International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 12, December 2025 **ijppr.humanjournals.com** ISSN: 2349-7203

Herbal Antidiabetic Agent: Current Trends and Future Prospective

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Received: 09 November 2025 Revised: 25 November 2025 Accepted: 10 December 2025

- **ABSTRACT**

The treatment of diabetes mellitus, particularly type 2 diabetes, has evolved remarkably in recent years with the development of innovative antidiabetic agents. Current trends emphasize therapies that not only control blood glucose but also address associated metabolic and cardiovascular complications. Modern agents such as glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and dual incretin agonists have demonstrated significant efficacy in glycemic control, weight management, and cardiorenal protection. Despite these advances, challenges such as drug cost, accessibility, and long-term safety persist. Future prospects in antidiabetic therapy focus on precision medicine, multi-target drugs, gene and stem cell-based treatments, and nanotechnology-based delivery systems aimed at restoring β-cell function and preventing disease progression. Overall, the future of antidiabetic pharmacotherapy lies in achieving holistic metabolic regulation with improved safety, efficacy, and patient adherence.

- **Keywords**: Antidiabetic agents, GLP-1 agonists, SGLT2 inhibitors, diabetes mellitus, future prospects, metabolic regulation.

- **INTRODUCTION**

Diabetes mellitus is one of the most prevalent and serious chronic metabolic disorders, characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is associated with long-term damage and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. According to the International Diabetes Federation (IDF), approximately 537 million adults (20–79 years) were living with diabetes in 2021, and this number is expected to rise to 643 million by 2030 and 783 million by 2045 (IDF Diabetes Atlas, 10th edition, 2021). The increasing global burden of diabetes poses a major challenge to healthcare systems worldwide.[1]

The management of diabetes primarily aims at maintaining optimal blood glucose levels to prevent acute and chronic complications. Conventional antidiabetic agents such as insulin, sulfonylureas, biguanides, thiazolidinediones, and α-glucosidase inhibitors have been the cornerstone of therapy for several decades. However, these agents often have limitations such as hypoglycemia, weight gain, gastrointestinal disturbances, and declining efficacy over time (Nathan et al., 2009).[2]

In recent years, major advances have been made in understanding the molecular mechanisms underlying diabetes, leading to the discovery of new therapeutic targets and innovative treatment strategies. The development of incretin-based therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, has revolutionized diabetes management by improving glycemic control with minimal risk of hypoglycemia (Drucker, 2018). Similarly, sodium-glucose co-transporter-2 (SGLT2) inhibitors have gained prominence due to their dual benefits in lowering blood glucose and providing cardiovascular and renal protection (Zinman et al., 2015).[3]

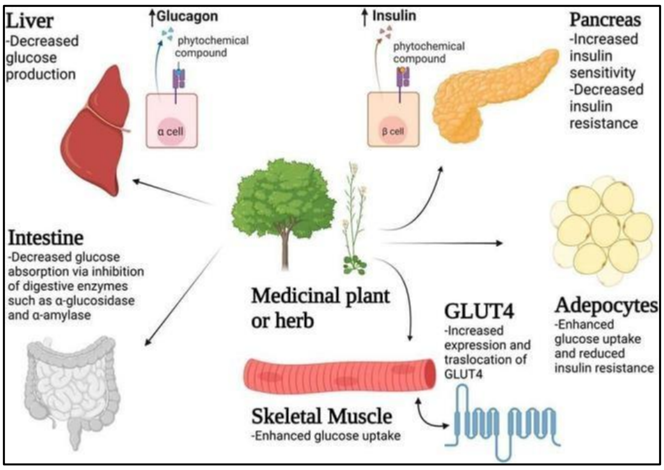
Current research trends also include the exploration of natural bioactive compounds with antidiabetic properties, nanotechnology-based drug delivery systems for targeted and sustained release, and the application of gene therapy to correct insulin signaling defects. The future prospects of antidiabetic therapy are moving toward personalized medicine, which integrates genetic, metabolic, and lifestyle factors to optimize treatment outcomes for individual patients (Ashcroft & Rorsman, 2020).[4]

Therefore, this project aims to present a comprehensive overview of current trends and future perspectives in the development of antidiabetic agents, focusing on novel mechanisms of action, emerging drug targets, and advanced therapeutic strategies that promise to transform diabetes care in the coming decades.[5]

- **PATHOPHYSIOLOGY OF DIABETES MELLITUS**

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The pathophysiology primarily involves disturbances in glucose metabolism, insulin signaling, and β-cell function.

Diabetes melllitus gradually affects multiple body organs including the pancreas, liver, muscles, kidneys, eyes, nerves, and cardiovascular system. Medicinal herbs play a significant role in preventing or reducing this damage through their antioxidant, anti-inflammatory, hypoglycemic, and insulin-sensitizing properties. Many herbs contain bioactive phytochemicals such as flavonoids, alkaloids, terpenoids, and phenolic compounds that modulate glucose metabolism and protect target organs.



1. **Mechanism of Glucose Metabolism[6]**

- Glucose metabolism is tightly regulated by insulin and glucagon to maintain normal blood glucose levels (70–110 mg/dL).
- After a meal, blood glucose levels rise, stimulating the pancreatic β-cells to secrete insulin.
- Insulin promotes glucose uptake by muscle and adipose tissue via glucose transporter type 4 (GLUT4).
- In the liver, insulin stimulates glycogenesis (conversion of glucose to glycogen) and inhibits gluconeogenesis (production of glucose from non-carbohydrate sources).

2. **Insulin Signaling Pathways[7]**

Insulin acts through binding to its receptor on target cells (muscle, adipose tissue, liver). The insulin receptor is a tyrosine kinase receptor consisting of α and β subunits.

Steps in Insulin Signaling:

1. **Insulin Binding**: Insulin binds to the α-subunit of the insulin receptor.
2. **Receptor Autophosphorylation**: The β-subunit undergoes autophosphorylation, activating tyrosine kinase activity.
3. **IRS Activation**: The receptor phosphorylates insulin receptor substrates (IRS-1, IRS-2).
4. **PI3K/Akt Pathway**: Activated IRS recruits phosphoinositide-3 kinase (PI3K) → converts PIP2 to PIP3 → activates Akt (Protein Kinase B).

This pathway stimulates GLUT4 translocation to the cell membrane, enabling glucose uptake.

It also promotes glycogen synthesis (via inhibition of GSK3), protein synthesis, and lipogenesis.

5. **MAPK Pathway**: Involved in cell growth and differentiation. During fasting, glucagon (secreted by pancreatic α-cells) increases hepatic glucose output through glycogenolysis and gluconeogenesis.

3. B-CELL DYSFUNCTION[8]

β-cells in the pancreatic islets of Langerhans are responsible for insulin synthesis and secretion.

Their dysfunction plays a central role in both Type 1 and Type 2 diabetes.

In Type 1 Diabetes Mellitus:

Autoimmune destruction of β-cells occurs due to genetic and environmental factors.

T-lymphocyte–mediated immune response targets β-cell antigens (e.g., GAD65, insulin, IA-2).

Leads to absolute insulin deficiency and lifelong dependence on exogenous insulin.

In Type 2 Diabetes Mellitus:

β-cells initially compensate for insulin resistance by increasing insulin secretion.

Chronic hyperglycemia and elevated free fatty acids cause glucotoxicity and lipotoxicity, leading to:

ER stress and oxidative stress in β-cells Loss of insulin gene expression Apoptosis and decreased β-cell mass

Progressive β-cell failure results in relative insulin deficiency and worsening hyperglycemia.

- **HERBAL DRUGS WITH ANTIDIABETIC POTENTIAL**

1. **Berberine** – An isoquinoline alkaloid present in Berberis aristata, Coptis chinensis, and Phellodendron amurense. It activates AMP-activated protein kinase (AMPK), improves insulin sensitivity, and reduces hepatic gluconeogenesis, resulting in decreased fasting glucose and HbA1c levels.

2. Moringa oleifera – Leaves and seeds contain flavonoids, phenolic acids, glucosinolates, and isothiocyanates. It enhances glucose uptake, improves insulin secretion, and reduces oxidative stress in diabetic conditions.

3. Momordica charantia (Bitter gourd) – Contains charantin, vicine, and polypeptide-p which possess insulin-mimetic and insulin-secretagogue activity, lowering fasting glucose and HbA1c.

4. Trigonella foenum-graecum (Fenugreek) – Rich in 4-hydroxyisoleucine and soluble fiber (galactomannan). Improves glucose tolerance, insulin sensitivity, and lowers lipid profile in diabetic patients.

5. Cinnamomum zeylanicum / C. cassia (Cinnamon) – Polyphenolic compounds act as insulin mimetics, enhance glucose uptake, and inhibit α-glucosidase. Shown to significantly reduce fasting plasma glucose in clinical studies.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 12, December 2025 ijppr.humanjournals.com ISSN: 2349-7203

6. **Gymnema sylvestre** – Contains gymnemic acids that suppress glucose absorption from the intestine and promote pancreatic β-cell regeneration, leading to improved glycemic control.

7. **Panax ginseng** – Ginsenosides improve glucose metabolism by enhancing insulin secretion and increasing peripheral glucose uptake.

8. **Aloe vera** – Aloe polysaccharides and phytosterols contribute to hypoglycemic effects by enhancing insulin sensitivity and reduceing blood glucose levels.

9. Ocimum sanctum (Holy basil) – Contains eugenol and ursolic acid; improves insulin secretion, lowers blood glucose, and reduces oxidative stress.

10. Curcuma longa (Turmeric) – Curcumin acts as an antioxidant and anti-inflammatory agent; improves insulin receptor signaling and reduces complications of diabetes

- **COMBINATION OF HERBAL DRUGS WITH ANTIDIABETIC POTENTIAL[9]**

POLYHERBAL COMBINATION	MAIN ACTIONS	OBSERVED EFFECT
Moringa + Fenugreek + Turmeric	Insulin secretion, glucose uptake, anti-inflammatory	↓ FBG, ↓ HbA1c
Bitter gourd + Gymnema + Neem	Insulin mimetic, antioxidant	Improved glycemic and lipid profile
Holy basil + Tinospora + Jamun	α-glucosidase inhibition, insulin release	Strong hypoglycemic activity
Moringa + Ficus + Jamun	β-cell regeneration, antioxidant	Improved antioxidant and glucose parameters
Garlic + Ginger + Cinnamon	Insulin sensitization, lipid regulation	Enhanced glucose tolerance
Turmeric + Amla	Anti-oxidative, anti-inflammatory	Better glycemic control

- **NOVEL APPROACHES AND CURRENT TRENDS IN HERBAL ANTIDIABETIC RESEARCH**

1. Standardization and Quality Control of Herbal Extracts

To ensure reproducible efficacy and safety, modern research emphasizes phytochemical standardization using chromatographic and spectroscopic techniques (HPLC, HPTLC, LC–MS, FTIR). Authentication of raw materials, marker-based quantification, and fingerprint profiling are now essential steps in herbal drug development.(10)

2. Polyherbal Formulations with Synergistic Activity

Combining multiple herbs enhances the overall pharmacological effect through multi-target synergy—addressing insulin secretion, glucose absorption, oxidative stress, and lipid metabolism simultaneously. For instance, Moringa + Fenugreek + Turmeric or Gymnema + Neem + Bitter gourd formulations show superior glycemic control compared to individual herbs.

3. Nanotechnology-Based Herbal Delivery Systems

Nanocarriers such as liposomes, phytosomes, and polymeric nanoparticles are employed to enhance the bioavailability and stability of poorly absorbed phytoconstituents like berberine and curcumin. These nanoformulations provide controlled release and improved cellular uptake.

4. Gut Microbiota Modulation

Emerging studies reveal that certain herbal compounds act through modification of gut microbiota, improving glucose metabolism and reducing inflammation. Phytochemicals such as berberine and polyphenols increase beneficial bacterial species linked with metabolic health.

5. Metabolomics and Network Pharmacology Approaches

Integration of omics-based tools (metabolomics, proteomics, and network pharmacology) helps identify multiple targets of herbal compounds and predict synergistic interactions at a systems- biology level.

6. Computational Drug Discovery and Molecular Docking

In-silico methods are used to screen herbal phytoconstituents against key diabetic targets such as α-glucosidase, DPP-IV, and PPAR-γ. Molecular docking and ADMET prediction accelerate drug discovery from herbal sources.

7. Herbal-Based Combination Therapy with Conventional Drugs

Researchers are exploring herb-drug combinations (e.g., berberine + metformin, cinnamon + insulin) to achieve additive or synergistic glycemic control, reduce side effects, and improve patient outcomes.

8. Clinical Evaluation and Regulatory Harmonization

Current trends include large-scale, multicentric randomized controlled trials (RCTs) of standardized herbal formulations. Global regulatory initiatives now promote GMP guidelines and pharmacovigilance for herbal drugs.[11]

- **ROLE OF AI IN ANTIDIABETIC DRUG DISCOVERY**

1. AI is used at various stages of drug discovery:

- Target identification: AI analyzes biological data to identify novel molecular targets involved in glucose metabolism, insulin resistance, or β-cell dysfunction.
- Drug design: Deep learning algorithms predict molecular structures that may interact effectively with specific diabetic targets (e.g., PPAR-γ, DPP-4, SGLT2, GLP-1 receptors).
- Virtual screening: AI models screen millions of compounds in silico, reducing the need for extensive lab testing.
- Drug repurposing: Machine learning helps identify existing drugs with potential new use as antidiabetic agents.[12]

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2. AI Applications in Antidiabetic Research.[13]

AI Application	Description	Example
Machine Learning Models	Predict and Compound activity optimize	Predicting inhibitors DPP-4 or α- for glucosidase.
	pharmacokinetics (ADMET properties).	
Deep Learning in Molecular Design	Generative models create novel chemical structures with high binding affinity.	Deep generative networks for GLP-1 agonists.
AI-based ockingand Simulation	Improves prediction accuracy of ligand–receptor binding.	AI-driven docking for SGLT2 inhibitors.
Pharmacogenomics and Personalized Therapy	AI analyzes patient data to tailor antidiabetic treatment.	Personalized insulin therapy using AI glucose monitoring.
AI-integrated Wearables	Predicts blood glucose fluctuations using continuous glucose monitoring (CGM).	AI in smart insulin pumps (e.g., Medtronic MiniMed).

3. AI in Natural Product Research

- AI is also accelerating the study of herbal and phytochemical antidiabetic agents:
- Predicts active compounds from medicinal plants (e.g., Gymnema sylvestre, Momordica charantia).
- Uses molecular docking and QSAR modeling to evaluate natural molecule efficacy.
- Identifies plant-based compounds that act as DPP-4, α-amylase, or α-glucosidase inhibitors.[14]

4. Advantages of AI in Antidiabetic Drug Development ▪

Reduces time and cost of research.

- Enhances prediction accuracy of drug efficacy and toxicity.
- Enables personalized and precision medicine.
- Facilitates identification of multi-target agents for complex metabolic disorders.[15]

5. Challenges and Limitations

- Limited availability of high-quality biomedical datasets.
- Lack of interpretability ("black-box" problem) in deep learning models.
- Need for integration of AI outputs with biological validation.
- Ethical and regulatory issues in AI-assisted clinical trials.

- **FUTURE PROSPECTIVE FOR ANTIDIABETIC AGENT**

1. Development of Multi-Target Antidiabetic Agents

● Future drug design will emphasize multi-target approaches rather than single-target drugs. ● These agents can simultaneously act on multiple pathways (e.g., insulin resistance, β-cell regeneration, and glucose uptake).

- Examples include dual-acting GIP/GLP-1 receptor agonists and PPAR-α/γ modulators, which improve glycemic control and reduce cardiovascular risk.[16]

2. Integration of Artificial Intelligence (AI) and Computational Tools

- AI and machine learning will transform antidiabetic drug discovery by:
- Predicting molecular interactions and potential drug candidates.
- Analyzing large datasets from genomics and metabolomics to identify new therapeutic targets.
- Enabling personalized diabetes treatment through predictive modeling and precision dosing.[17]

3. Advancements in Gene and Cell Therapy

- Future therapies may focus on genetic correction and β-cell regeneration:
- CRISPR/Cas9 gene editing can correct mutations responsible for defective insulin secretion.
- Stem cell-derived β-cells could replace damaged pancreatic cells, restoring natural insulin production.
- Such regenerative approaches hold promise for a long-term or even permanent cure.[18]

4. Nanotechnology and Targeted Drug Delivery Systems

- Nanotechnology will play a major role in improving the bioavailability and efficacy of antidiabetic agents:
- Nano-insulin formulations for sustained release and better absorption.
- Glucose-responsive nanoparticles that release insulin only when blood sugar rises.
- Targeted delivery systems to pancreatic β-cells or liver tissues for enhanced therapeutic outcomes and reduced side effects.[19]

5. Herbal and Phytochemical-Based Antidiabetic Drugs

- The exploration of medicinal plants and phytoconstituents will continue to expand:
- AI and molecular docking tools are helping identify active plant compounds (e.g., flavonoids, alkaloids, terpenoids).
- Future studies will focus on standardization, bioavailability improvement, and synergistic formulations combining herbal and synthetic agents.
- Herbal nanoformulations could bridge traditional and modern medicine.

6. Personalized and Precision Medicine

- The future of diabetes treatment lies in personalized therapy, where medication is tailored to an individual's:
- Genetic profile,
- Lifestyle, and
- Metabolic response.
- AI-driven predictive models and pharmacogenomic data will enable doctors to choose the most effective drug with minimal

adverse effects for each patient.

7. **Digital Health and Smart Devices**

- Advancements in digital therapeutics and wearable technology will play a significant role:
- Continuous glucose monitoring (CGM) devices integrated with AI.
- Smart insulin pens and closed-loop "artificial pancreas" systems.
- Mobile health applications for remote diabetes management and monitoring.
- These technologies will improve patient adherence and quality of life.

8. **Focus on Preventive and Disease-Modifying Therapies**

Future research aims to develop disease-modifying drugs that prevent or reverse diabetes progression by targeting early metabolic changes and immune dysfunctions, particularly in Type- 1 diabetes.

● CONCLUSION

Herbal antidiabetic agents have gained significant attention in recent years as safer and more sustainable alternatives to synthetic drugs. Various medicinal plants such as Momordica charantia, Gymnema sylvestre, Trigonella foenum-graecum, and Syzygium cumini have shown promising hypoglycemic activity through mechanisms like enhancing insulin secretion, improving glucose uptake, and protecting pancreatic β-cells. Current research trends emphasize the isolation of bioactive phytoconstituents, formulation of novel herbal combinations, and the application of advanced techniques such as nanotechnology and artificial intelligence for drug discovery and optimization.

Despite their potential, challenges such as lack of standardization, limited clinical validation, and regulatory hurdles remain major barriers. Future perspectives lie in integrating traditional knowledge with modern scientific approaches, conducting well-designed clinical trials, and developing standardized herbal formulations with proven efficacy and safety. Overall, herbal antidiabetic agents hold great promise for the development of effective, affordable, and holistic therapies for diabetes management.

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How to cite this article:
Ms. Bhagyashri Raju Rathod et al. Ijppr.Human, 2025; Vol. 31 (12):316-326.

Conflict of Interest Statement: All authors have nothing else to disclose.