

Phyto medicinal approaches to postprandial hyperglycemia: Plants with α -amylase and α -glucosidase inhibitory effects (Review)

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Abstract. Diabetes mellitus (DM), a non-communicable disease with a high disease burden, is characterized by insulin resistance and postprandial hyperglycemia. An estimated 589 million adults worldwide were suffering from DM in 2024, a number projected to exceed 853 million by the year 2050. Diabetes has an evolving epidemiological profile driven by rapid urbanization, dietary patterns characterized by the high consumption of refined carbohydrates, and longstanding ethnomedicinal practices involving native plants for glycemic management. Specific epidemiological data on the prevalence of diabetes for the present review were extrapolated from available regional and national estimates due to the lack of comprehensive population-level data estimates. The digestive enzymes, α -amylase and α -glucosidase, are crucial in mediating hyperglycemia. Acarbose, miglitol and voglibose are potent inhibitors of intestinal α -amylase and α -glucosidase, and are routinely used in clinical practice. However, these drugs are associated with gastrointestinal side-effects that affect patient compliance. The present review synthesized evidence from published *in vitro*, preclinical and clinical data, and highlights the potential of phytoconstituents, such as polyphenols, flavonoids, alkaloids, tannins, terpenoids and saponins, as α -amylase and α -glucosidase inhibitors. Accordingly, three botanicals of cultural and significant medicinal importance are highlighted: *Azadirachta indica*, *Trigonella foenum-graecum* and *Ocimum tenuiflorum*. The present review discusses the potential of plant-derived phytochemicals to modulate carbohydrate-digesting enzymes and delay glucose absorption and also highlights the potential of using advanced cultivation

techniques, such as hydroponics, CRISPR-Cas9 gene editing and plant tissue culture to enhance phytoconstituent yield and batch consistency, to improve clinical applications. Some limitations in the context of overcoming gaps in the literature are addressed, which remain largely confined to preclinical data and scarce clinical data.

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1. Introduction

Global burden of diabetes mellitus (DM). Non-communicable diseases, such as DM are currently acknowledged as the most challenging health challenges in society. In 2024, there were 589 million adults worldwide living with diabetes. This number is predicted to increase to 853 million by the year 2050 under current circumstances, based on a report by The International Diabetes Federation Diabetes Atlas 11th Edition (2025). The increasing global burden has had a significant socioeconomic impact, with >1 trillion USD spent on the treatment of diabetes to date (1).

DM poses a serious public health concern in India. Recent findings by the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) have reported an overall prevalence of DM of ~7.1% in the state of Gujarat, India, with high disparities between urban (9.5%) and rural (5.1%) populations, indicating the increased burden of metabolic diseases in the state. These epidemiological findings emphasize the

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need for continued research utilizing indigenously available medicinal plants to supplement glycemic control (1,2). This epidemic of global proportions has had its most severe impact on India. Indeed, a World Health Organization-supported study (ICMR-INDIAB National Prevalence Study) found that >101 million Indians suffered from diabetes in 2023, the highest number in a nation globally. With an additional 136 million Indians living with prediabetes (the most recent national data available), the high prevalence can be further justified in Gujarat, in urban areas, such as Ahmedabad, Surat and Vadodara, which have a higher rate of diabetes due to the increased intake of refined carbohydrates. By contrast, the rural areas of Gujarat exhibit an equal decrease in rate, which is attributable to the implementation of traditional agriculture and the use of native plants. Dedicated state-specific large-scale studies in Gujarat are limited; the reported numbers are estimates based on extrapolating national trends and are not directly measured at the state level (2,3).

The global, national and Gujarat-specific prevalence of diabetes is summarized in Table I. The table highlights the escalating worldwide burden of DM and the disproportionate share of this in India, with Gujarat exhibiting marked urban-rural differences. Of note, Gujarat-level figures are extrapolated from state- and national-level data rather than dedicated regional surveys.

Postprandial hyperglycemia and the enzyme gateway. Postprandial hyperglycemia is the main pathophysiological mechanism underlying the progression of type 2 DM (T2DM). The process of hydrolysis of dietary carbohydrate begins in the mouth, with salivary α -amylase acting on starch and cleaving its α -1,4-glycosidic bonds. The hydrolysis cascade is terminated by enzymes located in the brush border of the proximal small intestine (α -glucosidase, maltase and sucrase-isomaltase), which digest oligosaccharides into monosaccharides. The resultant sugars are absorbed into blood circulation in the presence of sodium-glucose cotransporter 1. This absorption occurs more rapidly than insulin release, resulting in postprandial hyperglycemia, which becomes particularly dangerous in the presence of underlying insulin resistance (4,5).

The Food and Drug Administration (FDA)-approved the α -glucosidase inhibitors, acarbose, miglitol and voglibose, competitively inhibit these brush-border enzymes, delaying carbohydrate digestion and reducing postprandial glucose spikes. The undigested carbohydrate reaching the large intestine undergoes colonic fermentation, producing flatulence, abdominal bloating and osmotic diarrhea, which are adverse effects that disproportionately affect acceptability, particularly in resource-limited rural settings. Plant-derived polyphenols and flavonoids have, therefore, attracted increasing interest as candidate *in vitro* inhibitors: Several exhibit half-maximal inhibitory concentration (IC₅₀) values that are 10- to 100-fold lower than that of acarbose under specific assay conditions, although this *in vitro* potency has not yet been confirmed using comparable *in vivo* or clinical head-to-head studies. Thus, these preliminary findings should not be interpreted as evidence of superior clinical efficacy (6,7). A mechanistic overview of the mechanisms through which dietary carbohydrates are hydrolyzed by salivary and pancreatic α -amylase and intestinal

α -glucosidase, leading to rapid glucose absorption is presented in Fig. 1. Plant-derived phytochemicals, such as polyphenols, flavonoids, terpenoids, tannins and alkaloids function at these enzymatic steps, effectively delaying digestion and reducing postprandial hyperglycemia.

The case for phytomedicinal research in the Indian context. For >2,000 years, traditional Indian medicine systems, including Ayurveda, Unani, Siddha and various Adivasi folk-medicine traditions, have used plant-based remedies for the treatment of DM. An estimated 1,200 plant species worldwide have been reported to exert antidiabetic effects, yet only ~500 have undergone controlled laboratory testing. This gap is particularly critical, given that India alone has >45,000 plant species, representing an exceptional and largely underexplored botanical resource (8-10).

Due to the marked reliance of agriculture, food and religious activities in Gujarat, India on local indigenous flora, all of which have received considerable ethnomedicinal and pharmacological attention, there is adequate scientific reason to focus on the study of the medicinal flora in Gujarat; however, the majority of evidence presented in the present review was obtained from either other regions of India or the world literature rather than from Gujarat-based research. The authors have endeavored to address these findings in the present review to the best of their abilities (11).

Literature search strategy. The present narrative review was based on a literature search conducted across the PubMed, ScienceDirect and Google Scholar databases, using the combinations of the key words ' α -amylase inhibition', ' α -glucosidase inhibition', 'postprandial hyperglycaemia/hyperglycemia', 'phytochemicals' and 'polyherbal', and the botanical/Latin nomenclature, *Azadirachta indica* (*A. indica*), *Trigonella foenum-graecum* (*T. foenum-graecum*) and *Ocimum tenuiflorum* (*O. tenuiflorum*). Articles published up to 2026 were considered, with an emphasis on peer-reviewed original research and review articles reporting *in vitro*, *in vivo*, or clinical enzyme-inhibition and antidiabetic data. Conference abstracts, non-peer-reviewed sources, and articles in languages other than English were excluded. As the present study is a narrative review rather than a systematic review, screening was not performed in duplicate, an inclusion/exclusion flow diagram was not generated, and formal risk-of-bias or quality assessments were undertaken. Consequently, the PRISMA compliant systematic review methodology was not used; hence, the conclusions presented herein should be interpreted as a qualitative synthesis rather than a quantitative or exhaustive appraisal of the literature.

2. Phytochemical classification and mechanisms of enzyme inhibition

The inhibitory activity of plant extracts against α -amylase and α -glucosidase is attributable to structurally diverse classes of secondary metabolites, each engaging distinct molecular interactions with the catalytic machinery of these enzymes. A comparative overview of the principal phytochemical classes, their representative compounds, enzyme targets and mechanisms of action documented in the literature is

Table I. Diabetes mellitus prevalence data: Global, India and Gujarat estimates.

Region/population	Year	Diabetic adults (millions)	Prevalence (%)	(Refs.)
Global	2021	537	~10.5	(1)
Global (projected)	2045	783	~12.2	(1)
India	2023	101	11.4	(2)
India (pre-diabetic)	2023	136	~15.3	(2)
Gujarat - Urban	2022-2023	~8.5 (est.)	~13.0	(3)
Gujarat - Rural	2022-2023	~3.2 (est.)	~7.5	(3)

Gujarat district-level estimates derived from ICMR-INDIAB state-level extrapolation and published epidemiological surveys. est., estimated.

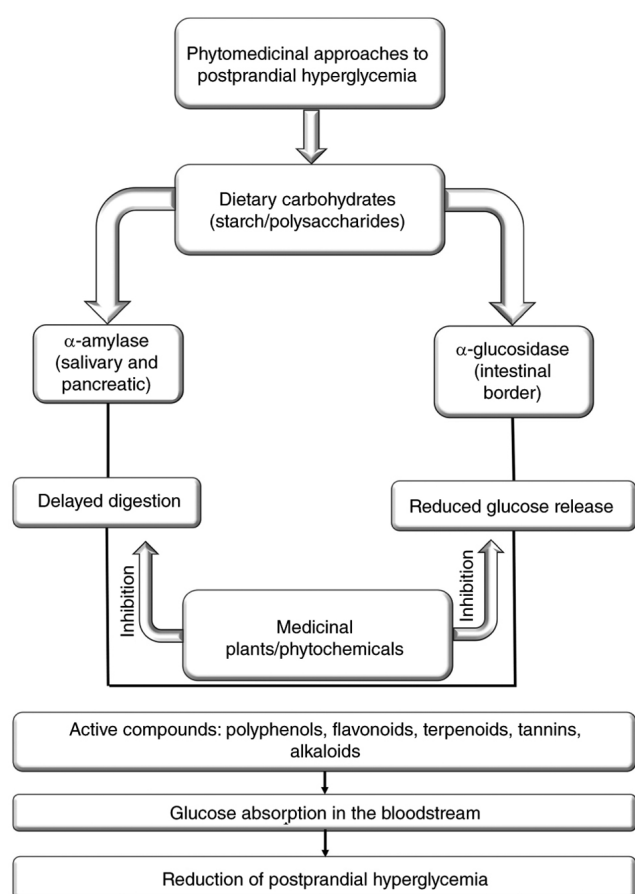


Figure 1. Phytomedicinal approaches for the treatment of postprandial hyperglycemia: Inhibition of α -amylase and α -glucosidase by plant-derived polyphenols, flavonoids, terpenoids, tannins, and alkaloids reduces glucose absorption and postprandial blood glucose levels.

provided in Table II (6,7,12-19). Unless otherwise stated, the mechanisms summarized in the table are derived from *in vitro* enzyme-inhibition assays rather than *in vivo* or clinical studies.

Polyphenols and flavonoids. Polyphenols are the most extensively researched group of plant-derived inhibitors of α -amylase and α -glucosidase, owing to the multiple aromatic rings containing hydroxyl groups, which facilitate hydrogen binding, as well as hydrophobic and van der Waals interactions in the active sites of the enzymes. *In vitro* studies have revealed that flavonoids, such as quercetin, kaempferol, rutin

and epigallocatechin-3-gallate as the most active inhibitors of these enzymes, with the IC₅₀ value of quercetin for the inhibition of α -amylase being 10-100-fold higher than that for acarbose under certain conditions, although direct clinical evidence remains lacking (6,7,14). Other potential antidiabetic mechanisms of action in preclinical settings include the antioxidant role of polyphenols in scavenging oxidative species, the attenuation of the secretion of inflammatory cytokines, and the upregulation of insulin receptor expression mediated by the AMP-activated protein kinase (AMPK) and phosphoinositide 3-kinase/protein kinase B pathways. These mechanisms, among others, can synergize with enzyme inhibition for a holistic approach to treat T2DM, although their impact on clinical outcomes warrants validation and elucidation (6).

Alkaloids, tannins, saponins and terpenoids. Trigonelline, isolated from *T. foenum-graecum*, inhibits α -glucosidase by mimicking its natural substrate. Berberine functions via a dual mechanism, combining direct enzyme inhibition with AMPK activation, -a pathway shared with metformin. Hydrolyzable tannins, including gallic acid and rosmarinic acid, inhibit α -glucosidase via multipoint binding to the enzyme surface. Saponins, including diosgenin and limonoid terpenoids, such as nimbolide from *A. indica*, contribute additional inhibitory activity through allosteric mechanisms and insulin-secreta-gogue effects. However, these findings are predominantly derived from *in vitro* and *in vivo* studies and have not yet been substantiated in randomized controlled trials (13,14,16,17).

3. Extraction methodology and analytical approaches

The selection of extraction solvent fundamentally governs the qualitative and quantitative profiles of phytochemicals derived from plants. 3,5-Dinitrosalicylic acid (DNSA) colorimetry is the most widely used laboratory technique for determining α -amylase inhibition *in vitro*. DNSA reacts with reducing sugars generated by α -amylase-mediated hydrolysis of starch, forming a chromophore that is quantifiable spectrophotometrically at 540 nm. The calculation of the IC₅₀ value from dose-response data enables standardized cross-study comparison and is the primary method used to identify candidate species for subsequent *in vivo* evaluation, although IC₅₀ values obtained under various assay conditions are not always directly comparable across studies (14,20).

Table II. Major phytochemical classes mediating α -amylase and α -glucosidase inhibition: Compounds, targets and mechanisms.

Phytochemical class	Key compounds	Target enzyme(s)	Mechanism of action	(Refs.)
Polyphenols/flavonoids	Quercetin, kaempferol, rutin, EGCG	α -amylase, α -glucosidase	Competitive and non-competitive active-site binding via H-bonds and hydrophobic interactions	(6,7)
Alkaloids	Trigonelline, berberine	α -glucosidase, AMPK	Substrate mimicry; AMPK activation suppressing hepatic gluconeogenesis	(12,13)
Tannins/phenolic acids	Gallic acid, rosmarinic acid, ellagic acid	α -amylase, α -glucosidase	Multi-point surface binding to basic enzyme residues; stable complex formation	(14-17)
Terpenoids/limonoids	Nimbolide, azadirachtin, charantin	α -glucosidase, α -amylase	Allosteric inhibition; insulin secretagogue activity at pancreatic β -cells	(9,10,18)
Saponins	Diosgenin, charantin glycosides	α -glucosidase	Lipid metabolism modulation; competitive enzyme inhibition	(19)
Soluble fibres	Galactomannan (methi)	Physical (non-enzymatic)	Viscosity-mediated delay of gastric emptying and glucose absorption	(19)

EGCG, epigallocatechin-3-gallate; AMPK, AMP-activated protein kinase.

A comparative evaluation of extraction solvents and traditional preparations used in phytomedicinal research and Ayurvedic practice, including their reported phytochemical yield profiles and relative *in vitro* enzyme-inhibitory potential is provided in Table III (3,9,21).

4. Ethnomedicinal plants of Gujarat: Phytochemical and pharmacological profiles

The three plants that are discussed herein, *A. indica*, *T. foenum-graecum* and *O. tenuiflorum*, represent the convergence of centuries of Gujarati ethnomedicinal practice with an increasingly robust scientific evidence base for antidiabetic activity. The taxonomic classification, phytochemical composition, enzyme-inhibitory profile and cultural significance of the three species are presented in Table IV (3,9,10,14,15,18, 19,22-24), which serves as a structured comparative overview.

A. indica (*neem/limbdo*). *A. indica* A. Juss. (family: Meliaceae), known as limbdo in Gujarat, holds special value in traditional Indian medicine. *A. indica* is extensively distributed throughout Gujarat and is commonly cultivated in both rural and urban environments. In traditional Ayurveda, different parts of the plant, including its leaves, bark, seeds and flowers, are used for the management of diabetes, skin diseases, infections and inflammatory disorders. Ethnobotanical investigations from Gujarat have documented the continued use of neem by tribal and rural communities as part of primary healthcare practices. Beyond its common applications, neem is used by Ayurvedic physicians and traditional healers in the Saurashtra region to treat 'meetha mutra', a condition characterized by sweet urine. The antidiabetic activity of *A. indica* is attributable to its high limonoid content, including nimbolide and azadirachtin. The reported IC₅₀ values for nimbolide-enriched fractions against α -amylase and α -glucosidase range from 100-250 μ g/ml *in vitro* (10,18).

In vivo studies have reported that neem extracts enhance glucose uptake by skeletal muscles by upregulating glucose transporter type 4, lowering fasting blood glucose and improving lipid profiles. Concurrent antioxidant effects, including reduced malondialdehyde and increased superoxide dismutase activity, have been proposed to protect pancreatic β -cells from oxidative stress-induced damage. These findings have been derived from preclinical studies using animal models and are not yet confirmed in human clinical trials (23,25).

T. foenum-graecum (*fenugreek/methi*). *T. foenum-graecum* L. (family: Fabaceae), known as methi, is used as both a culinary spice and medicinal plant in Gujarat, which is among the leading methi-producing states in India, with major cultivation in the Mehsana, Patan and Banaskantha districts. It has also long been used in traditional medicine for the management of diabetes and digestive disorders. Its antidiabetic phytochemical portfolio includes 4-hydroxyisoleucine (an insulin secretagogue), trigonelline (an α -glucosidase inhibitor), diosgenin (a lipid modulator) and galactomannan fibers (a physical barrier to glucose absorption). As indicated in a previous review, randomized controlled trials on Indian subjects have reported that fenugreek supplementation at 10-25 g/day is associated with significant reductions in fasting blood glucose, 2-h postprandial glucose and glycated hemoglobin (HbA_{1c}) levels, providing the strongest clinical-level evidence among the three plants reviewed herein (22). The beneficial effects of fenugreek are supported by small-scale randomized trials providing preliminary evidence in humans alongside *in vitro* and *in vivo* data.

O. tenuiflorum (*holy basil/tulsi*). *O. tenuiflorum* L. (family: Lamiaceae), known as tulsi, is among the most widely grown sacred plants in Gujarati courtyards. Its principal bioactive constituents include eugenol, reported as an α -glucosidase inhibitor and insulin secretagogue; ursolic acid, reported as

Table III. Comparative evaluation of extraction solvents and traditional Ayurvedic preparation methods for antidiabetic phyto-medicinal research.

Solvent/method	Polarity	Primary phytochemical yield	Advantages/limitations	(Refs.)
Hexane	Non-polar	Terpenoids, fatty acids, waxes	Isolates lipophilic compounds; poor flavonoid recovery	(21)
Chloroform/ethyl acetate	Intermediate	Moderate polyphenols, alkaloids	Good for aglycone flavonoids; solvent toxicity concerns	(21)
Ethanol (70-95%)	Intermediate-polar	Flavonoids, polyphenols, alkaloids (highest yield)	Superior enzyme inhibitory potency; safe for oral preparations; preferred for pharma	(21)
Methanol	Polar	Polyphenols, glycosides	High recovery; toxicity limits therapeutic use; mainly for research/analytical	(21)
Water (aqueous)	Highly polar	Tannins, saponins, polar glycosides	Lowest enzyme inhibitory potency; traditional kwath/decoction basis; safest for use	(3,9)
Fermented (Arishta)	Aqueous-ethanolic	Enhanced bioavailable phytochemicals via microbial biotransformation	Improved bioavailability; synergistic effects; long shelf-life; deeply traditional	(3,9)

Enzyme inhibitory potency ranking: Ethanol $\geq$ methanol $>$ ethyl acetate $>$ aqueous $>$ hexane for flavonoid-mediated α -amylase inhibition. Fermented Arishta preparations exhibit enhanced bioavailability relative to simple aqueous extracts.

Table IV. Comparative phytochemical, pharmacological, and ethnomedicinal profile of the three primary Gujarat-native antidiabetic plants.

Parameter	<i>Azadirachta indica</i> (neem)	<i>Trigonella foenum-graecum</i> (methi)	<i>Ocimum tenuiflorum</i> (tulsi)	(Refs.)
Gujarati name	Limbdo	Methi	Tulsi	—
Family	Meliaceae	Fabaceae	Lamiaceae	—
Key active compounds	Nimbolide, azadirachtin, flavonoids	4-Hydroxyisoleucine, trigonelline, diosgenin, galactomannan	Eugenol, ursolic acid, rosmarinic acid	(9,15,19)
Enzyme target(s)	α -glucosidase, α -amylase	α -glucosidase; physical glucose absorption barrier	α -amylase, α -glucosidase, PPARG	(15,18,19)
Reported IC50 (α -amylase)	100-250 μ g/ml (nimbolide fractions)	Not directly reported; HbA1c $\downarrow$ in RCTs	Comparable to acarbose <i>in vitro</i>	(14,18)
Secondary mechanisms	GLUT4 upregulation; antioxidant ($\uparrow$ SOD, $\downarrow$ MDA); β -cell protection	Insulin secretagogue (4-OHile); lipid regulation (diosgenin)	COX-2/NF- κ B inhibition; PPARG activation; insulin sensitisation	(15,23,24)
Ethnomedicinal use in Gujarat	Neem kadha; fresh leaves on empty stomach for meetha mutra (sweet urine)	seed powder for glycaemia	Morning infusion; courtyard worship plant	(3,10)
Major Gujarat districts	State-wide (urban roadsides, rural villages)	Mehsana, Patan, Banaskantha (regions of Gujarat)	Household cultivation-state-wide	(3)

IC50 values are approximate and vary by extraction method, solvent and assay conditions. 4-OHile, 4-hydroxyisoleucine; GLUT4, glucose transporter type 4; PPARG, peroxisome proliferator-activated receptor gamma; SOD, superoxide dismutase; MDA, malondialdehyde; RCT, randomised controlled trial.

a peroxisome proliferator-activated receptor gamma activator and insulin sensitizer; and rosmarinic acid, reported as an α -amylase inhibitor with anti-inflammatory effects. The

anti-inflammatory effects of tulsi, mediated via the inhibition of cyclooxygenase-2 and suppression of the NF- κ B pathway, are proposed to address chronic low-grade inflammation,

Table V. Emerging biotechnological platforms for the development of Gujarat-native antidiabetic phytomedicines: Mechanisms, demonstrated benefits and translational relevance.

Technology	Mechanism/application	Demonstrated benefit	Gujarat relevance	(Refs.)
Hydroponics	Soilless cultivation with optimised nutrient solutions	30% ↑ rosmarinic acid in <i>O. tenuiflorum</i> vs. soil; 95% less water usage	Saurashtra/Kutch water scarcity; year-round production of tulsi, neem and methi	(26,27)
CRISPR-Cas9	Targeted genomic editing of CHS and CHI biosynthetic genes	Enhanced flavonoid titres in pilot species; proof-of-concept in tulsi and neem	Contained greenhouse/hydroponic deployment; GEAC regulatory pathway	(28,29)
Plant tissue culture/hairy roots	<i>Agrobacterium rhizogenes</i> transformation; bioreactor scale-up	Nimbolide yield from neem hairy roots within 6 weeks; GMP-compatible batch production	Bypasses seasonal variability; enables pharmaceutical-grade raw material supply	(30,31)
Metabolomics/HPLC-MS	LC-MS/MS, NMR, chemometrics for phytochemical fingerprinting and QA	Batch-to-batch consistency; marker compound quantification; regulatory compliance	CSMCRI Bhavnagar analytical capability; aligns with EMA/FDA CMC requirements	(32,33)
Pharmacogenomics	CYP2C9, PPARG, TCF7L2 variant profiling for personalised dosing	Pilot cohorts at AIIMS Rajkot/Sterling Hospitals; genotype-guided response prediction	India Genomics Consortium Collaboration; Ayurvedic Prakriti Integration	(24,34,35)

CHS, chalcone synthase; CHI, chalcone isomerase; HPLC-MS, high-performance liquid chromatography-mass spectrometry; NMR, nuclear magnetic resonance; QA, quality assurance; PPARG, peroxisome proliferator-activated receptor gamma; GMP, good manufacturing practice; GEAC, Genetic Engineering Appraisal Committee; CMC, chemistry, manufacturing and controls; CSMCRI, Central Salt and Marine Chemicals Research Institute.

which is increasingly recognized as a component of the pathogenesis of T2DM. However, this link is based largely on preclinical rather than clinical evidence (14,15,24). The antidiabetic potential of tulsi is mainly supported by *in vitro* and preclinical studies, and evidence of its efficacy in humans is still limited (14).

5. Emerging biotechnological platforms for phytomedicinal development

The standardized, scalable production of antidiabetic phytochemicals from the native medicinal plants of Gujarat requires biotechnological platforms capable of overcoming the inherent variability of conventional agricultural cultivation. A summary of the five principal technologies reviewed, their demonstrated benefits, and their specific relevance to the research and agricultural infrastructure in Gujarat is presented in Table V (26-35).

Hydroponics. Hydroponic cultivation allows for the precise control of nutrients, light, CO₂, temperature and pH, and it has been used to increase the biosynthesis of phenolics, flavonoids and the yields of specific secondary metabolites associated with α -amylase and α -glucosidase inhibition. In *O. tenuiflorum*, hydroponic cultivation reportedly increased the rosmarinic acid content by 30% relative to the soil-based cultivation. Rosmarinic acid is an α -amylase inhibitor, providing a plausible route toward developing higher-potency

plant-derived materials. However, the enzyme-inhibitory activity of the resulting extracts was not reassessed in that study. Water-scarce regions, such as Saurashtra and Kutch could, in principle, use hydroponic systems, as they require only ~5% of the water required for soil-based cultivation to produce medicinal herbs throughout the year (26,27).

CRISPR-Cas9. CRISPR-Cas9 technology provides a precise and targeted approach for manipulating genes involved in secondary metabolite biosynthesis. Genome editing may improve the phytochemical profile of medicinal plants by enhancing the production of flavonoids, phenolic acids and terpenoids that are associated with the inhibition of digestive enzymes. Its applications to medicinal plants possessing antidiabetic effects remain largely experimental, and further studies are warranted to demonstrate its impact on the production of bioactive components with validated enzyme-inhibitory activity. The CRISPR-Cas9 enzymes chalcone synthase and chalcone isomerase, which are crucial for flavonoid production in medicinally important plants, such as tulsi and neem, can selectively upregulate production by using CRISPR technology. The hairy root cultures of *A. indica* produced by the transformation of *Agrobacterium rhizogenes* were found to produce an improved nimbolide yield in 6 weeks in the absence of seasonal factors. The bioreactor-based scale-up achieved good manufacturing practice (GMP)-compliant production under a controlled environment (29-31,36).

Table VI. Comparative regulatory frameworks for botanical/herbal antidiabetic products: Requirements and gaps for Indian phytomedicinal products seeking international approval.

Regulatory body	Framework/pathway	Key requirements	Gap for Indian botanicals	(Refs.)
WHO GACP guidelines	Good agricultural and collection practices	Seed sourcing, cultivation standards, post-harvest handling, storage	GACP widely unadopted by small-scale Indian botanical suppliers	(32)
EMA (EU)	Traditional Herbal Medicinal Products Directive (THMPD)	30 years traditional use (15 in EU); quality dossier; safety monitoring	EU use documentation absent for Gujarat-native species; origin traceability gaps	(32)
US FDA	Botanical Drug Development Guidance (IND/NDA pathway)	Full CMC; analytical characterisation; phase I-III clinical data	High cost and complexity; lack of standardised botanical API infrastructure in India	(32)
ICH Q1A/BIS (India)	Stability testing; pharmacopoeial monographs	Stability under defined climate zones; marker compound specifications	No BIS monographs for neem/methi/tulsi; stability data rarely generated	(37)

CDSCO, Central Drugs Standard Control Organization; WHO, World Health Organization; EMA, European Medicines Agency; FDA, US Food and Drug Administration; CMC, chemistry, manufacturing and controls; GACP, good agricultural and collection practices; IND, investigational new drug; NDA, new drug application; BIS, Bureau of Indian Standards; ICH, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

6. Regulatory landscape and standardization

Existing Indian regulatory standards require substantial strengthening to meet international benchmarks, a gap that currently limits the progression of Indian phytomedicinal research toward clinical development. A comparison of the regulatory frameworks and documentation requirements of the Central Drugs Standard Control Organization (CDSCO)/Ayush, World Health Organization (WHO), European Medicines Agency (EMA), FDA and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) for botanical drug products, highlighting gaps that would need to be addressed for the polyherbal antidiabetic products of Gujarat to reach international markets is provided in Table VI (32,37). The regulatory pathway for herbal drug development spans cultivation and harvesting, extraction and purification, phytochemical profiling, stability and safety testing, and final regulatory approval.

The implementation of advanced analytical quality assurance tools using high-performance liquid chromatography fingerprinting for phytochemical profiling, liquid chromatography-tandem mass spectrometry for the measurement of marker compounds, nuclear magnetic resonance spectroscopy together with metabolomics for the identification of secondary metabolites, and ICH Q1A stability testing for the assessment of product integrity throughout its shelf life will enable international regulatory bodies to achieve their alignment objectives. The WHO guidelines for Good Agricultural and Collection Practices (GACP) establish standardized procedures for seed selection, field management, and post-harvest processing, which help control upstream sources of variability in agricultural operations (32,33).

The Bureau of Indian Standards should work with the Ministry of Ayush to create complete quality monographs for neem, methi and tulsi, which will meet international

pharmacopoeial standards. The institutional ecosystem of Gujarat, which includes Anand Agricultural University and CSMCRI Bhavnagar and AIIMS Rajkot, possesses the necessary resources to advance the standardization process (37).

7. The polyherbal research gap

The reductionist approach, which currently controls modern phytomedicinal research, and the Ayurvedic treatment method, which uses multiple active ingredients to treat patients, create an essential conflict. The limonoids from neem inhibit α -glucosidase, whereas 4-hydroxyisoleucine and galactomannans from methi boost insulin production and delay glucose uptake, distinct mechanisms acting at three different pathophysiological points (9,15,24).

Isobolographic analysis and network pharmacology models are mathematical methods used by researchers to determine how different plants in polyherbal systems interact with each other through synergistic, additive or antagonistic effects. The present review mentions randomized controlled trials that have analyzed polyherbal formulations containing neem, tulsi and methi. The formulations were found to provide significant benefits in reducing fasting blood glucose and HbA1c levels compared with both monotherapy and placebo controls, thereby establishing an initial clinical support for the Ayurvedic system of medicine, which uses multiple herbs together (38-40).

Clinical and preclinical evidence supporting polyherbal synergy is summarized in Table VII (41-44), where combinations such as neem, tulsi and fenugreek are shown to exhibit superior glycemic control compared with monotherapy. Furthermore, to avoid different levels of evidence, Table VIII stratifies the findings into *in vitro*, preclinical and clinical categories for the three ethnomedicinal plants from Gujarat.

Table VII. Neem, tulsi and fenugreek combinations: Preliminary evidence for polyherbal synergy in multi-targeted enzyme inhibition^a.

Polyherbal formulation	Study design	Experimental model	Extract/ Formulation	Dose/ Concentration	Outcome measures	Main findings	(Refs.)
Neem (<i>Azadirachta indica</i>) + tulsi (<i>Ocimum tenuiflorum</i>) + fenugreek (<i>Trigonella foenum-graecum</i>)	Preclinical experimental study	STZ-induced diabetic rats	Hydroalcoholic polyherbal extract	200-400 mg/kg (oral)	FBG, oral glucose tolerance test (OGTT), serum insulin, antioxidant enzyme activity	Significantly improved glycaemic control and antioxidant status. Synergistic antihyperglycemic effects were suggested; however, direct evidence for enhanced α -amylase/ α -glucosidase inhibition was not demonstrated.	(41-43)
Neem (<i>Azadirachta indica</i>) + tulsi (<i>Ocimum tenuiflorum</i>) + jamun (<i>Syzygium cumini</i>)	Preclinical experimental study	Alloxan-induced diabetic rats	Polyherbal syrup	5-10 ml/kg (oral)	FBG, body weight, lipid profile, liver function markers	Improved fasting blood glucose and metabolic parameters compared with untreated diabetic animals. Evidence for synergistic enzyme inhibition remains indirect because α -amylase and α -glucosidase activities were not measured separately.	(41,43,44)

^aBased on the three studies identified in the present review (findings should be regarded as hypothesis-generating rather than conclusive). Study design and appraisal detail for the combinations above: i) Neem + tulsi + fenugreek - an Indian randomised controlled trial in patients with type 2 diabetes mellitus compared a standardised polyherbal formulation against monotherapy, with HbA1c reduction as the primary outcome measure; sample size and blinding details are as reported in the original source and should be verified there, as only a single trial of this combination was identified. ii) Neem + tulsi + jamun - evaluated as a herbal syrup formulation with fasting glucose control as the outcome measure in a preclinical/early-phase evaluation rather than a large-scale randomised trial. Given that each study was identified for each combination, with no independent replication, direct extract-type and dose/concentration comparators, or head-to-head comparison against standard antidiabetic drugs, the evidence for polyherbal synergy summarised here is preliminary and should not be interpreted as established clinical efficacy. FBG, fasting blood glucose.

Table VIII. Evidence stratified into *in vitro* (enzyme assays), preclinical (animal models) and clinical (human trials).

Plant	<i>In vitro</i> evidence (Refs.)	Preclinical (animal) evidence (Refs.)	Clinical (human) evidence (Refs.)
<i>Azadirachta indica</i> (neem)	Limonoids (nimbolide, azadirachtin) inhibit α -glucosidase with IC50 values ~100-250 μ g/ml (50).	Improves glucose uptake via GLUT4 upregulation; reduces oxidative stress markers in diabetic rats (49,51).	No robust RCTs; evidence limited to ethnomedicinal reports and small observational studies.
<i>Trigonella foenum-graecum</i> (fenugreek)	Trigonelline inhibits α -glucosidase; diosgenin modulates lipids; galactomannan fibres reduce glucose absorption (19).	Animal studies show improved insulin secretion, glucose metabolism and lipid profiles, including increased HDL and reduced LDL levels (52).	Small RCTs in Indian populations: 10-25 g/day fenugreek reduced fasting glucose, postprandial glucose, HbA1c, cholesterol, and triglycerides (22).
<i>Ocimum tenuiflorum</i> (tulsi)	Eugenol (α -glucosidase inhibitor), rosmarinic acid (α -amylase inhibitor), ursolic acid (PPARG activator) (14,15).	Animal models exhibit anti-inflammatory and insulin-sensitizing effects via activation of the GLUT4-AMPK signaling pathway (53).	Human evidence is lacking; current support is ethnomedicinal and preclinical only.

GLUT4, glucose transporter type 4; RCT, randomized controlled trial; PPARG, peroxisome proliferator-activated receptor gamma.

8. Limitations

Certain limitations should be acknowledged as the evidence base is dominated by *in vitro* enzyme-inhibition assays. *In vivo* data are comparatively limited, and data from randomized controlled trials are available for only a small subset of the discussed phytochemicals and plant combinations, most notably *T. foenum-graecum*. Claims that certain phytochemicals ‘match or exceed’ the effects of acarbose are based on *in vitro* IC50 comparisons under heterogeneous assay conditions and should not be considered evidence of superior clinical efficacy. *In vivo* studies provide mechanistic support, whereas evidence from clinical studies in humans is limited. Although direct evidence linking hydroponically grown plants with increased inhibitory potency remains limited, this review focuses on the plants from Gujarat. Dedicated Gujarat-specific epidemiological, ethnobotanical, and clinical data are scarce where used, and regional figures are largely extrapolated from national or broader Indian datasets rather than direct measurements. Furthermore, measurable improvements in α -amylase or α -glucosidase inhibitory activity and their inclusion are intended to inform future research directions rather than to imply established clinical relevance.

9. Future research directions

Future studies could focus on four main research areas that are connected to each other. The first research area is the systematic characterization of polyherbal synergy in neem-methi-tulsi formulations using isobolographic analysis, network pharmacology modeling and randomized clinical trials, which could use standardized preparations with metabolomic plasma profiling. The second research area could involve the use of hydroponic systems, CRISPR-Cas9 technology, and

tissue culture methods to create GMP-compliant facilities through joint efforts between Anand Agricultural University (AAU) and Central Salt and Marine Chemicals Research Institute (CSMCRI) and the pharmaceutical companies in Gujarat. The third focus area could involve developing pharmacogenomic research cohorts that utilize genetic variants in *cytochrome P450 2C9*, *PPARG*, *TCF7L2* and *SLC2A2* to investigate genotype-guided polyherbal antidiabetic treatment at AIIMS Rajkot through collaborative work under the India Genomics Consortium. The fourth research area could implement capacity-building programs that will help the medicinal plant production sector of Gujarat to adopt GACP and GMP, and thereby advance analytical quality-assurance methods (32,34,35,37,45).

Furthermore, future research is required to focus on generating Gujarat-specific evidence by performing comprehensive ethnobotanical surveys, moving into phytochemical profiling and metabolomic characterization, and by using standardized enzyme-inhibition studies, preferably using locally cultivated germplasm. Moreover, researchers could integrate traditional knowledge from tribal communities in regions, such as Dang, Panchmahal, Sabarkantha, Kutch and Narmada, with newer analytical methods to discover novel bioactive molecules, and then work toward region-tuned phytomedicinal formulations. This well-planned preclinical work could be followed by randomized clinical trials consisting of participants from Gujarat to validate traditional therapeutic claims and support the development of standardized, evidence-based botanical interventions for postprandial hyperglycemia. Such a multidisciplinary approach will not only strengthen the scientific backbone of the traditional medicinal knowledge in Gujarat, but may also create avenues for the discovery and clinical translation of plant-derived α -amylase and α -glucosidase inhibitors for the management of diabetes (46-48).

10. Conclusions

The present review summarizes scientific evidence that supports phytochemicals as compounds that inhibit α -amylase, α -glucosidase and carbohydrate-digesting enzymes *in vitro*, the main enzymes responsible for generating high blood glucose levels following a meal, in individuals with T2DM. The *in vitro* enzyme-inhibitory effects of polyphenols, flavonoids, alkaloids, tannins, terpenoids and saponins match or surpass the effects of acarbose, whereas quercetin and its related flavonoids appear to be particularly valuable owing to their medicinal uses (6,7,14,20).

Three traditional medicinal plants of Gujarat, i.e., *A. indica*, *T. foenum-graecum* and *O. tenuiflorum*, exert their anti-oxidant, antidiabetic and insulin-sensitizing effects through various pathways that target enzymatic, hormonal, and inflammatory processes (15,23). Among these three plants, methi has a reasonable level of preliminary evidence of efficacy in humans, whereas neem and tulsi are mainly supported by *in vitro* and *in vivo* data (19,22). The clinical efficacy of these plants has not yet been established. The deep integration of the population into the agricultural economy, culinary practices and religious culture of Gujarat creates an alignment between cultural familiarity, sustainable supply chain potential and pharmacological validity (15,23).

The development of internationally recognized herbal medicines requires international approval by means of clinical validation, which in turn demands coordinated efforts to address the three remaining challenges. Gujarat serves as the ideal location to implement this translational research agenda, as its institutional framework includes Anand Agricultural University and CSMCRI Bhavnagar and AIIMS Rajkot, its existing farming capacity and the traditional knowledge of residents of botanical remedies (32,41).

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Authors' contributions

GA searched the literature and wrote the original draft of the manuscript. JG and JL wrote the original draft of the manuscript. ST conceptualized the study, searched the literature for the purposes of the present review and wrote and modified the original draft of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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