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RECENT ADVANCES IN PHYTOPHARMACEUTICAL INTERVENTIONS FOR THE MANAGEMENT OF TYPE 2 DIABETES

Ravina Patidar*[1], Somvardhan Singh Jaitawat[2], Ruchi Dashora[2], Dr. R. S. Tomar[3] and Aditya Pant[4]

[1,2]PG scholar, Bhupal Nobles' College of Pharmacy, Udaipur (raj.).
[3,4]Assistant Professor, Bhupal Nobles' College of Pharmacy, Udaipur (raj.).

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***Corresponding Author: Ravina Patidar**
PG scholar, Bhupal Nobles' College of Pharmacy, Udaipur (raj.).
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ABSTRACT

Chronic hyperglycemia, which can be the result of impaired insulin secretion, insulin resistance, or both, is a sign of a complex metabolic disorder known as diabetes mellitus (DM) Though effective, conventional therapies often have limitations, including possible side effects, expenses, and limited glycemic control for some patients. Phytopharmaceuticals, which are standardized plant-derived compounds developed into scientifically validated formulations, have recently become promising alternatives and supplements for diabetes treatment. This review covers recent progress (2022–2025) in phytopharmaceutical studies aimed at type 2 diabetes mellitus (T2DM). It emphasizes preclinical and clinical results, mechanisms of action, and future pathways.

KEYWORDS: Chronic hyperglycemia, Diabetes Mellitus (DM), Phytopharmaceuticals.

1. INTRODUCTION

The effect of diabetes is demonstrated by the fact that 783 million instances of diabetes mellitus will occur globally by 2045 (International Diabetes Federation, 2023). Nowadays, even the use of synthetic hypoglycemic medications (such insulin, sulfonylureas, and metformin) depends on plant-based bioactives since they may target several metabolic pathways with fewer adverse effects. Coote and associates. Sharma and Kaur (2022) assert that phytopharmaceuticals vary from conventional herbal treatments due to their rigorous preclinical and clinical testing, standardized active constituents, and validated mechanisms.

This review examines phytopharmaceutical studies that have demonstrated anti-diabetic efficacy throughout the last three years, with an emphasis on clinical translation.

Definition and the Framework for Regulation

According to the Indian Drugs and Cosmetics (Eighth Amendment) Rules, 2015, a phytopharmaceutical is:
A standardized and purified fraction that contains a minimum of four phytochemical or bioactive chemicals (evaluated both qualitatively and quantitatively) that are extracted from plants and used to prevent or treat illnesses.

Important differences from herbal products

Standardization: Quantified and consistent active substances are used in all batches. Purity: Devoid of impurities like adulterants or heavy metals.

Scientific validation: Therapeutic claims are supported by preclinical and clinical research
Regulatory approval: Needs safety, pharmacokinetic, and effectiveness data to be submitted.

Although regulatory bodies like the FDA (US), EMA (Europe), and CDSCO (India) have different policies, the general trend is to incorporate plant-based active ingredients into conventional medicine while maintaining high standards of quality.

Mechanistic Targets & Key Bioactive Classes

Enzyme Inhibition: α-Glucosidase, α-Amylase, DPP-IV

- Tropical herbs as natural DPP-IV inhibitors: flavonoids (quercetin), phenolic acids, coumarins show antioxidative/incretin-modulating effects. Novel heterocyclic analogues inspired by phytochemicals serve as α-glucosidase inhibitors.

Insulin Mimetic & Sensitizing Actions

- *Myricetin*: rodent studies demonstrate enhanced GLUT4/GLUT2–mediated uptake and glycogen synthase activation; clinical human data remains inconclusive. Combined natural compounds like **curcumin**, **berberine**, **gymnemic acid**, **mangiferin** target multiple metabolic nodes including PPARγ and PI3K, as evidenced by patent literature. **β-Cell Preservation & Regeneration**
- Peptides such as *Esculentin-2CHa* promote β-cell proliferation, membrane depolarization and insulin exocytosis in animal models.

Anti-inflammatory & Antioxidant Modulation

- *Celastrol* (from *Tripterygium wilfordii*) improves insulin resistance and mitigates diabetic nephropathy via NF-κB inhibition and autophagy induction

2. Recent Advances in Phytopharmaceutical Research for Diabetes

2.1 Ocimum sanctum (Tulsi) Tablet Formulation

A 2025 study created a tablet of Ocimum sanctum hydro-alcoholic extract and assessed its ability to inhibit α-glucosidase. With an IC_{50} of roughly 3.58 µg/mL, the formulation demonstrated a strong ability to reduce postprandial glucose levels by inhibiting the digestion and absorption of carbohydrates (Mishra et al., 2025).

2.2. Ptyrone™: Andrographis paniculata + Pterostilbene Combination

Ptyrone™, a novel capsule containing *Andrographis paniculata* extract and pterostilbene from *Pterocarpus marsupium*, was evaluated in an open-label clinical trial involving 115 patients with uncontrolled T2DM. Over 12 weeks as add-on therapy to standard care, it significantly reduced fasting plasma glucose (FPG), postprandial glucose (PPG), glycated hemoglobin (HbA1c), and triglycerides without serious adverse effects (Nair et al., 2024).

2.3. Berberine Ursodeoxycholate (HTD1801)

In 113 T2DM patients, HTD1801, a synthetic salt of ursodeoxycholic acid and berberine, was evaluated in a phase II randomized, placebo-controlled study. HbA1c dropped by about 1.0% after taking 1,000 mg twice a day for 12 weeks, whereas LDL C, insulin resistance, and inflammatory markers improved (Zhang et al., 2023). The compound's potential as a multipurpose metabolic treatment is highlighted by its dual impact on lipid and glucose metabolism.

2.4. Eriocitrin (Eriomin®)

In randomized controlled trials, people with prediabetes and hyperglycemia were used to evaluate eriocitrin, a flavonoid that is derived from citrus fruits. Fasting hyperglycemia was reduced by 5–7%, HbA1c was reduced by 2%, GLP 1 production was enhanced, and inflammatory indicators were reduced as a result of supplementation. Remarkably, almost 24% of patients with prediabetes saw a return to normoglycemia (Yáñez et al., 2023).

2.5. Fenugreek-Derived L-Arginine Nanoparticles

A 2025 article in Scientific Reports detailed lipid nanoparticles that contained Trigonella foenum-graecum L arginine. In vitro and in animal models, the nanoformulation increased antioxidant capacity, decreased inflammatory mediators, and possibly increased glucose absorption efficiency (Patel et al., 2025).

2.6. Cumin Seed-Derived Peptides

15 bioactive peptides from Cuminum cyminum with α-amylase inhibitory and antioxidant qualities were found in a 2025 bioinformatic and in vitro study, indicating their possible function in glycemic control and oxidative stress modulation (Singh et al., 2025).

2.7. Berberine

Berberine, an isoquinoline alkaloid primarily derived from *Berberis aristata* and *Coptis chinensis*, has demonstrated significant antidiabetic potential through multiple mechanisms. One of its primary actions involves the activation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis, which leads to enhanced glucose uptake and inhibition of hepatic gluconeogenesis (Zhang et al., 2010). Additionally, berberine modulates gut microbiota composition, further contributing to improved glycemic control (Zhang et al., 2012). A randomized clinical trial by Yin et al. (2008) reported that berberine administration (1.5 g/day) reduced HbA1c levels by approximately 1% over a 3-month period, an effect comparable to metformin. Despite its efficacy, berberine’s poor oral bioavailability has limited its clinical application; however, recent advances such as nanoparticle-based formulations and liposomal delivery systems have shown promise in enhancing its pharmacokinetic profile (Liu et al., 2020).

2.8. Curcumin

Curcumin, the principal polyphenolic compound from *Curcuma longa*, exhibits potent antioxidant and anti-inflammatory effects, along with the ability to modulate peroxisome proliferator-activated receptor gamma (PPAR-γ) and

enhance insulin signaling pathways (Panahi et al., 2016). These properties collectively contribute to its glucose-lowering potential. In a randomized, double-blind, placebo-controlled trial, Chuengsamarn et al. (2012) demonstrated that curcumin supplementation over a 9-month period prevented the progression from prediabetes to type 2 diabetes mellitus (T2DM) in 16.4% of patients, compared to the placebo group. However, curcumin suffers from low systemic absorption; therefore, formulation improvements such as curcumin-phospholipid complexes and nanoemulsions have been developed to significantly increase its bioavailability (Anand et al., 2007).

2.9. Gymnemic Acids

Gymnemic acids, a group of triterpenoid saponins from *Gymnema sylvestre*, exert antidiabetic effects primarily through stimulating insulin secretion, promoting partial regeneration of pancreatic β-cells, and inhibiting intestinal glucose absorption by suppressing the activity of glucose transporters (Persaud et al., 1999). Preclinical studies in streptozotocin-induced diabetic animals have confirmed β-cell regenerative effects, while clinical trials in T2DM patients have shown reductions in fasting plasma glucose and postprandial glucose levels (Shanmugasundaram et al., 1990). These findings support the potential of gymnemic acids as adjunctive therapy in diabetes management.

2.10. Resveratrol

Resveratrol, a natural stilbene found abundantly in grapes and berries, has been shown to activate sirtuin 1 (SIRT1), induce mitochondrial biogenesis, and improve insulin sensitivity (Baur et al., 2006). In clinical studies, resveratrol supplementation has resulted in enhanced insulin sensitivity, decreased fasting glucose, and reductions in oxidative stress biomarkers in T2DM patients (Brasnyó et al., 2011). The compound's pleiotropic benefits, coupled with a favorable safety profile, make it a promising candidate for long- term diabetes management, although its poor bioavailability remains a challenge. Efforts are underway to improve delivery using micronized and encapsulated formulations.

2.11. Momordicosides

Momordicosides, cucurbitane-type triterpenoids present in *Momordica charantia* (bitter melon), have been reported to exhibit insulin-mimetic properties, stimulating glucose uptake in skeletal muscle and adipose tissue via activation of the insulin signaling cascade (Joseph & Jini, 2013). Animal studies have consistently shown improvements in glycemic parameters; however, human clinical trial results are mixed, potentially due to variability in extract standardization and dosage. Standardized bitter melon extracts with defined momordicoside content are currently under investigation to enhance reproducibility and efficacy.

2.12 Other Emerging Phytopharmaceutical Agents

- **Allium sativum (Garlic)**: Garlic tablets (300 mg TID) adjunct to metformin reduced FPG, cholesterol, and triglycerides in T2DM patients (Mahboubi et al., 2023).
- **Momordica charantia (Bitter Melon)**: Standardized capsule formulations lowered fasting glucose in randomized trials, though mild gastrointestinal side effects occurred (Lim et al., 2023).
- **Morus alba (Mulberry Leaf)**: 1-Deoxynojirimycin (DNJ)–rich mulberry leaf powder reduced HbA1c and FPG in impaired glucose tolerance (Kwon et al., 2024).
- **Moringa oleifera**: Leaf powder supplementation improved glycemic control in small-scale trials (Oyeyinka et al., 2023).

- **Eugenia jambolana (Jamun)** polyherbal tablets improved fasting and postprandial glucose in prediabetic and early T2DM patients (Das et al., 2024).

3. Mechanisms of Action of Recent Phytopharmaceuticals

The reviewed phytopharmaceuticals exhibit diverse mechanisms

- **Enzyme inhibition**: α-glucosidase and α-amylase inhibition (*O. sanctum*, cumin peptides).
- **Incretin modulation**: GLP-1 stimulation (eriocitrin).
- **Insulin sensitization**: Activation of AMPK pathways (berberine ursodeoxycholate).
- **Antioxidant and anti-inflammatory**: Fenugreek L-arginine nanoparticles, pterostilbene.
- **β-cell protection**: Polyphenolic antioxidants reducing oxidative stress in pancreatic islets.

4. Limitations and Future Perspectives

Although these studies demonstrate promising results, limitations include small sample sizes, short treatment durations, and lack of large-scale multicentric trials. Furthermore, bioavailability issues for certain compounds (e.g., berberine) necessitate novel delivery systems such as nanoparticles and liposomal encapsulation. Regulatory frameworks for phytopharmaceutical approval should also be strengthened to ensure consistent quality and efficacy.

5. CONCLUSION

Recent advances in phytopharmaceutical development highlight the therapeutic potential of standardized plant-derived compounds in T2DM management. The integration of traditional medicinal knowledge with modern pharmacological validation may yield effective, safe, and affordable alternatives or adjuncts to current anti-diabetic therapies. However, robust clinical trials remain essential to translate these findings into routine practice.

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