Journal of Pharmacological Biomolecules and Therapeutics

ETERNO PRESS

Review

Integrating Traditional Medicine in the Modern Management of Type 2 Diabetes Mellitus and Obesity: Mechanisms, Evidence, and Future Directions

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Abstract

The rising trend of Type 2 Diabetes Mellitus (T2DM) and obesity across the globe is one of the most significant health problems of the 21st century. In accordance with the current epidemiological statistics provided by the International Diabetes Federation and the World Obesity Federation, an incredible increase in prevalence is projected, and an excess of 853 million people are predicted to live with diabetes by 2050. Although there has been tremendous progress in the pharmacotherapy of metabolic syndrome, which is typified by insulin resistance, dysfunction of the beta-cell, and chronic low-grade inflammation, it may be assumed that the complexity of this disease will outweigh the current reductionist one-drug-one-target paradigm. This is a comprehensive narrative review with structured literature synthesis, Traditional Chinese Medicine, and Unani systems of Traditional Medicine may be integrated into the modern metabolic management. We critically analyze the ethnopharmacological foundations and molecular mechanisms of key medicinal plants, including *Gymnema sylvestre*, *Momordica charantia*, *Berberis aristata*, *Salacia reticulata*, and *Curcuma longa*. Emerging evidence from systems pharmacology reveals that bioactive phytoconstituents such as gymnemic acids, charantin, berberine, and curcumin exert potent pleiotropic effects. These compounds regulate key metabolic hubs such as Adenosine Monophosphate-activated Protein Kinase (AMPK), Peroxisome Proliferator-Activated Receptors (PPARs) and the incretin axis Glucagon-like peptide-1 (GLP-1) and tend to mimic or improve the activity of pharmacological agents such as metformin and acarbose. Furthermore, we examine the transformative role of modern technologies, including network pharmacology, metabolomics, and Artificial Intelligence, in decoding the synergistic interactions inherent in polyherbal formulations. Clinical evidence from randomized controlled trials is synthesized to evaluate efficacy in glycemic control Glycated haemoglobin (HbA1c reduction) and weight management, while acknowledging the heterogeneity and methodological limitations of current data. Finally, the report addresses the imperative of rigorous safety monitoring, detailing the risks of herb-drug interactions (e.g., serotonin toxicity with *Garcinia cambogia*) and the regulatory landscapes of the Food and Drug Administration, WHO, and AYUSH. By bridging ancient wisdom with modern systems biology, this report advocates for a paradigm shift toward a holistic, evidence-based integrative model to combat the metabolic pandemic.

Keywords

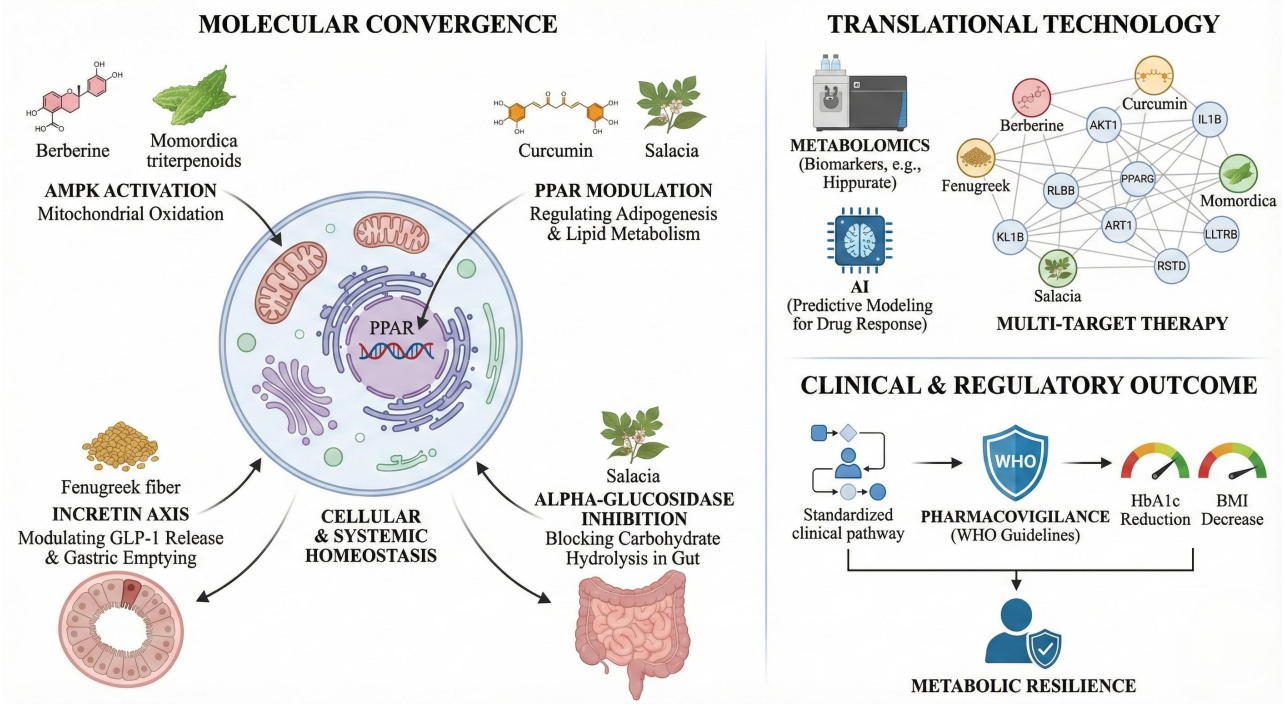
Diabetes melitus, Homeostasis, Metabolic resilience, Ayurveda, PPAR, Signaling

Article History

Received: 08 December 2025 Revised: 19 January 2026

Accepted: 11 February 2026 Available Online: 13 February2026

Graphical Abstract



Bridging ancient wisdom with modern science, this framework integrates Ayurvedic, Traditional Chinese Medicine, and Unani principles with systems-biology approaches to elucidate multi-target therapeutic strategies for diabesity. By mapping bioactive phytoconstituents to key metabolic pathways, including AMPK and PPAR signaling, through network-pharmacology and computational tools, it provides a translational framework for restoring metabolic homeostasis.

1. Introduction

1.1 The Global Metabolic Crisis: Epidemiology and Economic Burden

The 21st century is marked by a non-communicable disease crisis on a scale never before seen, with the twin epidemics of Type 2 Diabetes Mellitus (T2DM) and obesity leading the changing epidemiological landscape [1]. The scale of this public health emergency is captured vividly in the latest data from the International Diabetes Federation (IDF) Diabetes Atlas 2025. According to the IDF Diabetes Atlas, an estimated 589 million adults aged 20-79 years were living with diabetes globally in 2024, corresponding to a prevalence of approximately 11.1%, as reported in the 11th edition of the Atlas (2025 update) [2]. Projections from the same IDF edition indicate that the global diabetes burden is expected to rise to approximately 853 million adults by 2050 if current trends persist. Earlier IDF estimates from 2015 reported substantially lower global prevalence, reflecting the rapid acceleration of the diabetes epidemic over the past decade [3].

This escalating burden is not merely a statistical abstraction but a reflection of profound demographic and environmental shifts. Rapid urbanization, ageing populations, and the adoption of sedentary lifestyles have created an "obesogenic" environment that fuels metabolic dysregulation [4]. According to the 'Atlas 2025' Report of the World Obesity Federation, there are expected to be more than double as many adults living with obesity by 2030 (1.13 billion) as there were in 2010 (524 million). Such a combination of conditions has frequently been called “diabesity.” A high body mass index (BMI) contributes greatly to the burden of T2DM, particularly among men and women who have transitioned through the menopause or post-menopause state [5].

In addition to affecting morbidity, the trend also has a vast spreading effect of mortality and economic impact. Only in 2024, it was estimated that Diabetes caused a total of 3.4 million deaths or one death every nine seconds [6]. Furthermore, obesity-related complications account for nearly 10% of global deaths, a toll that now surpasses road traffic fatalities. The financial impact of diabetes has become enormous. Global health expenditures due to diabetes are projected to exceed USD 1 trillion in 2024, representing a growth of 338% in the last 17 years (as determined by various International health organisations). Crucially, over 80% of individuals with diabetes reside in low- and middle-income countries, where healthcare systems are often ill-equipped to manage chronic, progressive conditions, leading to a significant "treatment gap" [7].

1.2 Limitations of Current Pharmacotherapy and the Integrative Imperative

In recent years, modern pharmacotherapy for T2DM has progressed immensely as part of an expanding selection of available agents from the foundation of metformin and sulfonylureas to the development of new drug classes such as

Dipeptidyl Peptidase-4 (DPP-4s), Sodium-Glucose Cotransporter-2 (SGLT2), and (GLP-1) receptor agonists [8]. While these drugs have transformed diabetes care, they are not without limitations. Their accessibility and long-term adherence are restricted, especially in LMICs, by problems like gastrointestinal side effects, hypoglycemia risk, weight gain (with insulin and sulfonylureas), and high costs.

Furthermore, many of the current treatments for type 2 diabetes control hyperglycemia but are unable to stop the underlying pathophysiology of the disease, which is characterised by a progressive decline in pancreatic β-cell function [9].

Traditional Medicine (TM) systems, particularly Ayurveda, Traditional Chinese Medicine (TCM), and Unani, provide an appealing complementary approach in this regard. These systems, refined over millennia, do not view metabolic diseases as isolated glucocentric phenomena but as systemic dysregulations of physiological homeostasis. The World Health Organisation recognises the critical role of TM, pointing out that because of their perceived safety and cultural acceptability, the great majority of people worldwide rely on herbal medicines for primary healthcare [10].

However, the integration of TM into modern clinical practice is often hindered by a lack of rigorous scientific validation and standardization. The reductionist "silver bullet" approach of modern drug discovery struggles to evaluate the complex, multi-component nature of traditional formulations. Yet, the emergence of systems biology and network pharmacology offers a new lens through which to understand these complex therapeutics. By mapping the interactions between multiple bioactive phytoconstituents and biological networks, modern science is beginning to validate the holistic principles of TM. This report aims to bridge the gap between these two worlds, providing a rigorous, evidence-based analysis of how TMs can be integrated into the modern management of T2DM and obesity [11].

1.3 Aims and Objectives

This review aims to synthesize ethnopharmacological and mechanistic evidence on medicinal plants with putative antidiabetic and anti-obesity effects, evaluate the quality of preclinical and clinical data, and identify translational opportunities and limitations for integrating TM into modern metabolic care.

Specifically, the objectives are to critically appraise ethnobotanical and clinical evidence for key plants (e.g., *Gymnema sylvestre*, *Momordica charantia*, Berberine, Salacia, Curcuma), (2) consolidate molecular mechanisms using a pathway-centred approach (e.g., AMPK, Peroxisome Proliferator-Activated Receptors (PPARs), incretin axis), (3) assess safety profiles and herb-drug interaction risks, (4) propose a roadmap, drawing on network pharmacology and AI, for rigorous translational evaluation and standardization of herbal therapeutics for diabesity. The novelty of this review lies in its integrated, evidence-graded synthesis that links traditional systems (Ayurveda, TCM, Unani) with contemporary systems-biology tools to provide a practical translational framework focused on real-world applicability in low- and middle-income country settings.

2. Materials and Methods

A comprehensive literature search was conducted to identify relevant studies examining the role of TM in the management of T2DM and obesity. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were searched. The search covered publications from January 2000 to March 2025 using combinations of keywords such as “T2DM,” “obesity,” “traditional medicine,” “ethnopharmacology,” “medicinal plants,” “network pharmacology,” “systems biology,” and “artificial intelligence.” Peer-reviewed original research articles, randomized controlled trials (RCTs), meta-analyses, and mechanistic studies published in English were included. Studies focusing on *in vitro*, *in vivo*, or clinical evidence relevant to antidiabetic or anti-obesity mechanisms were considered. Conference abstracts, non-peer-reviewed articles, non-English publications, and studies lacking sufficient methodological detail were excluded. Titles and abstracts were initially screened for relevance, followed by full-text evaluation of eligible articles. Study selection was guided by relevance to ethnopharmacological use, molecular mechanisms, clinical outcomes, and translational significance. Discrepancies in selection were resolved through consensus. Key information including study design, sample size, intervention details, duration, primary outcomes, and mechanistic insights was extracted. Data were synthesized qualitatively with emphasis on mechanistic pathways, clinical relevance, and translational potential rather than quantitative meta-analysis. Clinical evidence was appraised based on study design, sample size, duration, consistency of outcomes, and reported methodological limitations. Evidence strength was graded as high, moderate, or low to allow transparent interpretation of reliability and clinical applicability.

2.1 Overview of Traditional Medicine Systems

To effectively integrate TM, it is essential to understand the theoretical frameworks that guide diagnosis and treatment in these systems. While the terminology differs from modern pathology, the physiological states described often correlate closely with contemporary understandings of metabolic syndrome [12]. Ayurveda, TCM, and Unani medicine converge on a shared conceptual understanding of metabolic disease as a disorder of systemic balance rather than a single biochemical abnormality. Ayurveda frames T2DM and obesity as outcomes of disturbed Agni and Ama accumulation leading to Medodushti and insulin resistance, with therapeutic decisions guided by body constitution

(Sthula versus Krisha). In TCM, Spleen Qi deficiency and the accumulation of Phlegm Dampness provide an explanatory model that aligns with contemporary observations of gut dysbiosis, altered metabolites, and chronic low-grade inflammation in metabolic syndrome. Unani medicine similarly emphasizes humoral disequilibrium and kidney dysfunction in Ziabetus, linking altered absorptive and retentive powers to polyuria and metabolic imbalance (Figure 1).

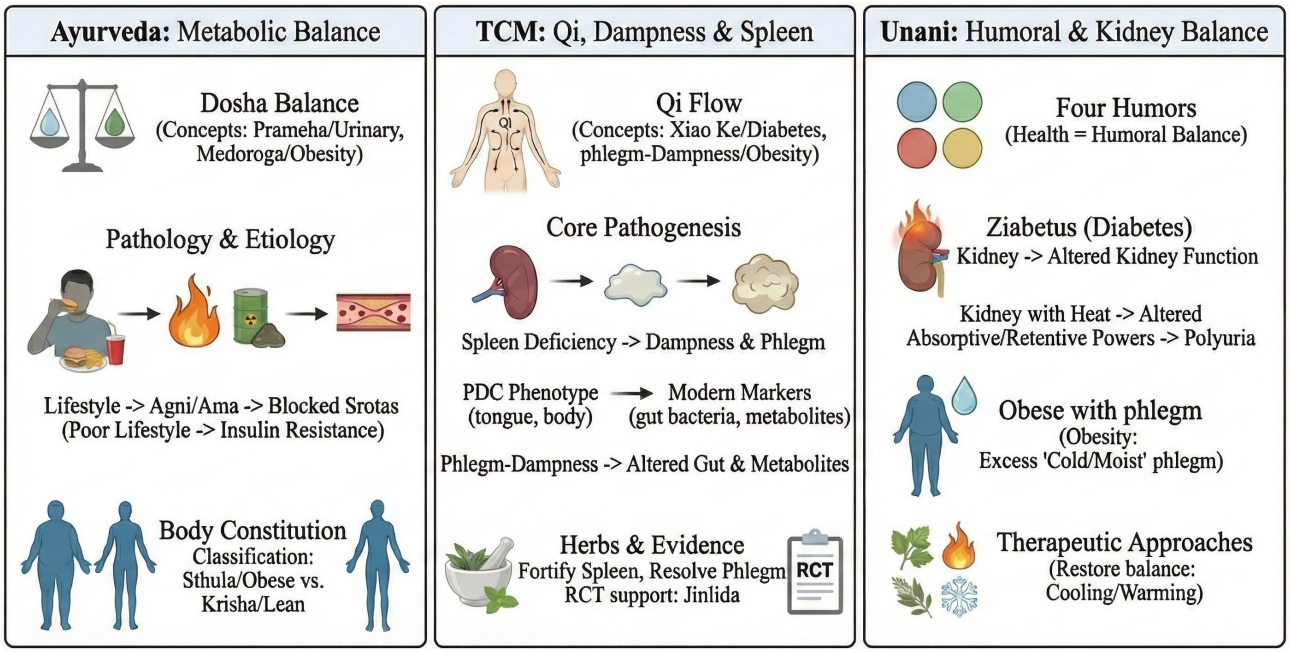


Figure 1. Conceptual overview of TM systems and their alignment with metabolic pathophysiology in T2DM and obesity.

2.1.1 Ayurveda: The Science of Metabolic Balance

Ayurveda, the ancient medical system of the Indian subcontinent, possesses a sophisticated classification of metabolic disorders, primarily conceptualized under *Prameha* (urinary disorders) and *Medoroga* (disease of fat) or *Sthaulya* (obesity) [13].

2.1.2 Pathophysiology of Prameha and Medoroga

The root words that describe excessive (Prakarsa) and turbid (Avila) urination (Mehati) are the source of the term Prameha, which is consistent with the polyuria and glycosuria seen in diabetes. 9 Ayurveda categorizes Prameha into 20 subtypes based on the dominance of the three Doshas (bio-energies): 10 Kaphaja (dominant in early diabetes/obesity), 6 Pittaja (associated with inflammation/infection), and 4 Vataja (associated with advanced wasting/neuropathy) types. Madhumeha (honey urine), a subtype of Vataja Prameha, is frequently associated with Type 1 Diabetes or terminal or uncontrolled T2DM [14,15].

The etiology of *Prameha* is explicitly linked to lifestyle factors. Ancient texts cite "sedentary habits" (*Asyasukham*), "excessive sleep," and the consumption of "Kapha-aggravating" foods such as dairy, sugar (*Ikshu*), and fresh grains as primary causes. This mirrors the modern risk factors of physical inactivity and high-glycemic diets [16]. Agni and Ama: Central to Ayurvedic pathology is the concept of *Agni* (digestive fire). In *Prameha*, the *Agni* is disturbed, leading to the formation of *Ama* (metabolic toxins) due to incomplete metabolism. This *Ama* blocks the *Srotas* (channels), causing insulin resistance at the tissue level [17]. Dhatu Dushya (Tissue Vitiation): The disease primarily affects the *Medas* (adipose tissue), *Mamsa* (muscle), and *Kleda* (body fluids). *Medodushti* (vitiation of fat) is the common pathological ground for both obesity (*Sthaulya*) and diabetes. In *Sthaulya*, there is an abnormal increase in *Meda Dhatu* which obstructs the path of *Vata*, leading to increased appetite (*Ati-agn*) and further weight gain. Classification by Body Constitution: Ayurveda distinguishes between *Sthula* (obese) *Pramehi*, who require *Apatarpana* (depletion/purification) therapies, and *Krisha* (lean) *Pramehi*, who require *Santarpana* (nourishment). This nuanced classification anticipates the modern distinction between obese T2DM phenotypes and lean/ketosis-prone diabetes.

2.2 Traditional Chinese Medicine: Qi, Dampness, and Spleen Function

In TCM, diabetes has been referred to as Xiao Ke or (Wasting-Thirst Syndrome) since ancient times due to symptoms such as polydipsia, polyphagia, and polyuria. It perceives obesity as a condition of accumulated Phlegm and Dampness [18]. The core pathogenesis of metabolic disorders in TCM revolves around the dysfunction of the Spleen and the accumulation of pathological products known as "Phlegm-Dampness" (Tan Shi) [18]. Spleen Deficiency (*Pi Xu*): In TCM physiology, the Spleen is responsible for the "transportation and transformation" of nutrients (*Gu Qi*) and fluids. When Spleen Qi is deficient often due to poor diet (excessive sweet/greasy food), overwork, or sedentary behaviour it fails to distribute fluids correctly. These fluids accumulate to form "Dampness," which over time condenses into

"Phlegm" [19]. Phlegm-Dampness Constitution (PDC): TCM typologies classify individuals with a "Phlegm-Dampness Constitution" as having a high susceptibility to metabolic syndrome. These individuals typically present with central obesity, a sticky sensation in the mouth, fatigue, and a thick, greasy tongue coating [20]. Modern Correlates: Recent research has successfully bridged TCM concepts with modern biomarkers. Patients with PDC have been shown to have distinct gut microbiota profiles (e.g., reduced *Flavonifractor plautii*) and altered serum metabolites (e.g., lower phytosphingosine), which are linked to PPAR-alpha signaling and lipid metabolism. This provides a biological basis for the "turbid pathogen" concept in TCM [21].

2.2.1 Therapeutic Principles

TCM management focuses on "fortifying the Spleen," "resolving Phlegm," and "clearing Dampness." Formulations often use aromatic and bitter herbs to revive the Spleen's transportive function and dissolve adipose accumulation [22].

2.2.2 Clinical and Patent Evidence of Chinese Medicine in T2DM

RCTs and several meta-analyses support the glycaemic benefits of specific Chinese patent medicines when used as monotherapy or as add-on therapy. Jinlida granules (a marketed Chinese herbal granule) have shown clinically meaningful effects: controlled trials and pooled analyses report improved glycaemic control and, importantly, a randomized clinical trial (n=889, median follow-up 2.2 y) found Jinlida reduced progression from impaired glucose tolerance to diabetes. Shorter RCTs also show HbA1c/FPG Fasting plasma glucose reductions when Jinlida is added to metformin.

Xiaoke (Xiaoke Decoction / Xiaoke Pill) formulations often combined with conventional agents have been evaluated in meta-analyses and RCTs showing improvements in FPG, 2-h PG and HbA1c versus Western medicine alone; however, heterogeneity in composition, dose and outcome reporting limits definitive interpretation.

Systematic reviews of Chinese patent medicines indicate overall favorable signals for FPG/2-hPG/HbA1c but emphasize small sample sizes, short durations and inconsistent standardization across trials; these limitations should temper clinical recommendations.

The patent landscape for TCM anti-diabetic preparations is active (multiple CN patents and families); representative filings include traditional formula patents and patented preparation methods (e.g., CN101190262A). A concise patent summary (number of families, major applicants, and key target mechanisms) is recommended when discussing translational/commercial prospects.

2.3 Unani Medicine: Humoral Equilibrium and Kidney Function

Unani medicine, based on the teachings of Hippocrates, Galen, and Avicenna (Ibn Sina), considers health as the balance of four humors: Blood-Dam, Phlegm-Balgham, Yellow Bile-Safra, and Black Bile-Sauda [23].

2.3.1 Concept of Ziabetus (Diabetes)

Unani literature describes Ziabetus primarily as a disorder of the kidneys. The pathophysiology is attributed to a "hot" temperament (Su-e-Mizaj Haar) of the kidneys, which weakens their "retentive power" (Quwate Masika) and increases their "absorptive power" (Quwate Jaziba). Consequently, the kidneys absorb fluids excessively from the circulation and excrete them immediately without proper metabolic utilization, leading to intense thirst and polyuria [24].

2.3.2 Concept of Obesity and Temperament

Obesity is frequently linked to an excess of the Balgham (Phlegm) humor, which is cold and moist in nature. Individuals with a "Phlegmatic" temperament are predisposed to a slow metabolism, fluid retention, and adipose accumulation. Conversely, Sanguine (Blood-dominant) individuals may develop metabolic disorders due to a robust appetite and "high living," leading to metabolic excesses [24].

2.3.3 Therapeutic Approach

Unani treatment (Ilaj bil Tadbeer) involves restoring the temperamental balance. For diabetes, cooling herbs are used to correct the hot temperament of the kidneys. For obesity, "desiccating" and warming therapies are employed to resolve excess Phlegm [24].

2.4 Ethnopharmacology and Key Medicinal Plants

The integration of these traditional systems into modern practice is largely mediated through their pharmacopoeia. Numerous plants identified in ancient texts have been subjected to rigorous scientific scrutiny, revealing bioactive compounds with potent antidiabetic and anti-obesity properties [25].

2.4.1 *Gymnema Sylvestre* (Gurmar): The "Sugar Destroyer"

Gymnema sylvestre, a woody climber from the Asclepiadaceae family, is revered in Ayurveda as *Gurmar*, literally translating to "sugar destroyer." It has a dual action on both taste perception and glucose metabolism. Bioactive Constituents: The primary active constituents are the group of saponins, triterpene gymnemic acids, and peptide gurmarin or gymnemas [26]. Taste Suppression: Gymnemic acids have a unique molecular structure similar to glucose. The acids present in the leaves when chewed, will connect to the sweet taste receptors located on the tongue, and will then block the feeling of sweetness for a short moment. This mechanism is utilized clinically to reduce sugar cravings in patients with obesity [27]. Intestinal Glucose Absorption: In the intestine, gymnemic acids attach to receptor sites in the absorptive surface: they are said to inhibit the uptake of glucose molecules. This reduces postprandial hyperglycemia [28]. β-cell functional preservation: β-cell effects (preclinical evidence) showed that several rodent studies report that Gymnema extracts are associated with increases in islet area and markers of β-cell function on histological and functional assays. These observations derive from diabetic animal models and suggest improved β-cell survival or restoration of function under experimental conditions; however, they remain preclinical and do not establish β-cell regeneration in humans [29].

2.4.2 *Momordica Charantia* (Bitter Melon): A Vegetable Insulin

Momordica charantia (Cucurbitaceae), widely used in Asian and African TMs, acts as a potent metabolic modulator. Bioactive Constituents: The plant is rich in charantin (a mixture of sterol glucosides), polypeptide-p (an insulin-like protein), and vicine [30]. Insulin-Mimetic Action: Polypeptide-p, often called "p-insulin," has been shown to lower blood glucose levels when administered subcutaneously, mimicking the action of endogenous insulin [31,32]. AMPK Activation: Modern research has identified that cucurbitane-type triterpenoids in bitter melon activate (AMPK). This route promotes the movement of (GLUT4) Glucose transporter type 4 to the plasma membrane in skeletal muscle, which leads to increased glucose absorption without the help of insulin [33]. Anti-adipogenic Effects: *Momordica* extracts suppress the differentiation of preadipocytes and reduce adipose tissue inflammation by inhibiting the (NF-κB) Nuclear factor kappa B and MAPK signaling pathways [34]. This dual action on glucose and fat metabolism makes it highly relevant for managing diabesity [35]. Critical factors contributing to heterogeneity: The variability in clinical outcomes for *Momordica charantia* is likely driven by differences in bioavailability of active constituents (e.g., charantin, polypeptide-p), inconsistent extract standardization (juice vs. aqueous vs. ethanolic extracts), dose and formulation differences (fresh fruit, dried powder, concentrated extract), and study-design heterogeneity (short durations, small sample sizes, and variable endpoints). Reported HbA1c reductions across clinical trials typically range from approximately 0.2-0.8%, with more consistent and larger reductions observed in studies that used standardized extracts, higher doses, and longer intervention periods. These ranges are approximate and reflect between-study variability; they should be interpreted cautiously.

2.4.3 *Berberis* Species and Berberine: The Natural Metformin

Berberine is a yellow isoquinoline alkaloid isolated from plants like *Coptis chinensis* (used in TCM) and *Berberis aristata* (used in Ayurveda). It is currently one of the most researched phytochemicals for metabolic syndrome. Mechanism of Action: Berberine shares a key mechanism with metformin. The drug inhibits the mitochondrial Complex I thus causing the AMP/ATP ratio to rise that later activates the AMPK [36]. Metabolic Effects: Activation of AMPK by berberine leads to: Inhibition of lipogenesis (via Acetyl-CoA Carboxylase inhibition). Increased fatty acid oxidation. Enhanced glucose uptake in muscle and liver. Lipid Regulation: Unique to Berberine is its ability to stabilize the mRNA of the Low-Density Lipoprotein Receptor (LDLR), preventing its degradation. This increases the clearance of LDL cholesterol from the blood, a mechanism distinct from statins [3,37].This dual efficacy on glucose and lipids addresses the dyslipidemia often co-occurring with T2DM [38].

2.4.4 *Curcuma Longa* (Turmeric): Targeting Metabolic Inflammation

Curcumin, the primary polyphenol in turmeric, addresses the inflammatory root of metabolic syndrome. Anti-inflammatory Action: Obesity is characterized by a state of chronic low-grade inflammation. Curcumin potently inhibits the NF-κB pathway, reducing the production of pro-inflammatory cytokines like TNF-alpha and IL-6, which are known drivers of insulin resistance [39,40]. Adipocyte Modulation: Curcumin modifies Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ). Unlike synthetic thiazolidinediones (TZDs) which are full agonists and can cause weight gain, curcumin suppresses adipocyte differentiation and lipid accumulation while maintaining insulin-sensitizing benefits Antioxidant Effects: It enhances the activity of antioxidant enzymes (SOD, catalase) and upregulates the (Nrf2) Nuclear factor erythroid 2-related factor 2 pathway, protecting pancreatic β-cells from glucotoxicity-induced oxidative stress [41,42].

2.4.5 *Salacia* Species (*S. Eticulata, S. Oblonga*): The Carbohydrate Blocker

Native to India and Sri Lanka, *Salacia* roots have been used for centuries to treat diabetes. Bioactive Constituents: The primary active compounds are thiosugar sulfonium sulfates, specifically salacinol and kotalanol [43]. Alpha-Glucosidase Inhibition: These compounds are potent competitive inhibitors of intestinal alpha-glucosidase enzymes. By

blocking the breakdown of disaccharides and oligosaccharides into glucose, *Salacia* extracts flatten the postprandial glucose curve, a mechanism analogous to that of acarbose alpha-glucosidase inhibition [44]. PPAR-alpha Activation: Additionally, *Salacia* has been shown to activate PPAR-alpha, promoting fatty acid oxidation and lowering triglyceride levels, providing a comprehensive metabolic benefit [45].

2.4.6 *Trigonella Foenum Graecum* (Fenugreek): Fiber and Incretin Modulation

Fenugreek seeds are unique in combining pharmacological activity with nutritional fiber. Bioactive Constituents: The seeds are rich in soluble fiber (galactomannan) and the amino acid 4-hydroxyisoleucine (4-OH-Ile) [46]. Gastric Emptying and GLP-1: The high viscosity of galactomannan delays gastric emptying, slowing the absorption of carbohydrates. This mechanism is similar to the physiological effects of GLP-1. By modulating the transit of nutrients, Fenugreek can enhance the secretion of incretin hormones, improving postprandial glycemic control [47]. Insulin Stimulation: 4-hydroxyisoleucine can directly stimulate insulin secretion from β-cells when glucose levels are high. This helps reduce the risk of hypoglycemia [48].

Figure 2 illustrates the mechanistic actions of selected traditional medicinal plants on glucose and lipid homeostasis. *Gymnema sylvestre* reduces sweet taste perception and intestinal glucose absorption, with reported preclinical evidence suggesting pancreatic β-cell functional support. *Momordica charantia* exhibits insulin-mimetic activity and enhances glucose uptake primarily through AMPK-mediated GLUT4 translocation while exerting anti-adipogenic effects. Berberine from *Berberis* species activates AMPK and improves lipid metabolism via LDL receptor stabilization. *Curcuma longa* modulates metabolic inflammation through NF-κB inhibition, PPAR-γ regulation, and antioxidant (Nrf2-dependent) pathways. *Salacia* species attenuate postprandial hyperglycaemia by α-glucosidase inhibition and activation of fatty-acid oxidation via PPAR-α. *Trigonella foenum-graecum* improves glycaemic control through delayed gastric emptying, incretin (GLP-1) modulation, and glucose-dependent insulin secretion. Collectively, these pathways converge on improved insulin sensitivity, reduced inflammation, and metabolic homeostasis.

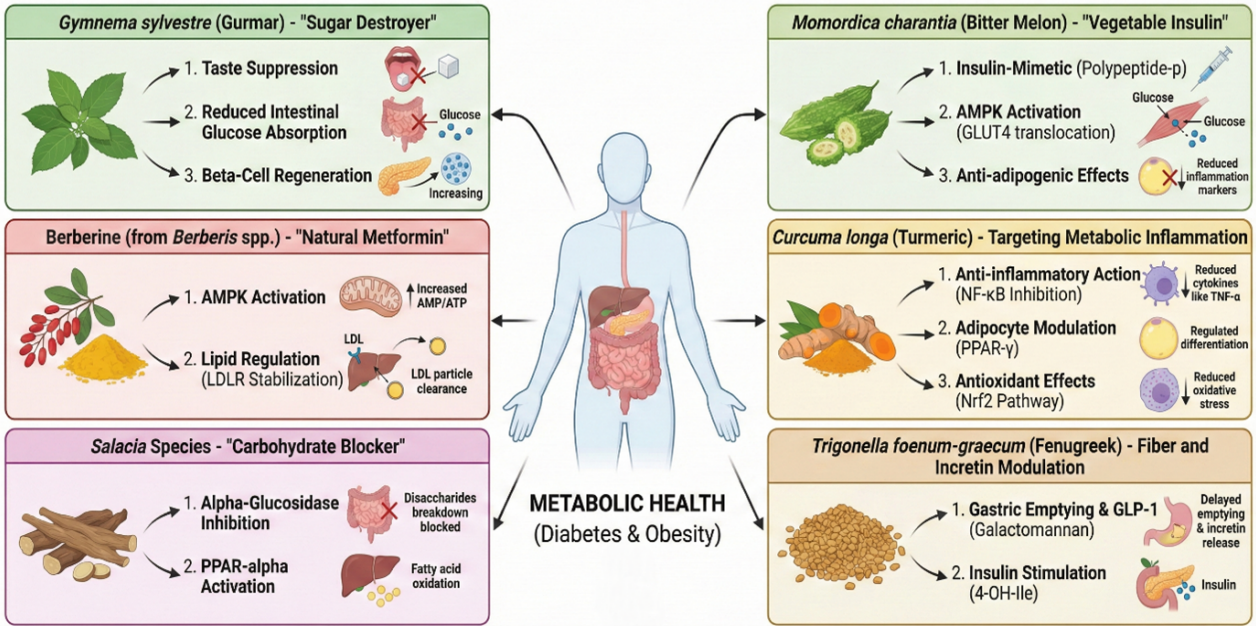


Figure 2. Proposed molecular mechanisms of key medicinal plants involved in the regulation of metabolic health in T2DM and obesity.

2.5 Experimental Evidence: Animal Models and Cell Lines

2.5.1 Preclinical Studies

In vitro cell assays and *in vivo* animal models provide the mechanistic foundation for many claims about traditional medicinal plants discussed in this review. To synthesise this body of evidence, the following summary highlights commonly used experimental models, typical mechanistic readouts, and the recurrent findings reported for key botanical candidates.

2.5.2 Models and Common Readouts

In vivo studies predominantly employ rodent models of diabetes and obesity, including streptozotocin- or alloxan-induced β-cell damage models, high-fat diet (HFD) or HFD in combination with streptozotocin models of insulin resistance, and genetic models where appropriate. Typical endpoints include fasting glucose, oral glucose tolerance tests, insulin tolerance tests, HbA1c (where measured), pancreatic histology (islet area, β-cell number, immunostaining for insulin), adipose/tissue inflammatory markers, and lipid profiles. *In vitro* investigations commonly use human hepatoma

cell line (HepG2), skeletal-muscle (L6 or C2C12 myotubes), L6 rat skeletal muscle cell line or C2C12 murine skeletal muscle myoblast cell line adipocyte, (3T3-L1) murine adipocyte precursor cell line, and pancreatic β-cell lines, rat insulinoma β-cell line (INS-1/INS-832/13) to probe glucose uptake, GLUT4 translocation, insulin secretion, enzyme inhibition (α-glucosidase/α-amylase), AMPK phosphorylation, NF-κB signalling, and oxidative stress markers.

Rodent studies investigating *Gymnema sylvestre* consistently report reduced postprandial glycaemia and improved glycaemic indices. Histological analyses in diabetic animal models demonstrate increased islet area and markers of β-cell function, findings that are consistent with enhanced β-cell survival and functional preservation under preclinical conditions. *In vitro* assays further indicate inhibition of intestinal glucose uptake and modulation of glucose transporter activity. However, evidence for β-cell regeneration remains limited to preclinical models and has not been established in humans.

For *Momordica charantia* (bitter melon), both *in vitro* and rodent studies demonstrate activation of AMPK, enhanced GLUT4 translocation in skeletal muscle cells, and suppression of adipogenesis in 3T3-L1 adipocytes. Animal models of dietary- and chemically induced diabetes show improvements in glucose tolerance and reductions in adipose tissue inflammation, although reported effects vary depending on extract composition and dosage.

Berberine derived from *Berberis* species has been extensively evaluated in cell-based and animal studies. *In vitro* investigations show that berberine inhibits mitochondrial complex I, leading to an increased AMP/ATP ratio and subsequent activation of AMPK. Corresponding animal models demonstrate improvements in glycaemic control and lipid profiles, supporting mechanistic overlap with established insulin-sensitising pathways.

Preclinical studies of *Curcuma longa* (curcumin) using high-fat diet and other diabetic rodent models reveal reductions in adipose tissue inflammation, decreased NF-κB activation, improved insulin sensitivity, and favourable modulation of adipokine profiles. Complementary *in vitro* studies further document inhibition of NF-κB signalling and activation of antioxidant responses through Nrf2-dependent pathways.

For *Salacia* species, enzyme-based assays confirm potent α-glucosidase inhibitory activity *in vitro*. These findings are supported by animal feeding studies demonstrating attenuation of postprandial hyperglycaemia and improvements in lipid handling, indicating a primary role in postprandial glucose regulation.

Studies of *Trigonella foenum-graecum* (fenugreek) using *in vitro* and *ex vivo* systems support delayed carbohydrate absorption mediated by viscous galactomannan fibre, incretin modulation, and glucose-dependent insulin secretion driven by 4-hydroxyisoleucine. Consistent with these findings, rodent models show improved postprandial glycaemia and enhanced insulin dynamics.

Interpretation of preclinical findings requires caution. Evidence derived from *in vitro* systems and animal models primarily supports mechanistic plausibility rather than clinical efficacy. While these studies provide valuable insights into molecular pathways such as AMPK activation, PPAR modulation, α-glucosidase inhibition, and incretin signaling, they do not establish therapeutic equivalence or predict clinical outcomes in humans. Accordingly, all preclinical observations discussed in this review should be regarded as hypothesis-generating and require confirmation through adequately powered, well-designed human clinical trials before definitive clinical conclusions can be drawn.

2.5.3 Molecular Mechanisms of Action

To avoid redundancy with the preceding ethnopharmacological descriptions, this section reorganizes mechanistic information by molecular pathway rather than by individual plant. While specific mechanisms such as AMPK activation, PPAR modulation, α-glucosidase inhibition, and incretin signaling are introduced within plant-centric contexts earlier, they are synthesized here in a pathway-centric framework to highlight shared molecular hubs and convergent mechanisms across diverse traditional medicinal systems.

Understanding the molecular targets of these TMs allows for a rational integration with modern pharmacotherapy [49,50]. These agents often act as "dirty drugs" or "poly-pharmacological agents," hitting multiple targets simultaneously to restore metabolic homeostasis.

2.5.4 AMPK Signaling Hub

AMPK serves as the cellular "fuel gauge." In states of nutrient excess (obesity/T2DM), AMPK activity is often suppressed [51]. Intervention: Both Berberine and *Momordica* triterpenoids activate AMPK. This activation triggers a cascade of metabolic corrections: it inhibits mTOR (promoting autophagy and cellular repair), translocates GLUT4 to the sarcolemma [52,53] (increasing glucose uptake), and inhibits Acetyl-CoA Carboxylase (promoting mitochondrial fatty acid oxidation). This overlaps with the mechanism of Metformin and exercise, suggesting that these herbs can act as "exercise mimetics" [54].

2.5.5 PPAR Modulation: Balancing Storage and Oxidation

PPARs are nuclear transcription factors that control lipid and glucose metabolism [55]. PPAR-gamma: Synthetic TZDs activate PPAR-gamma to improve insulin sensitivity but often induce adipogenesis (weight gain) [56]. Curcumin and *Momordica* compounds act as selective PPAR-gamma modulators (SPPARMs), improving insulin sensitivity while inhibiting adipogenesis, thus uncoupling the therapeutic benefit from the adverse effect of weight gain [57]. PPAR-

alpha: *Salacia* extracts activate PPAR-alpha, mimicking the effect of fibrates. This promotes the hepatic uptake and oxidation of fatty acids, directly addressing the dyslipidemia that contributes to cardiovascular risk in diabetics [58,59].

2.5.6 The Incretin Axis and Gastric Motility

The incretin hormones glucose-dependent insulinotropic polypeptide" are crucial for the "incretin effect"-the enhanced insulin response to oral glucose. Intervention: Fenugreek works by delaying gastric emptying through soluble fiber. This fiber modulates how nutrients interact with L-cells in the gut. As a result, it may help sustain GLP-1 release [60-62]. This mechanism offers a synergistic potential with DPP-4 inhibitors (which prevent GLP-1 degradation) or GLP-1 receptor agonists, potentially allowing for lower doses of synthetic agents [63-66]. Inhibition of Carbohydrate Digestion: Alpha-glucosidase enzymes in the brush border of the small intestine [67-69]. *Salacia* species and *Gymnema* contain inhibitors that block these enzymes [70-72]. By delaying carbohydrate digestion, they reduce the magnitude of postprandial glucose spikes [73-75]. This "peak flattening" effect [76], reduces glucotoxicity and the secretory burden on pancreatic β-cells [77-79].

3. Results

3.1 Synthesized Clinical Evidence and Translational Considerations

The clinical evidence supporting the use of traditional medicinal plants in the management of T2DM and obesity is derived primarily from RCTs, controlled clinical studies, and meta-analyses evaluating standardized extracts or defined formulations as monotherapy or adjunctive therapy. Overall, these studies report modest but consistent short-term improvements in glycaemic parameters, including fasting plasma glucose and HbA1c, along with variable effects on body weight and lipid profiles. However, the strength of evidence is constrained by heterogeneity in study design, extract standardization, dosage, intervention duration, and background pharmacotherapy, which complicates direct comparison across trials. As shown in Table 1, while certain phytochemicals such as berberine and curcumin demonstrate relatively reproducible metabolic signals across multiple studies, evidence for other interventions remains variable, underscoring the need for cautious interpretation and rigorous, standardized clinical evaluation.

Table 1. Clinical evidence summary for key medicinal plants: study design, sample size, duration, interventions, outcomes, and evidence quality.

Study (Author, Year)	Design	Sample size (n)	Duration	Intervention	Comparator	Primary outcome(s)	Key result	Evidence quality / Risk-of-bias
Wang et al. / various RCTs (Berberine vs Metformin)	RCTs / meta-analyses	Small-moderate (approx. 30-120)	8-24 weeks (varies)	Berberine (HCl)	Metformin	FPG, HbA1c	Short-term reductions in FPG and HbA1c; some trials report comparable short-term glycaemic reductions but heterogeneity across studies	Moderate (RCTs present but heterogeneity, short durations, small samples)
Gymnema clinical trials (multiple authors)	RCTs / controlled studies	Small (approx. 20-100)	4-24 weeks (varies)	Gymnema extract (e.g., 600 mg/day)	Placebo or standard care	HbA1c, FPG, insulin requirement	Reduced HbA1c and insulin requirement in some trials; evidence suggests insulin-sparing effect	Low-Moderate (many small trials, variable standardization of extracts)
Momordica charantia RCTs / meta-analyses	RCTs / meta-analyses	Small (varied; often <100 per arm)	4-12 weeks typically (varies)	Bitter melon preparationsjuice/extract	Placebo or standard care	FPG, HbA1c	Heterogeneous results; some studies show modest FPG/HbA1c reductions (0.2-0.8%) depending on formulation	Low (high heterogeneity, non-standardized formulations)
Salacia spp. RCTs	RCTs often food-format interventions	Small-moderate (approx. 30-150)	Single-meal to 12-24 weeks	Salacia extract (tea/biscuit)	Placebo or control food	Postprandial glucose, HbA1c	Consistent reductions in postprandial glucose excursions; modest HbA1c reductions (0.25-0.35%) in some trials	Moderate (consistent postprandial effects; variability in formulation/dose)
Curcumin meta-analyses (multiple RCTs)	RCTs pooled in meta-analyses	>1,600 across meta-analyses	Most trials 4-12 weeks; pooled analyses longer	Curcumin supplements	Placebo or standard care	BMI, weight, waist circumference, inflammatory markers	Meta-analyses report modest reductions in BMI/weight and improved adiponectin; overall beneficial signals	Moderate (larger pooled sample but heterogeneity in doses and formulations)

While preclinical data is compelling, the translation to clinical practice requires rigorous validation [80-82]. The following section synthesizes data from RCTs and meta-analyses [83-85]. Reported HbA1c changes should be interpreted in the context of modest baseline HbA1c levels, short follow-up durations, and frequent concomitant therapy.

The current clinical evidence supporting traditional medicinal plants in T2DM and obesity is characterized by modest efficacy signals accompanied by significant translational constraints (Figure 3). Among the evaluated agents, berberine shows the most reproducible short-term improvements in glycaemic indices across multiple RCTs and meta-analyses, yielding a moderate level of evidence. Gymnema sylvestre demonstrates clinically relevant HbA1c reductions and insulin-sparing effects, although the overall strength of evidence remains limited by small sample sizes and short intervention durations. In contrast, outcomes for Momordica charantia are highly variable, reflecting heterogeneity in formulations and study designs. Salacia species exhibit comparatively consistent postprandial glucose-lowering effects, while curcumin shows moderate evidence for weight-related and adipokine-mediated benefits rather than direct glycaemic control.

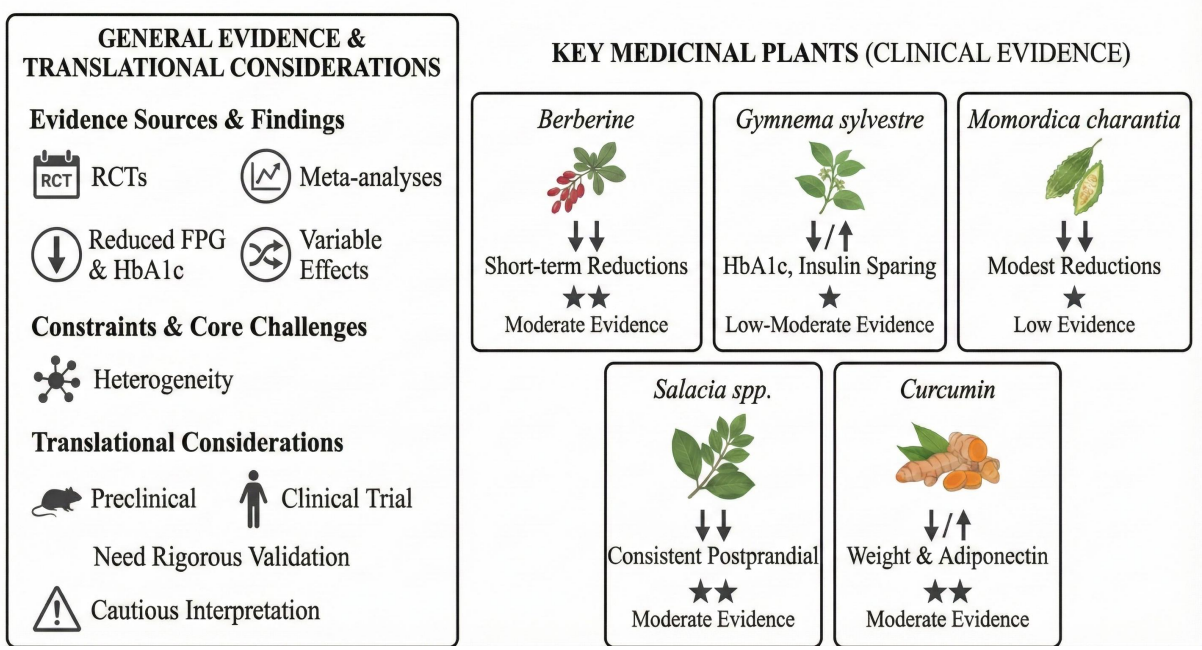


Figure 3. Clinical evidence and translational considerations for key medicinal plants used in the management of T2DM and obesity.

3.2 Berberine vs. Metformin: Comparative Efficacy

Several high-quality trials have benchmarked Berberine against Metformin, the gold standard for T2DM [86-90]. Glycemic Control: In a landmark RCT involving prediabetic patients, Berberine HCl was compared directly to Metformin [91-93]. The results showed short-term glycaemic reductions of comparable magnitude in small RCTs: Berberine reduced (FPG) from 109.8 mg/dl to 97.2 mg/dl, while Metformin reduced it from 110.2 mg/dl to 99.4 mg/dl. HbA1c reductions were also similar (0.31% vs. 0.28%) [94]. Lipid Profile: Berberine demonstrated a superior effect on lipid profiles, significantly lowering Triglycerides (TG) and LDL-Cholesterol, whereas Metformin had negligible effects on lipids [95-99]. Adverse Events: The safety profile of Berberine was favorable, with a 20% incidence of mild gastrointestinal side effects compared to 30% in the Metformin group [100-103]. This suggests Berberine is a viable alternative for patients intolerant to Metformin [104-106].

3.3 *Gymnema Sylvestre*: Clinical Outcomes

Insulin Sparing Effect: A key finding in clinical literature is *Gymnema's* ability to reduce insulin requirements [107-111]. In trials involving Type 2 diabetics on oral medications, supplementation with 600 mg/day of *Gymnema* extract significantly reduced HbA1c and FPG compared to placebo [112-116].It also facilitated a reduction in the dosage of conventional medicines, supporting its role as an adjunct therapy [117-120]. Regenerative Potential: Improvements in glycaemic control reported in some longer-term studies may reflect enhanced β-cell function or preservation, but direct evidence of β-cell regeneration in humans is lacking; available clinical data are insufficient to confirm regeneration and require dedicated translational biomarker studies (e.g., stimulated C-peptide) [121-124].

3.4 *Momordica Charantia*: Heterogeneity in Results

Meta-Analysis Data: Evidence for *Momordica* is mixed. Some meta-analyses report significant reductions in FPG and HbA1c, while others find low certainty of evidence due to high heterogeneity in study designs [125-128]. Formulation Matters: The inconsistency likely stems from the variation in preparations (juice vs. dried powder vs. extract) [129-132]. Trials using standardized extracts of polypeptide-p or charantin tend to show more consistent hypoglycemic effects compared to crude fruit preparations [133-136].

3.5 *Salacia* Species: Postprandial Control

RCTs using *Salacia* extracts (often incorporated into biscuits or tea) have consistently demonstrated significant reductions in postprandial glucose excursions and HbA1c (reductions of 0.25-0.35%). These studies highlight its utility as a "medical nutrition therapy" or functional food ingredient for prediabetes and early T2DM [137-140].

3.6 *Curcuma Longa*: Metabolic Syndrome Management

A comprehensive meta-analysis of 18 RCTs involving over 1,600 individuals concluded that Curcumin intake significantly reduces BMI, body weight, and waist circumference in patients with metabolic syndrome [141-143]. Crucially, it also increased levels of adiponectin an anti-inflammatory hormone inversely correlated with body fat confirming its role in ameliorating adipose tissue dysfunction [144,145].

3.7 Safety, Toxicity, and Regulatory Aspects

For clarity, safety concerns discussed in this section are distinguished between clinically documented adverse events and theoretical or preclinical risks. Documented clinical cases are derived from human case reports, clinical trials, or post-marketing surveillance, whereas theoretical risks primarily arise from preclinical toxicology studies, mechanistic considerations, or limited observational evidence. This distinction is important to avoid overestimation of risk and to contextualize safety findings appropriately for clinical practice.

The integration of TMs into mainstream healthcare is contingent upon rigorous safety assurances [146]. The perception that "natural" equates to "safe" is a dangerous fallacy that must be addressed through pharmacovigilance [147].

3.8 Herb-Drug Interactions and Toxicity Risks

Serotonin Toxicity: *Garcinia cambogia* containing Hydroxycitric Acid (HCA) is popular for weight loss [148]. However, HCA increases serotonin levels. Case reports have documented severe serotonin toxicity (manifesting as tremors, hypertension, and ocular clonus) in patients taking *Garcinia* concurrently with SSRIs (e.g., fluoxetine). This highlights a critical herb-drug interaction that clinicians must screen for [149]. Hepatotoxicity: In clinical practice, most commonly used medicinal plants are well tolerated; however, a small number of case reports have described unexpected liver injury associated with certain herbal supplements. Concerns about long-term hepatic toxicity from concentrated extracts remain largely theoretical and are primarily derived from preclinical studies, highlighting the importance of routine liver function monitoring during prolonged use [150]. Hypoglycemia: Clinically documented cases indicate that the glucose-lowering effects of herbs such as Gymnema, Berberine, and Momordica may precipitate hypoglycemia when used concomitantly with sulfonylureas or insulin. These events reflect additive pharmacodynamic effects rather than intrinsic toxicity, and often necessitate dose adjustment of conventional antidiabetic agents [151].

3.9 Global Regulatory Frameworks

WHO Pharmacovigilance: The WHO has established guidelines for safety monitoring of herbal medicines, advocating for their inclusion in national pharmacovigilance systems. However, implementation remains inconsistent. In countries like Tanzania, assessment of regulatory authorities revealed significant gaps, such as underreporting of adverse reactions and a lack of qualified pharmacovigilance personnel among herbal manufacturers [152].

FDA (USA): In the United States, botanical products are regulated differently from small-molecule drugs. The FDA's "Guidance for Industry on Botanical Drug Products" provides a way for these products to be approved as prescription drugs (NDA). This process requires strict Chemistry, Manufacturing, and Controls (CMC) data to ensure consistency in batches. However, most herbals are marketed as Dietary Supplements under Dietary Supplement Health and Education Act (DSHEA), which does not require pre-market proof of efficacy, leading to variability in product quality [153].

AYUSH (India): The Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) has formalized the management of *Prameha* through clinical protocols. These guidelines recommend a graded approach: starting with lifestyle and single herbs (*Amalaki*, *Guduchi*) for prediabetes, and escalating to polyherbal formulations for established T2DM. This structured approach offers a model for integrating traditional knowledge into national health programs [154].

3.10 Standardization Technologies FDA

Ensuring the reproducibility of herbal medicines is a major challenge. Modern analytical techniques are now essential. HPTLC/HPLC: High-Performance Thin-Layer Chromatography (RCT)/ High-performance liquid chromatography (HPLC) is commonly used to identify polyherbal formulations. By measuring specific marker compounds, such as mangiferin in Salacia and gymnemic acids in Gymnema, manufacturers can confirm that each batch provides a consistent therapeutic dose. This "marker-based standardization" is a prerequisite for reliable clinical trials and practice [155]. As shown in Table 2, key medicinal plants and their principal phytoconstituents converge on shared metabolic targets, including AMPK activation, PPAR modulation, α-glucosidase inhibition, and incretin pathway regulation, which collectively underpin their reported glycaemic and metabolic effects.

Table 2. Key phytochemicals, molecular targets, and supporting clinical evidence in T2DM.

Plant Species	Bioactive Constituents	Primary Mechanism of Action	Clinical Effect	Key Supporting Clinical Evidence
Gymnema sylvestre	Gymnemic acids, Gurmarin	Taste suppression; Intestinal glucose blockade; β-cell functional preservation.	HbA1c reduction; Reduced insulin requirement.	Small RCTs (n 20-100; 4-24 weeks) using standardized extracts (600 mg/day) reported reductions in FPG and HbA1c with insulin-sparing effects; evidence limited by small sample size and short duration.
Momordica charantia	Charantin, Polypeptide-p, Vicine	AMPK activation (GLUT4 translocation); Insulin mimetic; Anti-adipogenic.	FPG reduction; Improved insulin sensitivity.	Clinical trials show heterogeneous outcomes due to formulation and bioavailability differences; reported HbA1c reductions range from 0.2-0.8%, with greater consistency in standardized extract or polypeptide-p formulations.
Berberis aristata	Berberine	AMPK activation (mitochondrial inhibition); LDLR mRNA stabilization.	Comparable to Metformin; Significant lipid lowering.	RCTs and meta-analyses (8-24 weeks) demonstrate modest HbA1c (0.3%) and FPG reductions alongside lipid-lowering effects; evidence moderate but limited by heterogeneity and short follow-up.
Curcuma longa	Curcumin	NF-κB inhibition (Anti-inflammatory); PPAR-γ modulation (Anti-adipogenic).	Reduced BMI & waist circumference; Increased Adiponectin.	Meta-analyses of RCTs (pooled N >1,600; 4-12 weeks) indicate modest reductions in BMI and waist circumference with improved adiponectin and inflammatory markers.
Salacia reticulata	Salacinol, Kotalanol	Alpha-glucosidase inhibition; PPAR-α activation.	Postprandial glucose flattening; Lipid regulation.	Human trials (n 30-150) consistently demonstrate postprandial glucose attenuation and modest HbA1c reductions (0.25-0.35%), particularly with standardized formulations.
Trigonella foenum-graecum	Galactomannan, 4-Hydroxyisoleucine	Delayed gastric emptying (GLP-1 modulation); Direct insulin stimulation.	Reduced postprandial glucose; Insulin secretion.	Small clinical studies report reduced postprandial glucose levels and improved glycaemic control, attributed to soluble fiber and insulinotropic amino acids; evidence primarily short-term.

3.11 Modern Tools: Omics, Network Pharmacology, and AI

The modernization of TM is being revolutionized by the application of systems biology tools, which align perfectly with the holistic nature of TM.

3.11.1 Network Pharmacology: Decoding Synergy

Network pharmacology allows for the analysis of "multicomponent-multitarget" networks, moving beyond the single-target paradigm. An analysis of the TCM formula *Shen-Qi* revealed that its multiple herbal ingredients target a shared network of genes (*AKT1, IL1B, PPARG*) involved in insulin signaling and inflammation. This computational approach validates the "synergistic" theory, where different herbs hit different nodes of the same biological network to produce a robust therapeutic effect [156].

3.11.2 Metabolomics: Signatures of Efficacy

Metabolomics provides a snapshot of the organism's metabolic state. Studies have shown that herbal treatments can normalize specific metabolic biomarkers perturbed in diabetes (e.g., succinate, citrate, branched-chain amino acids). For instance, specific lipidomic profiles have been identified that correlate with TCM syndromes, offering objective biomarkers for traditional diagnoses [157].

3.11.3 Artificial Intelligence (AI): The Future of Discovery

AI and machine learning algorithms are being trained on large datasets to predict patient responses to herbal interventions. This paves the way for "Personalized Integrative Medicine," where a patient's genetic and metabolic

profile can be matched to the most effective herbal formulation [158]. Generative AI models are now screening vast libraries of phytochemicals to identify novel inhibitors of diabetic targets (e.g., SGLT2, DPP-4), accelerating the discovery of new drugs from ancient pharmacopoeias [159]. As shown in Table 3, traditional medical systems conceptualize diabetes and obesity as systemic disorders arising from functional imbalance, a perspective that aligns with the modern understanding of metabolic syndrome as a multi-pathway disease driven by insulin resistance, lipid dysregulation, and chronic inflammation.

Table 3. Comparative analysis of traditional vs. Modern metabolic concepts.

Concept Domain	Ayurveda (Prameha/Medoroga)	TCM (Xiao Ke/Phlegm-Dampness)	Unani (Ziabetus)	Modern Medicine (Metabolic Syndrome)
Primary Etiology	Sedentary lifestyle (*Asyasukham*), Kapha-aggravating diet (dairy, sugar).	Spleen Deficiency (*Pi Xu*), consumption of greasy/sweet foods.	Weakened Kidney retention (*Quwate Masika*), Hot temperament.	Insulin resistance, caloric excess, physical inactivity.
Pathophysiology	*Agni* disturbance leading to *Ama* (toxins) and *Medodushti* (fat vitiation).	Failure of fluid transport leading to Dampness and Phlegm accumulation.	Rapid renal absorption and excretion; Humoral imbalance (*Balgham* excess in obesity).	Glucotoxicity, Lipotoxicity, Chronic low-grade inflammation.
Clinical Features	Polyuria (*Prabhutavil Mutrata*), turbidity in urine.	Thirst, wasting, sticky sensation in mouth, central obesity.	Excessive thirst, polyuria, rapid transit of fluids.	Polyuria, Polydipsia, Central Adiposity, Dyslipidemia.
Therapeutic Goal	*Apatarpana* (depletion) for obese; *Samshodhana* (purification).	Fortify Spleen, resolve Phlegm, clear Dampness.	Correct temperament (*Mizaj*), strengthen kidney retention.	Glycemic control (HbA1c <7%), Weight loss, Lipid normalization.

3.12 Conceptual Workflow for Future Integrative Studies

This section outlines a conceptual framework illustrating how modern computational approaches may be applied in future integrative studies of TMs.

3.12.1 Compound Identification

To obtain a validated compound list and canonical chemical identifiers, compile chemical records from primary cheminformatics repositories (for example, retrieve berberine's SMILES, InChI/InChIKey and PubChem CID from PubChem or ChEMBL). If the subject is a plant (e.g., *Berberis* spp.), assemble reported bioactive constituents from phytochemical databases (TCMSP, KNApSAcK) and the primary literature. Store 2D/3D structures in standard formats (SDF/MOL2) and record canonical identifiers for each entry. In the manuscript methods, report the exact database names, accession numbers and download dates, and document any choices regarding stereochemistry or salt/protomer forms.

3.12.2 Target Prediction (*In Silico*)

To generate a prioritized list of putative protein targets, submit the canonical chemical identifiers (e.g., SMILES/InChI) to multiple complementary in-silico prediction platforms and aggregate results. Typical actions include ligand-based prediction (SwissTargetPrediction, SEA, TargetNet) and reverse/structure-based docking or pharmacophore matching (PharmMapper, idTarget). Record prediction scores or probabilities for each target and retain a consensus set (for example, targets predicted by ≥2 independent methods or above a pre-specified score threshold). Report the tools and versions, input identifiers, score cutoffs, and the date of access; provide UniProt IDs for predicted proteins and retain original prediction output files. Common pitfalls are server-specific scoring idiosyncrasies and false positives; mitigate these by using multiple methods, documenting cutoffs, and flagging low-confidence predictions for downstream orthogonal validation.

3.12.3 Disease Target Mapping

Assemble a curated list of diabetes-associated genes by querying disease databases (GeneCards, DisGeNET, OMIM) and relevant GWAS resources, applying transparent evidence filters (e.g., relevance score or GWAS p-value threshold). Harmonize gene identifiers (convert gene symbols to Entrez/GeneID/UniProt) and annotate each entry with source and evidence type (association, expression change, GWAS). Report database versions, query terms, thresholds, and the date retrieved. Beware of synonym redundancy and broad disease terms; avoid including genes with tenuous or non-specific evidence by applying pre-defined inclusion criteria and documenting them in Methods.

3.12.4 Network Construction

Construct a multi-layer network linking compound(s) to predicted targets and to disease genes, augmenting edges with high-confidence protein-protein interactions (PPI) from STRING or BioGRID (specify confidence score cutoff, e.g., STRING combined score >0.7). Build the network in Cytoscape or an equivalent graph tool, exportable as GraphML/XGMML, and compute topological metrics (degree, betweenness, closeness) for prioritization. Document PPI database version and cutoff, network construction rules (edge types, evidence thresholds), software and versions, and layout/visualization parameters. Common pitfalls include overly dense networks; apply filtering (confidence thresholds, retain top-N neighbours) to maintain interpretability and reproducibility.

3.12.5 Pathway Enrichment and Mechanistic Inference

Perform functional enrichment on the intersecting target set (compound targets disease gene list) and on high-degree subnetworks using GO, KEGG, and Reactome tools (DAVID, Enrichr, g: Profiler or cluster Profiler). Report the background/universe used for enrichment, multiple testing correction method (e.g., Benjamini-Hochberg), significance threshold (e.g., FDR < 0.05), and the version/date of pathway databases. Present ranked pathways with adjusted p-values and mapped gene counts, emphasizing canonical metabolic and signaling pathways relevant to diabetes (e.g., AMPK, PI3K-Akt, insulin signaling). Pitfalls include inappropriate background choice and pathway redundancy; address these by specifying the universe and by clustering or condensing related pathway terms for clarity.

3.12.6 AI-assisted Prioritization

Assemble a feature matrix where each candidate compound-target (or compound-target-pathway) entry is described by prediction scores, docking scores (if available), network metrics (degree, centrality), tissue-specific expression overlap (GTEx), and ADME/drug-likeness flags. Use transparent machine-learning approaches (ranking SVM, random forest, XGBoost) or an interpretable scoring function for prioritization; when supervised labels are unavailable, apply unsupervised or semi-supervised ranking with explicit weighting and sensitivity analysis. Report model type, feature definitions, training/validation strategy (e.g., k-fold cross-validation), hyperparameters, and performance metrics where applicable; if docking or MD was performed for top candidates, report software, scoring functions, and parameters. Crucially, treat ML outputs as hypothesis generators: document steps taken to avoid overfitting, provide feature-importance or SHAP explanations when possible, and plan orthogonal validation (docking, biochemical assay) for top-ranked hypotheses.

4. Discussion

4.1 Integration of Mechanistic and Clinical Evidence

This review integrates mechanistic and clinical evidence to construct a pragmatic translational narrative. Mechanistic studies identify recurrent pathways-AMPK activation, modulation of PPAR signaling, inhibition of α-glucosidase, enhancement of incretin responses, and anti-inflammatory effects-that plausibly underlie observed short-term improvements in glycaemic indices in several small clinical trials. Nevertheless, concordance between mechanistic and clinical datasets is incomplete: many mechanistic observations are limited to *in vitro* and animal models, while clinical studies are heterogeneous in extract standardization, dose, and duration. Accordingly, we recommend that mechanistic hypotheses be explicitly linked to clinical end-points via translational biomarkers (e.g., stimulated C-peptide, mixed-meal tolerance testing) in future trials to close the preclinical-clinical gap.

4.2 Strengths of the Review

The principal strengths of this review are its integrative scope and methodological transparency. By combining ethnopharmacological context, mechanistic summaries, and an evidence-graded clinical synthesis, the work moves beyond descriptive listing to a structured appraisal useful for translational planning. Inclusion of a clear Materials and Methods section, an evidence-quality table, and an illustrative network-pharmacology/AI workflow enhances reproducibility and provides practical tools for researchers prioritizing candidates for experimental follow-up. Emphasis on real-world considerations, standardization challenges, bioavailability, and LMIC applicability, further increases the review's policy and implementation relevance.

4.3 Limitations

Several limitations temper the conclusions of this review. First, the narrative design and qualitative synthesis, while intentionally broad, are susceptible to selection bias despite a comprehensive search strategy. Second, heterogeneity in intervention formulations, small sample sizes, and short follow-up across clinical studies limit the generalizability and magnitude estimation of therapeutic effects. Third, a sizable portion of mechanistic evidence derives from preclinical models; these findings, though valuable for hypothesis generation, do not establish clinical efficacy. Finally, language restrictions and possible publication bias may have excluded relevant data; these limitations underscore the need for standardized reporting and higher-quality trials.

4.4 Implications for Research and Clinical Practice

For research, priorities are clear: development of chemically standardized extracts, routine pharmacokinetic and bioavailability profiling, selection of translational biomarkers, and adequately powered RCTs with clinically meaningful endpoints [160,161]. Network pharmacology and AI should be deployed as hypothesis-generating approaches that feed into prioritized experimental validation (docking, biochemical assays, short-term human pharmacology studies). For clinical practice, current evidence supports cautious, context-specific adjunctive use of certain herbal preparations where clinical data exist, paired with active monitoring for efficacy and safety (glycaemia, liver function) and attention to herb-drug interactions. Clinicians should counsel patients about limited evidence and prioritize evidence-based therapies as first-line treatment while considering herbal therapies as complementary under monitored conditions.

4.5 Translational Aspects, Challenges, and Future Directions

Despite the promise, several barriers impede the full integration of TM into modern care: Standardization: The inherent biological variability of plants makes standardization difficult. Adopting rigorous "Seed-to-Shelf" quality control is essential [162]. Clinical Trial Design: Standard RCT designs may not capture the personalized nature of TM (e.g., treating based on *Dosha* or *Constitution*). Future trials should incorporate "whole system" research designs that allow for individualized formulations within a rigorous framework [163]. Intellectual Property: Protecting traditional knowledge while incentivizing commercial drug development remains a complex legal hurdle [164].

Reverse Pharmacology: Instead of the "molecule-to-man" approach, research should adopt "reverse pharmacology," starting with documented clinical success in TM practice and working backward to identify mechanisms and active fractions [165,166]. Integrative Clinics: establishing clinics where modern diabetologists and TM practitioners work in tandem can generate real-world evidence and optimize patient outcomes [167,168]. Global Harmonization: Harmonizing regulatory standards for herbal medicines across the WHO, FDA, and European Medicines Agency would facilitate the global acceptance and trade of high-quality TMs [169,170].

5. Conclusion

The global burden TDM and Obesity demands a paradigm shift in management strategies. The relentless rise in prevalence, coupled with the limitations of current pharmacotherapy, necessitates a broader, more inclusive therapeutic arsenal. TM systems-Ayurveda, TCM, and Unani-offer time-tested, multi-targeted strategies that address the root causes of metabolic dysregulation: diet, lifestyle, and physiological balance.

This report demonstrates that the efficacy of plants like *Gymnema sylvestre*, *Momordica charantia*, and Berberine is not merely folklore but is grounded in potent, scientifically validated molecular mechanisms involving AMPK activation, PPAR modulation, and incretin regulation. When integrated with modern tools like network pharmacology, AI, and rigorous pharmacovigilance, these ancient therapies offer a sophisticated "systems biology" solution to the complex problem of metabolic syndrome.

The path forward lies in the rigorous scientific validation and respectful integration of these systems. By bridging ancient wisdom with modern science, we can develop a more resilient, effective, and patient-centered approach to conquering the metabolic pandemic, offering hope to the hundreds of millions of individuals living with diabetes worldwide.

Acknowledgements

The authors would like to acknowledge Lovely Professional University, Phagwara for continuous support and encouragement.

Funding

This review did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

Ethics Statement

Not applicable.

Data Availability

Not applicable.

Author Contributions

Saminesh Kumar: Writing, original draft, Data curation. Shivank Sharma: Supervision, Validation, Visualization.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Generative AI Statement

The authors only used ChatGPT as a language-assistance tool for grammar and phrasing improvement. Besides, generative AI was not used. They take full responsibility for all content.

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