Herbal Medicines for Diabetes: Potential and Challenges in Modern Pharmacotherapy

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Abstract

A chronic metabolic disease called diabetes mellitus is typified by hyperglycemia brought on by either insufficient insulin production, insulin resistance, or both. Interest in herbal remedies as possible substitutes or supplemental therapies to traditional treatments has surged as a result of the rising prevalence of diabetes. Momordica charantia, Gymnema sylvestre, Tinospora cordifolia, and Trigonella foenum-graecum are among the medicinal plants that have shown notable antidiabetic activity through a variety of mechanisms, including insulin sensitization, pancreatic β-cell regeneration, and glucose uptake enhancement. Herbal remedies do, however, encounter difficulties with standardization, bioavailability, regulatory obstacles, and possible herb-drug interactions, despite their apparent effectiveness. Investigating the pharmacological potential, mechanisms of action, and difficulties related to the use of herbal medications for the treatment of diabetes is the goal of this review.

Keywords: Herbal medicine, diabetes, phytochemicals, antidiabetic activity, insulin resistance, pharmacotherapy

I. INTRODUCTION

Definition and Classification of Diabetes Mellitus

Diabetes mellitus (DM) is a long-term metabolic disease marked by persistently high blood sugar levels brought on by deficiencies in either the action or secretion of insulin, or both. It is divided into various categories according to its pathophysiology and etiology:

1. **Type 1 Diabetes Mellitus (T1DM):** An autoimmune disease that causes the death of pancreatic β-cells, which leaves the patient completely insulin deficient. About 5–10% of all cases of diabetes worldwide are caused by it (American Diabetes Association, 2022) [1].
2. **Type 2 Diabetes Mellitus (T2DM):** The most common kind, accounting for 90–95% of cases, is distinguished by relative insulin insufficiency and insulin resistance. It is

closely linked to genetic predisposition, obesity, and a sedentary lifestyle (WHO, 2023) [2].

3. **Gestational Diabetes Mellitus (GDM):** Hyperglycemia that is initially identified during pregnancy can raise the risk of difficulties for both the mother and the unborn child (ADA, 2022) [1].

Other Specific Types: Includes monogenic diabetes, secondary diabetes due to pancreatic diseases, endocrinopathies, and drug-induced diabetes (NIDDK, 2021) [3].

Global Prevalence and Burden of Diabetes

With 537 million individuals (aged 20–79) worldwide suffering from diabetes in 2021, the disease is expected to afflict 783 million people by 2045 (IDF Diabetes Atlas, 2021) [4].

Cardiovascular disorders, neuropathy, nephropathy, and retinopathy are among the major complications of the condition, which also adds significantly to morbidity, death, and healthcare expenses.

Regional Burden of Diabetes

- **South Asia:** The two countries with the greatest rates of diabetes are China and India; by 2045, it is predicted that over 134 million people in India alone will have the disease (IDF, 2021).
- **Africa:** The prevalence of diabetes is rising due to rapid urbanization and lifestyle changes, especially in sub-Saharan Africa (WHO, 2022) [5].
- **Western Countries:** Over 37 million people in the United States have diabetes, and their yearly medical expenses exceed $327 billion (CDC, 2023) [6].

The rising prevalence of diabetes emphasizes the need for therapeutic approaches— including herbal remedies—that are efficient, widely available, and reasonably priced.

II. LIMITATIONS OF CONVENTIONAL ANTIDIABETIC DRUGS

Conventional treatment for diabetes includes oral hypoglycemic agents (e.g., metformin, sulfonylureas, SGLT2 inhibitors) and insulin therapy. Despite their effectiveness, they have several limitations:

1. Side Effects of Conventional Antidiabetic Drugs

Drug Class	**Examples**	**Common Side Effects**
Biguanides	Metformin	Gastrointestinal discomfort, lactic acidosis [7]
Sulfonylureas	Glibenclamide, Glipizide	Hypoglycemia, weight gain [8]
Thiazolidinediones	Pioglitazone, Rosiglitazone	Fluid retention, risk of heart failure [9]
SGLT2 Inhibitors	Empagliflozin, Canagliflozin	Genital infections, ketoacidosis [10]
Insulin Therapy	Various forms	Hypoglycemia, injection site reactions [11]

2. HIGH COST OF DIABETES TREATMENT

- Insulin therapy is costly, particularly in low-income countries. In the United States, the price of insulin has increased three times over the past decade, making it unaffordable for many patients. (ADA, 2023) [12].
- Oral antidiabetic medications also present financial challenges, with newer drugs like GLP-1 receptor agonists being particularly expensive.

3. DRUG RESISTANCE AND TREATMENT FAILURES

- Prolonged use of sulfonylureas and insulin can result in β-cell exhaustion and diminished effectiveness over time. (DeFronzo, 2020) [8].

Insulin resistance continues to be a challenge, especially in obese and elderly patients. Due to these limitations, there is increasing interest in herbal medicines as potential alternatives or supplementary treatments.

III. RATIONALE FOR EXPLORING HERBAL MEDICINES IN DIABETES THERAPY

Herbal medicines have been utilized for centuries in traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani for the treatment of diabetes. The renewed interest in these therapies reflects their potential benefits.

The renewed interest in herbal medicine is driven by several factors:

1. MULTIPLE MECHANISMS OF ACTION

Herbal extracts often contain a variety of bioactive compounds that target multiple pathways, such as enhancing insulin secretion (Gymnema sylvestre) [13], reducing insulin resistance (Curcuma longa), and inhibiting carbohydrate digestion (Salacia reticulata).

2. LOWER INCIDENCE OF SIDE EFFECT

Herbal treatments generally cause fewer side effects compared to synthetic drugs when used appropriately. (Patel et al., 2020) [9].

3. COST-EFFECTIVENESS AND ACCESSIBILITY

Many herbal remedies are cost-effective and readily accessible in rural and developing areas.

4. POTENTIAL FOR DRUG DEVELOPMENT

Several plant-derived compounds, such as metformin from Galega officinalis, have contributed to significant pharmaceutical breakthroughs. (Bailey & Day, 2019) [7].
Despite these advantages, herbal medicines face challenges such as a lack of standardization, regulatory barriers, and potential drug interactions, which will be addressed in subsequent sections.

IV. OBJECTIVES OF THE REVIEW

This review aims to:

1. Provide a comprehensive overview of **herbal medicines with antidiabetic potential** and their **mechanisms of action**.
   Herbal medicines have long been used in traditional medicine systems for managing diabetes. These remedies typically contain bioactive compounds that target various pathways involved in glucose metabolism. Key mechanisms of action include enhancing insulin secretion (e.g., Gymnema sylvestre), improving insulin sensitivity (e.g., Curcuma longa), inhibiting carbohydrate digestion (e.g., Salacia reticulata), and protecting pancreatic β-cells. Many plants also possess antioxidant and anti-inflammatory properties that contribute to managing diabetes and its complications.

2. Summarize **preclinical and clinical evidence** supporting herbal antidiabetic therapies. Numerous preclinical studies on animals have demonstrated the effectiveness of herbal treatments like bitter melon, fenugreek, and turmeric in regulating blood glucose levels. Clinical trials have shown promising results with herbs such as Gymnema sylvestre, which has been found to reduce blood sugar levels in type 2 diabetes patients, and fenugreek, which can improve insulin sensitivity. However, while some herbal treatments show positive results in human studies, further large-scale clinical trials are needed to confirm their effectiveness and safety.

3. The **challenges and limitations** of herbal medicines
   Including standardization, bioavailability, and safety concerns. Despite their potential, herbal medicines face several challenges. One major issue is the lack of standardization, which leads to variations in potency and efficacy. Herbal remedies are also subject to regulatory hurdles, with insufficient oversight in some regions,

making it difficult to ensure product quality. Bioavailability, or the extent to which the body can absorb and utilize active compounds from herbs, can also be a concern, as many bioactive components are poorly absorbed. Furthermore, safety concerns arise due to the potential for herb-drug interactions, side effects, and lack of long-term safety data.

4. **Future perspectives** on integrating herbal medicines into mainstream diabetes treatment.

The future of herbal medicines in diabetes treatment involves overcoming the current challenges by developing standardized formulations, improving bioavailability, and ensuring rigorous clinical testing. Collaboration between traditional medicine practitioners and modern researchers can help bridge the gap. Additionally, regulatory agencies need to establish clearer guidelines to ensure the safety and efficacy of herbal treatments. As research progresses, herbal medicines could be integrated into complementary treatment regimens alongside conventional therapies to provide a holistic approach to managing diabetes.

By addressing these points, the review will contribute to a better understanding of how herbal medicine can be harnessed in modern pharmacotherapy for diabetes.

V. HERBAL MEDICINES WITH ANTIDIABETIC POTENTIAL :-

Mechanisms of Action of Herbal Antidiabetic Agents

Medicinal plants exert antidiabetic effects through a range of pharmacological mechanisms, including the enhancement of insulin secretion, reduction of insulin resistance, inhibition of carbohydrate digestion and absorption, antioxidant and anti-inflammatory activities, as well as the regeneration of pancreatic β-cells.

ENHANCEMENT OF INSULIN SECRETION (E.G., GYMNEMA SYLVESTRE) MECHANISM:

- Certain herbs stimulate insulin release from pancreatic β-cells, mimicking the action of sulfonylureas.
- They modulate calcium ion channels and increase glucose-induced insulin secretion.

Example: Gymnema sylvestre (Gurmar, "sugar destroyer")

- **Active compounds:** Gymnemic acids, saponins, flavonoids

MECHANISM:

- Gymnemic acids improve β-cell function and stimulate insulin secretion. [14]
- They inhibit glucose absorption in the intestines, reducing postprandial glucose spikes [13].
- Long-term use of Gymnema sylvestre has been linked to pancreatic β-cell regeneration [15].

CLINICAL EVIDENCE:

- A study on T2DM patients showed a significant reduction in fasting and postprandial glucose levels after supplementation with Gymnema sylvestre extract [15].

Reduction of Insulin Resistance (e.g., Curcuma longa)

Mechanism:

- Insulin resistance is a defining characteristic of Type 2 diabetes, where the body's cells become unresponsive to insulin.
- Certain herbs enhance insulin sensitivity by regulating pathways such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-gamma (PPAR-γ). **Example: Curcuma longa (Turmeric)**
- **Active compound:** Curcumin

Mechanism:

- Curcumin reduces insulin resistance by activating AMP-activated protein kinase (AMPK), enhancing glucose uptake in muscle cells, and decreasing inflammation. [16]
- Curcumin mitigates insulin resistance by activating AMP-activated protein kinase (AMPK), promoting glucose uptake in muscle cells, and reducing inflammation. [17]

Clinical Evidence:

- A randomized controlled trial (RCT) showed that curcumin supplementation enhanced insulin sensitivity and lowered HbA1c levels in prediabetic individuals.[18]

Inhibition of Carbohydrate Digestion and Absorption (e.g., Salacia reticulata)

Mechanism:

- It delays glucose absorption by inhibiting carbohydrate-digesting enzymes, such as α-amylase and α-glucosidase.
- Results in lower postprandial blood glucose levels.

Example: Salacia reticulata

- **Active compounds:** Salacinol, kotalanol

Mechanism:

- It inhibits α-glucosidase and α-amylase, thus delaying the digestion and absorption of carbohydrates in the small intestine [19].
- This results in a slower and more controlled release of glucose into the bloodstream.

Clinical Evidence:

- A study conducted with diabetic patients showed that Salacia reticulata extract significantly lowered postprandial glucose levels compared to a placebo. [20].

Antioxidant and Anti-Inflammatory Effects (e.g., Tinospora cordifolia)

Mechanism:

Chronic hyperglycemia leads to oxidative stress, which damages pancreatic β-cells and contributes to the onset of insulin resistance. Herbal antioxidants neutralize reactive oxygen species (ROS), thus minimizing oxidative damage.

Example: Tinospora cordifolia (Guduchi)

- **Active compounds:** Berberine, tinosporaside, alkaloids

Mechanism:

- Reduces oxidative stress in β-cells, preserving insulin secretion [21].
- Inhibits NF-κB signaling, reducing inflammation and insulin resistance.

- Enhances glucose uptake via the PI3K/Akt pathway.

CLINICAL EVIDENCE:

- Supplementation with Tinospora cordifolia in diabetic patients led to improved fasting blood glucose and HbA1c levels, as well as a decrease in markers of oxidative stress. [22].

REGENERATION OF PANCREATIC B-CELLS (E.G., MOMORDICA CHARANTIA)

Mechanism:

Certain herbs promote the regeneration and proliferation of β-cells, thereby restoring insulin production. Additionally, they reduce apoptosis (cell death) in pancreatic β-cells. **Example: Momordica charantia (Bitter melon)**

- **Active compounds:** Charantin, polypeptide-P, vicine

MECHANISM:

- Stimulates β-cell regeneration and increases insulin production [23].
- Polypeptide-P acts similarly to insulin, lowering blood glucose levels.
- Enhances glucose uptake in muscle and liver cells.

CLINICAL EVIDENCE:

- A clinical study revealed that bitter melon extract significantly lowered fasting blood glucose and HbA1c levels in patients with Type 2 diabetes mellitus (T2DM). [24].

VI. NOTABLE HERBAL MEDICINES FOR DIABETES MANAGEMENT

ALOE VERA

- **Active Compounds:** Aloin, Emodin, Polysaccharides

MECHANISMS OF ACTION:

- Stimulates pancreatic β-cell function and increases insulin secretion [14].
- Lowers fasting blood glucose by enhancing peripheral glucose uptake
- Reduces oxidative stress and inflammation in diabetic tissues.

CLINICAL EVIDENCE:

- A randomized clinical trial demonstrated that Aloe vera gel supplementation significantly decreased fasting blood glucose and HbA1c levels in patients with Type 2 diabetes mellitus (T2DM). [15].

CINNAMOMUM CASSIA (CINNAMON)

- **Active Compounds:** Cinnamaldehyde, Polyphenols

MECHANISMS OF ACTION:

- Mimics insulin action by activating insulin receptor signaling pathways [16].
- Increases glucose uptake in skeletal muscle via GLUT4 translocation [17].
- Reduces postprandial blood glucose by slowing gastric emptying.

CLINICAL EVIDENCE:

- A meta-analysis of 10 clinical trials concluded that cinnamon supplementation significantly reduced fasting blood glucose and improved lipid profiles in diabetic patients. [18].

TRIGONELLA FOENUM-GRAECUM (FENUGREEK)

- **Active Compounds:** Trigonelline, 4-Hydroxyisoleucine

MECHANISMS OF ACTION:

- Stimulates insulin secretion from pancreatic β-cells.
- Enhances glucose uptake by muscle and liver cells [19].
- Forms a gel-like matrix in the intestines, reducing carbohydrate absorption.

CLINICAL EVIDENCE:

- A study found that daily supplementation with fenugreek seed powder significantly lowered both fasting and postprandial blood glucose levels in diabetic patients. [20].

VII. CHALLENGES AND LIMITATIONS OF HERBAL MEDICINES FOR DIABETES

- **Standardization and Quality Control:** Variations in bioactive compound content can occur due to differences in plant species, cultivation conditions, and extraction methods. [25].
- **Herb-Drug Interactions:** Certain herbal medicines may interact with conventional antidiabetic drugs, potentially causing hypoglycemia or reducing the effectiveness of the medication.

Example: *Momordica charantia* may enhance the effect of metformin, increasing the risk of hypoglycemia [26].

VIII. PHARMACOKINETICS AND BIOAVAILABILITY OF HERBAL COMPOUNDS

Herbal medicines contain bioactive compounds that often face challenges such as poor absorption, rapid metabolism, and low bioavailability. Improving the pharmacokinetic profile of these compounds is crucial for their clinical efficacy.

- **ABSORPTION AND METABOLISM**

Many polyphenols and flavonoids present in antidiabetic herbs, such as Curcumin (from *Curcuma longa*) and Berberine (from *Berberis aristata*), exhibit low water solubility and poor gastrointestinal absorption.

Curcumin is rapidly metabolized in the liver and intestines, limiting its bioavailability. However, combining it with Piperine (from black pepper) enhances its absorption by inhibiting its metabolism. [27].

- **NANOTECHNOLOGY-BASED DRUG DELIVERY FOR HERBAL MEDICINES**

I. Nanoparticle formulations, liposomes, and phytosomes enhance the solubility and stability of herbal compounds, improving their bioavailability.

Example: *Curcumin* nanoparticles increase bioavailability by 27 times compared to regular curcumin powder [28].

II. *Berberine* loaded on lipid-based nanoparticles enhances intestinal absorption and antidiabetic effects [29].

IX. Herbal Drug Interactions with Metformin and Other Antidiabetic Drugs

- *Aloe vera* and *Momordica charantia* can potentiate the effect of metformin, increasing the risk of hypoglycemia [30].
- *Ginseng* can interfere with warfarin metabolism, leading to potential bleeding risks.

X. Comparative Analysis of Herbal vs Conventional Antidiabetic Drugs

Efficacy Comparison

- **Metformin vs. Herbal Alternatives**:
- Metformin is a first-line drug for type 2 diabetes, but some herbal alternatives have shown comparable efficacy in glucose regulation.
- *Gymnema sylvestre* enhances insulin secretion and reduces glucose absorption, showing effects similar to metformin in clinical trials [13].
- *Berberine* has been found to be as effective as metformin in lowering fasting blood glucose levels [31].

Side Effects Comparison

- Metformin Side Effects:

I. Gastrointestinal disturbances (diarrhea, bloating).
II. Lactic acidosis in rare cases.

- Herbal Drug Side Effects:

I. *Momordica charantia* can cause hypoglycemia if taken in excess.
II. *Aloe vera* can cause hepatotoxicity at high doses.

XI. Toxicity and Safety Concerns of Herbal Medicines

Potential Toxicity of Herbal Antidiabetics

Some herbal compounds may exhibit toxicity at high doses or with prolonged use.

Example:

- *Aloe vera* contains anthraquinones, which can cause liver toxicity in excessive amounts [32].
- *Momordica charantia* extract, if overused, can cause hypoglycemia and intestinal discomfort.

Herb-Drug Interactions

Berberine inhibits cytochrome P450 enzymes, affecting the metabolism of many drugs, including statins and anticoagulants [33].

Fenugreek has blood-thinning properties and can interact with aspirin and warfarin,

increasing bleeding risk.

XII. Role of Gut Microbiota in Herbal Antidiabetic

Effects Gut Microbiome and Diabetes

The gut microbiota plays a pivotal role in glucose metabolism and insulin sensitivity. Dysbiosis, or an imbalance in gut bacteria, has been associated with insulin resistance and the development of type 2 diabetes [34].

Herbal Modulation of Gut Microbiota

Berberine improves the composition of the gut microbiota by increasing beneficial bacteria such as *Akkermansia muciniphila*, which enhances insulin sensitivity [35].

Curcumin promotes the balance of the gut microbiota, reducing inflammation and improving glucose tolerance.

XIII. AI and Machine Learning in Herbal Drug Discovery

AI for Identifying Herbal Antidiabetic Compounds

AI-based screening facilitates the prediction of active phytochemicals in herbal medicines. Molecular docking studies driven by AI have identified compounds in *Punica granatum* with a strong binding affinity for diabetic target proteins [36].

XIV. AI in Drug Repurposing of Herbal Medicines

AI models analyze extensive datasets to uncover new therapeutic applications for established herbal compounds. For example, AI analysis revealed that Quercetin (from onions and green tea) targets multiple diabetes-related pathways, positioning it as a potential alternative to synthetic drugs [37].

XV. Government Policies and Global Acceptance of Herbal Medicines

WHO Guidelines on Herbal Medicines

WHO encourages the integration of traditional medicine into national healthcare systems but emphasizes standardization and safety testing [38].

Regulatory Challenges for Herbal Antidiabetic Drugs

- **FDA (USA):** Herbal supplements are regulated as dietary supplements, meaning they do not require clinical trials before being marketed.
- **AYUSH (India):** Regulates Ayurveda, Unani, Siddha, and Homeopathy medicines, ensuring standardization and safety compliance.

Global Acceptance of Herbal Diabetes Treatment

- China and India have fully integrated herbal medicine into diabetes care, while Western countries have stricter regulations.
- *Berberine* has been approved as an over-the-counter antidiabetic in China, but not in the USA.

XVI. Standardization and Quality Control Improvements in Herbal Medicines

Standardization and quality control are crucial for integrating herbal medicines into modern pharmacotherapy. In contrast to synthetic drugs, herbal formulations often experience batch-to- batch variability, contamination, and inconsistent efficacy. To guarantee their safety, efficacy, and reproducibility, it is essential to implement stringent quality control measures and establish regulatory frameworks.

1. Need for Standardization in Herbal Medicines

- Herbal medicines contain **multiple bioactive compounds**, making **quality control challenging**.
- Differences in **growing conditions, harvesting time, and extraction methods** lead to variation in potency.
- Standardization ensures that each batch of herbal medicine contains **consistent levels of active compounds**.39

2. Methods for Standardization and Quality Control

A. Phytochemical Standardization

- **High-Performance Liquid Chromatography (HPLC)**: Quantifies specific active compounds (e.g., **Curcuminoids in Turmeric**).
- **Gas Chromatography-Mass Spectrometry (GC-MS)**: Detects volatile bioactive compounds (e.g., **Essential oils in medicinal plants**).
- **Fourier Transform Infrared Spectroscopy (FTIR)**: Identifies functional groups in herbal compounds.
- **Thin Layer Chromatography (TLC)**: Used for rapid fingerprinting of herbal extracts.40 & 41

B. Biological Standardization

- **In vitro bioassays**: Testing biological activity (e.g., **antioxidant, antimicrobial, anti-inflammatory properties**).
- **Animal models**: Evaluating pharmacological effects (e.g., **hypoglycemic effects in diabetic rats**).
- **Cell culture studies**: Testing cytotoxicity and efficacy.42

C. DNA Barcoding for Herbal Authentication

- **Prevents adulteration and misidentification** of herbal species.
- Uses **genetic markers** to verify plant origin (e.g., **ITS, rbcL, and matK genes**).43

D. Quality Control for Heavy Metals and Contaminants

- **Atomic Absorption Spectroscopy (AAS)** and **Inductively Coupled Plasma Mass Spectrometry (ICP-MS)**: Detect heavy metals like **lead (Pb), arsenic (As), and cadmium (Cd)**.
- **Microbial Testing**: Ensuring absence of pathogens like **Salmonella, E. coli, and fungi**.

3. Regulatory Guidelines for Herbal Medicine Standardization

- **WHO Guidelines for Herbal Medicines**: Provides global standards for herbal drug safety and efficacy.44

- **US FDA Botanical Drug Guidelines**: Requires herbal drugs to pass **clinical trials** for approval.45
- **European Medicines Agency (EMA) Herbal Monographs**: Defines **quality and safety parameters** for herbal medicines.
- **Indian Pharmacopoeia (Ayush)**: Standardizes Ayurvedic, Siddha, and Unani medicines.46

4. **FUTURE DIRECTIONS IN HERBAL DRUG STANDARDIZATION**

- **AI and Machine Learning for Phytochemical Analysis**: Predicting active compounds in herbs.
- **Blockchain Technology for Supply Chain Transparency**: Tracking herbal medicine authenticity.
- **Advanced Extraction Techniques**: Supercritical fluid extraction for **higher purity herbal compounds**.

XVII. CONCLUSION

Herbal medicines represent a promising therapeutic option for diabetes management, with various plant-derived compounds exhibiting substantial antidiabetic effects through mechanisms such as insulin sensitization, regeneration of pancreatic β-cells, and improved glucose uptake. Plants like *Momordica charantia, Gymnema sylvestre, Tinospora cordifolia*, and *Trigonella foenum-graecum* show considerable potential as adjunct or alternative therapies to conventional pharmacological treatments. Nevertheless, the integration of herbal remedies into conventional pharmacotherapy is impeded by challenges such as inconsistent standardization, poor bioavailability, regulatory complexities, and possible herb-drug interactions. To optimize the clinical application of herbal medicines in diabetes care, these issues must be addressed through stringent quality control, extensive clinical research, and the establishment of comprehensive regulatory frameworks. Continued investigation is essential to substantiate the efficacy, safety, and long-term effectiveness of these herbal remedies, thereby facilitating their safe and effective incorporation into integrative diabetes treatment strategies.

REFERENCES

1. American Diabetes Association. "Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022." Diabetes Care, 2022.
2. World Health Organization. "Diabetes." WHO, 2023.
3. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). "Diabetes Overview." NIH, 2021.
4. International Diabetes Federation. "IDF Diabetes Atlas 10th Edition." 2021.
5. WHO. "Diabetes in Africa: A Rising Concern." 2022.
6. Centers for Disease Control and Prevention. "National Diabetes Statistics Report, 2023."
7. Bailey CJ, Day C. "Metformin: Its botanical background and mechanism of action."

Diabetes Care, 2019.
8. DeFronzo RA. "Sulfonylureas: A risk-benefit assessment." Diabetes Care, 2020.
9. Patel DK et al. "An overview on antidiabetic medicinal plants having insulin mimetic property." Asian Pac J Trop Biomed, 2020.
10. Kumar S et al. "SGLT2 inhibitors: New insights into diabetes treatment." J Diabetes Res, 2021.
11. Bnouham M et al. "Medicinal plants used in the treatment of diabetes." Int J Diabetes Metab, 2002.
12. ADA. "Rising insulin prices and affordability concerns." Diabetes Care, 2023.
13. Baskaran K, Kizar AB, Radha S, Shanmugasundaram ER. "Antidiabetic effect of leaf extract of Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients." **Journal of Ethnopharmacology.** 1990;30(3):295-300
14. Shanmugasundaram, K. R., et al. "Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus." *Journal of Ethnopharmacology*, 1990.
15. Khan, A., et al. "Gymnema sylvestre supplementation lowers blood glucose levels in type 2 diabetic patients." *Diabetes Care*, 2003.
16. Pan, M. H., et al. "Molecular mechanisms for the anti-inflammatory effect of curcumin and its derivatives." *Journal of Pharmacology and Experimental Therapeutics*, 2000.
17. Weisberg, S. P., et al. "Obesity is associated with macrophage accumulation in adipose tissue." *Journal of Clinical Investigation*, 2003.
18. Chuengsamarn, S., et al. "Curcumin extract for prevention of type 2 diabetes." *Diabetes Care*, 2012.
19. Yasuda, K., et al. "Inhibitory effect of Salacia reticulata extract on postprandial hyperglycemia in rats and humans." *Diabetes Research and Clinical Practice*, 2004.
20. Sridhar, R., et al. "Effect of Salacia reticulata on postprandial glucose and insulin levels in patients with type 2 diabetes." *Diabetes, Obesity & Metabolism*, 2010.
21. Stanely Mainzen Prince, P., et al. "Antioxidant action of Tinospora cordifolia root extract in alloxan diabetic rats." *Phytotherapy Research*, 2004.
22. Patel, M. B., Mishra, S. "Hypoglycemic activity of Tinospora cordifolia in diabetic rats." *Indian Journal of Pharmacology*, 2011.
23. Roffey, B., et al. "Effects of bitter melon (Momordica charantia) on blood glucose levels in diabetes." *Journal of Ethnopharmacology*, 2006.
24. Basch, E., et al. "Bitter melon (Momordica charantia): A review of efficacy and safety."
American Journal of Health-System Pharmacy, 2003.
25. Tripathi, U. N., Chandra, D. "Synergistic effects of polyherbal formulations in diabetes management." *Journal of Ayurveda and Integrative Medicine*, 2011.
26. Yeh, G. Y., et al. "Herbal medicine in the treatment of diabetes." *Diabetes Care*, 2003.
27. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. "Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers." **Planta Medica.** 1998;64(4):353-356.
28. Anitha P, Pankaj V. "Curcumin nanoparticles: A review on formulation and

bioavailability enhancement." **Journal of Drug Delivery Science and Technology.** 2022;67:103121.

29. Xie W, Du L. "Berberine-induced hypoglycemia is associated with decreased insulin degradation in rats." **Planta Medica.** 2011;77(16):1900-1905.
30. Gupta R, Mediratta PK, Singh S. "Aloe vera: A review of its medicinal properties and clinical applications." **Journal of Ethnopharmacology.** 2018;225:42-51.
31. Yin J, Xing H, Ye J. "Efficacy of berberine in patients with type 2 diabetes." **Metabolism: Clinical and Experimental.** 2008;57(5):712-717.
32. Ekor M. "The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety." **Frontiers in Pharmacology.** 2014;4:177.
33. Zeng X, Su W, Liu W, et al. "Berberine modulates gut microbiota and reduces insulin resistance in metabolic disorders." **Scientific Reports.** 2020;10(1):13654.
34. Cani PD, Jordan BF, Blouet C, et al. "Gut microbiota, glucose homeostasis, and metabolic health: A focus on the brain-gut axis." **Diabetes.** 2017;66(6):1770-1777.
35. Li W, Zhang K, Zhang C, et al. "Gut microbiota and diabetes: Link, mechanism, and potential therapies." **Frontiers in Endocrinology.** 2022;13:905004.
36. Mittal A, Tabasum S, Misra R, et al. "AI-driven molecular docking of Punica granatum metabolites for potential antidiabetic therapy." **Journal of Computational Biology.** 2023;30(5):245-258.
37. Kumar A, Singh VK, Chandel M. "Role of quercetin in diabetes treatment: A computational approach." **Bioinformatics and Biology Insights.** 2021;15:11779322211022614.
38. WHO. "Traditional and complementary medicine: WHO global report on traditional and complementary medicine 2019." Geneva, Switzerland: WHO Press, 2019.
39. **Ekor, M.** (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology, 4*, 177. https://doi.org/10.3389/fphar.2013.00177
40. **Pandey, A., & Tripathi, S.** (2014). Concept of standardization, extraction, and pre-phytochemical screening strategies for herbal drugs. *Journal of Pharmacognosy and Phytochemistry, 2*(5), 115-119.
41. **Sharma, V., & Agarwal, A.** (2011). Pharmacognostical and phytochemical evaluation of leaves of *Moringa oleifera*. *International Journal of Pharmacy & Life Sciences, 2*(10), 1106- 1110.
42. **Rajasekaran, A., & Arulselvan, P.** (2019). Standardization and pharmacological validation of traditional herbal medicine. *Journal of Ethnopharmacology, 239*, 111961. https://doi.org/10.1016/j.jep.2019.111961
43. **Chen, S., Pang, X., Song, J., Shi, L., & Yao, H.** (2014). A renaissance in herbal medicine identification: From morphology to DNA barcoding. *Pharmaceutical Biology, 52*(7), 885-892. https://doi.org/10.3109/13880209.2013.792040
44. **World Health Organization (WHO).** (2007). *Guidelines for assessing quality of herbal medicines with reference to contaminants and residues.*
45. **U.S. Food & Drug Administration (FDA).** (2004). *Guidance for industry: Botanical drug development.*

46. **Indian Pharmacopoeia Commission (IPC).** (2018). *Indian Pharmacopoeia.* Government of India