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NATURAL PLANT EXTRACTS USED IN THE MANAGEMENT OF *STREPTOZOTOCIN* (STZ) INDUCED *DIABETES MELLITUS* IN RODENTS

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ABSTRACT: Diabetes mellitus is an associated symptom of untreated high blood sugar, and it's linked to long-term organ damage, dysfunction, and failure in adults. The ongoing increased scale of *Diabetes mellitus* will severely impact the long-term health of the global population and the global economy unless appropriate prevention and management strategies are established. Plants were studied using streptozotocin-induced diabetes rodents' *in-vivo* animal models. As per the World Health Organization, more than 90% of people in underdeveloped countries use natural medicine (plants and their products) for primary health care. Approximately 800 plants have been identified to have anti-diabetic properties. The following are the most commonly utilized plant extracts to help regulate blood glucose: *Allium cepa* (Onion), *Allium sativum* (Garlic), *Aloe barbadensis* (Aloe vera), *Azadirachta indica* (Neem), *Beta vulgaris* (Beetroot), *Catharanthus roseus* (Vinca rosea), *Cinnamomum cassia* (Cinnamon), *Curcuma longa* (Curcumin), *Eugenia jambolana* (Jamun), *Hibiscus rosa-sinesis* (Gurhal), *Mangifera indica* (Mango), *Momordica charantia* (Karela), *Nigella sativa* (Kalonji), *Ocimum sanctum* (Tulsi), *Panax ginseng* (Ginseng), *Pterocarpus marsupium* (Vijyasar), *Psidium guajava* (Guava), *Tamarindus indica* (Tamarind), *Trigonella foenum-graecum* (Methi) and *Zingiber officinale* (Ginger). This study is conducted for pre-clinical testing and its pharmacological effects in the management of *Diabetes mellitus*. The primary goal of this review is to summarize herbal extracts and their glucose-lowering pathways, including insulin-mimetic activity, increased β-cell regeneration and glucose uptake.

INTRODUCTION: An ancient Indian medical system promotes a variety of medicinal herbs to treat and manage diabetes, obesity, and other metabolic diseases [1]. According to the WHO, up to 90% of underdeveloped countries use herbal medicine for primary health care [2]. Numerous plant actions have been studied and validated in animal models, suggesting that herbal therapies could be used as culturally appropriate complementary or alternative treatments and help search for new anti-diabetic medications [3].

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A wide variety of extraction methods are reported in various animal experiments employing different plants, which is vital in the phytochemical constituents of the extracts [9]. Diabetes mellitus (DM) is one of the world's most rapidly spreading diseases, brought on by a confluence of genetic and environmental variables [4, 16, 79]. It is a long-term metabolic condition of the endocrine system characterized by persistent hyperglycemia with abnormalities in macromolecule metabolism as a result of deficiencies of insulin, production or poor insulin consumption, or both, as well as disrupted β-cell activity [9, 16, 41].

Insulin insufficiency or resistance, which reduces insulin's inhibitory impact on 3-Hydroxyl Methyl Glutaryl- Co A (HMG- Co-A) reductase, an enzyme responsible for cholesterol metabolism, may contribute to a rise in low-density lipoprotein

cholesterol (LDL-C) [18]. The fact the fact that diabetes is a global pandemic and its consequences are significant causes of early death in many nations it is well known that diabetes is a global pandemic and its consequences are significant causes of early death in many nations [20]. Diabetes caused the deaths of around 1.60 million people in 2016, the deaths of about 4 million persons in 2017, with 46.1 percent of patients dying before reaching the age of 60 [17, 24]. Diabetes is expected to affect over 600 million people by 2040, rising to 629 million by 2045 [17, 46]. The main risk factors for developing type 2 diabetes mellitus (T2DM) include being physically inactive and being overweight or obese [84]. Regular exercise and physical activity can slow or stop the onset of type 2 diabetes through a number of biochemical processes [83].

Types of Diabetes, Prevalence and Management: Diabetes mellitus is a multi-organ disease that affects the pancreas, liver, muscles, kidney, and central nervous system. It also has a number of side effects, including hypertension, stroke, blindness, and kidney disease [68]. There are many kinds of Diabetes mellitus, the most common of which are Type-1 *Diabetes mellitus* (T1DM) and Type-2 *Diabetes mellitus* (T2DM), both of which are characterized by increasing β-cell destruction [9, 12].

T1DM- Type 1 *Diabetes mellitus*, also known as insulin-dependent diabetes, juvenile diabetes, or childhood diabetes [12], affects people under 30 [16]. The loss of pancreatic islet causes it β-cells and it is characterized by a lack of insulin synthesis in the body, which requires insulin therapy regularly [9, 12].

T2DM- Type 2 *Diabetes mellitus*, also known as non-insulin-dependent diabetes or adult-onset diabetes, is a condition that affects people over the age of 40 [12, 16]. It is caused by the body's inadequate use of insulin and hyperglycemia, even if its aetiology and pathogenesis remains unknown [9, 81]. Genetic factors (such as family history), obesity, poor diet, insufficient physical exercise, advancing age, ethnicity, high blood glucose during pregnancy, hypertension, and dyslipidaemia are all risk factors for Type-2 diabetes [6, 12]. Gestational diabetes is the third type of diabetes that develops during pregnancy due to glucose intolerance [12]. The syndrome may result in the mother's and the fetus's premature death and numerous consequences, including high blood pressure, pre-eclampsia, (such as macrosomia, shoulder dystocia, respiratory distress, hypoglycaemia, or childhood obesity and diabetes), and increased caesarean rates [12, 71, 72]. Although gestational diabetes is a transient condition, it increases the risk of Type-2 *Diabetes mellitus* in the long run [12].

Diabetes damages, malfunctions, and fails numerous organ systems over time (heart, blood vessels, eyes, kidneys, and nerves), resulting in impairment and death [9]. Peripheral vascular disease, nephropathy, neuropathy, retinopathy, morbidity and/or death are also associated with uncontrolled diabetes [2]. Uncontrolled diabetes can have a major influence on morbidity and mortality [80]. Hyperglycemia alone is sufficient evidence for the diagnosis of diabetes [78]. Insulin is the primary form of treatment for diabetes and managing the associated hyperglycemia, with a primary focus on reducing and maintaining blood glucose levels [68]. When insulin binds to its receptor, which is found on the plasma membrane of target cells, the mechanism of action of insulin is started. As a result, the insulin receptor substrate is phosphorylated by the enhanced receptor tyrosine kinase activity [70]. Oral hypoglycemic agents are the mainstay of clinical pharmacological management of diabetes [74]. Modern anti-diabetic medicines are costly, have significant side effects, and fail to regulate glycemia adequately. Herbal drugs have evolved as an important alternative for DM control, as they have few side effects and are widely available to the general public [26].

Streptozotocin (STZ) induced *Diabetes mellitus*: The most widely used mouse models for diabetes mellitus are those that are induced by streptozotocin (STZ) [82]. Streptozotocin (STZ) is an antibiotic produced by *Streptomyces achromogenes*, a soil bacterium [41]. A β-cytotoxin, Streptozotocin (STZ), causes 'chemical diabetes' in various animal species, including rats [5]. STZ damages the pancreas insulin-secreting β-cells selectively.

Intraperitoneal injection of STZ causes DNA fragmentation in pancreatic β-cells, which promotes poly (ADP ribose) and depletes NAD, finally leading to β-cell death [5], resulting in

increased hepatic gluconeogenesis and reduced glucose tolerance, ultimately leading to hyperglycemia [41].

Natural Plants with Anti-diabetic Potential: Natural plants have been the subject of extensive research [69]. Herbal medicines are widely used for a range of diseases, and the World Health Organization estimates that 75 percent of the world's population utilizes herbs for primary healthcare [16].

The most widely used potent anti-diabetic medicinal herbs in India are *Allium cepa* (Onion), *Allium sativum* (Garlic), *Aloe barbadensis* (Aloe vera), *Azadirachta indica* (Neem), *Beta vulgaris* (Beetroot), *Catharanthus roseus* (*Vinca rosea*), *Cinnamomum cassia* (Cinnamon), *Curcuma longa* (Curcumin), *Eugenia jambolana* (Jamun), *Hibiscus rosa-sinesis* (Gurhal), *Mangifera indica* (Mango), *Momordica charantia* (Karela), *Nigella sativa* (Kalonji), *Ocimum sanctum* (Tulsi), *Panax ginseng* (Ginseng), *Pterocarpus marsupium* (Vijyasar), *Psidium guajava* (Guava), *Tamarindus indica* (Tamarind), *Trigonella foenum-graecum* (Methi), and *Zingiber officinale* (Ginger) [2].

TABLE 1:

S. no.	Botanical name (Family)	Local Name	Part's used	Extract	Animal (n)	Extract dose	Duration of study	Chemical constituent	Metabolic and cellular effects	Ref.
1.	*Allium cepa (Amaryllidaceae)*	Onion	Fresh or dried bulbs	Chloroform	Male *wistar* rat, n=80	30 g kg−1,	6 weeks	L-cysteine sulfoxides and quercetin	↓-Serum cholesterol, TG, and LDL cholesterol	11, 15, 19
2.	*Allium sativum (Amaryllidaceae)*	Lahsun	Leaves and bulb	Ethanol, petroleum ether, ethyl ether	*Albino wistar* adult rat, n=24	100 mg/kg	30 days	Alliin, allicin, diallyl disulfide, diallyl trisulfide, diallyl sulfide, S-allyl cysteine, ajoene, and allyl mercaptan	Targets pancreatic β-cells ↓-blood insulin.	2, 20, 49
3.	*Aloe barbadensis (Liliaceae)*	Aloe vera	Leaves	Aqueous, ethanol	Male *wistar* rat, n=55	100 mg/kg	8 week	Anthraquinones, anthrones, chromones, coumarins.	↑ Insulin secretion and pancreatic β-cell function by recovering pancreatic islet mass and ↓ blood glucose, TG, LDL and TC	9, 14, 21,
4.	*Azadirachta indica (Meliaceaeis)*	Neem	Seeds, leaves, fruits, bark, and twigs	Chloroform	Male *wistar* rat, n=30	(200 mg/kg), 300 mg/kg),	30 days	Azadirone, protomeliacins, Nimbin, azadirachtin, limonoids, gedunin nonisoprenoids, genistein, and epicatechin	Inhibits advanced glycation end product, glucose-6-phosphatase, hepatic glycogen content, insulin plasma levels, ↓ glucokinase, and normalizes abnormal levels of serum insulin, lipid profile, and insulin signalling molecules as well as GLUT-4 proteins	11, 22, 61
5.	*Beta vulgaris (Chenopodiaceae)*	Beetroot	Root	Water	Male *Albino wistar* rat, n=42	10, 20 & 40 mg/kg	30 days	Sesquiterpenoids, coumarins, betalain, and carotenoids	↑ glucose tolerance; the extract also ↓ the non-enzymatic glycosylation of epidermal proteins	15, 23, 50, 51
6.	*Catharanthus roseus (Apocynaceae)*	Vinca rosea	Leaves and twigs	Ethanol	Male *wistar* rat, n=36	50 mg/kg	28 days	Vincristine and vinblastine	↑ The expression of the GLUT gene and ↓ blood glucose levels.	9, 24, 25
7.	*Cinnamomum cassia (Lauraceae)*	Cinnamon	The dried inner bark, trunk bark,	Ethanol	Male *wistar* rat, n=42	100 mg/kg and 200 mg/kg	28 days	Cinnamaldehyde, eugenol, and coumarin	↑ effects on fasting plasma glucose and HbA1c, ↓ in TG, total and LDL cholesterol, and ↑ HDL cholesterol.	9, 11, 13, 31

8.	*Curcuma longa (Zingiberaceae)*	Turmeric	Fresh & dried rhizomes	Ethanol	*Sprague dawley* rat, n=50	150 mg/kg	45 days	Curcuminoids-demethoxycurcumin, methoxycurcumin, and curcumin	↑ β-cell activities inhibit β-cell dying, and ↓ insulin resistance	8, 28, 48, 60
9.	*Eugenia jambolana (Myrtaceae)*	Jamun	Seeds, leaves, fruits, and bark	Aqueous	Male *Albino wistar* rat, n=30	10 mg/kg, 15 mg/kg, 20 mg/kg	8 weeks	Non-phenolic sesquiterpenoids and triterpenoids. Triterpenoids have oleanane, ursane, and lupine carbon skeletons, with maslinic acid ursolic acid, corosolic acid, and oleanolic acid	FIIc and glibenclamide ↑ insulin release from remnant β-cells or regenerated β-cells could be a possible mechanism by which FIIc exerts its anti-hyperglycaemic action	39, 40, 41
10.	*Hibiscus rosa (Malvaceae)*	Gurhal	Flowers, leaves	Ethanol	*Sprague dawley* rat, n=30	25 mg/kg	60 days	Ascorbic acid, anthocyanins, gentisic acid (GA)	↑ Insulin release from pancreatic β-cells or ↑ glycogen deposition in the liver.	4, 5, 15, 29, 30
11.	*Mangifera indica (Ancardiaceae)*	Mango	Seeds, leaves, bark, and fruits	Ethanol	*Albino wistar* rat, n=42	100 mg/kg, 150 mg/kg, 200 mg/kg	60 days	Xanthones, phenolic acid, mangiferin, gallic acid, catechins, quercetin, kaempferol, ellagic acids, rhamnetin, and anthocyanins	↓ body weight, blood glucose, insulin TNF	15, 32, 33, 59
12.	*Momordica charantia (Cucurbitaceae)*	Karela	Fresh or dried fruits, seed, leaves	Aqueous	Adult male *Albino* rat, n=32	10 mL/kg	21 days	Stigmasterol glucoside, β-sitosterol glucoside, karaviloside IX, momordicosides, ribosome inactivating, aglycones momordicosides A, B, Q, R, and T	↓ body weight, blood glucose, insulin TNF	9, 11, 13, 58
13.	*Nigella sativa (Ranunculaceae)*	Kalonji	Seeds	Methyl alcohol	Male *Albino* rat, n=40	20% w/w	4 weeks	Thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine-N-oxide, nigellicine, nigellidine, and alpha-hederin	↓ Fasting blood sugar levels at lower doses. Partially repaired hepatic glycogen content and preserved pancreatic islet β-cells	10, 12, 34, 35
14.	*Ocimum sanctum (Lamiaceae)*	Tulsi	Whole plant	Hexane	Male *wistar* rat, n=21	46.54 mg/kg/ day	3 weeks	Eugenol, methyleugenol, and α- and β-caryophyllene	↓ in blood glucose levels, ↑ fasting blood glucose, glucose tolerance, and correction of the aberrant lipid profile	2, 11, 15, 53
15.	*Panax ginseng (Araliaceae)*	Ginseng	Dried roots	Aqueous ethanol	*Sprague dawley* male rat, n=42	250 mg/kg	4 weeks	Ginsenosedes and protopanaxadiols	↓ Hyperglycemia via ↑ glucagon-like peptide-1. The stimulation of peroxisome proliferator-activated receptors (PPARs), which govern glucose and lipid metabolism and the transcription of proteins involved in glucose and fatty-acid absorption, is thought to be the mechanism through which ginsenosides regulate metabolic	11, 13, 36, 37, 62

									processes	
16.	*Pterocarpus marsupium (Fabaceae)*	Vijyasar	Wood, leaves, flowers, bark, gum	Aqueous	*Albino wistar* rat, n=30	100 mg/kg, 200 mg/kg	4 weeks	β Sitosterol, lupenol, aurone glycosides, and epicatechins	Hypoglycaemic activity, β-cell protecting, and regenerating qualities.	2, 38, 63
17.	*Psidium guajava (Myrtaceae)*	Guava	Fruit and leaves	Aqueous	Male *wistar* rat, n=30	200 mg/kg	45days	4-hydroxy benzoic acid, 4-hydroxy 3,5-dimethoxy benzoic acid, Gallic acid, protocatechuic acid, ferulic acid, sinapic acid, chlorogenic acid, and vanillic acid	↓ Fasting blood sugar, total cholesterol, triglyceride, glycated serum protein, creatinine, and malonaldehyde.	45, 46, 47
18.	*Tamarindus indica* (*Caesalpiniaceae*)	Tamarind	Fruit pulp, leaves, and seed	Aqueous	Male *wistar* rat, n=40	120 mg/kg, 240 mg/kg	4 weeks	Phenolic compounds, cardiac glycosides, malic acid, tartaric acid, pectin, arabinose, xylose, galactose, glucose, uronic acid, arabinose, xylose, Organic acids, such as acetic acid, citric acid, formic acid, succinic acid, amino acids, β-amyrin, campesterol, β-sitosterol, procyanidins, epicatechin and two triterpenes, lupanone, lupeol	Anti-diabetic effect, ↓ blood sugar levels	12, 52, 57
19.	*Trigonella foenum-graecum (Fabaceae)*	Methi	Dried mature seeds, leaves	Ethanol	Male *Sprague dawley* rat, n=18	0.5 g	28 days	Aglycones- apigenin and luteolin C-glycosides- xylose, arabinose, glucose, galactose, and rhamnose	↓ Of blood glucose via an insulin signal route and the stimulation of glucose absorption in peripheral tissues. Renewal of pancreatic β-cells and stimulation of insulin production	2, 8, 11, 12, 42
20.	*Zingiber officinale Roscoe (Zingiberacea)*	Ginger	Fresh and dried rhizomes	Hydro-alcoholic	CD1 mice, n=56	250 mg/kg	4 weeks	Gingerols, shogaols, paradols and zingiberene	Improve hyperglycemia by ↑ insulin sensitivity and production and glucose uptake by tissues, ↓ oxidative stress, and repairing pancreatic β-cells	11, 13, 56

***Allium cepa* (Onion):** *Allium cepa* L. is a biennial herbaceous plant, An *Amaryllidaceae* family member [19, 64]. The onion bulbs, which can be fresh or dried, are the plant portions that are used. The principal chemical ingredients are sulfur-containing chemicals, such as L-cysteine sulfoxides and flavonoids, such as quercetin and its glycosides [11]. Preclinical and clinical investigations have shown that onions provide many health advantages, including anti-diabetic, antithrombotic, and hypocholesterolemic effects [19]. *Allium cepa* (7 percent freeze-dried onion powder added to a control diet) may be an encouraging anti-hyperglycaemic dietary adjunct for diabetic therapy, as it lowers serum cholesterol, TG, and LDL-cholesterol in streptozotocin-induced diabetic rats while leaving cholesterol and HDL-cholesterol levels unchanged. Hyperglycemia produces glucose autoxidation, decreased mitochondria bioenergetics and the formation of reactive oxygen species (ROS), resulting in intracellular pathway impairment (*e.g.*, JAK/STAT, JNK, p38, ERK/MAPK) and insulin resistance [11].

***Allium sativum* (Lahsun):** The *Amaryllidaceae* family includes lahsun, an aromatic annual spice [65]. The leaves and bulb are the most commonly used portions [2]. Alliin, allicin, diallyl disulfide, diallyl

trisulfide, diallyl sulfide, S-allyl cysteine, ajoene, and allyl mercaptan are some of the active components in garlic that have been linked to its health benefits. In recent research, S-allyl cysteine, the major organosulfur bioactive component in old garlic extract, has been shown to have anti-diabetic, antioxidant, anti-inflammatory, and neuroprotective activities. The anti-diabetic potential of garlic contains; Hyperinsulinemia, hypoglycemia, hypocholesterolemia, hypotriglyceridemia and anti-glycation and anti-lipid peroxidation activities [13].

Severe hyperglycemia and albuminuria were reported in STZ-induced diabetic rats. In diabetic rats, treatment with allicin for 12 weeks improved diabetes-induced kidney morphological changes and reduced FBG, BUN, sCr, triglyceride (TG). Allicin therapy, which targets pancreatic β-cells, dramatically reduced the expression levels of collagen I, TGF-β1 and p-ERK1/2, resulting in blood insulin reduction [49].

***Aloe barbadensis* (Aloe vera):** Indian Aloe, True Aloe, Barbados Aloe, and Burn Aloe are various names for the *Aloe barbadensis* plant from *Liliaceae* family [14]. Its triangular, trifocal, meaty, and spiky leaves [66]. *Aloe vera* is high in alkaloids, anthraquinones, anthrones, chromones, coumarins, flavonoids, phenols, tannins, vitamins, enzymes, minerals, proteins, and carbohydrates other phytochemicals [21]. Stimulation of cell growth, restoration of damaged cells, restoration of damaged stomach mucous membrane, alleviation of various gastrointestinal tract (GIT) disturbances, hemorrhoid treatment, wound healing, thermal burn or sunburn, and body immune system stimulation are some of the diseases for which the plant is used. In vitro studies have revealed anti-inflammatory, modulatory, antiprotozoal, ultraviolet (UV) protecting, anti-microbial, and antifungal action. The plant's wound healing, hypoglycemia, hypolipidemic, and antioxidant effects in rabbits and rodents have been studied *in-vivo* [14]. *Aloe vera* extract improved insulin secretion and pancreatic β-cell function in streptozotocin-induced diabetic rats by recovering pancreatic islet mass and a significant drop in blood glucose, TG, LDL, and TC [9].

***Azadirachta indica* (Neem):** *Azadirachta indica*, widely known as neem, is a *Meliaceaeis family* evergreen tree [11, 22]. The dried leaves of portions that are used of the plant. Secondary metabolites abound in Isoprenoids (azadirone, protomeliacins, Nimbin, azadirachtin, limonoids and gedunin) and nonisoprenoids (proteins, sulfur compounds, carbohydrates, dihydrochalcones polyphenolics, and their glycosides). Genistein 7-O-glucoside, a high-potential antioxidant flavonoid, and (–) epicatechin are also significant components of seeds. Antifungal, antiviral, antibacterial, anti-inflammatory, antifeedant pesticides, sterilant, antiscabic, anti-allergenic, analgesic, and nematicidal pharmacological properties of the plant. The leaf extracts were hypoglycaemic, hypolipidemic, hepatoprotective, antifertility, and hypotensive properties. Seeds have antihelmintic, antileprotic, and anti-poisonous properties. Spermicidal, antipyretic, antiarthritic, diuretic, antimalarial, and hypoglycaemic properties were found in seed oil. The tree's flowers are employed as astringents and anthelmintics, and its fruit has anti hemorrhoidal properties. Worm infestation, anorexia, vomiting, and dental problems are treated with bark and twigs [22].

It inhibits advanced glycation end product (AGE), glucose-6-phosphatase, hepatic glycogen content, and insulin plasma levels, lowers glucokinase, and normalizes abnormal levels of serum insulin, lipid profile, and insulin signalling molecules as well as GLUT-4 proteins. The inhibition of alpha-amylase and alpha-glucosidase is the primary mode of action of azadirachtins (e.g., azadirachtolide, azadiradione, gedunin, and meliacinolin) [11].

***Beta vulgaris* (Beetroot):** The *Chenopodiaceae* family includes red beets (*Beta vulgaris rubra*, BVr) [50]. Various glycosides were extracted from Beta vulgaris root extract [15]. Carbohydrates, fiber, protein, essential and non-essential amino acids, phytosterols, fatty acids, vitamins and minerals, as well as bioactive compounds such as flavonoids, triterpenes/steroids, saponins, sesquiterpenoids, coumarins, betalain, carotenoids, alkaloids and volatile constituents, are abundant in red beetroot [23]. The saponins in the extract are thought to have a hypoglycemic effect because they stop gluconeogenesis and glycogenolysis [67].

Patients with metabolic syndrome can benefit from red beetroots, which can help them feel better and

lose weight. Like antioxidants and anti-inflammatory agents, Betalains have a significant role in releasing NO, blood pressure reduction, and hyperlipidemia reduction. The blood glucose reducing the effect of red beetroots was linked to flavonoids and fiber in addition to betalain the red beets and their components effectively neurodegenerative illnesses like Alzheimer's and Parkinson's [23].

In a rat OGTT, they have been demonstrated to improve glucose tolerance. In STZ diabetic rats, the extract also reduced the non-enzymatic glycosylation of epidermal proteins [15].

***Catharanthus roseus* (Vinca rosea):** *Catharanthus roseus (C. roseus),* a flowering plant in the *Apocynaceae* family, is a common periwinkle synonym. This plant produced alkaloids, the most important of which were vincristine and vinblastine, used to treat Hodgkin lymphoma, blood cancer, malaria and diabetes [24].

In RINm5F cells, stem cells influence insulin secretion and expression. RINm5F, an insulin-producing cell line generated from a pancreatic islet, significantly increased the presence of the GLUT gene and lowered blood glucose levels [9, 25].

***Cinnamomum cassia* (Cinnamon):** Cinnamon can be obtained botanically from the dried inner bark of *Cinnamomum cassia (L.);* from *Lauraceae* species. Which primarily contains cinnamaldehyde, eugenol and coumarin. Essential oil, contains up to 95 percent cinnamaldehyde 1% coumarins, along with higher levels of benzaldehyde and methoxycinnamaldehyde [11]. Spice plants are known for their antioxidant, antibacterial, diuretic, antiseptic, anthelmintic, stimulant, anti-inflammatory, analgesic and carminative effects in traditional medicine [27].

Oral consumption or supplementation with cinnamon has been linked to modest effects on fasting plasma glucose and hemoglobin A 1c, as well as a decrease in triglycerides, total and LDL cholesterol, and an increase in HDL cholesterol when used in combination with traditional hypoglycaemic medications or other lifestyle therapies [11]. *Cinnamomum cassia* extract promotes lipid accumulation in adipose tissue and the liver. In contrast, *Cinnamomum tamala* extracts improve insulin concentrations in the blood and pancreas [13]. *Cinnamomum cassia* and *Cinnamomum japonica* bark extracts reduced blood glucose levels significantly. In addition, cinnamon extracts significantly boosted extracellular glucose consumption in insulin-resistant HepG2 cells and normal HepG2 cells compared to controls, showing an improvement in insulin sensitivity [9.]

***Curcuma longa* (Turmeric):** A perennial herb with rhizomes, *curcuma longa* belongs to the *Zingiberaceae* family [28, 70]. *Curcuma longa L.* rhizome's dried powder has been used as a medicinal agent, particularly an anti-diabetic drug [8]. Several molecules that are structurally similar to curcuminoids coexist in turmeric. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the three primary curcuminoids found in commercial turmeric extracts. Curcumin's bioavailability is a significant concern when using it as a nutritional supplement. Curcumin contains antioxidant, cardioprotective, anti-inflammatory, anti-microbial, nephroprotective, anti-neoplastic, hepatoprotective, immunomodulatory, hypoglycaemic, and anti-rheumatic properties [28].

Curcumin extract delays the development of diabetes in animal models, increases β-cell activities, inhibits β-cell dying, and lowers insulin resistance [28]. Turmeric supplementation in the diet could be a promising approach as a safe and effective alternative therapy for T2DM nephropathy because TGF plays a crucial role in the pathogenesis of diabetic nephropathy, and elevated serum TNF and urinary levels of IL-8 are associated with a decline in renal function in Type-1 diabetic nephropathy [8].

***Eugenia jambolana* (Jamun):** The *Myrtaceae* family contains the Eugenia jambolana Lam (EJ) tree. Jamun, Black plum, or Indian Blackberry are some of the common names [39]. Fruits are oval to elliptical, 1.5–3.5 cm long, dark purple or practically black in color, delicious, fleshy and edible [40]. Seeds, leaves, fruits, and bark are the most used plant parts. Eugenia jambolana is an evergreen tropical tree with smooth, glossy turpentine-scented leaves that grows to a height of 8 to 15 meters [2]. We found anthocyanins in the fruit pulp of the Jamun. We proved their anti-proliferative properties against breast cancer cells,

as well as α-glucosidase inhibitory hydrolyzable tannins and protein tyrosine phosphatase 1B inhibitory phloroglucinols in the seed extract. Jamun also has non-phenolic components, such as sesquiterpenoids and triterpenoids, which we extracted from its seeds and fruit pulp. Jamun fruit triterpenoids have oleanane, ursane, and lupine carbon skeletons, with maslinic acid (1), ursolic acid (2), corosolic acid (3), and oleanolic acid (4) being the most prominent. In non- diabetic mice, Triterpenoid-rich Jamun fruit extract (TJFE) increased glucose tolerance and reduced hepatic gluconeogenesis [41]. *E. jambolana* has anti-inflammatory and neuropsychic pharmacological properties, as well as antibacterial and anti-HIV activity and anti-diarrheal properties [39].

The active chemical FIIc and glibenclamide dramatically improved serum insulin and C-peptide levels in diabetic mice. Treatment with the FIIc resulted in a significant increase in insulin levels in the blood and a significant decrease (P 0.001) in FBG and GHb levels in diabetic rats. The enhanced release of insulin from remnant β-cells or regenerated β-cells could be a possible mechanism by which FIIc exerts its anti-hyperglycaemic action [40].

***Hibiscus rosa* (Gurhal):** Rosemallows are also called *Hibiscus rosa sinesis*, *Malvaceae* family. Yellow, white, pink, or red is the most common blossom colors in other Hibiscus species [29]. Phenolic acids, tannins, ascorbic acid, and anthocyanins make up the chemical makeup of *Hibiscus rosa Sinensis* [4]. Gentisic acid (GA) is a phenolic acid linked to anti-inflammatory, antigenotoxic, hepatoprotective, neuroprotective, antibacterial, and mainly antioxidant properties [30].

The activity was equal to that of tolbutamide. It was thought to be attributable to increased insulin release from pancreatic β-cells or increased glycogen deposition in the liver [15].

***Mangifera indica* (Mango) -** An evergreen tree from the *Anacardiaceae* family known for its sweetness, *Mangifera indica* L [32, 73]. The tree may be found all over India, and its seeds and fruits have traditionally been used to treat various diseases [15]. Polyphenols (flavonoids, xanthones, and phenolic acids) are the most prevalent chemical compound types. The primary polyphenolic components detected in *M. indica* are mangiferin, gallic acid, catechins, quercetin, kaempferol, protocatechuic acid, ellagic acids, propyl, propyl methyl gallate, rhamnetin, and anthocyanins. Mangiferin is a polyphenolic substance [33]. The bark of the mango plant has traditionally been treated for diarrhea, cancer, diabetes, prostatitis, toothaches, coughs, and infections of the urinary tract and skin. Emetic, diuretic, antibacterial, astringent, and hepatoprotective agents are employed in the stem bark. The stem bark was shown to have anti-inflammatory and anti-amoebic qualities, and studies have demonstrated that it shielded rats from DNA oxidation and inflammation [32]. In STZ-induced diabetic rats, oral administration of aqueous extract of the leaves did not affect blood glucose levels. However, when administered 60 minutes before or simultaneously with glucose, the extract showed anti-diabetic efficacy, attributable to a reduction in glucose absorption in the intestine [15].

***Momordica charantia* (Karela):** The fresh or dried fruits of bitter melons, an annual climber plant belonging to the *Cucurbitaceae* family are the plant parts employed. Sterols, triterpenes, and bioactive proteins are the primary chemical ingredients [11, 13]. The cucurbitane-type triterpenoids charantin (a steroidal glycoside that is an equal mixture of stigmasterol glucoside and β-sitosterol glucoside), karaviloside IX, momordicoside S, and its aglycones momordicosides A, B, Q, R and T, as well as polypeptide-p, vicine, and the ribosome-inactivating the hypoglycaemic effects of bitter melon extracts have been linked to several mechanisms [13].

Bitter melon preparations have been reported to restrict glucose absorption in the intestine, block major glucogenic enzymes, and reduce hepatic gluconeogenesis [13]. Using ethanol extracts significantly reduced body weight, blood glucose, insulin TNF-α, and interleukin 6 (IL-6) in streptozotocin-induced diabetic rats [9].

***Nigella sativa* (Kalonji):** NS is a member of the *Ranunculaceae* biological family and is a flowering annual herbaceous plant with linear, finely split leaves known as "black seed" or "kalonji" [12, 34, 75].

Thymoquinone, thymo-hydroquinone, dithymo-quinone, thymol, carvacrol, nigellimine-N-oxide, nigellicine, nigellidine, and alpha-hederin, as well as flavonoids, all have been identified from *N. Sativa* seeds and oil [10]. Traditional medicine has used various forms of NS, such as extract, oil, and powder, to treat various diseases, including fever, cough, diarrhea, bronchitis, and gastrointestinal problems [34, 35]. The components of black seeds have a wide range of metabolic, immunological, and pharmacological effects, including bronchodilatory and hypoglycaemic effects. In STZ-induced diabetic rats, the anti-diabetic efficacy of a hydro-alcoholic extract of *N. Sativa* was investigated. Compared to the control, *N. Sativa* extracts considerably boosted body weight gain and significantly reduced fasting blood sugar levels at lower doses. Its extract partially repaired hepatic glycogen content and preserved pancreatic islet cells [12].

***Ocimum sanctum* (Tulsi):** The *Lamiaceae* family includes *Ocimum sanctum L.* (holy basil or tulsi). Every portion of the plant is utilized to treat a variety of illnesses [2, 11]. Tulsi is a herb or shrub that grows 1 meter tall. The primary chemical components are tannins and essential oil (primarily constituted of eugenol, methyl eugenol, and α-and β-caryophyllene) [11]. *OS* is useful in treating various illnesses, including bronchitis, diarrhea and dysentery, leaf extracts have anti-hyperglycaemic properties and protect organs from multiple stressors, including hyperlipidemia, inflammation, cancer, and heavy metal toxicity [53].

OS extract showed a significant improvement in fasting blood glucose and glucose tolerance and a correction of the aberrant lipid profile. Reduced glutathione levels and improved antioxidant enzyme activity (*i.e.*, glutathione peroxidase, glutathione S-transferase, superoxide dismutase, and catalase) have been proposed as mechanisms of action for the decreased lipid peroxidation generated by tulsi [11]. On average, glucose-fed hyperglycaemic and STZ (50 mg/kg IP) induced diabetic rats, Ocimum sanctum has been proven to generate a considerable drop in blood glucose levels [15].

***Panax ginseng* (Ginseng):** Panax ginseng is a perennial herb native to Korea, China and Japan, a member of the Araliaceae family [36]. Among the natural substances used in human healthcare, the Panax genus is crucial [76]. The dried roots contain saponins, polysaccharides, polyacetylenes, phenols, and alkaloids. Ginseng saponins, also known as ginsenosides, are a type of natural triterpene saponin believed to be responsible for ginseng's anti-diabetic properties [36]. Protopanaxadiol (*e.g.*, ginsenoside Rb1) and protopanaxatriol are two types of ginsenosides (*e.g.*, ginsenoside Rg1). There are essential oil components, phenol compounds, polysaccharides, alkaloids, nitrogen compounds, and ginsenosides. Clinical outcomes improved significantly in patients with cancer, amyotrophic lateral sclerosis, skin wrinkles and allergic rhinitis chronic sickness, weariness, and impaired functions or organs [37].

Total ginseng saponins in high fat and low STZ induced diabetic rats effectively decreased hyperglycemia *via* elevating glucagon-like peptide-1 [11]. The stimulation of peroxisome proliferator-activated receptors (PPARs), which govern glucose and lipid metabolism and the transcription of proteins involved in glucose and fatty-acid absorption, is thought to be the mechanism through which ginsenosides regulate metabolic processes [13].

***Pterocarpus marsupium* (Vijyasar):** The *Fabaceae* family includes *Pterocarpus marsupium* (Indian kino tree, bijasar). The most widely used plant parts are heartwood, leaves, flowers, bark, and gum. β - sitosterol, lupenol, aurone glycosides, epicatechins, and iso-flavonoids are terpenoids and phenolic substances found in *Pterocarpus marsupium* [2]. It could be a source of anti-inflammatories, skin problems, diabetes, diarrhea, asthma, bronchitis medications, Antiobesity, anthelmintic, antitumorigenic, ant-hyperglycaemic, antihyperlipidemic, hepatoprotective, antiulcer, and antioxidant effects [2, 38]. *Pterocarpus marsupium* has been claimed to have hypoglycaemic, *β* cell-protecting and regenerating qualities, which have been related to the flavonoid content of the plant. In many experimental models of diabetes, complete restoration of normal insulin secretion and β-cell regeneration has been documented [2].

***Psidium guajava* (Guava):** Guava (*Psidium guajava L.*) is a tropical fruit plant that can find in a variety of tropical and subtropical climates from

Myrtaceae [45, 46]. The anti-hyperglycaemic effect of an aqueous soluble extract of guava leaves against Type-2 *Diabetes mellitus* has been proved [45]. Polyphenols, carotenoids, and vitamin A are all found in yellow-green guava (a retinoid source). α -amylase and α-glucosidase are bound by polyphenols and antioxidants [46]. The availability of several phytochemicals, particularly flavonoids, allows for the above actions. 4-hydroxybenzoic acid, 4-hydroxy3,5-dimethoxybenzoic acid, Gallic acid, protocatechuic acid, ferulic acid, sinapic acid, chlorogenic acid, vanillic acid, and other phytochemicals are present in guava leaf extract [47]. Diarrhea, dysentery, and Diabetes mellitus are treated with fresh fruit and leaf tea [46]. Guava leaf extract has antibacterial, antifungal, analgesic, hepatoprotective, antioxidant and anti-microbial properties [46, 47].

Polysaccharides from guava leaves (GLP) were isolated and tested for antioxidant activity in vitro and anti-diabetic benefits in diabetic mice caused by streptozotocin and a high-fat diet. According to the findings, GLP had good DPPH, OH, and ABTS free-radical scavenging capacities and significantly reduced fasting blood sugar, total cholesterol, total triglycerides, glycated serum protein, creatinine, and malonaldehyde [45].

***Tamarindus indica* (Tamarind):** *T. indica* is a tree that belongs to the family *Caesalpiniaceae*. Although the seed coat is brownish-black in appearance, the kernel is white. It's a dicotyledonous (two-headed) plant. It is a traditional medication for *Diabetes mellitus* control [12]. Phytochemical ingredients such phenolic compounds, cardiac glycosides, malic acid, tartaric acid, mucilage and pectin, arabinose, xylose, galactose, glucose, and uronic acid. Organic acids, such as tartaric acid, acetic acid, citric acid, formic acid, malic acid, succinic acid, amino acids, two triterpenes, lupanone, and lupeol are found in the pulp. Limonene and benzyl benzoate are located in the leaf oil. The root bark included n-hexacosane, eicosanoic acid, β -sitosterol, octacosanol ferulate, 21-oxobehenic acid and (+)-pinitol, according to phytochemical analysis. Furan and carboxylic acid were the volatile components of the fruit pulp. Palmitic acid, oleic acid, linoleic acid, and eicosanoic acid were seeds' most abundant fatty acids. β-amyrin, campesterol, β-sitosterol was found in the seed oil. Proanthocyanidins in various forms, such as apigenin, catechin, procyanidin B2, epicatechin, procyanidin dimer, trimer taxifolin, eriodictyol, and naringenin, were found in Tamarind pericarp polyphenolics. Only procyanidins and small epicatechin were found in Tamarind seeds [52].

Compared to the diabetic group, liver glucose- 6-phosphatase was significantly reduced in the aqueous extract-supplemented group. *T. indica* has been reported to have a significant anti-diabetic effect, lowering blood sugar levels in diabetic male rats induced by STZ [12].

***Trigonella foenum-graecum* (Methi):** The *Fabaceae* family includes *Trigonella foenum-graecum* (fenugreek, methi) [2]. The mature dried seeds contain mucilage and a range of other secondary metabolites, such as trigonelline [11]. Fenugreek includes 1–2% flavonoids, with the primary aglycones consisting of apigenin and luteolin, and the C-glycosides consisting of xylose, arabinose, glucose, galactose, or rhamnose [42]. Fenugreek has many medicinal benefits, including easing delivery, increasing milk flow, alleviating menstrual symptoms, treating body weakness, anti-diabetic, antithrombotic, hypocholesterolemic actions, and antioxidant effects [11, 43].

Fenugreek has been shown to have hypoglycaemic effects in humans by enhancing glucose-dependent insulin secretion from pancreatic cells, increasing the number of insulin receptors, decreasing α-amylase and sucrase activity [8], via an insulin signal route as well as stimulating of glucose absorption in peripheral tissues [11]. Renewal of pancreatic β-cells and stimulation of insulin production are among the hypoglycaemic mechanisms reported, as are anti-oxidative effects, promotion of adipocyte differentiation, and improvement of insulin-dependent glucose uptake [12].

***Zingiber officinale Roscoe* (Ginger):** The rhizome of ginger belongs to the *Zingiberaceae* family [13]. *Zingiber officinale*, widely known as ginger, is a harmless spice with few negative impacts [44]. Among its constituents, gingerols, shogaols, parasols, and zingiberene have anti-oxidative, glucose, lipid-lowering properties, immunomodulatory, anti-inflammatory and

antiapoptotic properties. It's been used as a herbal drug to treat cancer, rheumatism, toothaches, digestive issues and diabetes in the past [13]. *Zingiber officinale* Roscoe has been shown to improve hyperglycemia by enhancing insulin sensitivity and production, glucose uptake by tissues, lowering oxidative stress, and repairing pancreatic β-cells [11]. In individuals with Type-2 *Diabetes mellitus*, a recent study found increased insulin sensitivity, lower total cholesterol, triglycerides, and lower C-reactive protein and prostaglandin E2 [13]. In addition, ginger extract therapy increased insulin sensitivity in rats with metabolic syndrome [77].

CONCLUSION: Ayurveda has a wide range of herbs with anti-diabetic properties. Only a few have been scientifically verified, and many more are still being researched and proven. Isolation, purification, and characterization of bioactive chemicals found in these plants may focus on future research. WHO evaluates and lists medicinal plants with anti-diabetes properties that have been formally acknowledged in one or more world regions and are verified by clinical evidence in WHO monographs on medicinal plants.

The current trend in the therapy of DM characterized by hyperglycemia involves the use of natural plants. However, oral hypoglycaemic medications (OHAs) are known to cause undesired side effects; hence, the necessity to research-rich and useful plants with anti-diabetic activity. Several plants have been discovered with anti-diabetic, anti-hyperglycaemic and hypoglycaemic properties and inhibition of α-amylase and α-glucosidase. Plant extracts are believed to have anti-diabetic properties due to a combination of phytochemicals, alkaloids, phenolic acids, flavonoids, glycosides, saponins, polysaccharides, stilbenes, and tannins. The focus of this review was on anti-diabetic plants and their ability to increase insulin sensitivity and the cellular and metabolic impacts of these plants. Streptozotocin-induced diabetic rats and high-fat diet rodents' *in-vivo* animal models were used for plant study.

The prospective plants were shown to target insulin action worldwide through numerous mechanisms, including inhibiting hepatic glucose synthesis or potentiating peripheral glucose use in muscles and adipocytes by altering the activity and expression of critical enzymes and glucose transporters. Furthermore, many medicinal plants increased insulin sensitivity by stimulating the recognized insulin-signalling pathways of InsR-, IRS-1, PI3K, tyrosine-induced phosphorylation of insulin receptor substrate, AMPK/ACC, and MAPKs.

According to the research findings, various natural plant extracts may have positive effects in the two forms of *Diabetes mellitus*, which raises the prospect of a new generation of anti-diabetic medications. Although several medicinal plants have been shown to promote insulin sensitivity, there is inadequate evidence to draw definite conclusions on their efficacy in treating diabetic patients through improved insulin sensitivity. We discussed the use of herbal medicinal plants to treat *Diabetes mellitus.* Some attractive novel sources should be examined, and their active principles studied soon. The possible effect on specific or new targets identified in T2DM is another topic to explore for future research. Because the outcomes of several of these substances are preliminary or not well documented, more study and development are required before they can be used as new anti-diabetic medications.

The researchers discovered several phytochemicals found in medicinal herbs that can impact diabetogenic genes, clearing the way for nutritional therapy to modify diabetes-related genes in the future. Furthermore, the medicinal plants described could be helpful in the development of new functional meals with anti-diabetic qualities or avoid the hyperglycaemic effects of specific diets, such as those high in simple carbs, in the future. To summarise, natural products, particularly those derived from plants, are valuable sources of molecules with various chemical structures that, acting through multiple pathways, could provide a treatment alternative for T2DM.

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