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Plant-derived bio actives for type 2 diabetes: Therapeutic strategies and future outlook

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Abstract
Type 2 Diabetes Mellitus (T2DM) is a widely occurring metabolic disorder with a severe need for appropriate therapy. This review illustrates the therapeutic effects of natural products for T2DM. Bioactive substances such as flavonoids, alkaloids, polyphenols, and saponins modulate biological processes like glucose homeostasis, enhance insulin sensitivity, and inhibit oxidative stress. Each bioactive compound has its significant role in T2DM treatment. Mulberry leaf extract-MLE (DNJ, flavonoids) inhibits α-glucosidase, curcumin of turmeric is anti-inflammatory, and bitter melon (Charantin, p-insulin) enhances insulin release. Fenugreek (4-hydroxy isoleucine, galactomannan) lowers blood glucose, cinnamon promotes the activity of the insulin receptor, and berberine from *Berberis aristata* activates AMPK for enhanced glucose metabolism. *Gymnema Sylvestre* inhibits the absorption of glucose and contributes to enhancing insulin release. These drugs are potential add-on therapies but require further investigation to optimize bioavailability as most of the bioactive compound's availability is very limited. Synergistic formulations, stability and permeability enhancement, and molecular mechanisms of the bioactive compounds need to be explored. Advanced drug delivery platforms like Nano formulations and targeted therapy can amplify their efficiency. Combining traditional knowledge with modern diabetes medications can offer safer, multi-targeted treatments for improved glycemic control and overall metabolic health.

Keywords: Type 2 Diabetes Mellitus (T2DM), traditional medicine, phytocompounds, inflammation, oxidative stress, insulin, multi targeted treatment

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic syndrome that encloses insulin resistance, sustained hyperglycemia, and progressive β-cell failure [1]. Up to 90% of the total diabetes mellitus cases across the world are due to T2DM [2]. It is mostly the result of genetic predisposition, environmental influences, and lifestyle disorders such as obesity, physical inactivity and diet [3]. T2DM is a consequence of the inability of insulin-sensitive tissues to effectively utilize glucose, which in turn leads to impaired insulin secretion whereas Type 1 diabetes results from autoimmune β-cell destruction. Unless managed, T2DM can result in severe complications like cardiovascular disease, neuropathy, nephropathy, and retinopathy that impact quality of life and increase healthcare costs. T2DM is estimated to impact over 642 million persons by the year 2040 [4]. This is due to several important factors like speedy urbanization, the inactive lifestyle, and the increased rate of obesity all over the globe. Diabetes imposes a great economic burden on healthcare and comes with costs valued at over $1 trillion annually around the globe [5]. Due to side effects, high costs, and diminished long-term effectiveness, new approaches to the management of diabetes are increasingly being contemplated. Disturbed insulin signaling is a consequence of chronic inflammation, oxidative stress, mitochondrial dysfunction, and deregulated lipid metabolism. At the molecular level, T2DM is brought about by peripheral tissue insulin resistance in muscles, liver, and fat tissue and β-cell dysfunction.

TCF7L2, PPARG, KCNJ11, and IRS1 are the most critical genes associated with T2DM, all of which regulate insulin secretion, glucose regulation, and β-cell function [3]. Epigenetic modifications, such as DNA methylation and histone modification, also add to sensitivity to the condition. However, protective genetic alleles, efficient metabolic compensatory mechanisms, and intact antioxidant protective machinery have no impact whatsoever on the individuals who are sensitive to the condition due to epigenetic modifications. At the cellular level, mitochondrial damage, Endoplasmic Reticulum (ER) stress, chronic inflammation, and oxidative stress occur due to T2DM, all of which disrupt insulin signaling and β-cell viability. TNF-α and IL-6 are the Pro-inflammatory cytokines which increase insulin resistance, provoking metabolic control further [4]. Current available therapies like insulin therapy, oral hypoglycemic agents (metformin, sulfonylureas, SGLT2 inhibitors, and DPP-4 inhibitors), and bariatric surgery is prone to side effects and do not cure the root causes of the disease but can only control blood glucose levels. The therapeutic potential of plant bioactive compounds in the additive treatment of T2DM has been of significant interest [4]. Bioactive molecules from mulberry, turmeric, bitter melon, fenugreek, cinnamon, berberine, and *Gymnema sylvestre* [Fig 2] are found to possess promising anti-diabetic activities. Their Bioactive compounds [Fig 3] show their effects through enhanced insulin sensitivity, antioxidant activity, α-glucosidase inhibition and modulation of vital metabolic pathways like AMPK activation, GLUT4 translocation, and insulin receptor signaling. They also possess anti-inflammatory action which protects β-cells from damage. The difference between normal and diseased conditions in Insulin signaling pathway is depicted in through a pathway [Fig 1]. Future research must involve maximizing the bioavailability of such drugs utilizing nanotechnology-mediated drug delivery systems, discovering synergism of bioactive compounds with existing antidiabetic drugs, and carrying out large-scale clinical trials [5]. Elucidation of their mode of action could lead to personalized, multi- targeted therapies, combination therapies potentially revolutionizing T2DM care while restricting the adverse effects of standard treatment.

2. Natural bioactive compounds for Type 2 Diabetes Mellitus (T2DM) management mulberry (*Morus alba* L.)

Mulberry leaves (*Morus alba* L.) contain some bioactive substances that show the potential therapeutic effects in Type 2 Diabetes Mellitus (T2DM) like flavonoids (Isoquercitrin, Hyperoside, rutin), organic acids (protocatechuic acid, caffeic acid), phenolic acids (gallic acid), alkaloids (1-deoxynojirimycin or DNJ), coumarins (scoparone), and other substances such as resveratrol and β-sitosterol [6]. These bioactive compounds have been made into a variety of products such as Reducose, a 5% DNJ patented mulberry leaf extract which will block glucose absorption, mulberry tea, which reduces postprandial blood glucose, and drug extracts used in Traditional Chinese Medicine (TCM) [7]. Experiments with diabetic animal models have established that mulberry leaf extract significantly lowers FBG (Fasting Blood Glucose), improves insulin sensitivity, and regulates amino acid and lipid metabolism. Mulberry leaf extract works well in T2DM treatment due to the presence of DNJ which controls α-glucosidase inhibition, this leaf extract also regulates lipid and carbohydrate metabolism (by isoquercitrin and caffeic acid), it corrects Insulin Resistance (IR) by the activation of AMPK, and anti-inflammatory and antioxidant effects based on phenolic acids and flavonoids [8]. The therapeutic potential of mulberry extracts suggests their use as a subsidiary treatment to traditional anti-diabetic medications, nutraceuticals for prediabetes control, and also potential new drug leads have been proposed due to their multi- targeted metabolic actions. Future research needs to include large-scale clinical trials to confirm efficacy, synergism of mulberry leaf extract with other bioactive compounds for improved glucose control, and personalized medicine approaches to tailor mulberry-derived therapies to specific metabolic conditions.

Mulberry (*Morus* spp.) is also reported to have strong therapeutic value, particularly for diabetes, cardiovascular disease [9], neurodegeneration [10], liver disease [11], sepsis [12] and cancer. Its bioactive compounds (flavonoids, anthocyanins, fisetin, mulberry side A, and morusin) work by reducing oxidative stress [13], modulating immune functions, enhancing insulin sensitivity, and inhibiting vascular impairment [14]. To extend its health benefits, several Ayurveda formulations and clinical applications are being researched.

Turmeric (*Curcuma longa*)

Turmeric (*Curcuma longa*), its active principle is known as curcumin, which consists of anti- inflammatory, antioxidant, hypoglycemic, and lipid-lowering activity, which makes it a potential therapeutic drug for Type 2 Diabetes Mellitus (T2DM). Though curcumin has a lot of potential, it has poor bioavailability due to the rapid metabolic degradation and limited absorption by the body, making its overall effectiveness very low. To overcome this, scientists have developed more efficient versions of curcumin, that includes phytosome curcumin, which is easier for the body to absorb; curcumin combined with piperine, where piperine will help boost its availability in the body; nano-curcumin, that dissolves better and enters into the cells more efficiently; and curcumin-lipid nanoparticles, to enhance its stability and also to extend its operational lifespan. Curcumin was found to effectively decrease fasting glucose levels, HbA1c, and Insulin Resistance (HOMA-IR), to improve lipid profile by reducing Low-Density Lipoprotein (LDL), Very Low-Density Lipoprotein (VLDL), and triglycerides, and raising High-Density Lipoprotein (HDL) and also has anti-inflammatory properties owing to NF-κB inhibition, TNF-α, IL-6, and MCP-1 [15]. Increased levels of Superoxide Dismutase (SOD), catalase, and glutathione peroxidase lowers oxidative stress, thereby avoiding damage to cells. β-cell integrity has been preserved by curcumin by inhibiting apoptosis and stimulating insulin release through PPAR-γ activation [16]. Clinical studies suggest its potential to avert T2DM development, enhance liver and kidney function, and maintain cardio- vascular integrity, as it can enhance endothelial function and suppress oxidative stress [17]. Future studies must aim to introduce newer drug delivery systems to improve the bioavailability of curcumin, determining optimal doses and safety by performing long-term clinical trials, exploring combination therapy with standard anti-diabetic drugs, and investigating molecular mechanisms further to elucidate its exact role in glucose homeostasis and insulin action.

Turmeric (*Curcuma longa*) is a highly in- fluential medicinal herb with dynamic anti- inflammatory, neuroprotective [18], anti- cancer, cardioprotective [19], and antimicrobial activity [20]. The active compound, curcumin, has antioxidant [21], immune-modulating, and antiviral action, and it is beneficial in Alzheimer's [22], cardiovascular disease, cancer, diabetes, arthritis, and COVID-19 [23]. Increasing its bioavailability using nanotechnology and finding its use in neu-rodegenerative and viral infections are the current studies.

Bitter Melon (*Momordica charantia*)

Bitter melon (*Momordica charantia*) is a combi- nation of bioactive constituents with antidiabetic activity, such as cucurbitane-type triterpenoids (Momordicosides, Karavilosides, Kuguacins, goya glycosides), Charantin (a blend of β-sitosterol glucosides), p-insulin (a polypeptide of insulin- like character), vicine, and *Momordica charantia* Polysaccharide (MCP), which consists of an activity related to glucose regulation as well as immunomodulatory activity [24]. For increased therapeutic application, bitter melon is made available in different consumable forms like juice (unripe fruits), decoctions (herbal infusions), tablets/capsules (with powder extracts), polysaccharide extracts (MCP), and soft extracts [25]. Experimental evidence shows that bitter melon employs its hypoglycemic action by increasing GLUT4 translocation and AMPK activation, stimulate glucose uptake in muscle and adipose tissues, suppress α-glucosidase to slow down the process of glucose absorption, stimulate insulin secretion from β-cells, and suppress oxidative stress by applying its antioxidant effect. Therapeutic ap- plications of bitter melon confine enhancement of insulin sensitivity, preservation of β-cell function, reduction in postprandial glycemic peaks, and resistance towards metabolic disorders like dyslipidemia and fatty liver. Preclinical trials reveal a reduction in blood glucose and HbA1c, and mixed outcomes are seen in clinical trials, some studies present clear improvements in HbA1c and fasting blood glucose without any side effects, but meta- analyses show mixed results [26]. However, additional research is required to standardize extract concentrations, explore synergies with available diabetes drugs, perform large-scale placebo-controlled clinical trials, enhance the bioavailability of key constituents like Charantin and p-insulin, and more exploration of molecular mechanisms to completely understand how Mo- mordica charantia influences diabetes-associated metabolic pathways.

Bitter melon (*Momordica charantia*) has proved strong therapeutic activity against diabetes [27], cancer [28], obesity, inflammation, hypertension, and microbial infections. The bioactive pep- tides, flavonoids, and saponins in bitter melon supplement their action by modulating glucose metabolism [29], apoptosis of cancer cells [30], inhibiting Angiotensin-Converting Enzyme In- hibitors(ACE) for blood pressure control, and skin health maintenance [31]. Recent research is focusing on nanomedicine, drug formulation, and clinical translation, which is expected to lower the side effects of currently available drugs.

Fenugreek (*Trigonella foenum-graecum* L.)

Fenugreek (*Trigonella foenum-graecum* L.) consists of various bioactive phytochemicals that are involved in its antidiabetic activities, such as 4-hydroxy isoleucine (an amino acid with insulin-releasing and glucose transport functions), diosgenin (a saponin with glucose action-modulation and insulin-sensitization properties), Furostanol saponins (reduces blood cholesterol and glucose levels), galactomannan fiber (a soluble dietary fiber with slowing of glucose absorption rate and peak postprandial suppression), and trigonelline and alkaloids (play roles in lipid metabolism and the regulation of blood glucose). Fenugreek has been used in many forms in diabetes management, which includes fenugreek seed powder (10–15 g/day will lower blood glucose), fenugreek water extract (soaked seeds with glucose-lowering effect), fenugreek seed isolates (5 g isolates lowering postprandial glucose levels to a very high degree), fenugreek- cinnamon combinations (which lowered HbA1C and cholesterol), and fenugreek gum extracts (helps in glucose metabolism and lipid profile) [32]. Fenugreek supplementation was shown to reduce fasting blood glucose, postprandial glucose, and HbA1C effectively, and reduced diabetic status by 20.83% in the subjects has been found in some clinical trials [33]. This has been supplemented by animal research due to its activity in insulin release enhancement, glucose uptake, and lipid metabolism. Therapeutic effects of fenugreek in diabetes are insulin sensitization, reduction of HbA1C, blood glucose stabilization, enhancement of lipid metabolism (reduction of LDL and triglycerides, enhancement of HDL), prevention of diabetic complications such as cataracts, kidney impairment, and cardiovascular disorders. Larger scale clinical trials in the future must confirm its safety and efficacy, dosage optimization and formulation change for different patient groups, molecular mechanism studies to identify its definite antihyperglycemic action, integration of fenugreek into individualized nutrition and diabetes management schemes and combination treatment regimes with drugs and other herbal medications.

Fenugreek possess a wide range of therapeutic potential in diabetes, cardiovascular disease, cancer, PCOS [34], wound healing [35], and inflammatory conditions, due to its antioxidant, anti-inflammatory, insulin-sensitizing [36], and antiproliferative effects [37] which can be further explored using *in silico* and *in vitro* approaches.

Cinnamon (*Cinnamomum verum*) and Stevia (*Stevia rebaudiana*)

Cinnamon (*Cinnamomum verum*) and Stevia (*Stevia rebaudiana*) have bioactive compounds that exhibit great antidiabetic properties. Cin- namon has significant levels of cinnamaldehyde and polyphenolic polymers (A-type procyani- dins), which have antioxidant, anti-inflammatory, insulin-sensitising, and α-amylase inhibitory properties. Stevia includes steviosides that reduce glucose consumption, lower blood glucose, and improve insulin sensitivity. Numerous formu- lations are available for diabetic management using cinnamon and stevia extract [38]. An active ingredient preparation which was also proven to be successful is cinnamon supplementation as a capsular dose that lowers oxidative stress, inflammation and improved insulin sensitivity of diabetics [39].

The therapeutic activities of these compounds in type 2 diabetes are inhibition of major enzymes of glucose metabolism, i.e., α-amylase and α-glucosidase, and inhibiting carbohydrate absorption. Cinnamon polyphenols activate insulin receptors and glucose uptake and inhibit insulin resistance. The anti-inflammatory action of cinnamon is NF-kB pathway inhibition and decreasing high-sensitivity C-reactive protein (hs-CRP) levels, which is the reverse of diabetes-associated chronic inflammation. Further, the antioxidant potential of polyphenolic substances helps to search for Reactive Oxygen Species (ROS), preventing oxidative damage in diabetic subjects.

Further studies must be conducted to evaluate synergistic interactions of cinnamon with other anti-diabetic herbs and its possible use in multi- ingredient foods. Personalised nutrition through genetic and metabolic profiling would allow the production of individualised functional foods for better diabetes control.

Cinnamon (*Cinnamomum* spp.) is of very high therapeutic importance in diabetes [40], Parkinson's disease [41], cardiovascular disease, neurodegeneration, cancer, inflammation, and obesity. Its bioactive compounds (cinnamaldehyde, polyphenols, and procyanidins) improve insulin sensitivity, inhibit oxidative stress [42], inhibit neurodegeneration, and modulate lipid metabolism. Its neuroprotective, anticancer, and metabolic actions are of interest to ongoing stud- ies, qualifying it as a potential natural therapeutic drug.

Indian Barberry (*Berberis aristata*)

Indian barberry (*Berberis aristata*) abounds with countless bioactive compounds such as berberine, epi berberine, palmatine, jatrorrhizine, quercetin, columbamine, and pakistanine that reveal an-tidiabetic, antioxidant, and anti-inflammatory activity. These compounds have complicated roles in diabetic management through insulin sensitivity stimulation, oxidative stress inhibition, and gluco- neogenesis inhibition in the liver. *Berberis aristata* exists in various formulations that are used for diabetes treatment. Classical Ayurvedic and Unani preparations are decoctions, powders, and ex- tracts that are typically supplemented with Amla, Guduchi, and Haritaki [43]. Another preparation, Rasaunt, is also employed in gastrointestinal and cutaneous disorders. Pharmaceutical preparations now consist of ethanolic and methanolic extracts, capsules or powdered formulations and combi- nation therapy with metformin, sulfonylureas, or statins for improved glycaemic and lipid control.

The effectiveness of *Berberis aristata* in T2DM is confirmed with high-quality clinical trial data and substantial drop in Fasting Blood Sugar (FBS), improved insulin sensitivity, and lipid profile regulation. Mechanistically, berberine is an AMPK activator that increases insulin receptor expression and regeneration and β-cell regeneration but inhibits hepatic gluconeogenesis. The anti-inflammatory and antioxidant properties re- duce pancreatic β-cell inflammation and oxidative stress, thus decreasing diabetic complications.

Apart from glycaemic control, *Berberis aristata* also possesses lipid regulation activity by lowering Low-Density Lipoprotein (LDL) and triglycerides and raising High-Density Lipoprotein (HDL), decreasing the cardiovascular risk in diabetic patients. Its anti-inflammatory activity by suppressing pro-inflammatory cytokines like TNF-α and IL-6 aids in enhancing overall metabolic health. Combination therapy must be the future re- search priorities with a study of synergy with other antidiabetic drugs and/or probiotics to improve the therapeutic level. Personalized medicine models can possibly modify the treatment based on effects on individual response at the genomic level and planning biomarker-driven combination dosing regimens. Drug delivery by nanotechnology, e.g. nanoparticle encapsulation of berberine and prolonged release formulations, would enhance bioavailability as well as long-term efficacy, thus rendering *Berberis aristata* a valuable natural drug for the management of diabetes.

Berberis aristata possesses all of the therapeutic potential, namely in bacterial infection (meningitis) [44], cancer (melanoma and cervical), neurodegenerative disease (Alzheimer's), and inflammatory disease [45]. Berberine is known to be involved in the initiation of apoptosis, immune modulation, inhibition of bacteria, and neuro- protection [46]. Its use along with conventional treatment is the focus of ongoing research for greater efficacy against different diseases [47].

Gurmar (*Gymnema sylvestre*)

Gurmar (*Gymnema sylvestre*) is a very powerful anti-diabetic herb containing many bioactive compounds that are responsible for blood sugar control. The bioactive compounds incorporate gymnemic acids (I, II, IV, X), gymnemagenin, gymnema side VI, stigmasterol, deacylgymnemic acid, beta-amyrin acetate, longispinogenin, phytic acid, orcinol, and curcumin, each of which is responsible for the inhibition of glucose uptake, stimulation of insulin release, enhancement in lipid metabolism, and inhibiting inflammation.

Different forms of *Gymnema sylvestre* have been studied, such as OSA-Om Santal Adivasi (lyophilized Gymnema extract), methanolic and ethanolic extracts, and alcoholic extracts (GS4, F2, F43). Among these, OSA extract has been shown to grow insulin release and β-cell mass, while methanolic extracts have high inhibitory effect on α-glucosidase and decrease postprandial peak levels of glucose [48].

The efficacy of *Gymnema sylvestre* in T2DM has been established by clinical as well as animal experiments. Gymnemagenin and gymnemic acids stimulate insulin release, while Gymnemagenin also stimulates lipid metabolism genes to boost triglyceride hydrolysis, insulin sensitivity, and glucose uptake [49]. Clinical trials of OSA extract have been found to decrease fasting blood sugar and HbA1c levels significantly, confirming its therapeutic value for diabetes. Furthermore, network pharmacology studies demonstrate that gymnemic acid I targets key diabetes-related proteins such as AKT1, TNF (Tumor necrosis factor), and Peroxisome Proliferator-Activated Receptor Gamma (PPARG), as well as influences the insulin signaling pathway and inflammation processes [50].

In addition to the control of glycaemia, *Gymnema sylvestre* also possesses therapeutic action in lipid metabolism and is therefore a potential anti-obesity supplement. Its anti-inflammatory action (inhibition of TNF-α and IL-1B) and induction of adiponectin expression also suggest other metabolic effects, reducing diabetes com- plications. Clinical trials need to be performed to confirm standardised extracts such as OSA and develop combination therapies with present anti-diabetic drugs to improve efficacy and reduce side effects. Network pharmacology approaches also predict synergistic action with PPARγ agonists and AKT modulators, which would further increase insulin signalling. Gymnema-derived nutraceuticals and phytomedicine formulations for specific site targeting are likely to be cost-effective and sustainable approaches for diabetes management. Further molecular docking and dynamics studies of Gymnemic Acid and its interaction with AKT1 could initiate novel drug applications, making *Gymnema sylvestre* a strong force in herbal drug therapy for diabetes.

Gymnema sylvestre is also a potential tradi- tional drug against diabetes [51], cancer, obesity, cardiovascular disease, and inflammation [52]. Its gymnemic acids and bioactive compounds slows glucose uptake, induce apoptosis in cancer cells, and regulate lipid metabolism [53]. Recent research highlight its nanotechnology-derived applications and combination therapies with improved therapeutic outcomes [54].

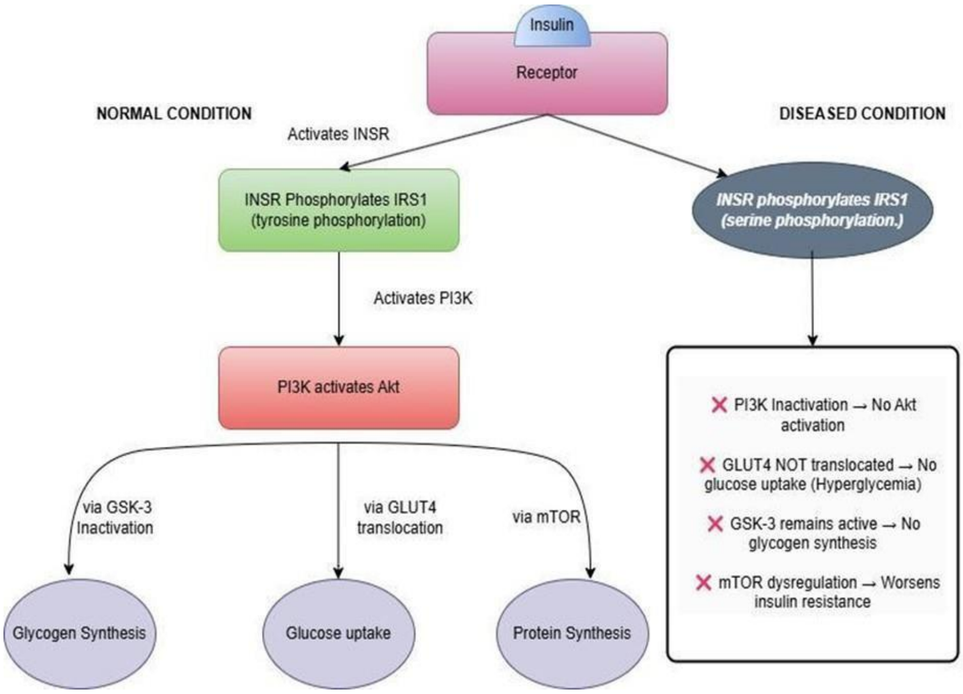

Fig 1: Insulin signalling pathway in normal and diseased conditions

This Pathway illustrates Insulin signaling pathway. The insulin signaling pathway regulates blood glucose levels to prevent diabetes and insulin resistance. It facilitates glycogen synthesis to store energy, supports muscle growth via protein syn- thesis, and maintains cellular function to prevent metabolic disorders, ensuring overall well-being.

However, in diseased condition, IRS1 gets phosphorylated with serine rather than tyrosine which prevents PI3K activation leading to occurrence of a series of events which are responsible for T2DM.

Table 1: Plant-derived medicines for managing diabetes and related disorders

Plant	Active Compounds	Diseases Cured	References
Mulberry (*Morus alba* L.)	1-Deoxynojirimycin (DNJ), Isoquercitrin, Hyperoside, Rutin, Protocatechuic acid, Caffeic acid, Gallic acid, Scoparone, Resveratrol, β-Sitosterol	Type 2 Diabetes Mellitus (T2DM)	Chang, C. L., Lin, Y., Bartolome, A. P., Chen, Y. C., Chiu, S. C., & Yang, W. C. (2013) [1]
Turmeric (*Curcuma longa*)	Curcumin	T2DM, Inflammation, Oxidative Stress	Abbas, S., Latif, M. S., Shafie, N. S., Ghazali, M. I., & Kormin, F. (2020) [18]; Qin, S., Huang, L., Gong, J., Shen, S., Huang, J., Ren, H., & Hu, H. (2017) [19]
Bitter Melon (*Momordica charantia*)	Vicine, Momordico- sides, Karavilosides, Kuguacins, Goyaglycosides, Charantin, P-Insulin, Vicine, *Momordica charantia* Polysaccharide (MCP)	T2DM, Breast Cancer, Fatty Liver Disease	Saliu, J. A. (2024) [28]; Hussain, A., Korma, S. A., Kabir, K., Kauser, S., Arif, M. R., Fatima, H., & Ali, A. (2024) [29]
Fenugreek (*Trigonella foenum- graecum L.*)	Diosgenin, 4-Hydroxyisoleucine, Furostanol Saponins, Galactomannan Fiber, Trigonelline, Alkaloids	T2DM, PCOS	Zafar, U., Amjad, U. A., Ghaffar, B., Fatima, A., Habiba, U. E., Malik, R., & Ashraf, R. (2024) [34]
Cinnamon (*Cinnamomum verum*)	Cinnamaldehyde, A-type Procyanidins	T2DM, Inflammation, Insulin Sensitivity	Ziegenfuss, T. N., Hofheins, J. E., Mendel, R. W., Lan- dis, J., & Anderson, R. A. (2006) [40]
Stevia (*Stevia rebaudiana*)	Stevioside	T2DM, Blood Glucose Regulation	Hameed, A., Ashraf, F., Anwar, M. J., Amjad, A., Hussain, M., Imran, M., & Jbawi, E. A. (2024) [38]
Indian Barberry (*Berberis aris- tata*)	Berberine, Epiberberine, Palmatine, Jatrorrhizine, Berbamine, Quercetin, Columbamine, Pakistanine	T2DM, Oxidative Stress, Cervical Cancer	Vaghasia, H., Patel, R., Prajapati, J., Shah, K., Saraf, M., & Rawal, R. M. (2025) [46]
Gymnema (*Gymnema sylvestre*)	Gurmarin, Gymnemic Acids (I, II, IV, X), Gymnemagenin, Gymnemaside VI, Stigmasterol, Deacylgymnemic Acid, Beta-Amyrin Acetate, Longispinogenin, Phytic Acid, Orcinol, Curcumin	T2DM, Insulin Regulation, Lipid Metabolism	DasNandy, A., Patil, V. S., Hegde, H. V., Harish, D. R., & Roy, S. (2022) [51]

This table summarizes various medicinal plants commonly used in traditional medicine for managing Type 2 Diabetes Mellitus (T2DM) and associated disorders. The active compounds present in these plants contribute to their therapeutic potential, addressing disease conditions.

Fig 2: Plants and plant parts consisting of phytocompounds used for their reliable phytocompounds which are significant in treating Type 2 Diabetes Mellitus (T2DM)

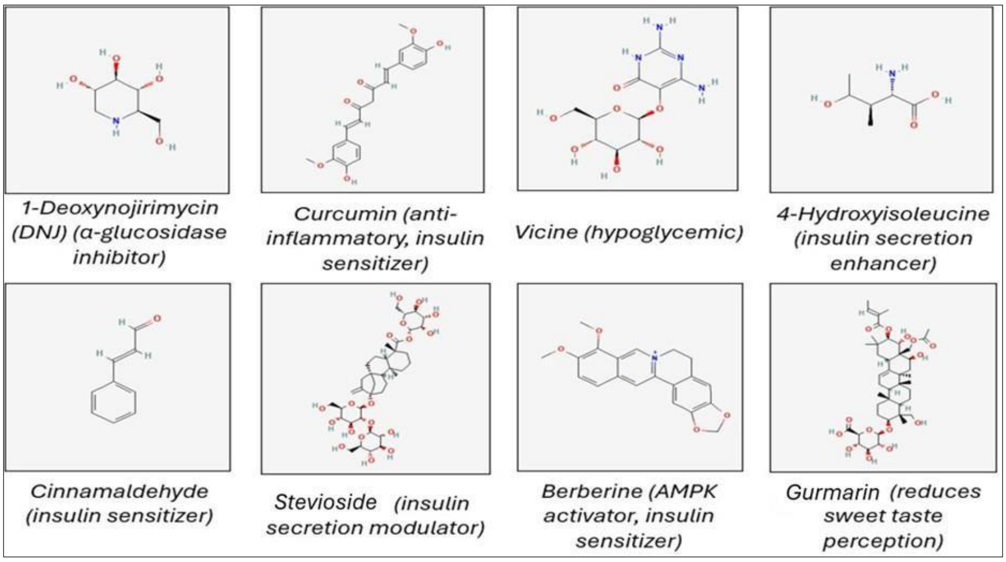

Fig 3: Bioactive compounds with potential antidiabetic activity

This figure illustrates the molecular structures and functional activities of several bioactive compounds with potential antidiabetic activity from different plant parts of Mulberry, Turmeric, Bitter melon, Fenugreek, Cinnamon, Stevia, Indian barberry and Gurmar. These compounds possess varied mechanisms of action, including insulin sensitization, modulation of glucose metabolism, and alteration of taste perception.

3. Future perspectives

The usage of plant extract molecules as a treatment mode is highly encouraged for studying molecular interactions. A blend or "cocktail" of plant bioactive molecules can be studied for their synergistic interaction in binding to a particular protein or gene. The process can increase binding efficiency and therapeutic effectiveness and this might be the reason for promising drug discovery strategies. More sophisticated computational methods, like molecular docking and dynamics simulation, could be applied to explore these interactions, and thereafter, experimental validation could be used to measure their efficiency in biological systems. The finest drugs for protein or gene interaction need to be identified and optimized for drug development strategies.

Screening of various plant-derived molecules with higher binding affinity and biological activity is the area of future inquiry. High-throughput screening, structural bioinformatics, and network analysis serve as critical methodologies for the identification and prioritization of potential candidates.

And also, the genomic and proteomic data can be combined to get insightful observations of these com- pounds' modulation in disease pathways and the ability to identify novel drugs. Identifying biomarkers is also key to formulate personalized medicine based on the correlation between molecular interactions and disease mechanisms. Through disease-specific biomarkers, it becomes possible to generate alternative therapeutic options based on specific patient profiles and thus facilitate individualized treatment schemes in lieu of traditional targeted therapy. Plant bioactive compounds employed in biomarker-based therapy can result in new treatment procedures that are customized and effective. More research is necessary for confirming these biomarkers in heterogeneous populations to determine their validity for clinical use, eventually leading to precision medicine.

4. Conclusion

The rising global prevalence of Type 2 Diabetes Mellitus (T2DM) underscores the imperative to explore novel therapeutic agents along with existing pharmacological therapies for enhancing treatment effects and disease management. The treatment developing from natural agents like mulberry, turmeric, bitter melon, fenugreek, cinnamon, berberine, and *Gymnema Sylvestre* for regulating the critical metabolic pathways rules the glucose homeostasis, insulin sensitivity, and relief of oxidative stress has been investigated here. These bioactive molecules shows different mechanisms, such as α-glucosidase inhibition, AMPK activation, insulin receptor modulation, and anti-inflammatory effects, are the potential adjunct therapies for diabetes treatment. In spite of showing promising preclinical results, limitations like low bioavailability, poor metabolic stability, and unavailability of large-scale clinical trials inhibit their clinical applicability. To bridge these gaps, new drug delivery systems, such as nanotechnology-based formulations, encapsulation technologies, and combination therapies, must be investigated. In addition to this, the application of systems biology and personalized medicine strategies will allow the creation of targeted interventions based on metabolic and genetic profiling, optimizing the treatment's efficacy.

Further research is needed to bridge the gap between computational predictions and experimental vali- dation with *in vitro*, *in vivo*, and clinical studies of efficacy, safety, and optimal dose of such therapeutic compounds. merging molecular simulations, bioinformatics-directed drug discovery, and experimental pharmacology also promises to be a major study to enhance the plant-derived therapies for T2DM towards a safer, multi-targeted, and sustainable diabetes regimen.

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