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Beyond Insulin: Unveiling the role of plants in Diabetes- A review of recent research

Riya Shikha[1]*, Mohd Qasid Lari[1], Deepak Kumar[1], Anushka Singh[2]

[1]Sardar Patel College of Pharmacy, Medical College Road, Gorakhpur 273013, (U.P.), India.
[2]Era University, Lucknow, Uttar Pradesh, India.

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ABSTRACT: Pharmaceutical interventions, notably insulin, have long been the cornerstone of conventional diabetes management. However, recent research has shed light on the promising potential of botanical remedies in both preventing and treating diabetes. This comprehensive review endeavours to delve into the burgeoning significance of plant-derived medicines in diabetes care, offering a nuanced exploration of their efficacy supported by the latest scientific findings.

Delving into the realm of phytochemicals, this review elucidates their diverse mechanisms of action, elucidating how they modulate insulin sensitivity, regulate glucose metabolism, and mitigate the complications of diabetes. Furthermore, it meticulously scrutinizes the ability of these bioactive compounds to combat inflammation, oxidative stress, and other pathophysiological pathways implicated in the onset and progression of diabetes mellitus. Moreover, the review underscores the synergistic advantages of amalgamating plant-based therapies with conventional pharmacological agents, thereby advocating for an integrative approach to diabetes management. By synthesizing evidence from various studies, it underscores the tangible benefits of incorporating botanical interventions either as adjuncts to existing therapies or as standalone alternatives. The implications of this review extend beyond academia, potentially reshaping clinical paradigms by fostering greater exploration into plant-derived drugs for diabetes treatment and mitigation of associated complications. Embracing the wealth of nature's pharmacopeia, we embark on a journey towards a future where the synergy between pharmaceutical and botanical therapies heralds new horizons in diabetes management. By elevating the discourse surrounding plant-based interventions, this review endeavours to stimulate further research, ultimately contributing to the evolution of diabetes care towards more holistic and efficacious approaches.

Corresponding author:
Mr. Riya Shikha
Assistant professor
Sardar Patel College of Pharmacy
Vill-Bangai, Gulharia
Gorakhpur-273013, Uttar Pradesh, India
Tel: +917546999243
E. Mail ID: riyashikhasiwan@gmail.com

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INTRODUCTION:

In recent decades, diabetes, a prevalent and persistent medical condition, has evolved into a significant global health challenge [1]. This complex metabolic disorder affects millions of individuals worldwide, resulting in abnormally elevated blood glucose levels (hyperglycemia) [2], the presence of glucose in the urine (glycosuria) [3], elevated blood lipid levels (hyperlipidemia) [4], negative nitrogen balance, and occasional ketonemia [5]. The pathology of diabetes

involves widespread changes, including thickening of the capillary basement membrane, increased matrix within vessel walls, and cellular proliferation, leading to vascular complications such as narrowed lumens, early atherosclerosis, glomerular capillary sclerosis, retinopathy, neuropathy, and peripheral vascular insufficiency [6].

In the case of Insulin-dependent diabetes mellitus (IDDM/ type I), it results from the destruction of pancreatic β-cells responsible for insulin production [7]. On the other hand, in Noninsulin-dependent diabetes mellitus (NIDDM/ type II), reduced peripheral tissue sensitivity to insulin or insufficient insulin production by β-cells hampers glucose metabolism within the body [8]. Besides the conventional complications associated with diabetes, emerging issues such as cancer, infections, liver diseases, functional disability, cognitive impairment, and dementia demand serious attention [9].

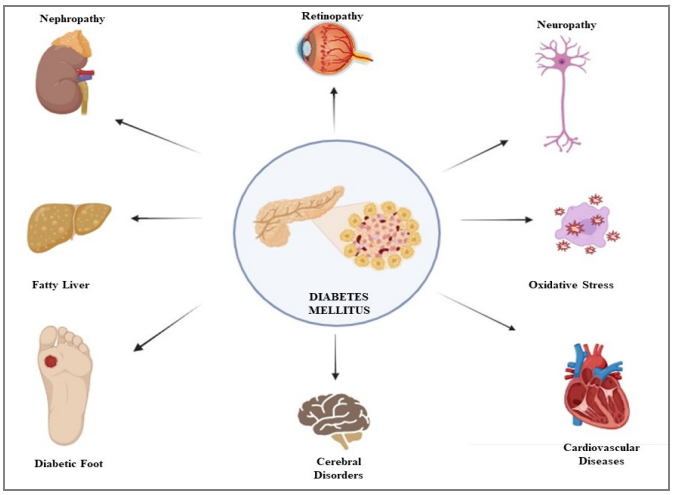

Fig 1. Complications of Diabetes Mellitus.

The impact of diabetes extends beyond the individual and their family, imposing substantial economic burdens on healthcare systems and national economies through direct medical expenses and losses in productivity and wages. According to a report from the United Nations General Assembly on non-communicable disease prevention and control, global GDP losses attributable to diabetes, encompassing both direct and indirect costs, are projected to reach US$ 1.7 trillion between 2011 and 2030 [10]. This estimate is divided, into US$ 900 billion for high-income nations and US$ 800 billion for low- and middle-income countries. In 2021, diabetes accounted for a substantial 11.5 % of global health expenditure, highlighting its significant impact on healthcare budgets. Diabetes is a prevalent condition, affecting 1 in every 10 adults aged 20 to 79 years worldwide. Alarmingly, three out of every four individuals with diabetes reside in low- and middle-income countries, underscoring the need for equitable access to care and resources [11].

Of particular concern is the link between poor glycemic management and adverse COVID-19 outcomes. By the close of 2022, the global COVID-19 pandemic had recorded over 700 million confirmed cases, demonstrating its far-reaching impact on public health. Notably, adults with diabetes faced a 35 to 40 % higher risk of hospitalization due to COVID-19, emphasizing the vulnerability of this population to severe disease and the urgent need for targeted interventions and prevention measures [12].

Currently, there are several medications available for the treatment of diabetes. Insulin is the mainstay for managing type-I diabetes, while type-II diabetes primarily relies on oral hypoglycemic agents (OHAs) such as Biguanides (e.g., Metformin) [13], Sulfonylureas (e.g., Tolbutamide) [14], Thiazolidinediones (e.g., Pioglitazone) [15], and Alpha-glucosidase inhibitors (e.g., Voglibose) [16]. These drugs work through different mechanisms to lower blood glucose levels, but they also come with notable side effects, including reduced vitamin B_{12} absorption, hepatic injury with metformin, hypoglycemia, weight gain, and skin reactions with sulfonylureas [17].

Despite their use, these medications may not adequately control blood sugar levels and the progression of diabetes [18]. To address these challenges, combination therapy has been introduced as a new approach. However, this approach still requires thorough evaluation to ensure its safety and effectiveness. In the context of combination therapy of dapagliflozin and metformin, significant adverse effects include renal dysfunction, hypertension, and constipation. Additionally, patients may experience severe hypoglycemia, nausea, back pain, and diarrhea [19]. It's important to be aware that using multiple antidiabetic medications appears to elevate the risk of hypoglycemic events, particularly when combining sulfonylurea and insulin [20].

To address these challenges, researchers are directing their attention toward natural products. This review will delve into the phytoconstituents, and their substantial impact on regulating blood glucose levels in individuals with diabetes.

The objective of this work is to present a thorough analysis of current research investigating the possible

functions of different plant-based therapies in the control and treatment of diabetes.

MOLECULAR PATHWAYS UNDERLYING DIABETES MELLITUS:

Diabetes Mellitus (DM) is the most common metabolic illness in humans. The two main cellular substrates, fats and carbohydrates, are metabolised differently in people with diabetes mellitus (DM), which disrupts metabolic pathways and produces harmful metabolites [21]. Even though a lot of in vitro and in vivo research has been done to clarify the underlying molecular pathways of diabetes mellitus, the exact pathophysiology remains unclear [22]. Yet, a wide range of causes have been linked to this condition, including inflammation, insulin resistance, oxidative stress, mitochondrial malfunction, beta cell dysfunction, and apoptosis with reduced levels of circulating insulin.

Insulin resistance:

The primary underlying pathology of type 2 diabetes is insulin resistance, which results in cells' inadequate absorption of glucose due to an inability to respond to insulin [23]. Through the use of GLUT-4 (glucose transporter-4) transporters, normal insulin signal transduction (IST) involves a complicated series of successive phases involving several enzymes and mediators, which permit glucose entrance into adipocytes, muscles, and cardiac cells [24]. Insulin receptors (IRs), which are members of the transmembrane tyrosine kinases made of α and β chains and activated by insulin as well as IGF- (insulin-like growth factor-) 1 and IGF-2, attach to the α chain of insulin to start the insulin secretion cycle (IST) [25]. By auto phosphorylating tyrosine residues in the β chain, this interaction causes structural modifications in the β chain. Subsequently, various adaptor proteins, such as insulin receptor substrates (IRSs), Shc (SHC-transforming) protein, and APS protein (adapter protein with a PH and SH2 domain), are recruited. These procedures give the IRS-1 (insulin receptor substrate-1) a suitable binding site [26]. A variety of insulin-dependent kinases, including AMPK (AMP-activated protein kinase) and GSK-3 (glycogen synthase kinase 3) and atypical PKC (protein kinase C), S6K1 (ribosomal protein S6 kinase beta-1), SIK2 (serine/threonine-protein kinase 2), Akt (protein kinase B), mTOR (mammalian target of rapamycin), and ROCK1 (rho-associated protein kinase 1) are among the insulin-dependent kinases that can phosphorylate and activate IRSs [27]. PIP2 (phosphatidylinositol 4,5-bisphosphate) is converted to PIP3 (phosphatidylinositol 3,4,5-trisphosphate) by the action of activated IRS-1, that binds to and activates phosphoinositide 3-kinase. PIP3 is a strong activator of Akt by itself, which helps glucose reach cells by directing GLUT-4 to specific locations and by blocking glycogen synthase kinase, which increases the formation of glycogen [28]. Any disruption to these processes may impede normal IST, which could lead to insulin resistance and diabetes.

β-Cell Dysfunction/Insulin Production and Secretion:

Normal glucose homeostasis requires a healthy and functional mass of pancreatic beta cells, and diabetes mellitus is associated with variable degrees of beta-cell malfunction [29]. Gradual decrease of beta-cell mass and function is a critical factor in the development of diabetic mellitus [30]. Under these circumstances, postprandial glucose rises above normal because beta cells' unregulated and declining glucose-induced insulin production occurs [31]. The process starts with a flaw in the prior or first-phase release of insulin, which is subsequently followed by a decrease in the maximum ability of glucose to trigger the secretion of insulin after meals, which results in an error in the steady-state and basal production of insulin, which is followed by total beta-cell failure. Oxidative stress and a variety of pathogenic mechanisms can lead to beta-cell malfunction [32].

Mutations of GLUT-4:

The normal functioning of insulin-dependent cells is dependent on the transportation of glucose by GLUT-4, and any deficiencies in this protein can hinder its performance [33]. Any point mutation that modifies this transporter has the potential to seriously hinder cells' ability to absorb glucose and the signalling pathways that follow

For instance, a 1998 study showed that GLUT-4's activity was compromised by mutations in two consecutive arginine residues at positions 333 and 334, which greatly reduced the carrier's ability to transport glucose [34].

Mitochondrial dysfunction:

Double-membrane cellular organelles called mitochondria play crucial roles in the synthesis of energy, the storage of calcium, the synthesis of fatty acids, the generation of heat, and the survival of cells. They also participate in cellular signalling networks [35,

[36]. Diabetes is one of the many disease disorders linked to mutations in mitochondrial DNA (mtDNA). Diabetes is significantly associated with specific mutations in mtDNA, such as the A3243G mutation in the mitochondrial DNA-encoded tRNA(Leu,UUR) gene [37]. One of the main characteristics of type 2 diabetes mellitus is insulin resistance, which has been linked to mitochondrial dysfunction in its development. Enhancing mitochondrial function could be a useful treatment strategy to increase insulin sensitivity [38]. Mitochondria are essential for the tight regulation of glucose-stimulated insulin secretion (GSIS) in pancreatic beta cells by connecting insulin exocytosis to glucose metabolism. Mitochondrial dysfunction can have an effect on this procedure [39].

OXIDATIVE STRESS BROUGHT ON BY HYPERGLYCEMIA DEACTIVATES THE INSULIN SIGNALLING SYSTEM:

Oxidative stress has been linked to the dysfunction of the primary glucose regulation mechanisms in diabetes, namely insulin production and insulin action [40]. The insulin signalling cascade is a biochemical system that regulates both mechanisms. The pancreatic islet beta cells alone are in charge of secreting insulin, and they do so only after the enzyme glucokinase serves as a glucose sensor in the organ. When blood glucose levels rise, beta cells absorb glucose at a faster rate, and glucokinase (also known as glucose-stimulated insulin secretion) starts the process of secreting insulin [41]. This enzyme easily phosphorylates the glucose molecule to glucose-6-phosphate due to its high affinity or low Km for glucose at high concentrations. This phosphorylation commits the glucose molecule to ATP-generating pathways such as glycolysis, the Kreb cycle, and the electron transport chain. It is known that an elevated intracellular ATP level will block an ATP-sensitive K^+ channel [42]. It concurrently encourages sodium (Na^+) influx, which causes a disruption in the typical Na^+-K^+ ratio. The voltage-dependent T-type calcium (Ca^{2+}) and sodium (Na^+) channels open as a result of this occurrence, depolarizing the membrane and causing an increase in the influx of Na^+ and Ca^{2+} as well as additional membrane depolarization [43]. In the end, elevated intracellular Ca^{2+} stimulates insulin-containing secretory granules to fuse with the plasma membrane, releasing insulin as a result. After being released into the portal circulation, insulin travels to its intended locations, or peripheral tissues, where it attaches to its receptor to initiate the process of releasing glucose into bodily cells. A sequence of phosphorylation and protein coupling processes are part of the cascade of events that the insulin-receptor complex triggers [44, 45].

It has been observed that hyperglycaemia-induced oxidative stress, among other activities, activates uncoupling protein-2 (UCP-2) and lowers the ATP/ADP ratio, which in turn prevents the ATP-dependent sequence of occurrences that leads to the secretion, discharge, and function of insulin [46]. Similarly, the quantity and quality of insulin released by pancreatic islet beta cells are also compromised by the oxidative harm caused by reactive species (ROS and RNS) created by hyperglycaemia [47]. A study's findings indicate that oxidative stress-induced loss of beta-cell function, which results in reduced secretory capability and elevated insulin resistance, is a significant factor in the aetiology of type 1 and type 2 diabetes. Furthermore, changes in the form, volume, and function of the mitochondria may result from hyperglycaemia-mediated increased mitochondrial metabolism and the formation of ROS in the beta-cell. This could uncouple ATP-dependent K+ channels and impede glucose-stimulated secretion of insulin ultimately leads to diabetic condition [48].

ANTIDIABETIC MEDICINAL PLANTS:

Rytigynia senegalensis:

Rytigynia senegalensis, a plant from the *Rubiaceae* family within the Blume genus, is native to tropical and southern regions of Africa. In Africa, it has been traditionally used for the treatment of various health issues such as diabetes mellitus, malaria, dysentery, constipation, and hemorrhoids. Through a phytochemical screening, an aqueous extract of *R. senegalensis* (AERS) demonstrated the presence of several secondary metabolites, including flavonoids, phenols, tannins, terpenoids, coumarins, glycosides, and anthraquinones, while alkaloids quinones, saponins, and sterols were not detected.

AERS exhibited promising antidiabetic properties in both Type 1 (T1D) and Type 2 (T2D) diabetes models induced by streptozotocin (STZ) and dexamethasone, respectively. Additionally, AERS demonstrated lipid-lowering, cardioprotective, and antioxidant effects when tested on Wistar rats. Notably, AERS showed effects similar to the reference compounds Glibenclamide and metformin, suggesting that in T1DM, AERS may act by inhibiting ATP-sensitive K+ channels, stimulating insulin secretion. In T2DM, the reduction in blood

glucose levels after AERS treatment could be attributed to its ability to enhance the translocation of GLUT4 transporters from the inner membrane to the plasma membrane of muscle cells, possibly accompanied by changes in the total amount of GLUT4 or its gene expression. Furthermore, one of the major challenges in diabetes management is weight loss, and AERS effectively addresses this issue by increasing food intake. Histological analysis of the pancreas in T1DM revealed an increase in the size and number of islets of Langerhans, indicating a potential regenerative effect. Importantly, no adverse side effects were observed in animals treated with AERS. Additional research is necessary to elucidate the structure of phytoconstituents and to clarify the precise cellular and molecular mechanisms of action.

AERS effectively reduces postprandial glycemia by inhibiting the activity of α-Amylase and α-glucosidase enzymes. Additionally, it exhibits antioxidant properties by acting as a hydrogen donor, and the phenolic group within it can efficiently scavenge free radicals. The inhibition of α-Amylase enzymes prevents the hydrolysis of complex polysaccharides into oligosaccharides and disaccharides. Subsequently, the inhibition of α-glucosidase enzymes delays the further hydrolysis of these compounds into monosaccharides, leading to a slowed digestion and absorption of carbohydrates. This dual enzymatic inhibition contributes to the reduction of postprandial glucose levels [49, 50].

Corni fructus:

Corni fructus is a versatile herbal remedy with a wide array of potential health advantages, particularly in the areas of managing diabetes [51], promoting liver health [52], and enhancing general well-being. Its extensive traditional use in medicine continues to stimulate contemporary research into its healing attributes and possible uses. *C. fructus*, derived from the mature and dried fruit of *C. officinalis*, is rich in key phytoconstituents such as iridoid glycosides, saponins, and tannins, which play a significant role in its therapeutic properties [53]. This natural resource can be found in regions spanning Anhui, Gansu, Jiangsu, Jiangxi, Shandong, and Shanxi in China, as well as in Korea and Japan. The extraction process involves using 70 % ethanol for saponin extraction, 80% methanol for iridoid glycoside extraction, and 42 % ethanol for tannin extraction. A key driver of insulin resistance in type 2 diabetes mellitus (T2DM) is dyslipidemia, marked by the excessive buildup of lipids, notably triglycerides, in the liver. *C. Fructus* extracts, aside from their role in regulating T2DM via the AMPK/ACC/CPT-1 signaling pathway, also effectively target a range of related health issues. These include rectifying abnormal lipid metabolism, aiding in liver damage repair, improving insulin secretion and sensitivity, restoring proper islet functions, facilitating weight loss, and reducing hyperglycemia in Streptozocin-mice model. The key bioactive components of the extract include protocatechuic acid, gallic acid, 5-hydroxy-methyl furfural, morroniside, sweroside, loganin, and cornuside [54].

Eclipta prostrata:

Eclipta prostrata (EP), also known as Bhringraj, Bhumiraj, and Nash jhar, is a plant belonging to the *Asteraceae* family [55]. It is widely distributed in tropical and subtropical regions of Africa, South America, and Asia. This plant contains several key phytoconstituents, including Wedelolactone, Catechin, Chlorogenic Acid, Epigallocatechin Gallate, Epicatechin, Epicatechin gallate, Vitexin, Salicylic acid, Isovitexin, Rutin, Apigetrin, Myricetin, Quercetin, Kaempferol, and Apigenin, which contribute to its diverse range of pharmacological activities [56]. Studies conducted *in vitro* and *in vivo* have demonstrated the anti-glycation and anti-diabetic properties of Wedelolactone. It accomplishes this by reducing the formation of Advanced Glycation End Products (AGEs), which are known to cause tissue damage, including damage to pancreatic β-cells in rats induced with Streptozocin. AGEs generate harmful free radicals, which are responsible for cellular and tissue damage, ultimately leading to β-cell dysfunction, a primary contributor to diabetes mellitus [57].

Furthermore, *E. prostrata* extracts have shown significant anti-glucosidase and anti-amylase activity, indicating their potential role in diabetes management. In particular, the aqueous leaf extract of *E. prostrata* (AEEP) has demonstrated its ability to effectively regulate blood glucose levels, lipid profiles, and the histological condition of the pancreas, kidney, and liver. AEEP alone has been found to improve damage to the liver and pancreas associated with diabetes while increasing the excretion of urea, uric acid, and creatinine [58].

Tapinanthus cordifolius:

Tapianthus cordifolius, a plant rich in phytoconstituents and belonging to the *Loranthaceae* family, is native to Nigeria. It is renowned for its ability to aid in the management of diabetes mellitus by reducing post-meal glucose levels. This is achieved by inhibiting carbohydrate hydrolyzing enzymes like α-amylase, a crucial approach in diabetes control. Out of the 43 bioactive compounds found in the ethanolic extract of *T. cordifolius*, Benzaldehyde, 4-(Ethylthio-2,5-dimethoxy, α-tocopherol-β-D-mannoside, and 5-Ergosterol have been identified as the most stable compounds when interacting with the target protein α-amylase [59]. They form bonds through hydrogen interactions, π-π stacking, and ionic connections with specific amino acids. This provides strong evidence of their efficacy in inhibiting α-amylase and underscores *T. cordifolius*'s potential in this regard. Additionally, α-tocopherol found in *T. cordifolius* contributes to better metabolic control in diabetes due to its antioxidant properties, which help combat lipid oxidation, protein glycation, and enhance insulin sensitivity. Diabetic patients often lack sufficient α-tocopherol. Both in-vitro α-glucosidase assay and *in-silico* studies have further confirmed *T. cordifolius's* inhibitory activity against α-glucosidase. The presence of phytosterols in plants contributes to cholesterol-lowering, anti-inflammatory, and anticancer effects, as these compounds share a structural similarity with cholesterol. In addition to its medicinal benefits, *T. cordifolius* is considered safe for use, as it shows no signs of mortality or apparent toxicity symptoms. Moreover, it does not impact the hematological, biochemical, and histological parameters in rats [60].

Gynura procumbent:

Gynura procumben, also known as Longevity spinach, has a rich history as a herbal remedy for various health issues, including kidney discomfort, inflammation [61], viral diseases [62], and rheumatism [63]. Indigenous communities worldwide have embraced its therapeutic properties, incorporating it into their diets without worry of toxicity. In Bangladesh, it goes by the local name "diabetic leaf" due to its association with managing diabetes. Belonging to the *Asteraceae* family, this resilient plant thrives in regions like China, Africa, and Southeast Asia, particularly Indonesia, Thailand, and Malaysia [64]. The methanolic leaf extract of *G. procumbens*, along with its fractions in different solvents, is packed with phytoconstituents. The ethyl acetate soluble fraction (EASF) stands out, containing phytol, lupeol, stigmasterol, friedelanol acetate, β-amyrin, and a mix of stigmasterol and β-sitosterol, as confirmed by spectroscopic data analysis. Remarkably, the petroleum ether soluble fraction (PESF) exhibited potent glucose-lowering activity, surpassing the effectiveness of the standard drug Glibenclamide in Alloxan-induced diabetic rats. Additionally, oral administration of Chloroform soluble fraction (CSF), Ethyl acetate soluble fraction (EASF), and Aqueous soluble fraction (AQSF) demonstrated blood glucose reduction. Beyond its antidiabetic effects, EASF showcased significant antioxidant activity in the DPPH assay and a robust antithrombotic effect in the methanolic leaf extract of *G. procumbens*. Although these findings are promising, further studies are essential to delve into the mechanisms behind these activities [65].

Prosopis strombulifera:

The root cause of type 1 diabetes mellitus is the autoimmune destruction of pancreatic β-cells, orchestrated by T-cells, leading to hyperglycemia due to insufficient insulin production [66]. *Prosopis strombulifera*, a rhizomatous shrub native to Argentina and belonging to the *Fabaceae* family, is recognized for its astringent, anti-inflammatory, and antidiabetic properties [67]. The aqueous extract of *P. strombulifera* (AEPS) contains a diverse array of compounds, including catechin, kaempferol glucoside, myricitrin 3-O-glucoside, naringoside, rutin, protocatechuic acid, and xilonic acid. In both *in-vitro* and *in-vivo* studies involving non-obese diabetic mice, PsAE exhibited immunosuppressive effects. PsAE lowered CD69 expression post polyclonal activation, diminished CD69 expression in isolated CD4+ and CD8+ T cells following CD3/CD28 stimulation, and alleviated IFN-γ cytokine release. Furthermore, PsAE improved type 1 diabetes in NOD mice by reducing lymphocyte infiltration in beta-islets and modulating the mRNA expression levels of PRF-1 and GRZ-B. The immunosuppressive actions of PsAE were ascribed to its ability to inhibit key immune activation signaling pathways. Protocatechuic acid in PsAE reduced the production of FN-g, IL-6, and IL-8 by suppressing the NF-KB activation pathway. Rutin hindered the proliferation of splenocytes and thymocytes under ConA stimulation, resulting in decreased IFN-g production. The flavanols present in PsAE delayed the onset of type 1 diabetes by preventing chronic inflammation and influencing the physiology of CD8+ T

cells. Significantly, the NOD mice model illustrated the antidiabetic activity of PsAE through diverse underlying mechanisms, and PsAE demonstrated these therapeutic effects without inducing any discernible side effects [68].

Oldenlandia umbellate and Oldenlandia corymbose:

Oldenlandia umbellate, commonly referred to as Choy root or Chaaya Ver, is a medicinal plant indigenous to India. Similarly, *Oldenlandia corymbosa*, recognized as a medicinal herb, is cultivated in tropical regions such as China, India, Sri Lanka, and other tropical East Asian countries. These plants are notably abundant in oleanolic acid and ursolic acid [69]. In the investigation, the petroleum ether, ethanolic, and aqueous extracts of *O. umbellate* whole plant parts (OUWP) and *O. corymbosa* whole plant part (OCWP) were scrutinized for various properties, including total phenolic content, flavonoids, tannins, flavanols, proanthocyanidins, vitamin-E, enzyme inhibitory activity (α-amylase and α-glucosidase enzymes), as well as anti-inflammatory, antioxidant, and antibacterial effects. The qualitative phytochemical analysis of petroleum ether, ethanolic, and aqueous extracts of OUWP and OCWP revealed the presence of proteins, carbohydrates, alkaloids, phenols, flavonoids, tannins, cardiac glycosides, and phytosterols. Notably, saponins were exclusively identified in the aqueous extract. Among the extracts, the ethanolic extracts of OUWP and OCWP demonstrated the highest TPC, with the ethanolic extract of OUWP exhibiting greater TVE and TPAC compared to the ethanolic extract of OCWP. Remarkably, the ethanolic extract of OUWP and the aqueous extract of OCWP displayed notable α-amylase inhibitory effects, while the petroleum ether extract of both plants exhibited significant α-glucosidase inhibitory effects. These inhibitory effects were found to be comparable to the standard drug acarbose [70].

Heteromorpha arborescens:

Heteromorpha arborescens, a medicinal plant belonging to the *Apiaceae* family and widely distributed in tropical Africa, boasts a rich array of phytoconstituents. Various parts of the plant, including the bark, leaves, milky exudate, roots, and root barks, have been traditionally utilized for medicinal purposes. Despite this extensive traditional use, there is a notable absence of in-vivo studies substantiating the plant's antidiabetic activity [71]. Notably, a polyene found in the leaves of *H. arborescens* exhibits antifungal and analgesic properties [72].

In an effort to explore its potential antidiabetic effects, different fractions of *H. arborescens* leaves—hydro-methanolic, hexane, ethyl acetate, and water—were evaluated using an STZ-induced diabetic mice model. The water fraction yielded 78 %, hexane 16 %, and ethyl acetate 6 %, with an overall crude extract yield of 11 %. Phytochemical screening revealed that the ethyl acetate fraction exhibited positive results for a wide range of constituents, including alkaloids, flavonoids, anthraquinones, phenols, glycosides, saponins, steroids, tannins, and triterpenoids. The hexane fraction, while negative for triterpenoids, and the distilled water fraction, lacking in steroids and alkaloids, were also subjected to screening.

In diabetic mice, both the crude extract and n-hexane fraction demonstrated a dose-dependent reduction in blood glucose levels, while the ethyl acetate fraction proved effective across all doses (100, 200, and 400 mg/kg). Notably, the 400mg/kg doses of the crude extract and ethyl acetate fraction did not impact body weight, and groups treated with these doses exhibited lower cholesterol levels, indicating an antihyperlipidemic effect [73].

While the current studies propose potential mechanisms, including increased insulin sensitivity, enhanced insulin production from β-cells facilitated by essential oils, and inhibition of α-amylase and α-glucosidase by polyphenols and flavonoids, it is acknowledged that, more research is essential to precisely elucidate the underlying mechanisms behind the antidiabetic and antihyperlipidemic activities of *H. arborescens*.

***Trapa Bispinosa Roxb.*:**

Trapa Bispinosa, a notable herb in the Indian Ayurvedic system, holds significance in addressing issues related to the stomach, liver, genitourinary system, and spleen. Belonging to the *Trapaceae* family, it is indigenous to Eurasia and was introduced to North America in the 1870s. In India, it is commonly known as Paniphal and thrives abundantly in the lakes of Kashmir. Commercially cultivated in tropical regions like Pakistan, Sri Lanka, Ceylon, Indonesia, and Africa, it is also found in Southeast Asia, Southern China, Japan, Italy, and tropical America [74].

A phytochemical analysis of *T. Bispinosa* Roxb. reveals the presence of carbohydrates, vitamins, alkaloids, flavonoids, saponins, and other secondary metabolites. The polyphenols in TBR, such as Gallic acid, Ellagic acid, Camptothin B, Rubuphenol, Eschweilenol A,

Cornusiin G, Acarbose, and Tellimagrandin II, and exhibit α-Glucosidase inhibitory activity. Some of these polyphenols also demonstrate inhibitory effects on advanced glycation end products (AGEs), which are implicated in conditions like Alzheimer's Disease and contribute to the complications of Diabetes [75].

Autophagy, a cellular self-preservation mechanism, regulated by the AKT/WNK pathway, declines in type 2 diabetes due to reduced activity caused by high insulin levels. The AKT signaling and WNK1 pathways play a role in autophagy regulation. *T. bispinosa Roxb* Extract (TBE) treatment in obese mice reduces AGEs, indicating an antiglycation effect in type 2 diabetes. mRNA expression levels of AKT1 and WNK1 are affected by TBE, suggesting its involvement in the regulation of autophagy. TBE, rich in ellagitannins that hydrolyze into ellagic acid and its intestinal metabolite urolithin, acts as an inhibitor on the insulin-dependent AKT signaling pathway. This inhibitory action, as observed in the study, implies that TBE may induce autophagy. Notably, a normal diet containing *T. Bispinosa* can potentially improve diabetic retinopathy or cataracts [76].

CONCLUSION:

Although insulin is still the mainstay of treatment for diabetes, new studies are revealing the enormous potential of plants in the management of this illness. Plant-based medicines provide a promising supplementary approach by lowering oxidative stress, enhancing insulin sensitivity, and regulating blood sugar levels. To completely comprehend the mechanisms of action, optimise doses, and guarantee safety and efficacy, more research is necessary. With more investigation, the lives of those with diabetes may be considerably enhanced by combining the benefits of plants with traditional therapies.

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