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Medicinal Plants As Sources Of Antidiabetic Bioactive Compounds: A Systematic Review Of Extraction, Isolation, And Pharmacological Evaluation Methods

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ABSTRACT

Background: Diabetes mellitus (DM) is a global metabolic pandemic with an estimated 451 million people affected worldwide, with this figure being projected to increase to 693 million by 2045. Although effective, conventional antidiabetic pharmacotherapy is plagued by adverse effects, drug resistance, and high cost, fostering renewed scientific interest in plant-derived therapeutics. India contains an abundant source of ethnomedicinal plants with traditional applications in glycaemic management, many of which have not been fully characterized at the molecular level.

Purposes: This is a review in which the evidence is systematically consolidated on (i) pharmacology of antidiabetic phytoconstituents, (ii) already established and emerging strategies of extraction and isolation, (iii) already validated pharmacological models of antidiabetic screening, and (iv) spectroscopic methodologies of structural characterization of bioactive compounds.

Methods: A thorough literature review was performed in PubMed, Scopus, Web of Science and Google Scholar using the following keywords: antidiabetic plants, phytoconstituents, bioactive compounds, α-amylase inhibition, α-glucosidase inhibition, LC-MS, GC-MS, and Indian medicinal plants. After quality appraisal, articles that were published between 2000 and 2024 were included.

Findings: More than 400 plant species have been reported to have hypoglycaemic potential, with flavonoids, alkaloids, terpenoids, glycosides and tannins being the major pharmacologically active classes. One of them is the inhibition of carbohydrate-hydrolyzing enzymes (α-amylase and α-glucosidase), stimulation of pancreatic insulin secretion, upregulation of GLUT4, and AMPK activation. Soxhlet extraction, Maceration, and Ultrasound-assisted extraction have been commonly used for isolation, whereas HR-LC-MS and GC-MS have been employed as gold standards for structural elucidation. The alloxan- and streptozotocin-induced rodent models continue to predominate as in vivo systems for the validation of antidiabetic agents.

Conclusion: India harbors a scientifically underexplored phytochemical reservoir with high potential for the discovery of antidiabetic drugs. Fractionation guided by bioactivity, coupled with high-resolution spectroscopic detection, is a strong pipeline for revealing new, safe, and effective lead compounds. Molecular docking, ADMET profiling, and phase I/II clinical trials should be the focus of future research to translate preclinical results into therapeutic applications.

Keywords: *Antidiabetic; Bioactive compounds; Ethnopharmacology; Extraction; Fractionation; Isolation; LC-MS; GC-MS; Medicinal plants; Phytoconstituents; α-Amylase inhibition; α-Glucosidase inhibition*

1. INTRODUCTION

Diabetes mellitus (DM) is a multifactorial, complex metabolic disorder characterized by persistent hyperglycemia caused by defects in insulin secretion, insulin action, or both. The socioeconomic burden of diabetes is enormous: an estimated 4.2 million deaths in 2019 can be attributed to diabetes and its complications, and worldwide spending on healthcare is estimated to exceed USD 760 billion per year. [3]

Although synthetic agents biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and SGLT-2 inhibitors form the basis of modern antidiabetic therapy, they are associated with adverse effects including hypoglycemia [1,2], weight gain, lactic acidosis, fluid retention, and genitourinary infections [5], compelling both patients and clinicians to find safer alternatives.

The use of plant-based remedies in glycaemic control has long been a part of ethnobotanical traditions world-wide, and especially within the Indian subcontinent. More than 400 species of plant have been reported as having hypoglycaemic activity, although most of these are not fully characterized in phytochemical and molecular pharmacological terms.

Several regions of Maharashtra, India, including districts such as Nanded, Aurangabad, Latur, Osmanabad, Hingoli, Parbhani, Beed, and Jalna, harbor a rich array of ethnomedicinal flora used by indigenous communities to manage hyperglycemia. [9] Although this region's extensive botanical riches and systematic

scientific exploration, especially bioactivity-guided isolation and structural characterization of antidiabetic compounds, have long been understudied. [6,7]

The present review summarises the latest state of knowledge on: (i) the pathophysiology and classification of DM; (ii) the limitations of current pharmacotherapy; (iii) phytoconstituents whose antidiabetic mechanisms have been validated; (iv) modern methodologies of extraction, fractionation and isolation; (v) pharmacological screening models; and (vi) advanced analytical strategies of bioactive compound identification. The review is intended as a scholarly framework to support current and future studies on antidiabetic bioactive compounds in Indian medicinal plants.

2. PATHOPHYSIOLOGY AND CLASSIFICATION OF DIABETES MELLITUS

2.1 Definition and Aetiology

Four main aetiological mechanisms have been identified: (i) inadequate production of insulin by the pancreas in response to dysfunction of the beta-cell; [1] (ii) peripheral tissue resistance to insulin action; (iii) dys-regulated production of counter-regulatory hormones (glucagon, cortisol, growth hormone); and (iv) increased production of reactive oxygen species (ROS) secondary to chronic hyperglycaemia, which maintains oxidative damage in the beta-cell. [2,3]

2.2 Classification

Type 1 DM (T1DM): A type of autoimmune disease, which is characterized by the selective destruction of insulin-secreting pancreatic β-cells (or β cell group). T1DM has been estimated to account for 5–10% of all DM and is most commonly found in children and young adults. [4]

Type 2 DM (T2DM): The most common type (>90% of cases), T2DM is a form of diabetes characterized by progressive insulin secretory deficiency superimposed on a background of peripheral insulin resistance. The main risk factors are obesity, sedentary lifestyle and genetic predisposition. Pathologically, sustained hyperglycemia drives glucotoxicity and lipotoxicity, further impairing β-cell function. [2,3]

Gestational DM (GDM): Intolerance to glucose, first recognized during pregnancy, which could be attributed to the placental hormones (cortisol, estrogen, HPL) antagonizing insulin action. GDM has an estimated burden of 21.3 million live births each year, and poses long-term risk of T2DM in both the mother and her offspring. [9]

Other Specific Type: Include monogenic DM (MODY), drug-induced DM (glucocorticoids, antipsychotics), cystic fibrosis-related DM and latent autoimmune diabetes in adults (LADA). A condition of insensitivity of ADH to reabsorb water in the kidneys, causing diabetes insipidus, which is not DM but shares the symptom of polyuria.

2.3 Biosynthesis and Secretion of Insulin.

Insulin is a polypeptide consisting of 51 amino acids synthesized in pancreatic β -cells as preproinsulin (110 amino acids), which is cleaved into 2 by the cleavage furrow. [4] The process of insulin secretion (GSIS) is

characterized by: (i) the uptake of glucose through GLUT2; (ii) the production of ATP through glycolysis and the Krebs cycle; (iii) closing of KATP channels; (iv) membrane depolarisation; (v) influx of calcium via the voltage-gated Ca^{2+} channel; and (vi) exocytosis of insulin granules. The metabolism of insulin is then mainly first-pass extraction in the liver (50% first-pass extraction) and some small amounts of clearance by the kidney and skeletal muscle.

3. Existing therapeutic approaches to therapy and their shortcomings.

Present-day antidiabetic pharmacotherapy includes six major oral drug classes and two types of injectable. [5,6] Although effective in insulin sensitizing, the thiazolidinediones (pioglitazone, rosiglitazone) are associated with weight gain, fluid retention, peripheral edema, heart failure, and, in the case of pioglitazone, with a hypothetical risk of bladder cancer. Sulfonylureas have a risk of hypoglycemia, especially in the elderly and renal-impaired patients. DPP-4 inhibitors and GLP-1 agonists are more tolerable, but prohibitively costly in resource-constrained environments. Cardiorenal protective, but predisposing to genitourinary infections and diabetic ketoacidosis, SGLT-2 inhibitors are. [5]

This pharmacological environment underscores the clinical need to identify novel, more effective antidiabetic agents with respect to efficacy, safety, affordability, and tolerability. Plant-derived compounds present a scientifically appealing pool of lead molecules whose mechanisms of action are often complementary or additive to those of current therapies, making ethnopharmacology a paradigm for scientifically compelling drug discovery. [6,7]

4. MEDICINAL PLANTS having ANTIDIABETIC POTENTIAL.

A survey of the ethnobotanical literature indicates that more than 400 plant species across various botanical families have been reported to have hypoglycaemic properties. [6] Table 1 lists 10 major medicinal plants, their phytoconstituents, and their proven antidiabetic mechanisms, some of which are widely distributed across India.

Table 1. Key Medicinal Plants with Antidiabetic Potential: Phytoconstituents and Mechanisms of Action

Medicinal Plant	Family	Plant Part	Key Phytoconstituents	Antidiabetic Mechanism(s)
Momordica charantia	Cucurbitaceae	Fruit	Charantin, Polypeptide-p, Vicine	α-glucosidase inhibition, insulin secretion stimulation
Trigonella foenum-graecum	Fabaceae	Seed	4-Hydroxyisoleucine, Diosgenin	Insulin secretagogue, GLUT4 upregulation
Azadirachta indica	Meliaceae	Leaf, Bark	Nimbolide, Azadirachtin	Pancreatic β-cell regeneration, oxidative stress reduction
Gymnema sylvestre	Apocynaceae	Leaf	Gymnemic acids, Gurmarin	SGLT2 inhibition, glucose absorption reduction
Pterocarpus marsupium	Fabaceae	Heartwood	Pterostilbene, Epicatechin	PPAR-γ activation, insulin sensitization
Tinospora cordifolia	Menispermaceae	Stem	Berberine, Tinosporin	AMP kinase activation, hepatic glucose regulation
Allium sativum	Amaryllidaceae	Bulb	Allicin, S-allyl cysteine	Insulin release stimulation, glycogen synthesis
Emblica officinalis	Phyllanthaceae	Fruit	Ellagic acid, Emblicanin A & B	Antioxidant, α-amylase inhibition
Cinnamomum zeylanicum	Lauraceae	Bark	Cinnamaldehyde, Procyanidin B2	Insulin receptor sensitization, GLUT4 translocation
Swertia chirayita	Gentianaceae	Whole plant	Swertiamarin, Mangiferin	Insulin secretagogue, DPP-IV inhibition

Abbreviations: GLUT4, glucose transporter type 4; PPAR-γ, peroxisome proliferator-activated receptor gamma; SGLT, sodium-glucose cotransporter; AMPK, AMP-activated protein kinase; DPP-IV, dipeptidyl peptidase-IV.

4.1 Flavonoids

Flavonoids are among the most well-researched groups of plant polyphenols with antidiabetic properties. Potent inhibition of α-amylase and α-glucosidase, which are essential in the digestion of carbohydrates in the intestines and postprandial glycemia [5,8], has been demonstrated by flavonoids interacting with the active site of these enzymes using hydrogen bonding and hydrophobic forces, which reduces the kinetics of glucose absorption. Moreover, flavonoids have antioxidant properties by neutralizing ROS through direct radical scavenging, metal chelation, and up-regulation of endogenous antioxidant enzymes (SOD, CAT, GPx), thereby alleviating oxidative injury to β-cells.

4.2 Alkaloids

Berberine, an isoquinoline alkaloid abundant in Tinospora cordifolia and Berberis aristata, is possibly the most well-characterized plant alkaloid antidiabetic agent. Berberine has been shown to have glycaemic efficacy similar to metformin in T2DM patients and a no-gastrointestinal-toxicity profile. [8] Gurmarin is a polypeptide antidiabetic agent derived from Gymnema sylvestre that inhibits the perception of sweet taste and blocks intestinal glucose transport, providing a unique antidiabetic mechanism of gastrointestinal targeting.

4.3 Terpenoids and Saponins

Charantin, a steroidal mixture of glycosides isolated from the fruit of Momordica charantia, has shown insulin-secretagogue-like activity and improved glucose tolerance in alloxan-diabetic rodents. [6] Piagrindioxin (p-Diosgenin) in the seeds of fenugreek stimulates PPAR-γ and enhances insulin signaling via the PI3K/AKT/mTOR pathway. An unusual amino acid of Trigonella foenum-graecum, 4-hydroxyisoleucine, directly stimulates insulin secretion in response to glucose in β-cells.

4.4 Phenolic Acids and Tannins.

Ellagic acid, gallic acid and chlorogenic acid, phenolic acids, which are abundant in Phyllanthus emblica, Terminalia chebula and Coffea arabica respectively, have been reported to induce moderate alpha-glucosidase inhibitory activity and significant antioxidant activity on skeletal muscle cells via AMPK activation. [11] Tannins, by their astringency and protein-precipitating effects, retard the digestion of starch in the intestine and the absorption of glucose through the intestine into the bloodstream. By their astringency and their precipitation of proteins, tannins slow the digestion of starch in the intestine and the absorption of glucose from the intestine into the bloodstream. [12]

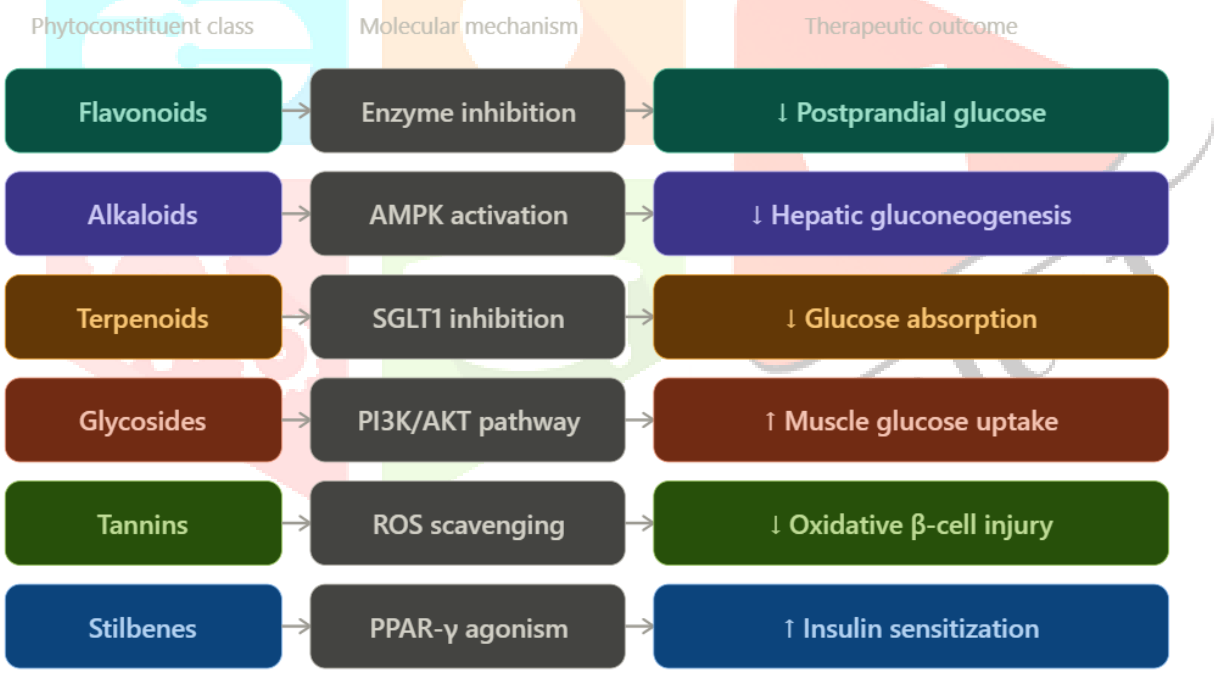

Figure 1. Molecular mechanisms of action of key antidiabetic phytoconstituent classes. Arrows indicate the pathway from the compound class through the molecular target to the therapeutic outcome.

5. Extraction, fractionation and isolation Strategies.

5.1 Extraction Techniques

The choice of a suitable extraction method is a decisive factor in the amount and quality of extractable bioactive compounds. [26] The polarity selectivity and the range of extracted phytoconstituents of a plant

depend on the solvent used, which could be either non-polar (hexane, petroleum ether) or polar (methanol, ethanol, water). Differential partitioning of classes of compounds can be achieved using a sequential extraction strategy, which employs solvents of increasing polarity.

Modern green extraction processes such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE) and pressurised liquid extraction (PLE) have the benefits of high efficiency, short processing time, and low levels of thermal degradation of labile compounds. The UAE uses acoustic cavitation to break cell walls and promote mass transfer, including lipophilic compounds, without solvent residues; SFE uses supercritical CO_2 to selectively extract lipophilic compounds, without solvent residues. [29]

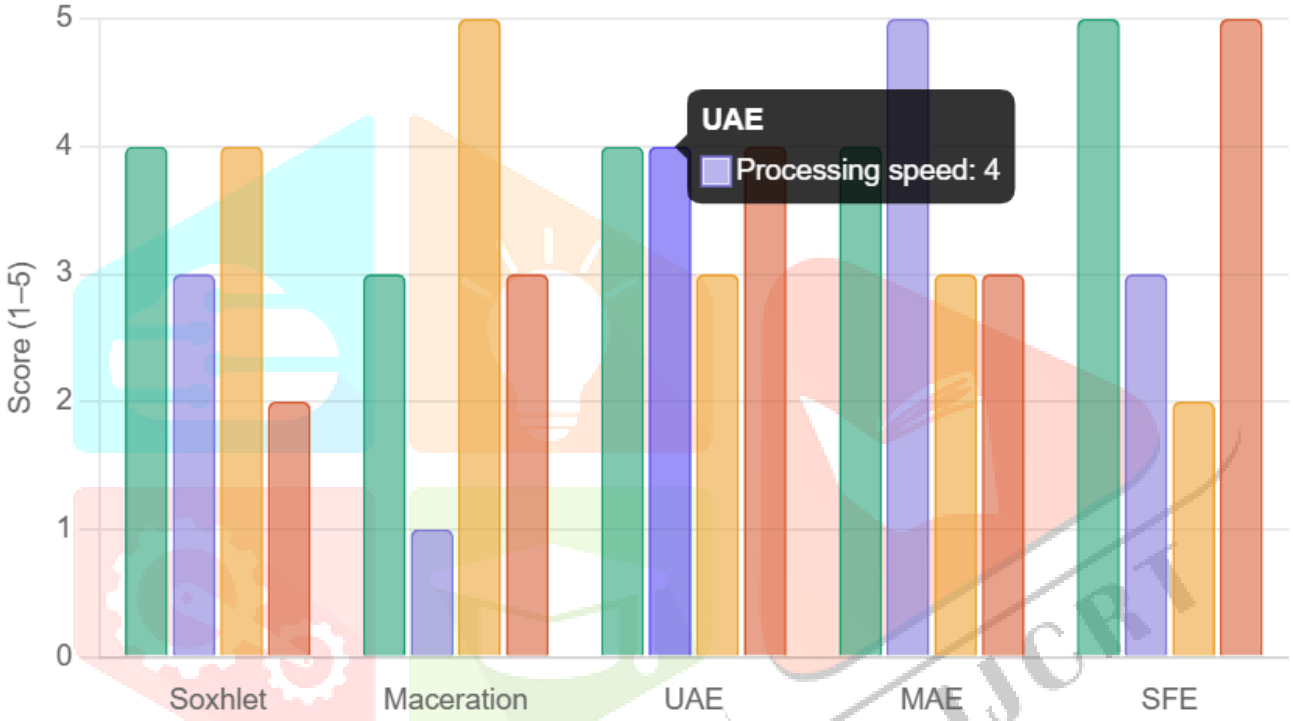

Figure 3. Comparative evaluation of conventional and modern extraction techniques for antidiabetic bioactive compounds. Scores (1–5) reflect relative performance across yield efficiency, processing speed, cost-effectiveness, and thermal safety of labile compounds.

5.2 Phytochemical Standardization

Standardization of plant material and extracts is part and parcel of research reproducibility. Pharmacognostic parameters, including morphological characterization, microscopical evaluation of transverse sections and powder microscopy, and physicochemical standards[27], including loss on drying, extractive values, ash content, and so on.

5.3 Chromatographic Fractionation

The methodological backbone of the process of discovering lead compounds in plant extracts is bioactivity-guided fractionation. After pharmacological screening, the best crude extract is subjected to progressive fractionation. Solvent-solvent partitioning (hexane, ethyl acetate, n-butanol, aqueous) separates compounds based on being polar or apolar. Further open-column chromatography on silica gel, Sephadex LH-20, or reverse-phase C18 packing could then allow the isolation of enriched fractions based on TLC and HPTLC observations. [27,28]

High-performance liquid chromatography (HPLC), especially in preparative mode with photodiode array (PDA) or mass spectrometric detectors, can provide high-resolution separation and purity determination of the separated compounds. Gas chromatography-mass spectrometry (GC-MS) is specifically well-suited to volatile and semi-volatile phytoconstituents, whereas high-resolution liquid chromatography-mass spectrometry (HR-LC-MS) is more suitable to provide the correct mass information and fragmentation patterns that can be used to provide a structural elucidation of polar and thermolabile molecules. [29,30,31]

Figure 2. Stepwise methodology for extraction, isolation, and identification of antidiabetic bioactive compounds from medicinal plants.

6. PHARMACOLOGICAL SCREENING MODELS FOR ANTIDIABETIC EVALUATION

Strict pharmacological validation of antidiabetic activity would require a hierarchical system of screening that would include in vitro enzyme inhibition assays, cell-based assays of glucose uptake, acute and repeated-dose toxicity studies, and in vivo animal models. Table 2 gives a cumulative summary of validated models which have been used in preclinical studies on antidiabetic drugs.

Table 2. Validated Pharmacological Models for Preclinical Antidiabetic Screening

Model	Type	Inducing Agent / Method	Mechanism of Induction	Parameters Evaluated
Alloxan-induced DM	In vivo	Alloxan monohydrate (150 mg/kg, i.p.)	Selective destruction of pancreatic β-cells via oxidative stress	FBG, insulin, HbA1c, lipid profile, body weight
STZ-induced Type 1 DM	In vivo	Streptozotocin (60 mg/kg, i.p.)	Alkylation of DNA in β-cells causing necrosis	FBG, serum insulin, oral GTT, hepatic enzymes
STZ + HFD-induced Type 2 DM	In vivo	STZ (35 mg/kg) + High-fat diet	Peripheral insulin resistance + partial β-cell destruction	HOMA-IR, lipid panel, adipokines, liver histology
α-Amylase Inhibition	In vitro	Porcine pancreatic α-amylase + starch	Competitive inhibition of starch hydrolysis	IC50, % inhibition, comparison with acarbose
α-Glucosidase Inhibition	In vitro	Rat intestinal α-glucosidase + p-NPG	Inhibition of disaccharide hydrolysis at brush border	IC50, Km, Vmax, kinetic mode of inhibition
DPPH Free Radical Scavenging	In vitro	DPPH radical (0.1 mM in methanol)	Donation of H-atom or electron to stable radical	IC50, % RSA, correlation with antidiabetic activity
Glucose uptake – 3T3-L1 cells	In vitro	Differentiated adipocytes + 2-NBDG	GLUT4 translocation and glucose transport	Fluorescence intensity, GLUT4 expression (WB)

Abbreviations: FBG, fasting blood glucose; GTT, glucose tolerance test; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; i.p., intraperitoneal; IC50, half-maximal inhibitory concentration; p-NPG, p-nitrophenyl-α-D-glucopyranoside; RSA, radical scavenging activity; 2-NBDG, 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose; WB, western blot.

6.1 In Vitro Antioxidant Assays

The most commonly used in vitro antioxidant assay, which offers a rapid, reproducible spectrophotometric assessment of hydrogen-atom/electron-donating capacity, is the DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay. The IC50 values are compared with those of conventional antioxidants (ascorbic acid, Trolox, BHT). Orthogonal estimates of antioxidant mechanisms are provided by complementary assays ABTS, FRAP, and ORAC, and the connection between antioxidant and antidiabetic actions is assessed statistically. [8]

6.2 Enzyme Inhibition Assays

The liberation of p-nitrophenol at 405 nm is used to determine the α-glucosidase inhibition. p-nitrophenyl-α-D-glucopyranoside (p-NPG) is the substrate used to assess the 4-hydroxy-2-deoxyuridine (H2O2) effect on the nucleic acid, p-DNA. Kinetic analyses of both assays[8] (Michaelis-Menten, Lineweaver-Burk, Dixon plots) are used to determine the mode of inhibition (competitive, non-competitive, mixed) and the corresponding kinetic constants.

6.3 In Vivo Diabetic Models

Alloxan-induced diabetes acts via DNA alkylation in β-cells, producing a Type 1-like phenotype at high doses (>60 mg/kg). [9,10] The combined STZ + high-fat diet (HFD) protocol is closer to the human pathophysiology of T2DM as it induces peripheral insulin resistance and partial β-cell failure. The following key outcome parameters are used: fasting blood glucose, oral glucose tolerance test (OGTT), serum insulin,

HbA1c, HOMA index of insulin resistance, lipid profile, hepatic and renal functional biomarkers, and the histopathological examination of pancreatic islets.[14,15]

6.4 Toxicity Studies

The OECD Guidelines: Acute Oral Toxicity (OECD 423, class method) were used to safety-profile plant extracts and determine the LD50 and a safe dose for use in efficacy studies. Repeated dose 28-day oral toxicity (OECD 407) is used to assess subacute systemic toxicity using hematological, biochemical, and histopathological parameters. The studies are required by ethical and regulatory consent for the preceding pharmacological research studies. [9]

7. Analytical Techniques for Structural Characterization

7.1 High-Resolution Liquid Chromatography–Mass Spectrometry (HR-LC-MS)

HR-LC-MS has become the most prominent platform for comprehensive metabolite profiling of complex plant matrices. Examining mass data at sub-ppm accuracy using reverse-phase C18 chromatographic separation and high-resolution mass analyzers (Orbitrap, Q-TOF) yields accurate mass measurements, permitting unambiguous assignment of molecular formula.[29,30] The HR-LC-MS technique is especially useful in the polar, thermolabile phenolics, glycosides, and alkaloids that cannot be analyzed using GC.

7.2 Gas Chromatography -Mass Spectrometry (GC-MS).

Combined with retention index (RI) comparisons, mass spectral library matching (NIST, Wiley) allows reliable identification of the compounds.[26] GC-MS has been used regularly for the characterization of essential oils and the metabolic fingerprinting of plant extracts.

7.3 Spectroscopic Confirmation

Isolated compounds are structurally confirmed using a multi-spectroscopic approach: UV-Visible spectroscopy identifies chromophore systems and conjugation patterns, Fourier-transform infrared (FT-IR) spectroscopy characterizes functional groups, Nuclear Magnetic Resonance (NMR ^{1}H, ^{13}C, DEPT, COSY, HMBC, HSQC) provides definitive three-dimensional structural elucidation. X-ray crystallography can determine the absolute stereochemistry of crystalline isolates. The combination of HR-LC-MS and NMR data is the gold standard for unambiguously assigning the structure of novel phytoconstituents. [31]

Table 3 Molecular *mechanisms of key phytoconstituent classes in antidiabetic action.*

Phytoconstituent Class	Mechanism of Antidiabetic Action
Flavonoids & Polyphenols	Inhibit α-amylase and α-glucosidase → reduce postprandial glucose absorption
Alkaloids (Berberine)	Activate AMPK → decrease hepatic gluconeogenesis & enhance GLUT4 translocation
Terpenoids (Gymnemic acids)	Block intestinal glucose transport (SGLT1) & stimulate insulin secretion from β-cells
Glycosides (Charantin)	Increase insulin sensitivity; activate PI3K/AKT pathway → glucose uptake in muscles
Tannins & Ellagic acid	Scavenge ROS, reduce oxidative stress on islet cells; mild α-glucosidase

Phytoconstituent Class	Mechanism of Antidiabetic Action
	inhibition
Stilbenes (Pterostilbene)	PPAR-γ agonism → adipogenesis regulation; reduce hepatic lipid accumulation

8. DISCUSSION

The evidence synthesized in this review highlights the high pharmacological richness of medicinal plants as sources of antidiabetic compounds. Although synthetic drugs may be more effective than traditional natural products in treating DM, the complexity of DM pathophysiology, with multiple metabolic derangements occurring simultaneously, favors multi-target phytochemical preparations over single-target synthetic molecules. Pleiotropic effects are common among phytoconstituents: a single phytoconstituent may have multiple actions simultaneously. [5,6,7]

Several regions of India, with their own distinct agroclimatic zones and rich ethnobotanical heritage, are particularly promising areas for exploratory studies in phytopharmacology. Plants commonly used historically in these regions, such as Azadirachta indica (neem), Gymnema sylvestre (gurmar), Tinospora cordifolia (giloy), Momordica charantia (bitter gourd) and Pterocarpus marsupium (Indian kino), were historically used in glycaemic control, although systematic bioactivity-directed isolation of their respective active constituents using locally collected specimens is sparse in the literature.

The proposed methodology pipeline encompassing authentication, standardization, sequential extraction, multi-model pharmacological screening, bioactivity-guided fractionation and HR-LC-MS identification is compatible with internationally recognized frameworks of natural product drug discovery. There is a critical scientific gap in the translation of in vitro observations to clinically meaningful outcomes; however, the IC50 values of 0.3-0.4 µg/mL are in the low 0.3-0.4 mU/mL range that does not necessarily predict equivalent in vivo efficacy due to bioavailability limits, metabolic conversion, and the complex intestinal environment. Future research should thus include the factors of pharmacokinetic characterization (oral bioavailability, plasma half-life, protein binding, tissue distribution) and metabolic stability assessment. [11,12,13]

The analysis of network pharmacology, which is a map of the polypharmacology of phytoconstituents in the context of disease-relevant protein networks, provides a holistic mechanistic framework for understanding multi-target antidiabetic activity. [30]

9. RESEARCH GAPS and Future perspectives.

Some of the major gaps in research that should be given priority investigations include: (i) Most of the published studies of antidiabetic plants use crude extracts or broad fractions, but not isolated pure compounds, which limits the ability to understand their mechanisms and their translatability. The minimum acceptable standard of scientific work should be bioactivity-guided isolation to chemical purity. (ii) There is a dearth of clinical trial data to support plant-derived antidiabetic compounds; strong phase I/II randomized controlled trials (RCTs) using standardized phytochemical preparations are urgently needed to determine clinical efficacy and safety. (iii) Nanoformulation approaches nanoparticles, phytosomes, and self-nanoemulsifying drug delivery systems, could significantly improve the oral bioavailability of poorly soluble phytoconstituents and should be systematically studied. (iv) Antidiabetic phytoconstituents modulating the gut microbiome is an emerging mechanism that should be characterized using a shotgun metagenomics/metabolomics approach. (v) Region-specific profiling (various Indian ecotypes versus other geographic sources) can detect chemotypic variation in bioactive content, highlighting the importance of standardization of the collection and the authenticity of voucher specimens.[7,13]

10. CONCLUSION

Diabetes mellitus still stands as one of the leading global health issues of the 21st century, and the shortcomings of the currently used synthetic pharmacotherapy still motivate the idea of seeking a safer, more effective therapeutic alternative. Medicinal plants, especially those from the ethnobotanically rich regions of India, are a largely under-explored source of structurally novel and pharmacologically diverse antidiabetic lead compounds. The conceptual framework of a scientifically sound and internationally validated drug discovery route is the rigorous pharmacological validation of bioactivity-guided fractionation, supported by pharmacological validation using standardized in vitro and in vivo models, and culminating in the systematic structural characterization of drugs using HR-LC-MS/GC-MS-boards.

This review establishes important phytoconstituent families, including flavonoids, alkaloids, terpenoids, glycosides, and phenolic acids, as primary antidiabetic scaffolds that act through complementary and synergistic mechanisms, including enzyme inhibition, insulin secretion stimulation, GLUT4 upregulation, AMPK activation, and ROS scavenging. Future research needs to address the translational gap by incorporating computational pharmacology, pharmacokinetic profiling, nanotechnological delivery optimization, and clinical validation to bridge the gap between phytochemical discovery and the development of medicines that can significantly reduce the global burden of diabetes mellitus.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise, related to this work.

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