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Plant-Based Therapeutics Agents for Glycemic Control: A Comprehensive Review of Stevia, Monk Fruit, Licorice Root, Mulberry Leaf and Fenugreek

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Abstract: Diabetes mellitus (DM) remains one of the most prevalent metabolic disorders worldwide, imposing significant health and economic burdens. Type 2 diabetes mellitus (T2DM), characterized by insulin resistance and impaired insulin secretion, requires long-term management strategies to control hyperglycemia and prevent complications. Conventional pharmacotherapies, while effective, are associated with adverse effects and limitations that have spurred interest in natural alternatives. Plant-derived bioactive compounds offer promising adjunct or alternative therapeutic options due to their multifaceted mechanisms and generally favorable safety profiles. This comprehensive review focuses on five botanicals—*Stevia rebaudiana* (stevia), *Siraitia grosvenorii* (monk fruit), *Glycyrrhiza glabra* (licorice root), *Morus alba* (mulberry leaf), and *Trigonella foenum-graecum* (fenugreek)—all widely studied for their antidiabetic properties. We explore their phytochemical constituents, molecular mechanisms of action, preclinical and clinical evidence, and potential integration into diabetes management. Emphasis is placed on their effects on insulin secretion and sensitivity, modulation of glucose metabolism enzymes, antioxidant and anti-inflammatory activities, and impacts on carbohydrate digestion and absorption. This review aims to provide an in-depth synthesis of current knowledge to inform future research and clinical applications of these natural agents in glycemic control.

Keywords: *Stevia Rebaudiana, Monk Fruit, Licorice Root, Glycyrrhiza Glabra, Mulberry Leaf, Fenugreek, Antidiabetic Agent, Herbal Medicine, Hypoglycemic Effect.*

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I. INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by persistent hyperglycemia, affects an estimated 537 million adults worldwide, with the number projected to rise to 783 million by 2045 (IDF, 2021). The majority of cases (90–95%) are type 2 diabetes mellitus (T2DM), which results from a combination of peripheral insulin resistance and pancreatic β-cell dysfunction. The disease substantially increases risks for cardiovascular disease, nephropathy, neuropathy, retinopathy, and overall mortality, making effective management a global priority.

Current therapeutic approaches predominantly involve pharmacological agents such as metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and insulin therapy. Despite advancements, these treatments often cause adverse effects including hypoglycemia, gastrointestinal discomfort, weight gain, and, in some cases, cardiovascular risks (American Diabetes Association, 2023). Furthermore, the lifelong cost and medication adherence challenges encourage exploration of alternative or complementary therapies.

Traditional medicinal plants have been a cornerstone of diabetes management in various cultures for centuries. Their bioactive compounds exhibit a diverse range of pharmacological effects, including enhancement of insulin secretion and sensitivity, inhibition of carbohydrate-digesting enzymes, antioxidative and anti-inflammatory properties, and modulation of glucose metabolism pathways (Patel et al., 2012; Kumar & Kalra, 2018). Modern scientific research has increasingly validated these effects and begun elucidating the molecular mechanisms involved.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1163

Among such botanicals, *Stevia rebaudiana* (stevia), *Siraitia grosvenorii* (monk fruit), *Glycyrrhiza glabra* (licorice root), *Morus alba* (mulberry leaf), and *Trigonella foenum-graecum* (fenugreek) are notable due to their extensive traditional use, growing scientific interest, and commercial availability as dietary supplements or functional foods. Each possesses unique phytochemical profiles and biological activities that contribute to their antidiabetic potential.

This review aims to synthesize comprehensive information on these five botanicals, covering their chemical constituents, pharmacodynamics, experimental and clinical evidence, and safety profiles. By integrating current knowledge, this review seeks to support evidence-based use and guide future research on plant-based therapeutics for glycemic control.

II. STEVIA (*STEVIA REBAUDIANA*): A NATURAL ZERO-CALORIE SWEETENER WITH ANTIDIABETIC PROPERTIES

A. Botanical Overview and Traditional Applications

Stevia rebaudiana Bertoni is a perennial shrub belonging to the Asteraceae family, native to the subtropical and tropical regions of South America, particularly Paraguay and Brazil. It thrives in well-drained soils under warm climates and is cultivated worldwide for its leaves, which are characterized by intense natural sweetness.

Indigenous Guaraní peoples have traditionally used *Stevia* leaves for centuries to sweeten beverages and foods and to treat ailments such as diabetes, hypertension, and digestive disorders (Brandle et al., 1998; Kinghorn et al., 2017). The plant's medicinal use primarily focuses on its ability to reduce blood glucose levels, promote weight management, and improve cardiovascular health.

B. Chemical Composition and Sweetening Components

The sweetness of *Stevia* is mainly due to a group of diterpenoid glycosides called **steviol glycosides**. These compounds consist of the aglycone steviol bound to varying numbers and types of sugar moieties, which greatly influence their sweetness intensity and taste profile.

Fig 1: Stevia Plant

➢ *The Major Steviol Glycosides Include:*

- **Stevioside:** Constitutes about 5–10% of dried leaves; approximately 200–300 times sweeter than sucrose.
- **Rebaudioside A:** Less abundant but sweeter and less bitter than stevioside; approximately 300 times sweeter than sucrose.

Other rebaudiosides (B, C, D, E, F, M), dulcoside A, and rubusoside also contribute minor sweetness and improve flavor complexity (Geuns, 2003; Chatellier et al., 2020).

The purification and extraction of these glycosides enable the production of stevia-based sweeteners widely used as sugar substitutes in beverages, food products, and dietary supplements.

C. Metabolism and Pharmacokinetics

After oral ingestion, steviol glycosides are resistant to digestion in the upper gastrointestinal tract due to their glycosidic bonds. Instead, they reach the colon where gut microbiota hydrolyze the glycosides to release the aglycone steviol. Steviol is then absorbed into the bloodstream and undergoes hepatic conjugation primarily to steviol glucuronide, which is excreted via the urine (Nikiforov et al., 2017; Chatsellier et al., 2020).

The slow metabolism and lack of caloric contribution make stevia an ideal natural sweetener for glycemic control.

D. Mechanisms of Antidiabetic Action

Extensive research has elucidated multiple pathways by which stevia and its bioactive compounds modulate glucose homeostasis:

➢ *Enhancement of Insulin Secretion and β-Cell Protection*

Steviol glycosides stimulate insulin secretion from pancreatic β-cells by modulating intracellular calcium influx and activating cyclic AMP (cAMP)-dependent pathways (Chan et al., 2000; Geuns et al., 2008). They also exhibit protective effects on β-cells against oxidative and inflammatory damage by scavenging reactive oxygen species (ROS) and inhibiting pro-apoptotic signaling (Chakrabarti & Raychaudhuri, 2013).

➢ *Inhibition of Intestinal Glucose Absorption*

Stevia compounds inhibit digestive enzymes such as α-glucosidase and sucrase, thereby reducing the breakdown and absorption of complex carbohydrates and sucrose in the gut. This results in decreased postprandial blood glucose spikes (Jeppesen et al., 2000; Chatellier et al., 2020).

➢ *Improvement of Insulin Sensitivity*

Experimental studies show that stevia enhances peripheral insulin sensitivity by upregulating insulin receptor substrate (IRS) phosphorylation and activating the PI3K/Akt signaling pathway, leading to increased glucose uptake in skeletal muscle and adipose tissue (Chen et al., 2019).

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1163

➢ *Anti-Inflammatory and Antioxidant Effects*

Chronic inflammation and oxidative stress contribute significantly to insulin resistance and diabetic complications. Stevia extracts reduce inflammatory cytokines such as TNF-α and IL-6 by inhibiting NF-κB signaling and upregulate endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase, mitigating oxidative damage in metabolic tissues (Tadhani et al., 2007; Jeppesen et al., 2000).

➢ *Modulation of Gut Microbiota*

Recent studies highlight the prebiotic potential of stevia, showing that it fosters the growth of beneficial gut bacteria (e.g., *Bifidobacterium*, *Lactobacillus*) while suppressing pathogenic strains, which contributes to improved metabolic regulation and inflammation reduction (Ruiz-Ojeda et al., 2019).

E. Preclinical Evidence

➢ *Animal Studies*

In diabetic rodent models (streptozotocin-induced and high-fat diet-induced), administration of stevioside or rebaudioside A reduced fasting blood glucose levels, improved oral glucose tolerance, and enhanced insulin secretion (Jeppesen et al., 2000; Hsieh et al., 2003). These treatments also ameliorated diabetic dyslipidemia by lowering triglycerides and LDL cholesterol while increasing HDL cholesterol (Boonkaewwan et al., 2008).

Histopathological analysis showed improved pancreatic islet morphology and reduced inflammatory infiltration in treated animals (Chakrabarti & Raychaudhuri, 2013).

➢ *Cellular Studies*

In vitro studies on pancreatic β-cell lines and adipocytes demonstrated that steviol glycosides promote insulin gene expression, enhance glucose uptake via GLUT4 translocation, and reduce inflammatory signaling (Chen et al., 2019).

F. Clinical Evidence

➢ *Clinical Trials have Evaluated the Safety and Efficacy of Stevia Extracts and Purified Glycosides in Human Subjects:*

- Several randomized controlled trials (RCTs) report that stevia supplementation significantly reduces postprandial blood glucose and insulin levels in healthy, prediabetic, and type 2 diabetic subjects compared to sucrose controls (Gregersen et al., 2004; Chan et al., 2000).
- A meta-analysis concluded that stevia glycosides produce modest but significant reductions in blood glucose without adverse effects on lipid profiles or liver and kidney function (Anton et al., 2010).
- Stevia is generally well tolerated; common side effects are minimal and include mild gastrointestinal discomfort (Geuns et al., 2008).

G. Safety and Regulatory Status

Stevia extracts and purified glycosides such as rebaudioside A have been granted Generally Recognized As Safe (GRAS) status by the U.S. FDA since 2008 and approved by the European Food Safety Authority (EFSA). Toxicological studies reveal no carcinogenic, genotoxic, or reproductive toxicity at dosages much higher than normal dietary intake (Chatsellier et al., 2020).

Fig 2: Monk Fruit

III. MONK FRUIT (*SIRAITIA GROSVENORII*): A NATURAL NON-CALORIC SWEETENER WITH ANTIDIABETIC POTENTIAL

A. Botanical Description and Traditional Uses

Siraitia grosvenorii, commonly known as monk fruit or luo han guo, is a perennial, climbing vine native to southern China's subtropical regions, especially Guangxi province, and parts of northern Thailand. The plant belongs to the Cucurbitaceae family, which includes melons and cucumbers. The fruit is round to oblong, approximately 6–8 cm in diameter, with a greenish-brown rind and sweet, fleshy pulp inside.

Historically, monk fruit has been used for over 400 years in Traditional Chinese Medicine (TCM) primarily as a natural sweetener and remedy for respiratory conditions such as cough, sore throat, and constipation (Wang et al., 2018). Its use as a low-calorie sweetening agent has gained attention globally in recent decades.

B. Phytochemical Composition and Sweetening Principles

The unique sweetness of monk fruit is attributable to a class of cucurbitane-type triterpene glycosides known as **mogrosides**. Among these, **mogroside V** is the major and most potent component, estimated to be 250–450 times sweeter than sucrose on a weight basis (Zhang et al., 2017). Structurally, mogrosides comprise a triterpenoid backbone conjugated with several glucose units, which confer intense sweetness without contributing calories.

In addition to mogrosides, monk fruit contains flavonoids (kaempferol, quercetin derivatives), polysaccharides, essential oils, and other phytochemicals that contribute to its antioxidant and biological effects (Chen et al., 2021).

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C. Molecular and Metabolic Mechanisms Underlying Antidiabetic Effects

Recent studies have illuminated multiple pathways through which monk fruit exerts beneficial effects on glucose metabolism and diabetes control:

➢ *Inhibition of Carbohydrate-Hydrolyzing Enzymes*

Mogrosides have been shown to inhibit key digestive enzymes — α-glucosidase and α-amylase — responsible for breaking down dietary carbohydrates into absorbable glucose. This inhibitory action slows carbohydrate digestion and glucose absorption, attenuating postprandial blood glucose spikes, which is a therapeutic goal in type 2 diabetes management (Liu et al., 2019; Chen et al., 2020).

➢ *Antioxidant and β-Cell Protective Effects*

Oxidative stress induced by chronic hyperglycemia damages pancreatic β-cells, impairing insulin secretion. Mogrosides and associated flavonoids scavenge reactive oxygen species (ROS), thereby reducing oxidative damage. Experimental evidence indicates that treatment with monk fruit extracts increases activities of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px), promoting β-cell survival and function (Wang et al., 2021).

➢ *Anti-Inflammatory Action*

Low-grade chronic inflammation plays a central role in insulin resistance. Monk fruit extracts inhibit pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) by downregulating the NF-κB signaling pathway in adipose and hepatic tissues. This leads to a reduction in systemic inflammation and improved insulin sensitivity (Chen et al., 2020).

➢ *Modulation of Insulin Signaling*

Preliminary research suggests mogrosides enhance insulin sensitivity by promoting phosphorylation of the insulin receptor substrate (IRS) and activating downstream signaling via the PI3K/Akt pathway. This improves glucose uptake in peripheral tissues such as muscle and adipose tissue, counteracting insulin resistance (Zhou et al., 2019).

➢ *Effects on Gut Microbiota*

Emerging evidence points to monk fruit components modulating the gut microbiota composition by increasing populations of beneficial bacteria like *Bifidobacterium* and *Lactobacillus*, which are linked to better glucose metabolism and reduced inflammation (Liu et al., 2020).

D. Pharmacokinetics and Bioavailability

The oral bioavailability of mogrosides is limited due to their large molecular size and poor intestinal absorption. However, intestinal microbiota metabolize mogrosides into smaller bioactive metabolites that may exert systemic effects. Animal studies show that mogroside metabolites circulate in plasma and are responsible for some of the antioxidant and anti-inflammatory activities (Huang et al., 2021). Detailed human pharmacokinetic data remain insufficient, highlighting an area for further research.

E. Preclinical Evidence from Animal and Cellular Studies

➢ *Animal Models of Diabetes*

In streptozotocin (STZ)-induced diabetic rats, oral administration of mogroside V-enriched extracts significantly reduced fasting blood glucose levels and improved glucose tolerance tests compared to untreated controls (Zhang et al., 2019). Treated animals also exhibited improved lipid profiles with reduced serum triglycerides and total cholesterol.

➢ *High-Fat Diet-Induced Obesity Models*

Mice fed a high-fat diet and supplemented with monk fruit extract showed reduced adiposity, amelioration of insulin resistance, decreased hepatic fat accumulation, and lowered inflammatory markers (Wang et al., 2021). Pancreatic histology revealed preserved islet structure and reduced β-cell apoptosis.

➢ *In Vitro Cellular Studies*

Experiments on pancreatic β-cell lines exposed to oxidative stress demonstrated that mogrosides reduce ROS production, suppress inflammatory gene expression, and maintain insulin secretion (Li et al., 2020).

F. Clinical Evidence

Clinical studies on monk fruit as an antidiabetic agent remain limited but promising.

- In healthy volunteers, a randomized crossover study showed monk fruit sweetener elicited no significant increase in postprandial glucose or insulin levels compared to sucrose, indicating its safety as a non-caloric sweetener (Koyama et al., 2017).
- Safety trials confirm good tolerability with no serious adverse effects reported; mild gastrointestinal discomfort is rare and transient (FDA, 2023).
- However, robust randomized controlled trials (RCTs) in diabetic or prediabetic populations are still needed to establish definitive clinical efficacy.

G. Safety Profile and Regulatory Status

Monk fruit extract, and purified mogrosides have GRAS status by the U.S. FDA since 2010. Toxicological studies reveal no genotoxicity, carcinogenicity, or reproductive toxicity at consumption levels far exceeding typical human use (FDA, 2023). Its natural origin, historical use, and comprehensive safety data support its potential as a safe sugar substitute and therapeutic adjunct in diabetes management.

Fig 3: Licorice Root

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IV. LICORICE ROOT (*GLYCYRRHIZA GLABRA*): A PHYTOTHERAPEUTIC ALLY IN GLYCEMIC CONTROL

A. Introduction

Licorice root, derived from the **Glycyrrhiza glabra** plant, has been one of the most extensively used herbal remedies in traditional medicine across cultures, particularly in **Unani, Chinese, Ayurveda, and Greco-Arabic systems**. Known for its sweet taste—attributed to the triterpenoid glycoside **glycyrrhizin**, which is approximately 50 times sweeter than sucrose—licorice has been employed historically for respiratory, gastrointestinal, and inflammatory conditions. However, in recent years, its **potential role in modulating glucose metabolism and insulin function** has become a topic of scientific curiosity and clinical relevance.

The pharmacological properties of licorice root relevant to diabetes management arise from a **complex array of bioactive compounds**, including **glycyrrhizin, glabridin, liquiritin, isoliquiritigenin,** and **licochalcone A**, which exhibit **antioxidant, anti-inflammatory, aldose reductase-inhibiting**, and **insulin-sensitizing** activities.

B. Phytochemistry and Bioactive Constituents

Licorice root contains more than 400 identified phytoconstituents. The most studied among these in the context of diabetes are:

- **Glycyrrhizin**: A pentacyclic triterpenoid saponin known for mimicking corticosteroid activity and modulating hepatic enzymes.
- **Glabridin**: A prenylated isoflavonoid with potent antioxidant and estrogenic effects, known to improve insulin sensitivity.
- **Liquiritin and isoliquiritigenin**: Flavonoids that influence oxidative stress pathways and modulate cytokine production.
- **Licochalcone A**: A chalconoid that regulates lipid metabolism and exerts hepatoprotective and anti-inflammatory actions.

These phytochemicals act synergistically to influence glycemic parameters through a multitude of biological pathways.

C. Mechanisms of Antidiabetic Action

➢ *Enhancement of Insulin Sensitivity*

Licorice root constituents, particularly glabridin and glycyrrhizin, have been shown to enhance insulin sensitivity by improving GLUT-4 translocation in peripheral tissues, reducing insulin resistance in adipocytes, and modulating adiponectin and leptin levels.

➢ *Inhibition of Aldose Reductase and AGEs Formation*

In hyperglycemic states, excessive glucose is diverted through the polyol pathway, where aldose reductase converts glucose into sorbitol, leading to osmotic stress and diabetic complications. Licorice flavonoids such as licochalcone A have shown aldose reductase-inhibiting activity, thus offering protection against retinopathy, nephropathy, and neuropathy.

➢ *Anti-inflammatory and Antioxidant Effects*

Chronic inflammation and oxidative stress are central to the pathogenesis of both type 1 and type 2 diabetes. Isoliquiritigenin and glabridin scavenge reactive oxygen species (ROS), inhibit the NF-κB pathway, and downregulate inflammatory cytokines like TNF-α and IL-6, thereby reducing insulin resistance.

➢ *Hepatoprotective and Lipid-Modulating Effects*

Glycyrrhizin modulates hepatic enzymes involved in gluconeogenesis and lipogenesis, leading to improved lipid profiles and a reduction in hepatic insulin resistance. This is particularly beneficial in individuals with metabolic syndrome or non-alcoholic fatty liver disease (NAFLD) associated with diabetes.

D. Evidence from Preclinical and Clinical Studies

➢ *Preclinical Evidence*

A study by Wang et al. (2013) demonstrated that glycyrrhizin significantly reduced fasting blood glucose levels and increased plasma insulin in streptozotocin-induced diabetic rats. Another study by Lee et al. (2014) showed that glabridin improved glucose tolerance and lipid metabolism in high-fat diet-induced insulin-resistant mice, with a concurrent reduction in markers of oxidative stress.

➢ *Clinical Evidence*

Clinical data on licorice and diabetes remain limited but promising. A randomized trial conducted by Derosa et al. (2012) indicated that patients receiving a combination of licorice extract with metformin experienced better glycemic control, reduced HbA1c, and improved lipid profile compared to metformin alone. However, these findings call for further validation through large-scale, placebo-controlled trials.

E. Safety, Toxicology, and Contraindications

While licorice is generally considered safe in low to moderate doses, its **prolonged or high-dose use** may lead to **pseudoaldosteronism**, characterized by **hypertension, hypokalemia, and edema**, primarily due to glycyrrhizin's mineralocorticoid-like effects. Therefore, deglycyrrhizinated licorice (DGL) preparations are often recommended for therapeutic use, particularly in individuals with cardiovascular comorbidities.

Patients on antihypertensives, corticosteroids, or diuretics should be cautious, and healthcare provider supervision is recommended during supplementation. Pregnant and lactating women should avoid licorice due to potential hormonal and uterotonic effects.

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V. MULBERRY (*MORUS ALBA*): A COMPREHENSIVE REVIEW OF ITS ANTIDIABETIC POTENTIAL

A. Introduction

Mulberry (*Morus alba*), a member of the Moraceae family, is a deciduous tree indigenous to China and extensively cultivated in many parts of Asia, Europe, and North America. Its leaves, fruits, and roots have been used for centuries in traditional medicine systems such as Traditional Chinese Medicine (TCM) and Ayurveda, treating ailments ranging from fever and inflammation to diabetes and hypertension. The plant's antidiabetic properties have recently gained scientific validation through a plethora of in vitro, in vivo, and clinical studies, positioning mulberry as a promising phytotherapeutic agent for glycemic control and diabetic complication prevention.

Diabetes mellitus, especially type 2 diabetes, is characterized by hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both. The chronic elevation of blood glucose triggers a cascade of metabolic disturbances and oxidative stress, culminating in microvascular and macrovascular complications. Conventional antidiabetic drugs, while effective, are often associated with adverse effects, motivating the search for safer, natural alternatives.

Mulberry's efficacy in diabetes is primarily attributed to its rich phytochemical profile. This review explores the bioactive compounds in mulberry leaves and their molecular targets, mechanisms of action, pharmacological evidence, clinical applicability, and safety considerations.

Fig 4: Mulberry Leaf

B. Phytochemical Constituents of Mulberry Relevant to Diabetes Management

The therapeutic potential of mulberry derives from a complex mixture of bioactive substances distributed across its leaves, fruit, and roots. For antidiabetic activity, mulberry leaves are the most extensively studied part, containing:

- **Iminosugars**: The most notable is 1-deoxynojirimycin (DNJ), a potent α-glucosidase inhibitor that structurally mimics glucose and competitively inhibits enzymes that digest carbohydrates in the intestine.
- **Flavonoids**: Including rutin, quercetin, kaempferol, and isoquercetin, which possess antioxidant, anti-inflammatory, and insulin-sensitizing properties.
- **Polyphenols**: Such as chlorogenic acid and resveratrol, known for modulating glucose metabolism and improving endothelial function.
- **Polysaccharides**: High molecular weight compounds with immunomodulatory and hypoglycemic effects.
- **Alkaloids and Coumarins**: Which contribute to the antioxidative capacity and cellular protection.
- **Vitamins and Minerals**: Including vitamin C, E, and trace elements that support metabolic health.

Each of these constituents targets different aspects of glucose homeostasis, collectively providing a multitargeted approach to diabetes management.

C. Mechanisms of Antidiabetic Action

➢ *Inhibition of α-Glucosidase and Reduction of Postprandial Hyperglycemia*

The most extensively documented mechanism of mulberry's antidiabetic action is the inhibition of intestinal α-glucosidases by DNJ and its derivatives. α-Glucosidases are enzymes that hydrolyze complex carbohydrates into absorbable monosaccharides. Inhibition of these enzymes delays carbohydrate digestion, thereby attenuating postprandial blood glucose spikes, which are significant contributors to the overall glycemic burden in diabetic patients.

The efficacy of DNJ in this role rivals that of pharmaceutical α-glucosidase inhibitors such as acarbose, but with a better side effect profile. Multiple in vitro studies have demonstrated DNJ's competitive inhibition kinetics against maltase and sucrase enzymes. Furthermore, animal studies confirm the significant reduction in postprandial glucose levels following oral administration of mulberry leaf extracts rich in DNJ.

➢ *Improvement of Insulin Sensitivity and Glucose Uptake*

Insulin resistance, a hallmark of type 2 diabetes, results in impaired glucose uptake by peripheral tissues. Flavonoids such as quercetin and kaempferol found in mulberry leaves have been shown to enhance insulin signaling pathways. They promote the phosphorylation of insulin receptor substrate-1 (IRS-1) and activate phosphoinositide 3-kinase (PI3K)/Akt pathways, leading to increased translocation of glucose transporter type 4 (GLUT4) to the cell membrane in skeletal muscle and adipose tissue. This process facilitates glucose entry into cells, reducing circulating glucose concentrations.

In addition, mulberry polyphenols improve pancreatic β-cell function by protecting against oxidative damage and enhancing insulin secretion in response to glucose stimulation.

➢ *Antioxidant and Anti-inflammatory Activities*

Chronic hyperglycemia induces oxidative stress by increasing reactive oxygen species (ROS) production, which

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damages cellular components and promotes inflammation. The antioxidant components of mulberry, including flavonoids and polyphenols, neutralize ROS and upregulate endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase.

Simultaneously, mulberry compounds inhibit nuclear factor kappa B (NF-κB) signaling, reducing the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). This dual action protects pancreatic β-cells and vascular endothelium, mitigating the progression of diabetic complications such as nephropathy and retinopathy.

- *Modulation of Lipid Metabolism and Cardiovascular Protection*

Dyslipidemia is common in diabetes, characterized by elevated triglycerides, LDL cholesterol, and reduced HDL cholesterol. Mulberry leaf extract administration has been shown to improve lipid profiles by inhibiting HMG-CoA reductase activity, enhancing LDL receptor expression, and stimulating bile acid synthesis.

These effects reduce atherogenic risk and promote cardiovascular health. Animal studies also report reduced oxidative damage to cardiac tissues and improved endothelial-dependent vasodilation following mulberry supplementation.

- *Hepatoprotective Effects*

The liver plays a central role in glucose and lipid metabolism. Mulberry extracts exhibit hepatoprotective properties by attenuating fat accumulation, fibrosis, and inflammation in the liver. These effects are partly mediated by the activation of AMP-activated protein kinase (AMPK) pathways, which regulate energy homeostasis and inhibit lipogenesis.

D. Preclinical Studies: Evidence from Animal and In Vitro Models

Extensive preclinical research supports the antidiabetic efficacy of mulberry. Streptozotocin (STZ)-induced diabetic rat models have demonstrated significant reductions in fasting blood glucose, improved oral glucose tolerance, and enhanced insulin levels after treatment with mulberry leaf extracts.

For example, a study by Kim et al. (2015) found that administration of mulberry leaf aqueous extract (200 mg/kg body weight) over 8 weeks decreased fasting blood glucose by 30%, improved insulin sensitivity, and reduced lipid peroxidation markers in diabetic rats. Histological examination revealed preservation of pancreatic islets and reduced inflammatory infiltration.

In vitro studies with 3T3-L1 adipocytes and HepG2 hepatocytes have elucidated molecular mechanisms, showing mulberry flavonoids upregulate glucose uptake, inhibit lipid accumulation, and suppress pro-inflammatory gene expression.

E. Clinical Evidence

While preclinical findings are compelling, clinical trials on mulberry's antidiabetic efficacy are relatively limited but growing.

A randomized, double-blind, placebo-controlled trial conducted by Hwang et al. (2016) enrolled 60 prediabetic subjects who received 1 g/day of mulberry leaf extract standardized to 5% DNJ for 12 weeks. Results showed a statistically significant reduction in postprandial blood glucose levels at 30, 60, and 120 minutes after a carbohydrate load compared to placebo ($p < 0.01$). HbA1c levels were modestly reduced, and no severe adverse events were reported.

Another study by Lu et al. (2019) investigated the effects of mulberry leaf extract combined with lifestyle modification in type 2 diabetic patients over 24 weeks. The treatment group demonstrated significant improvements in fasting plasma glucose, insulin resistance indices (HOMA-IR), and lipid parameters relative to controls. Patient-reported quality of life and oxidative stress biomarkers also improved.

Despite these promising results, larger, multicenter trials with longer follow-up durations are necessary to establish mulberry leaf extract as a standard adjunct therapy for diabetes.

F. Safety and Toxicological Considerations

Mulberry leaf extract is generally regarded as safe when consumed orally at therapeutic doses. Acute and subchronic toxicity studies in rodents indicate high LD50 values, with no significant hepatotoxicity or nephrotoxicity observed.

Mild gastrointestinal discomfort such as bloating or diarrhea has been occasionally reported, likely due to the delayed carbohydrate digestion effect. Caution is advised when combining mulberry with pharmaceutical α-glucosidase inhibitors or insulin to avoid hypoglycemia.

Long-term safety studies in humans are sparse but essential to fully understand chronic exposure risks.

Fig 5: Fenugreek

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VI. FENUGREEK (*TRIGONELLA FOENUM-GRAECUM*): A DETAILED REVIEW OF ITS ANTIDIABETIC PROPERTIES

A. Introduction

Fenugreek (*Trigonella foenum-graecum*), a leguminous herb native to the Mediterranean region and Western Asia, has been widely used in traditional medicine and culinary applications for thousands of years. It is recognized for its distinctive aromatic seeds, which serve as a common spice, and its leaves that are used as vegetables in many cultures. Beyond its culinary role, fenugreek seeds and leaves have been extensively investigated for a broad spectrum of therapeutic properties, notably in the management of metabolic disorders including diabetes mellitus.

Diabetes mellitus, a chronic metabolic disease characterized by hyperglycemia, arises due to defects in insulin secretion, insulin action, or both. The prevalence of type 2 diabetes has escalated globally, posing a significant public health burden. Conventional pharmacological agents, while effective, are frequently associated with undesirable side effects and high costs. Consequently, there is a pressing demand for alternative therapies that are safe, affordable, and efficacious.

Fenugreek has gained significant attention as a natural antidiabetic agent due to its rich composition of bioactive compounds that modulate various biochemical pathways implicated in glucose homeostasis. This review comprehensively explores fenugreek's phytochemistry, molecular mechanisms of antidiabetic action, preclinical and clinical evidence, safety profiles, and the challenges in its therapeutic use.

B. Phytochemical Profile of Fenugreek Relevant to Diabetes Management

The therapeutic effects of fenugreek primarily derive from the complex array of bioactive constituents in its seeds and, to a lesser extent, leaves. These compounds include:

- **Soluble dietary fibers**: Fenugreek seeds are rich in galactomannan, a soluble fiber that delays gastric emptying and carbohydrate absorption.
- **Alkaloids**: Trigonelline is a prominent alkaloid with insulinotropic and neuroprotective properties.
- **Saponins**: Fenugreek saponins, such as diosgenin, exhibit anti-inflammatory, antioxidant, and lipid-lowering effects.
- **Flavonoids and polyphenols**: These include vitexin, quercetin, and isovitexin, which contribute to antioxidant and insulin-sensitizing effects.
- **Amino acids**: Particularly 4-hydroxyisoleucine, an unusual amino acid unique to fenugreek, known for its potent insulinotropic activity.
- **Other constituents**: Including essential oils, vitamins (such as vitamin C), and minerals (chromium, magnesium) that support metabolic health.

The synergy of these bioactives orchestrates fenugreek's multi-faceted antidiabetic actions.

C. Mechanisms of Antidiabetic Action

➢ *Modulation of Carbohydrate Absorption and Glycemic Control*

One of the primary mechanisms by which fenugreek exerts glycemic control is through its high content of soluble dietary fiber, particularly galactomannan. This viscous fiber forms a gel-like matrix in the gastrointestinal tract, slowing gastric emptying and delaying the absorption of glucose and other carbohydrates. The resulting effect is an attenuation of postprandial hyperglycemia, a critical factor in the management of diabetes.

Moreover, fenugreek seeds inhibit digestive enzymes such as α-amylase and α-glucosidase, further reducing carbohydrate breakdown and absorption. This dual inhibition has been demonstrated in vitro and validated in animal models, supporting fenugreek's role as a natural α-glucosidase inhibitor.

➢ *Insulinotropic Effects of 4-Hydroxyisoleucine and Trigonelline*

The amino acid 4-hydroxyisoleucine is a distinctive component of fenugreek seeds that has received significant attention for its ability to stimulate insulin secretion from pancreatic β-cells in a glucose-dependent manner. Unlike sulfonylureas, which stimulate insulin irrespective of glucose concentration and can cause hypoglycemia, 4-hydroxyisoleucine enhances insulin release only when glucose levels are elevated, thereby reducing the risk of hypoglycemia.

Trigonelline, another key alkaloid, not only improves insulin secretion but also exhibits neuroprotective and lipid-lowering effects. It modulates key enzymes involved in glucose metabolism, improves insulin sensitivity, and reduces oxidative stress in pancreatic cells.

➢ *Improvement of Insulin Sensitivity and Glucose Uptake*

Fenugreek flavonoids and saponins have been shown to enhance peripheral insulin sensitivity through multiple pathways. They activate the AMP-activated protein kinase (AMPK) signaling pathway, a master regulator of energy homeostasis, leading to increased glucose uptake in muscle and adipose tissues by promoting GLUT4 translocation to the cell membrane.

In addition, fenugreek components inhibit protein tyrosine phosphatase-1B (PTP1B), a negative regulator of insulin signaling, thereby potentiating insulin receptor activity.

➢ *Antioxidant and Anti-inflammatory Effects*

Chronic hyperglycemia induces oxidative stress and inflammation, key drivers of diabetic complications. Fenugreek's polyphenols and saponins possess robust antioxidant properties, scavenging free radicals and upregulating endogenous antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase.

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Fenugreek also suppresses the activation of pro-inflammatory transcription factors like NF-κB, reducing the expression of cytokines such as TNF-α, IL-6, and IL-1β. These anti-inflammatory effects protect pancreatic β-cells from cytokine-mediated apoptosis and preserve their function.

➢ *Lipid-Lowering and Cardioprotective Effects*

Fenugreek's saponins, particularly diosgenin, reduce serum total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol. These lipid-modulating effects improve the lipid profile of diabetic patients and lower cardiovascular risk.

Fenugreek also reduces oxidative stress in vascular tissues and improves endothelial function, contributing to its cardioprotective effects.

D. Preclinical Studies: Animal and Cellular Evidence

Extensive preclinical studies corroborate the antidiabetic efficacy of fenugreek. In streptozotocin (STZ)-induced diabetic rat models, oral administration of fenugreek seed extract resulted in significant reductions in fasting blood glucose, HbA1c levels, and improved glucose tolerance tests. Histopathological studies revealed restoration of pancreatic islet architecture and β-cell regeneration.

In vitro assays with pancreatic β-cell lines demonstrated that 4-hydroxyisoleucine enhances glucose-stimulated insulin secretion and protects against cytokine-induced apoptosis. Cellular studies in adipocytes and hepatocytes showed enhanced glucose uptake and reduced lipid accumulation.

One pivotal study by Sharma et al. (2014) reported that fenugreek seed powder administered to diabetic rats over 8 weeks reduced fasting blood glucose by 40%, improved insulin sensitivity indices, and decreased oxidative stress markers. These findings strongly support fenugreek's potential as a natural antidiabetic agent.

E. Clinical Evidence

Several clinical trials have evaluated fenugreek's efficacy in human subjects with type 2 diabetes or impaired glucose tolerance.

A randomized controlled trial by Gupta et al. (2001) involving 60 type 2 diabetic patients demonstrated that supplementation with 10 g/day of fenugreek seed powder for 3 months significantly reduced fasting blood glucose, postprandial glucose, and HbA1c levels compared to controls.

In another study, Neelakantan et al. (2014) conducted a meta-analysis of randomized controlled trials assessing fenugreek's effect on glycemic control. They reported a significant mean reduction of 0.88% in HbA1c and improved insulin sensitivity markers.

Additionally, fenugreek has been tested in gestational diabetes with favorable outcomes in controlling maternal blood glucose and reducing insulin requirements.

Despite promising results, variation in dosage forms (seed powder, extracts, capsules), doses, and study durations necessitates further well-designed, large-scale clinical trials to confirm fenugreek's role as a complementary therapy in diabetes.

F. Safety and Toxicological Profile

Fenugreek is generally considered safe with a long history of dietary and medicinal use. However, high doses may cause gastrointestinal disturbances such as diarrhea, bloating, and flatulence.

Rare allergic reactions have been reported, especially in individuals sensitive to peanuts or chickpeas, due to cross-reactivity.

Fenugreek's anticoagulant properties may potentiate bleeding risk when combined with anticoagulant drugs. Pregnant women should use fenugreek cautiously, as it can induce uterine contractions.

Overall, toxicological studies have confirmed a wide margin of safety, but clinicians should consider potential interactions and contraindications.

Table 1: Comparative Table of Selected Botanicals for Diabetes Management

Plant	Key Bioactives	Primary Mechanisms	Clinical Outcomes	Dosage/Forms	Cautions
Stevia (*Stevia rebaudiana*)	Stevioside, Rebaudioside A	Stimulates insulin secretion, α-glucosidase inhibition, antioxidant action	↓ Fasting glucose, ↑ insulin, safe for T2DM patients	Leaves, extracts, sweeteners (1-4 g/day)	Caution with hypotensive meds
Monk Fruit (*Siraitia grosvenorii*)	Mogroside V, Squalene, Triterpenoids	Antioxidant, insulin sensitizer, glucose uptake enhancer	Emerging clinical data; ↓ glucose in preclinical models	Fruit extract, mogroside concentrates	Insufficient human trials
Licorice Root (*Glycyrrhiza glabra*)	Glycyrrhizin, Glabridin, Liquiritigenin	β-cell protection, AMPK activation, PPAR-γ agonist	Improved insulin sensitivity, ↓ glucose in animal models	Dried roots, decoctions, extracts (50–200 mg/day)	Avoid in HTN, edema, pregnancy

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Mulberry Leaf (*Morus alba*)	DNJ, Rutin, Quercetin, Morusin	α-glucosidase inhibition, ↓ hepatic glucose production, ↑ GLUT4	↓ Postprandial glucose, ↓ HbA1c, ↑ insulin sensitivity	Capsules, tea, powder (1–2.5 g/day)	Mild GI discomfort
Fenugreek (*Trigonella foenum-graecum*)	Galactomannan, 4-Hydroxyisoleucine, Trigonelline	Delayed glucose absorption, insulin secretion, anti-inflammatory	↓ FBG, ↓ HbA1c, ↑ HDL, ↓ LDL/TG in human trials	Powdered seeds, soaked seeds, capsules (5–25 g/day)	Hypoglycemia with concurrent antidiabetics

VII. CONCLUSION

Diabetes mellitus, particularly type 2 diabetes, continues to impose a massive global health burden, with current therapeutic modalities facing limitations in terms of cost, accessibility, side effects, and long-term efficacy. Against this backdrop, plant-derived therapeutics are gaining prominence as complementary and alternative options, particularly in the form of dietary adjuncts, nutraceuticals, or phytopharmaceutical agents.

This review explored five extensively studied botanicals—Stevia (*Stevia rebaudiana*), Monk Fruit (*Siraitia grosvenorii*), Licorice Root (*Glycyrrhiza glabra*), Mulberry Leaf (*Morus alba*), and Fenugreek (*Trigonella foenum-graecum*)—all of which demonstrate promising antihyperglycemic potential through diverse biochemical mechanisms.

Stevia primarily exerts its antidiabetic activity via steviol glycosides, especially stevioside and rebaudioside A, which stimulate insulin secretion, enhance β-cell function, and inhibit glucose absorption enzymes such as α-glucosidase. Its non-caloric sweetening property and high safety index make it highly valuable for diabetic dietary interventions.

Monk Fruit contains unique mogrosides, particularly mogroside V, which act as potent antioxidants and insulin sensitizers. While human clinical data is still emerging, its historical use and strong mechanistic backing provide a solid foundation for further nutraceutical development.

Licorice Root offers a unique blend of triterpenoid saponins (e.g., glycyrrhizin) and flavonoids (e.g., glabridin), contributing to improved glucose uptake, insulin sensitization, and β-cell preservation. However, its mineralocorticoid effects warrant dosage control and caution in patients with hypertension.

Mulberry Leaf is rich in DNJ (1-deoxynojirimycin), flavonoids, and alkaloids that inhibit α-glucosidase, suppress hepatic gluconeogenesis, and improve peripheral insulin sensitivity. Its role in reducing postprandial hyperglycemia and insulin resistance has been repeatedly verified in both preclinical and clinical models.

Fenugreek combines the mechanical effects of high-fiber content (galactomannan) with the insulinotropic properties of 4-hydroxyisoleucine and trigonelline. It is perhaps the most extensively researched among the five, showing efficacy in improving glycemic control, lipid profile, and pancreatic histoarchitecture.

Together, these botanicals reflect a multitargeted, systems biology approach to diabetes management—modulating digestion, absorption, insulin secretion, β-cell protection, hepatic metabolism, and inflammation. When used under supervision, they present minimal adverse effects and align well with preventive health strategies. However, to translate these findings into mainstream clinical practice, standardized extract formulations, larger randomized trials, and pharmacovigilance frameworks are essential.

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