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THERAPEUTIC POTENTIAL OF VARIOUS PHYTOCHEMICALS IN THE MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes Mellitus (DM) is among the most common disorder that is faced by the majority of the population. It is a set of conditions characterized by a rise in the level of glucose in the blood because of the inability of the pancreas to secrete insulin or insulin resistance by the body. There are two common types of diabetes, type-1 diabetes mellitus, and type-2 diabetes mellitus. Other types include gestational diabetes mellitus, maturity-onset diabetes of the young (MODY) as well as latent autoimmune diabetes in adults (LADA). Furthermore, a marked increase in blood glucose levels may cause acute complications like diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS) and hypoglycemia as well as serious complications like microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (cerebrovascular, cardiovascular and peripheral vascular/arterial disease). Numerous medications have been employed for the management of diabetes mellitus and its complications, which range from allopathic like meglitinides, dipeptidyl peptidase-4 inhibitors (DPP-4), thiazolidinediones, sodium-glucose cotransporter-2 inhibitors (SGLT-2). Apart from that, phytochemicals have emerged as a potential therapy worldwide due to their efficacy, fewer side effects, and cost-effective benefits. Phytochemicals are classes of compounds found naturally in plants that, importantly, benefit humans, such as alkaloids, glycosides, polyphenols, terpenoids, flavonoids, and steroids. In the last few years, many phytochemicals (quercetin, kaempferol,

mangiferin, curcuminoids) have been reported to produce therapeutic effects in diabetes mellitus.

Keywords: Diabetes mellitus, phytochemicals, complications, glucose

INTRODUCTION

Diabetes mellitus (DM) is a set of metabolic disorders that are characterized by increased levels of glucose in the blood (hyperglycemia) due to defects in insulin

secretion, the action of insulin, or both. The Blood Sugar level can be differentiated by diagnostic ranges as per the World Health Organization (WHO) in 2006 [1].

Table 1: Diagnostic criteria for Diabetes Mellitus

	Fasting (mg/dl)	2 Hours Post Meal (mg/dl)
Normal	70-99	<140
Prediabetes	100-125	140-199
Diabetes Mellitus	>126	>200

Types of Diabetes Mellitus

Diabetes mellitus is mainly classified into two types, these include:

- ◆ **Type-1 Diabetes mellitus:** it is also known as ‘juvenile diabetes’ [1] and ‘Insulin-dependent diabetes mellitus (IDDM)’ [2]. It occurs due to autoimmune destruction of the β -cells in the pancreas, due to which the pancreas is unable to secrete insulin. It usually occurs during childhood but may occur in adults less than 35 years [3], particularly due to family history. The onset of the symptoms may be sudden, which includes polyuria, polydipsia, polyphagia, blurry vision, slow wound healing, mood changes, irritability, fatigue, and unexplained weight loss. Furthermore, type-1

diabetes mellitus patients usually present with ketoacidosis if not treated at the earliest.

The treatment includes insulin therapy like Rapid-acting insulin (Insulin Aspart, glulisine, and lispro), short-acting Insulin (regular insulin), Intermediate-acting Insulin (NPH insulin), long-acting insulin (Insulin detemir and glargine), and Ultralong-acting Insulin (Insulin degludec) [4].

- ◆ **Type-2 Diabetes mellitus:** It is also known as ‘non-insulin-dependent diabetes mellitus (NIDDM)’ [2]. It occurs due to insulin resistance, that is when the body does not respond to Insulin or due to inadequate secretion of insulin from the pancreatic β -cells. It usually occurs in older age (greater

than 40 years) due to unhealthy eating, lack of exercise, obesity, and family history. The onset of symptoms is gradual, and it includes polydipsia, polyphagia, polyuria, blurred vision, hands and feet numbness, slow wound healing, and fungal infections like balanitis in men. Furthermore, ketoacidosis in patients with type-2 diabetes mellitus is rare, but not uncommon. It can be managed by modifications in diet and exercise along with oral hypoglycemic agents like sulphonylurea (glipizide, glimepiride), biguanide (metformin),

meglitinide (Repaglinide, Nateglinide), α -glucosidase inhibitors (Acarbose, Miglitol), thiazolidinediones (pioglitazone and Rosiglitazone), Glucagonlike peptide-1 agonists (semaglutide, Exenatide), Dipeptidyl peptidase IV (DPP-4) inhibitors (sitagliptin, linagliptin) and selective sodium-glucose transporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin) [3]. Patients with type-2 diabetes mellitus may require insulin therapy when their diet and antidiabetic drugs do not reach the targeted blood glucose level.

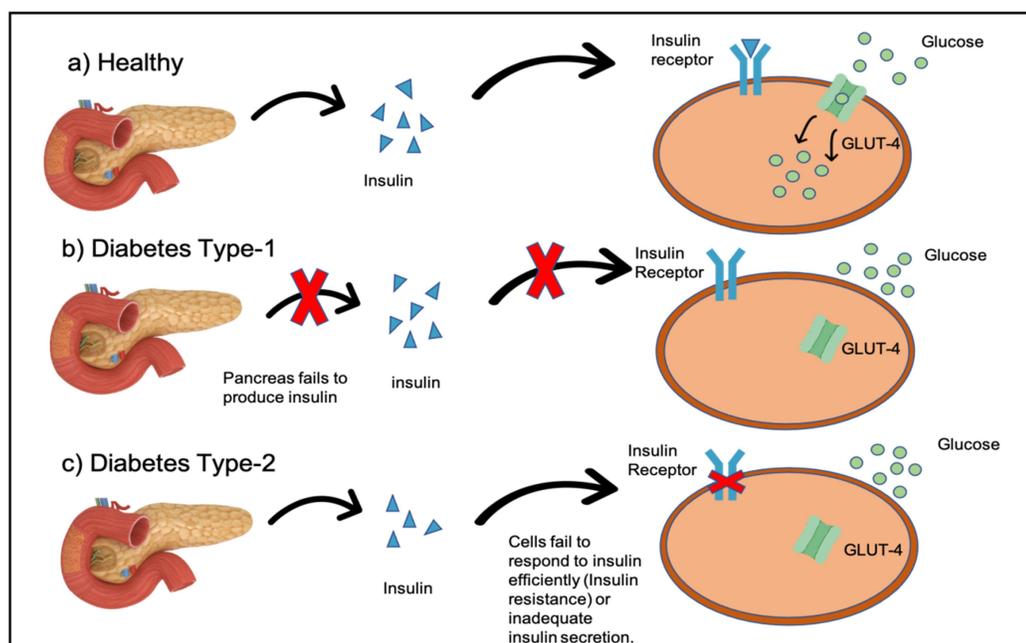


Fig. 1: a) In healthy individuals, Pancreas secretes insulin and is taken up by the insulin receptor and in turn stimulates the uptake of glucose by GLUT-4 present on the membrane into the cell, b) In diabetes type-1, Pancreas is unable to secrete insulin and the GLUT-4 is recycled back to the cytoplasm, hence there is an increase in glucose in the blood, c) In diabetes type-2, Pancreas secretes an inadequate amount of insulin or the cell does not respond to insulin and GLUT-4 is recycled back to the cytoplasm, hence an increase in glucose in the blood is observed

Other forms of diabetes Mellitus

◆ Gestational Diabetes Mellitus

(GDM): This develops during pregnancy, especially in the 2nd and 3rd trimester due to carbohydrate intolerance or insulin resistance, and resolves after the birth of the baby. The risks associated with this type are prenatal morbidity and mortality [5]. Women with GDM give birth to heavier babies with a weight of greater than 4.5kg (macrosomia) [6]. Also, women with GDM may develop diabetes mellitus 5 to 10 years after pregnancy [7].

◆ Maturity-Onset Diabetes of the young (MODY):

It is a form of diabetes mellitus from a single gene [3]. It occurs before the age of 25 years and is because of genetic defects in the functioning of the β -cell of the pancreas. Six forms of MODY are developed which is due to gene mutations like hepatocyte nuclear

factor-4 α (HNF-4 α), glucokinase gene (MODY 2), HNF-1 α (MODY 3), Insulin promoter factor-1 (IPF-1), HNF-1 β , and NEUROD1 [8]. It is treated with insulin therapy and oral hypoglycemic agents.

◆ Latent Autoimmune diabetes in adults (LADA):

It is a form of autoimmune type-1 diabetes mellitus in which the body attacks the β -cells leading to insulin-dependency and is often misdiagnosed as diabetes type-2[9], patients are diagnosed with LADA after the age of 35 years and it is managed with sulfonylureas and insulin therapy.

Risk Factors of Diabetes mellitus

Many factors increase the risk of diabetes mellitus onset and play a major part in insulin resistance or non-functionality of insulin causing an escalation in the number of patients with diabetes mellitus.

Table 2: Most common types of diabetes mellitus and their risk factors [10]

Type of diabetes mellitus	Risk Factors
Type-1	Family history
	Infections that cause injury to the pancreas like pancreatitis.
	Viruses like coronavirus disease-2019 (covid-19), influenza, and Human immunodeficiency virus (HIV).
	Physical stress like surgery.
Type-2	Drugs like antipsychotics, β -blockers, diuretics, and corticosteroids.
	Obesity $\geq 120\%$, higher than desired body weight or body mass index (BMI) $>27\text{kg/m}^2$.
	Age (>40 years)
	Sedentary lifestyle and unhealthy eating
	Family History
	Hypertension ($>140/90\text{mmHg}$) and dyslipidemia (HDL level $<35\text{mg/dl}$ or triglyceride $>250\text{mg/dl}$)
	Race (Native American, Hispanic, Asian American, and African American).
History of gestational diabetes.	

Gestational	Polycystic ovarian syndrome (PCOS)
	History of cardiovascular disease.
	Smokers
	Family history
	Overweight before pregnancy.
	Age >25 years
Glucose intolerance or history of gestational diabetes mellitus.	

Epidemiology of Diabetes mellitus

Diabetes mellitus is a major burden worldwide due to changing lifestyles and the prevalence of obesity. About 422 million people in the world have diabetes whereby a majority of them live in low and middle-income countries and each year, approximately 1.6 million people die due to diabetes [11].

From 1980 to 2014, the rise in diabetic cases was from 108 million to 422 million. From 2000 to 2016, there was a 5% increase in premature mortality from diabetes and it is estimated that by 2030 diabetic patients will rise to 552 million [12]. The latest prevalence shows a rate of 11.1% in diabetes and it is estimated to rise to 13% by 2045 in North America and Caribbean regions while it is observed that Africa has the lowest prevalence of 4.7% and by 2045 it is expected to rise to 5.2% [7]. China has the highest number of diabetic patients (116 million), the second-highest is observed to be India (77 million)

Phytochemicals in the Management of Diabetes mellitus

Phytochemicals are classes of compounds found naturally in plants that, importantly, benefit humans, such as

followed by the United States of America (31 million) [7].

Complications of Diabetes mellitus

Diabetes mellitus is a major cause of co-morbidities and death, this is due to uncontrollable blood sugar levels. Different organs in the body are affected due to increased blood sugar levels. The complications may be episodic or progressive and may be reversible or irreversible. Poor control of blood glucose in patients with diabetes mellitus may cause major complications which may be life-threatening. The acute complications include hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS), and the chronic complications can be categorized into microvascular complications like retinopathy, nephropathy, and neuropathy as well as macrovascular complications like cardiovascular diseases, peripheral vascular/arterial disease, and stroke [13].

alkaloids, glycosides, polyphenols and their derivatives, terpenoids, flavonoids, and steroids. These phytochemicals are isolated from different parts of the plants, like the stem, roots, bark, flower, leaf, and,

fruit. Phytochemicals have been observed as an important pathway in diabetes therapy and as per Ethnobotanical information, there are about 800 plants that have been reported to possess antidiabetic activity [14]. The increasing demand for pharmacotherapy with the use of herbal drugs worldwide is a result of the fewer side effects as well as cost-effective treatment as compared to the allopathic ones.

In diabetes, Phytochemicals decrease oxidative stress by the reduction of the formation of advanced glycation end products (AGEs) [15]. Some of the phytochemicals that have antidiabetic value and the plants that they have been isolated from include: curcumin and ferulic acid (*Curcuma longa*), mangiferin (*Mangifera indica*), momorcharins, momordin, charantin, and vicine (*Momordica charantia*), berberine (*Tinospora cardifolia* and *Berberis aristata*) and capsaicin (*Capsicum annum*) [16, 17].

Phytoconstituents in the Management of Diabetes mellitus

◆ Quercetin

Quercetin is a flavonoid found in many fruits and vegetables, like apples, berries, broccoli, onions, citrus fruits, and parsley. It protects the pancreatic β -cells from destruction and oxidative stress hence

showing antioxidant properties. Also, it inhibits the activity of α -glucosidase, hence inhibiting the digestion of carbohydrates in the small intestine and therefore decreasing the blood sugar level [18]. Also, Maltase activity reduction was observed, which decreased the blood sugar by decreasing carbohydrate digestion. Furthermore, quercetin has shown to have protective effects against liver injury in a rat model induced by STZ by lessening morphological damage to hepatocytes in the liver and improving lipid metabolism [19].

◆ Capsaicin

Capsaicin is a pungent phytochemical found in chili pepper fruit (*Capsicum frutescens*) belonging to the family Solanaceae. It is used as a spice and as a flavoring agent and is also used topically as patches and creams for the management of pain in diabetic neuropathy [20]. Capsaicin has been observed to improve insulin sensitivity, as anti-obesity, reduce blood glucose levels, as anti-inflammatory, anticancer, and improve liver and heart function [15].

◆ D-Limonene

D-Limonene is a monoterpene obtained in *Citrus* fruits such as lemons and oranges and has antioxidant, anticancer, antidiabetic, cardioprotective, anti-inflammatory, and antibacterial

properties. Apart from that, it is also used as a scent in essential oils. A study by Praveen Kumar *et al.* presented that cataract in diabetes was delayed by D-limonene by inhibition of aldose reductase in a rat model [21].

◆ Ginsenosides

Ginsenosides are active phytoconstituents of the triterpenoid saponin class, found in the roots and rhizomes of the ginseng plant (*Panax ginseng*, family: Araliaceae). Ginsenosides have anti-inflammatory, anticancer, antidiabetic, antioxidant, anti-obesity properties as well as, reduce cognitive impairment in Alzheimer's disease. In diabetic patients, Ginsenoside Rb1 has shown neuroprotective benefit, increased insulin sensitivity, decreased fasting blood glucose, and decreased effect of diabetic retinopathy [22].

◆ Mangiferin

Mangiferin is a polyphenol flavonoid isolated from the leaves, bark, and rhizomes of the mango plant (*Mangifera indica*, family: Anacardiaceae). Mangiferin is an anticancer, antiviral, immunomodulatory agent, and antioxidant. In addition to that, it possesses antidiabetic benefits by reducing high blood sugar levels and inhibiting the formation of fatty deposits in the arteries [23].

◆ Curcumin

Curcumin is an active polyphenolic isoflavonoid present in the roots and rhizomes of turmeric (*Curcuma longa*, family: Zingiberaceae). It possesses numerous health benefits like anti-inflammatory, antioxidant, wound-healing properties, boosts the immune system, antibacterial, antiviral, immunity booster, reduces the risk of cardiovascular diseases, boosts liver functioning, and antihypertensive. Furthermore, it is useful in patients with diabetes and has been stated to lower the level of blood glucose, improve insulin sensitivity and attenuate diabetic nephropathy, neuropathy, and vascular disease [24].

◆ Glabridin

Glabridin is an isoflavonoid isolated from roots of licorice (*Glycyrrhiza glabra*, family: Fabaceae). It possesses benefits like anti-inflammatory, anticancer, antioxidant, antibacterial, anti-obesity, used in the management of Alzheimer's disease, treatment of osteoporosis, treatment of kidney and cardiovascular diseases, and as a substitute for estrogen hormone [25]. Also, it possesses antidiabetic properties and has been stated to improve tolerance of glucose, hence reducing blood glucose levels and reducing the incidence of atherosclerosis in diabetic models as well as reducing biomarkers that are increased in renal and

hepatic damage by its antioxidant property [26].

◆ Naringin

Naringin is a flavonoid that is found in tomatoes, grapefruit, and citrus fruits and has anti-inflammatory, antioxidant, anti-obesity, antiulcer, cardioprotective, nephroprotective, hepatoprotective, and antimicrobial properties. In addition to that, it possesses hypoglycemic and hypolipidemic properties and has been stated to suppress oxidative stress and inflammation in diabetic retinopathy as well as ameliorate diabetic kidney disease [27]. Also, it improves diabetic ketoacidosis, lipid peroxidation, and insulin production [28].

◆ Kaempferol

Kaempferol is a flavonoid noticed in green leafy vegetables like spinach, cabbage, and broccoli, as well as in fruits like grapes

and tomatoes. It possesses anticancer, anti-inflammatory, antioxidant, hepatoprotective, anti-asthma, and antihypertensive benefits. Also, it is used as a hypoglycemic agent as it reduces hepatic gluconeogenesis and improves metabolism in the liver and skeletal muscles [29].

◆ Diosgenin

Diosgenin is a steroidal saponin obtained from yam and fenugreek and is an anticancer, antioxidant, analgesic, anti-inflammatory, hypolipidemic, cardioprotective, and hypoglycemic. In addition to that, diosgenin has been observed to be beneficial in improving the resistance of insulin, promoting insulin secretion, and in diabetic nephropathy, neuropathy, vascular disease, cardiomyopathy, and also in diabetic liver disorders [30].

Table 4: List of phytoconstituents along with their therapeutic potential in the control of diabetes as well as its complications

Phyto-constituent	Dose	Route of administration	Animal used	Model used/injury induced by	Observations/outcomes	Reference
Quercetin	100mg/kg	Oral	Sprague-Dawley Rat	Streptozotocin	↓ Blood glucose, ↑ insulin secretion, protects β-cell from oxidative stress, inhibits α-glucosidase in the intestine.	[18]
Capsaicin	6mg/kg	Oral	Sprague-Dawley rats	Streptozotocin	↓ Blood glucose, ↑ insulin secretion, ↑ glycogen content, ↓ intestinal absorption of glucose.	[31]
D-Limonene	100mg/kg	Oral	Wistar Rats	Alloxan	↓ blood glucose, ↓ creatinine, NO, and urea levels, ↑ GLUT1 hence prevent oxidative stress.	[32]
Ginsenoside Rb1	10mg/kg	Intraperitoneal	Long-Evans rats	Ad libitum-diet	↓ bodyweight, ↓ food intake, ↓ fasting blood glucose, improved impaired glucose tolerance.	[33]
Mangiferin	40mg/kg	Oral	Wistar Rats	Streptozotocin	↓ Advanced glycation end products (AGEs), ↓ urinary albumin, BUN, creatinine, and uric acid levels, ↓	[34]

					plasma glucose, improved diabetes-induced oxidative stress, and showed an anti-fibrotic effect in kidney tubules.	
Curcumin	300mg/kg	Oral	Albino Wistar rats	Streptozotocin	↓ blood glucose, triglycerides, LDL, cholesterol, urea, creatinine, ↓ body weight, and ↓ kidney lipid peroxidation.	[35]
Glabridin	25 and 50 mg/kg	Oral	Albino male rats	Streptozotocin	↓ blood glucose level, ↓ oxidative stress, ↓ lipid peroxidation, high dose improved hyperlipidemia hence ↓ risk of atherosclerosis, ↓ renal and hepatic biomarkers.	[26]
Naringin	80mg/kg	Oral	Albino male rats	Streptozotocin	↓ blood glucose level, ↑ insulin secretion, ↓ cholesterol, and triglyceride level, and ↓ free radicals.	[36]
Kaempferol	50mg/kg	Oral	C57BL/6 male mice	Streptozotocin	↑ glycogen content, ↑ hexokinase activity hence ↓ glucose uptake by muscles, ↑ glucose tolerance, ↓ gluconeogenesis.	[29]
Diosgenin	50 and 100mg/kg	Intragastric	C57BL/6 mice	Diet rich in fat + low dose streptozotocin	↓ blood glucose level, ↓ MDA hence ↓ oxidative stress, ↓ hyperalgesia, improved endometrial edema, myelinolysis and axon degeneration in the sciatic nerve.	[37]

Herbal Plants in the Management of Diabetes mellitus

◆ Bitter gourd

Bitter gourd or bitter melon or Karela (*Momordica charantia*) belongs to the family Cucurbitaceae. Its fruit and seeds are reported to have curative potential in the treatment of various diseases/disorders like diabetes, cardiovascular diseases, malaria, jaundice, bacterial infections, rheumatic arthritis, cancer, and kidney and liver damage [38]. In diabetic patients it has been stated to improve tolerance of glucose by enhancing glucose uptake, consumption, and utilization, inhibiting gluconeogenesis and glycogenolysis, delaying glucose absorption, protecting β -cells of the pancreas, as an antioxidant and anti-inflammatory agent and also,

beneficial in the growth of granulation tissues in diabetic wounds, as cardioprotective in treating diabetes-induced cardiac fibrosis and as a nephroprotective agent [39]. The phytoconstituents involved in the antidiabetic action of bitter gourd are glycosides like charantin, momordin, momorcharins, goyasaponins, anthranoids like vicine as well as polypeptide-P and galactose-binding lectin [40].

◆ Insulin plant

The insulin plant or spiral flag (*Chamaecostus cuspidatus*, *Costus igneus*, or *Costus pictus*) belongs to the family Costaceae [16]. Its leaves, stem, and rhizomes are reported to be beneficial as a diuretic, antioxidant, antidiabetic, anticancer, hypolipidemic, hepatoprotective, nephro-

protective, immunity booster, antiasthma, and antihypertensive. The leaves are rich in antioxidants like β -carotene and α -tocopherol, protein, iron, triterpenoid like corosolic acid, and β -amyrin, glycosides, phenols, tannins, and flavonoids, the rhizomes contain quercetin and diosgenin and the stem contains lupeol and stigmasterol [41, 42]. In diabetes, the insulin plant has shown to increase insulin release, decrease the hyperglycemic effect, increase liver glycogen, decrease triglyceride and cholesterol level, possess antioxidant effects [42].

◆ **Neem**

Neem or Indian lilac (*Azadirachta indica*) belongs to the family Meliaceae and possesses various health benefits like antiulcer, antioxidant, antileprosy, antidiabetic, anti-inflammatory, antipyretic, antimalarial, hypolipidemic, antibacterial, and antiviral [43, 44]. All parts (roots, leaves, seeds, fruit, bark, and flowers) of the neem plant are beneficial and possess antioxidants like azadirachtin, chlorogenic acid, quercetin, kaempferol, nimbin, nimbolide as well as tannins, polyphenols, triterpenoids, and flavonoids [45]. In diabetes, neem has been reported to reduce glucose level in the blood by increasing the insulin release from the pancreatic β -cells, decreasing triglyceride, very-low-density lipoprotein (VLDL),

low-density lipoprotein (LDL), and cholesterol level as well as having a wound-healing benefit in diabetic foot ulcer and beneficial in peripheral neuropathy [45].

◆ **Holy Basil**

Holy basil or Tulsi (*Ocimum sanctum*, or *Ocimum tenuiflorum*) belongs to the family Lamiaceae. It possesses antibacterial, hepatoprotective, antiviral, antioxidant, antimalarial, anticancer, antiprotozoal, antithrombotic, anti-hypertensive, anti-arthritis, antiulcer, neuroprotective, and antidiabetic properties [46]. In diabetes, holy basil is found to have a wound-healing effect, hypoglycemic, antioxidant, and anti-hyperlipidemic effects as well as increased insulin secretion from β -cells of the pancreas. The leaves and stems of tulsi contain ursolic acid, apigenin, estragole, eugenol, rosmarinic acid, carvacrol, cirsilineol, cicimaritin, linalool, orientin, and vicenin [47].

◆ **Black plum**

Black plum is or Jamun (*Eugenia jambolana* or *Syzygium cumini*), belongs to the family Myrtaceae. It possesses many health benefits like antibacterial, antiallergic, anti-inflammatory, antioxidant, antiarthritic, antiulcer, antidiabetic, antihyperlipidemic, nephroprotective, hepatoprotective, and antidiarrhoeal [48].

In diabetes, it has been reported to decrease blood sugar, increase insulin release, increase in glycogen content, decreased liver enzymes, decreased cholesterol and urea levels. The seeds, fruit, leaves, and stems of Jamun have been reported to be beneficial as it contains active constituents like quercetin, kaempferol, eugenin, ellagic acid, rutin, β -sitosterol, betulinic acid, myricetin, jamboline, and jambosine [38, 48].

◆ Papaya

Papaya or pawpaw (*Carica papaya*) belongs to the family Caricaceae. It possesses many health benefits like antioxidant, anti-inflammatory, anti-hypertensive, wound-healing properties, anthelmintic, antiulcer, nephroprotective, antihyperlipidemic, antidiabetic, and antifertility [49]. In diabetes, it has been stated to lower the level of blood glucose, decrease triglyceride, and cholesterol level, further preventing diabetes-induced cardiac complications like atherosclerosis, along with antioxidant effects preventing the advancement of diabetic nephropathy, neuropathy as well as retinopathy. Also, it has shown promising effects as a dressing on diabetic wounds. The active phytoconstituents in papaya leaves, stem, fruit, seeds, and latex include papain, chymopapain, ascorbic acid, α -tocopherol,

cystatin, myricetin, quercetin, and kaempferol.

◆ Amla

Amla or Indian gooseberry or myrobalan (*Emblica officinalis*) belongs to the family Euphorbiaceae. The fruits of amla possess numerous pharmacological properties like anti-inflammatory, neuroprotective, antioxidant, anti-hyperlipidemic, antitussive, analgesic, cardioprotective, nephroprotective, hypoglycemia, and anticancer [50, 51]. In diabetes, it has been reported to have hypoglycemic effects, hypolipidemic effects and prevents diabetic-induced complications like cataracts, nephrotoxicity, cardiovascular complications, increase body weight, and decreases advanced glycation end products (AGEs) hence showing the antioxidant property as well as inhibits α -glucosidase actions [52]. The active constituents present in amla fruit are gallic acid, chebulagic acid, kaempferol, ellagic acid, vitamin C, corilagin, phyllantin, quercetin, and geraniin [50].

◆ Indian Kino Tree

Indian kino tree or bijasar or vijayasar (*Pterocarpus marsupium*) belongs to the family Fabaceae. It possesses many pharmacological benefits, among them include anticancer, antidiabetic, antihyperlipidemic, anti-cataract, analgesic, antibacterial, anti-inflammatory, anti-

fungal, hepatoprotective, antiulcer, antidiarrheal, cardiogenic, and antioxidant [53]. In diabetes, it is reported to have hypoglycemic, and lipid-lowering properties, protect and regenerate β -cells of the pancreas, enhances insulin release, as well prevents further progression of diabetes-induced complications like cataracts [54]. The leaves, heartwood, gum, bark, and flowers contain phytoconstituents like marsupin, pterostilbene, epicatechin, liquiritigenin, propterol, pterostilbene, carpucin, lupeol, and vijayosin [55].

◆ **Garlic**

Garlic or Lasan (*Allium sativum*) belongs to the family Amaryllidaceae. It possesses many health benefits like anti-bacterial, anti-fungal, anti-parasitic, anti-thrombotic, anti-hypertensive, anti-hyperlipidemic, anti-diabetic, anti-oxidant, neuro-protective, nephroprotective, wound healing properties, cardio-protective, immunomodulator, anti-atherosclerotic, antioxidant, and anti-inflammatory [56]. In diabetes, it is reported to reduce the level of blood glucose, decrease triglycerides and cholesterol levels, scavenge free radicals, treat diabetic wounds, reduce the

progression of cardiac and renal complications. Garlic bulbs contain bioactive compounds like allicin, apigenin, allyl cysteine alliin, ajoene, allyl disulfide, ascorbic acid, amino acids, oleanic acid, palmitic acid, and linoleic acid [57].

◆ **Fenugreek**

Fenugreek or Chandrika or methi (*Trigonella foenum-graceum*) belongs to the family Fabaceae. It possesses many health benefits like antioxidant, antidiabetic, carminative, anticancer, antihyperlipidemic, anti-inflammatory, antibacterial, anti-gallstone, nephro-protective, hepatoprotective, and antiulcer [58]. In diabetes, fenugreek has been reported to show hypoglycemic effect by stimulating glucose uptake into the cells, hypolipidemic effect by lowering triglycerides, cholesterol, and LDL level, and decrease the intake of fat-diet as well as showed antioxidant effect hence preventing progression of diabetic complications. Fenugreek seeds and leaves contain 4-hydroxy isoleucine, diosgenin, trigonelline, methyl coumarin, naringenin, kaempferol, quercetin, fenugrin, yamogenin, β -pinene, ascorbic acid, and nicotinic acid [59].

Table 5: List of Herbal Plants along with their therapeutic potential in the control of diabetes mellitus as well as its complications

Plant	Dose	Route of administration	Animal used	Model used/ injury induced by	Observations/outcomes	Reference
Bitter gourd	10ml/kg	Oral	Albino Wistar rats	Streptozotocin	↓ Blood glucose level, ↑ insulin levels due to increased β -cell functioning, ameliorated islet destruction, ↓ lipolysis, and ↓ oxidative stress.	[60]
Insulin plant	120mg/kg	Oral	Albino Wistar rats	Alloxan	↓ blood glucose, ↑ glycogen content in the liver, ↑ insulin level, ↓ protein level, improved cholesterol and triglyceride levels, and improved morphology of kidney and liver.	[61]
Neem	400mg/kg	Oral	Charles-Foster rats	High-fat diet	↓ blood glucose level, ↓ lipid peroxide level, ↑ glutathione, catalase, and superoxide dismutase (SOD) level hence showing antioxidant property.	[62]
Holy Basil	2.5mg/kg	Oral	Albino Wistar rats	Alloxan	↓ blood glucose level, ↓ triglyceride, and cholesterol, ↓ creatinine, ↓ bilirubin, SGOT, SGPT, ALP.	[63]
Black plum	100mg/kg	Oral	Albino Wistar rats	Streptozotocin	↑ bodyweight, ↑ glucose metabolism, ↑ insulin secretion, ↓ blood glucose, ↓ cholesterol level, ↓ protein level, ↑ glycogen by ↑ glycogen synthase and ↓ glycogen phosphorylase.	[64]
Papaya	100mg/kg	Topical	Sprague-Dawley rats	Streptozotocin + excised wound/dead space wound	↓ wound size, ↑ hydroxyproline (collagen marker), the proliferation of granulation tissues, ↑ wound contraction, and antimicrobial activity.	[65]
Amla	10mg/kg	Oral	Sprague-Dawley rats	Diet rich in fat + low dose Streptozotocin	↓ blood glucose, ↓ axonal degeneration of sciatic nerve, ↓ MDA, ↑ glutathione, SOD, and catalase.	[66]
Indian Kino tree	2,4, and 8g/kg	Oral	Albino Wistar rats	Streptozotocin	↓ blood glucose level, inhibition in the activity of aldose reductase, ↑ glutathione level in the lens tissue.	[67]
Garlic	2g/kg	Oral	Albino Wistar rats	Streptozotocin	↓ blood glucose level, ↓ SGOT, SGPT, ALP, ↓ NO, and MDA and ↑ TAC.	[68]
Fenugreek	5% in the diet	Oral	Albino rats	Alloxan	↓ blood glucose levels, ↑ glutathione, SOD, catalase level, ↓ IL-6, ↓ urea, creatinine, and ↓ MDA.	[69]

CONCLUSION

Diabetes is the most rapid-growing disorder and is the main cause of death across the globe, appropriate therapies are necessary for managing diabetes hence, apart from the modern allopathic medications, phytochemicals are now

being used. Phytochemicals have been put-to-use for a long time in folk medicine and have now emerged as an effective alternative in the prophylaxis, management, and treatment of various disorders. Many phytochemicals have undergone scientific validation in the

control of diabetes as well as its complications and have been proven to be

efficacious, cost-effective, and easily available with fewer side effects.

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