic β-cells	100 and 300 mg/kg administered to animals, in-vivo	[100]
	Morinda citrifolia	Fruit	Antioxidant activity on pancreatic β-cells	A dose rate of 100 mg/kg body weight administered to wistar rats, in-vivo	[101]
Hypoxidaceae	*Hypoxis hemerocallidea*	Fruit	Antioxidant activity on pancreatic β-cells	Both dosages 200 mg/kg and 800 mg/kg administered to animals, in-vivo	[102]
Piperaceae	*Piper betle*	Leaf	Antioxidant activity on pancreatic β-cells	50, 100 and 200 mg/kg administered to 30 no of rats, in-vivo	[103]
Scrophulariaceae	*Scoparia dulcis*	Whole plant	*Stimulates the peripheral glucose uptake*	A dose of 200 mg/kg body weight administered to animals, in-vivo	[104]
Combretaceae	*Terminalia chebula*	Seed, Fruit	*Reduces Insulin Resistance*	A dose of 500 and 1000 mg/kg administered to animals, in-vivo	[105]
	Terminalia catappa	Fruit	Activates PI3K/AKT signaling, improves glucose transport, and reverses insulin resistance.	400 and 800 mg/kg administered to animals, in-vivo	[105]
	Tremella mesenterica	Fruit	Antioxidant activity on pancreatic β-cells	A dose of 100 mg/kg administered to animals, in-vivo	[106]
Rhamnaceae	*Ziziphus spina-christi*	Leaf	Antioxidant activity on pancreatic β-cells	100 mg/kg butanol extract administered to animals, in-vivo	[107]
Caricaceae	*Carica papaya*	Fruit	Antioxidant activity on pancreatic β-cells	A dose of 1000 mg/kg body weight of papaya leaf ethanol extract is more effective in reducing blood glucose levels in diabetic Wistar mice	[108]
Malvaceae	*Thespesia populnea*	Fruit	Antioxidant activity on pancreatic β-cells	200 mg/kg administered to animals, in-vivo	[109]
	Abelmoschus esculentus	Fruit	Antioxidant activity on pancreatic β-cells	a dosage of 150 mg/kg, 200 mg/kg administered to animals, in-vivo	[110]

Family	Botanical name	Plant parts	Mechanism of action	Description	Ref
	Diospyros lotus	Fruit	Increases the expression of the insulin mRNA in MIN6 cells cultured in conditions of prolonged high glucose, which in turn stimulates insulin secretion.	500, 750, 1000, and 1500 mg/kg administered to 50 animals, in-vivo	[111]
Ganodermataceae	*Ganoderma lucidum*	Fruit	Increases plasma insulin levels and lowers plasma sugar levels	A dose of 100 mg/kg administered to animals, in-vivo	[112]
Meripilaceae	*Grifola frondosa*	Fruit	significantly increases the uptake of glucose	150 and 300 mg/kg administered to animals, in-vivo	[113]
Sterculiaceae	*Helicteres isora*	Fruit	Antioxidant activity on pancreatic β-cells	125 and 250 mg/kg administered to animals, in-vivo	[114]
Punicaceae	*Punica granatum*	Fruit	Antioxidant activity on pancreatic β-cells	In this study, Alloxan-diabetic male Wistar rats were administrated with aqueous extract (PE) in different doses of 100, 200, and 350 mg/kg in-vivo	[115]
Araliaceae	*Panax ginseng*	Fruit	Regulation of insulin secretion, glucose uptake, anti-oxidative stress	150 mg/kg extract–treated ob/ob mice, in-vivo	[116]
Cactaceae	*Opuntia dillenii*	Fruit	Pancreatic α-amylase and intestinal α-glucosidase inhibition	2 mg/ administered to rats, in-vivo	[117]
Lyophyllaceae	*Lyophyllum decastes*	Fruit	Antioxidant activity on pancreatic β-cells	Oral administration of 400 mg/kg/d for 4 weeks administered animals, in-vivo	[118]
Caprifoliaceae	*Viburnum opulus*	Fruit	protective Potential on *Insulinoma MIN6* Cells Relevant for Diabetes Mellitus and Obesity	25–75 mg/kg administered to animals, in-vivo	[119]
Papilionaceae	*Butea monosperma*	Fruit	Antioxidant activity on pancreatic β-cells	100 mg/kg/day administered to animals, in-vivo	[120]
Sterculiaceae	*Abroma augusta*	Leaves	Inhibits oxidative stress and inflammatory response	100 and 200 mg/kg, p.o.) was measured in streptozotocin-nicotinamide induced type 2 diabetic (T2D) rat.	[121]

DISCUSSION

This comprehensive review shows that the most common families and species with antidiabetic properties are Fabaceae, Rutaceae, and Combretaceae. We have included details about the nature of the research in this review and the in-vitro, pre-

clinical, and clinical studies on the plants. These plants work in various ways, including controlling insulin release and glucose absorption, preventing oxidative stress, and promoting antioxidant activity in pancreatic β-cells. Furthermore, *Diospyros lotus*, a member of the Malyaceae family, exhibits mechanisms such as enhanced insulin mRNA expression in MIN6 cells cultivated under conditions of sustained high glucose, which in turn promotes insulin production.

Plants with similar mechanisms of action and antioxidant activity on pancreatic β-cells include *Thespesia populnea*, *Abelmoschus esculentus*, *Helicteres isora*, *Punica granatum*, and *Lyophyllum decastes*. Plants like *Cassia auriculata* and *Glycine max* lower serum TG and TC levels and can be used to treat diabetes linked to obesity. The bark of *Acacia farnesiana* has a protective impact on the ability to scavenge radicals against the production of DPPH+, ABTS+, and TBARS. Additional methods of hypoglycaemic effect include suppression of alpha-amylase, reduction of the peroxisome proliferator-activated receptor (PPARY), modulation of adiponectin, which encourages the reversal of insulin resistance, and inhibition of α-amylase and α-glucosidase, among others. In preclinical research, the dose of the plant extracts can range from 100 to 2000 mg/kg body weight of the chosen animals. Studies on humans showed no negative effects from plants like *Curcuma longa*, which belongs to the Zingiberaceae family. Taking 6 g of curcumin daily for 4–7 weeks was safe.

CONCLUSION

Plants' anti-diabetic effects can be attributed to various mechanisms, including increased insulin secretion by the enlarged pancreas, decreased liver glucose synthesis, increased muscle and adipose tissue glucose uptake, and antioxidant activity on pancreatic β-cells. Anti-diabetic medications derived from plants are affordable, widely accessible, and have minimal adverse effect risks. Therefore, they are promising as novel antidiabetic drugs. As research on medicinal plants advances, scientists and doctors are creating newer classes of antidiabetic medications by studying the pharmacology of the phytochemicals isolated from these plants. However, the medicinal plant industry does have several drawbacks, including a slow rate of production for many medicinal plants, a long gestation period, inadequate cultivation technology, small-scale production, amateur harvesting, and a lack of research on high-yielding variants. There is also a knowledge gap between preclinical and clinical trials, such as variations in species, doses, etc. However, among the safety concerns regarding dietary and herbal supplements are the potential for drug interactions, direct toxicities, and contamination with active pharmaceutical agents. Research has shown that botanical products and herbs in dietary supplements pose the same risks as other pharmacologically active substances despite the general public's belief that they are safe. Identifying all clinically significant interactions can be difficult because interactions can happen between prescription medication, over-the-counter medications, dietary supplements, and even tiny molecules in food. However, to effectively treat and control diabetes mellitus on a global scale, more research is needed to fully understand these recently discovered anti-diabetic medications at the molecular, therapeutic, and physiological levels.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Lorie Dehury took the lead in writing the manuscript and contributed to conceptualization, data curation, formal analysis, investigation, and methodology. Satyapriya Mahapatra and Anshuman Gouda did formal analysis and validation and performed the text mining analysis. Ghanshyam Panigrahi contributed to the investigation, methodology, formal analysis, validation, and supervision. Laxmidhar Maharana contributed to the investigation, methodology, formal analysis, validation, project administration, supervision, writing, review, and editing. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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ABBREVIATIONS

SU	Sulfonylurea
TZDs	Thiazolidinediones
SGLT-2	Sodium-glucose cotransport-2
SOD	Superoxide dismutase
DPP-4	Dipeptidyl peptidase-4
GLP-1	Glucagon-like peptide-1