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Review Article

Development and Evaluation of Herbal Antidiabetic Tablet Containing Gymnema sylvestre and Momordica charantia Extracts

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to insulin deficiency or resistance, leading to severe complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy. The global prevalence of diabetes continues to rise, highlighting the urgent need for effective and safe therapeutic strategies. Herbal antidiabetic therapy has gained attention due to its multi-target mechanisms, minimal side effects, and potential to improve glycemic control naturally. This review focuses on two well-known medicinal plants, Gymnema sylvestre and Momordica charantia, which have demonstrated significant antidiabetic properties through mechanisms such as insulin secretion stimulation, glucose absorption inhibition, and pancreatic β-cell regeneration. The paper summarizes pharmacological studies, formulation approaches for herbal tablets, and evaluation parameters including physicochemical characteristics, in vitro dissolution, and in vivo efficacy. The findings suggest that a combination tablet containing standardized extracts of Gymnema sylvestre and Momordica charantia could serve as a promising adjunct or alternative to conventional antidiabetic drugs, offering potential benefits in glycemic management and patient compliance. Further clinical studies are recommended to confirm their safety, efficacy, and therapeutic dose optimization.

INTRODUCTION

1.1 Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin

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action, or both. It is broadly classified into three main types: [1]

- Type 1 Diabetes (T1DM): An autoimmune condition marked by the destruction of pancreatic β-cells, leading to absolute insulin deficiency. [2]
- Type 2 Diabetes (T2DM): The most prevalent form, caused by a combination of insulin resistance and relative insulin deficiency, often associated with obesity and lifestyle factors. [3]
- Gestational Diabetes Mellitus (GDM): Hyperglycemia diagnosed during pregnancy in women without a prior history of diabetes, posing risks to both mother and fetus. [4]

Globally, diabetes has emerged as a major public health challenge, with over 537 million adults affected in 2021, a number projected to rise to 783 million by 2045. The disease is associated with severe microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications (cardiovascular diseases), contributing significantly to morbidity and mortality worldwide. The pathophysiology involves impaired insulin secretion from pancreatic β-cells, insulin resistance in peripheral tissues, and chronic hyperglycemia, which triggers oxidative stress and inflammation. [5]

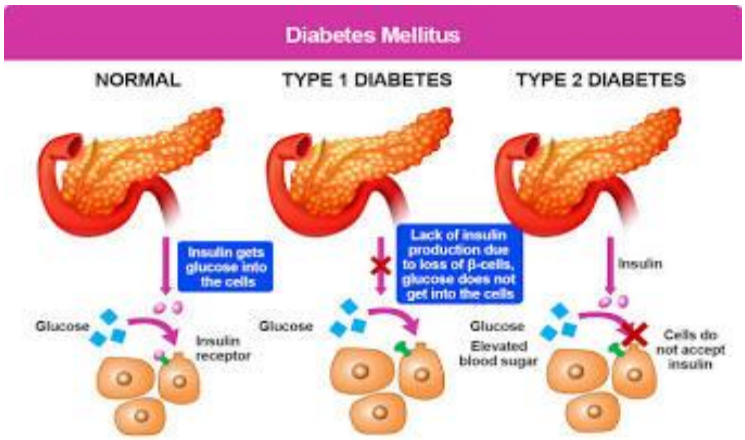


Figure no. 1 Diabetes mellitus

1.2 Limitations of Conventional Antidiabetic Drugs

Despite the availability of various pharmacological interventions, conventional antidiabetic drugs often present significant limitations. [6] Commonly prescribed medications, including sulfonylureas, biguanides, and insulin analogs, may cause adverse effects such as hypoglycemia, gastrointestinal disturbances, weight gain, and hepatotoxicity. [7] Additionally, long-term adherence is often hindered by high treatment costs and complex dosing regimens. These challenges highlight the need for alternative or adjunct therapies that are safer, cost-effective, and sustainable. [8]

1.3 Role of Herbal Therapy in Diabetes

Herbal therapy has garnered considerable attention as a complementary or alternative approach to diabetes management. [9] Medicinal plants often provide multi-targeted mechanisms, such as enhancing insulin secretion, improving glucose uptake, modulating carbohydrate metabolism, and exerting antioxidant and anti-inflammatory

effects. [10] Compared to synthetic drugs, herbal preparations are generally associated with fewer side effects and better patient compliance. [11] Several plants have been traditionally used for their antidiabetic potential. Among these, Gymnema sylvestre (commonly known as "gurmar") has shown the ability to stimulate insulin secretion and regenerate pancreatic β-cells, while Momordica charantia (bitter melon) exhibits insulin-mimetic properties and promotes glucose utilization. [12] The combination of these plants in a standardized herbal formulation holds promise for effective glycemic control and overall metabolic health. [13] [14]

2. Phytochemistry and Pharmacology

2.1 Gymnema sylvestre

Botanical Profile:
Gymnema sylvestre R.Br., commonly referred to as "gurmar" or "sugar destroyer," belongs to the Apocynaceae family. Native to India and parts of Southeast Asia, this perennial climbing vine has been used for centuries in Ayurveda to manage diabetes and obesity. The leaves, stems, and roots are used for therapeutic purposes, with the leaves being the primary source of antidiabetic compounds. [15]



Figure no. 2 Gymnema sylvestre

Phytochemical Composition:
The antidiabetic activity of *Gymnema sylvestre* is largely attributed to its diverse phytoconstituents:

- **Gymnemic acids:** A group of triterpenoid saponins; the primary bioactive compounds responsible for hypoglycemic activity. They suppress sweet taste perception and inhibit intestinal glucose absorption. [16]
- **Saponins:** Contribute to β-cell regeneration and improve lipid metabolism.
- **Flavonoids and phenolic compounds:** Exhibit strong antioxidant activity, reducing oxidative stress-induced β-cell damage.
- **Polysaccharides:** Modulate carbohydrate metabolism and enhance insulin sensitivity. [17]

Table 1: Phytochemical Composition of Gymnema sylvestre

Phytochemical	Constituent Type	Reported % or Range	Reference / Note
Gymnemic acids	Triterpenoid saponins	10–25%	Standardized extracts
Flavonoids	Polyphenols	2–5%	Antioxidant activity
Alkaloids	Nitrogen-containing compounds	Trace	May contribute to glucose modulation
Sterols	Phytosterols	1–3%	Lipid-lowering effect
Tannins	Polyphenolic compounds	1–4%	Antioxidant and anti-inflammatory

Mechanism of Action:

1. **Stimulation of insulin secretion:** Gymnemic acids and saponins enhance β-cell function, promoting endogenous insulin release.

2. **Inhibition of glucose absorption:** Gymnema compounds interfere with intestinal sugar receptors, reducing glucose uptake from the gut.

3. **β-cell regeneration:** Preclinical studies suggest that Gymnema extracts can regenerate damaged pancreatic islets.

4. **Reduction of sugar cravings:** Gymnema temporarily suppresses sweet taste perception, which may indirectly reduce sugar intake.

5. **Antioxidant activity:** Protects pancreatic β-cells from oxidative damage induced by hyperglycemia. [18]

Pharmacological Studies:

- **In vitro studies:** Gymnema extracts inhibit carbohydrate-digesting enzymes like α-glucosidase and α-amylase, limiting postprandial glucose spikes. [19]

- **In vivo studies:** In streptozotocin (STZ)-induced diabetic rats, Gymnema leaf extract significantly lowered fasting blood glucose, improved lipid profiles, and increased serum insulin levels.

- **Clinical studies:** Trials in Type 2 diabetic patients have demonstrated improved glycemic control, reduced HbA1c, and minimal adverse effects, confirming its safety and efficacy. [20]

2.2 Momordica charantia

Botanical Profile:
Momordica charantia L., commonly known as bitter melon, belongs to the Cucurbitaceae family. It is a tropical and subtropical vine widely cultivated in Asia, Africa, and South America. Traditionally, the fruit, leaves, and seeds have been used to treat diabetes, inflammation, and infections. [21]



Figure no. 3 Momordica charantia

Phytochemical Composition:
Bitter melon contains a variety of bioactive compounds:

- **Charantin:** Steroidal saponin with potent hypoglycemic activity.

- **Polypeptide-p:** An insulin-mimetic peptide that directly lowers blood glucose.

- **Vicine:** Alkaloid that contributes to antidiabetic effects.

- **Flavonoids, triterpenes, and phenolic compounds:** Provide antioxidant and anti-inflammatory benefits.

- **Other compounds:** Lectins and momordicosides enhance glucose uptake and lipid metabolism. [22]

Table 2: Phytochemical Composition of Momordica charantia

Phytochemical	Constituent Type	Reported % or Range	Reference / Note
Charantin	Steroidal saponin	0.1–0.3%	Hypoglycemic effect
Polypeptide-p	Peptide insulin mimetic	0.5–1%	Insulin-like activity
Flavonoids	Polyphenols	1–3%	Antioxidant activity
Alkaloids	Nitrogen-containing compounds	Trace	May modulate glucose metabolism
Triterpenoids	Bitter principles	0.5–2%	Antidiabetic and anti-inflammatory

Mechanism of Action:

1. **Insulin-mimetic activity:** Polypeptide-p binds to insulin receptors, facilitating glucose uptake in muscle and adipose tissue.

2. **Enhancement of β-cell function:** Promotes proliferation and regeneration of insulin-secreting pancreatic cells.

3. **Inhibition of gluconeogenesis:** Modulates key enzymes in the liver, reducing endogenous glucose production.

4. **Glycogen synthesis stimulation:** Increases glucose storage in liver and muscle, lowering circulating glucose.

5. **Antioxidant and anti-inflammatory effects:** Protects pancreatic tissue from oxidative stress and chronic inflammation associated with diabetes. [23]

Pharmacological Studies:

- **In vitro studies:** Bitter melon extracts improve glucose uptake in cultured myocytes and adipocytes, inhibit α-glucosidase, and reduce lipid peroxidation. [24]

- **In vivo studies:** In STZ- and alloxan-induced diabetic rats, Momordica fruit and leaf extracts reduce fasting blood glucose, HbA1c, and oxidative stress markers, while improving lipid profile and liver function.

- **Clinical studies:** Supplementation in Type 2 diabetic patients has shown moderate reduction in fasting and postprandial glucose levels, with good tolerability and minimal adverse effects. [25]

2.3 Synergistic Effects of Combination Therapy

- Combining *Gymnema sylvestre* and *Momordica charantia* is hypothesized to offer **multi-targeted therapeutic effects**:

  - Gymnema enhances endogenous insulin secretion and reduces intestinal glucose absorption. [26]

  - Momordica mimics insulin action and supports β-cell regeneration.

- **Potential Benefits:** [27]

  - Improved glycemic control

  - Reduction of oxidative stress

  - Favorable modulation of lipid profile

  - Enhanced patient compliance due to herbal origin[28]

- **Evidence from studies:** Animal models and preliminary clinical investigations indicate that the combination can exert additive or synergistic effects, providing stronger glucose-lowering action compared to individual extracts. [29]

3. Formulation Development

3.1 Selection of Extracts

The successful formulation of an herbal antidiabetic tablet critically depends on the quality and consistency of the plant extracts used. Standardization ensures reproducible therapeutic efficacy and safety. [30]

Standardization of extracts:

- **Marker compounds:**
- For *Gymnema sylvestre*, gymnemic acids are typically used as the primary bioactive marker.
    - For *Momordica charantia*, charantin and polypeptide-p serve as key indicators of potency. [31]
- **% Bioactive content:** Quantitative estimation of these markers ensures uniformity across batches, commonly determined using High-Performance Liquid Chromatography (HPLC), UV-Visible spectrophotometry, or Thin Layer Chromatography (TLC).
- **Importance:** Standardization reduces batch-to-batch variability, ensures reproducible pharmacological activity, and meets regulatory requirements for herbal formulations. [32]

Solvent extraction methods:

- **Ethanol extraction:** Efficient for extracting saponins, flavonoids, and other polar compounds; widely used for both Gymnema and Momordica leaves/fruits.
- **Aqueous extraction:** Mimics traditional herbal decoctions; preserves water-soluble polysaccharides and peptides. [33]
- **Hydroalcoholic extraction:** Combines the advantages of both polar and semi-polar solvents; maximizes yield of active constituents.
- **Optimization:** Extraction parameters such as solvent concentration, temperature, duration, and plant-to-solvent ratio are optimized to ensure maximal recovery of bioactives. [34]

Table 3: Comparison of Extraction Methods

Plant	Extraction Solvent	Method	Yield (%)	Bioactive Content	Advantages	Limitations
Gymnema sylvestre	Ethanol	Soxhlet	12–18	15–20% gymnemic acids	High extraction efficiency	Time-consuming, solvent use
Gymnema sylvestre	Water	Maceration	8–12	10–12% gymnemic acids	Safe, non-toxic	Lower yield
Momordica charantia	Hydroalcoholic	Soxhlet	10–15	0.2–0.3% charantin	Efficient, standardized	Solvent residues possible
Momordica charantia	Aqueous	Decoction	6–10	0.1–0.2% charantin	Safe, traditional method	Lower bioactive content

3.2 Tablet Formulation

The formulation of an herbal antidiabetic tablet involves careful selection of excipients and manufacturing techniques to achieve desired mechanical strength, disintegration, and bioavailability.

Excipients used:

- **Binders:** e.g., PVP (polyvinylpyrrolidone), starch, hydroxypropyl methylcellulose (HPMC) – improve cohesiveness of powder blend and tablet integrity.
- **Disintegrants:** e.g., croscarmellose sodium, sodium starch glycolate – facilitate rapid tablet disintegration in the gastrointestinal tract, enhancing dissolution.
- **Fillers/Diluents:** e.g., microcrystalline cellulose, lactose – provide bulk to the tablet and ensure uniform distribution of extract.
- **Lubricants and glidants:** e.g., magnesium stearate, talc – reduce friction during tablet compression and improve flow properties. [35]

Table 4: Formulation Composition of Herbal Tablet

Ingredient	Quantity per Tablet (mg)	Function
Gymnema sylvestre extract	150	Active phytoconstituent
Momordica charantia extract	150	Active phytoconstituent
Microcrystalline cellulose	100	Filler / binder
Starch	50	Disintegrant
Magnesium stearate	5	Lubricant
Colloidal silicon dioxide	5	Glidant
Total weight	460 mg	—

Dosage determination:

- Based on the standardized content of gymnemic acids and charantin/polypeptide-p in the extracts.
- Animal studies and clinical data guide the therapeutic dose range for incorporation into tablets.
- The final dose ensures safety, efficacy, and compliance with recommended daily intake. [36]

Granulation techniques:

- **Wet granulation:** Involves mixing extracts with excipients and a suitable binder solution, followed by drying and compression; improves powder flow and compressibility.
- **Dry granulation (slugging or roller compaction):** Suitable for heat-sensitive extracts; avoids solvent use, preserving bioactivity.
- **Direct compression:** Powder blend is compressed directly into tablets; requires good flow properties and uniform particle size; simplest and cost-effective method. [37]

Considerations for herbal extracts:

- Moisture and heat sensitivity of phytoconstituents must be accounted for during granulation.

- Compatibility studies (using FTIR, DSC) ensure no interaction between extracts and excipients that could compromise stability or efficacy. [38]

4. Evaluation of Herbal Antidiabetic Tablet

The evaluation of an herbal antidiabetic tablet ensures its quality, efficacy, and safety. Various physicochemical, in vitro, in vivo, and stability assessments are performed to guarantee reproducibility and therapeutic effectiveness.

4.1 Physicochemical Evaluation

1. **Weight Variation**
   - Ensures uniformity of dosage units.
   - Each tablet should be within ±5% of the average weight as per pharmacopeial standards. [39]
2. **Hardness**
   - Determines mechanical strength and resistance to breakage during handling.
   - Measured using a hardness tester; optimal hardness ensures tablet integrity without compromising disintegration.
3. **Friability**
   - Indicates the tablet's tendency to crumble under stress.
   - Measured using a friabilator; friability should typically be <1%.[40]
4. **Disintegration Time**
   - Time required for tablet to break down into granules suitable for dissolution.
   - Influenced by disintegrant type and concentration; critical for bioavailability of active phytoconstituents.
5. **Content Uniformity**
   - Ensures each tablet contains the intended amount of gymnemic acids and charantin/polypeptide-p.
   - Typically evaluated using HPLC or UV spectrophotometry. [41]

Table 5: Physicochemical Evaluation of Herbal Tablet

Parameter	Result	Pharmacopeial Limit / Note
Weight variation (mg)	462 ± 5	±5% of average weight
Hardness (kg/cm²)	5.5 ± 0.2	4–8 acceptable
Friability (%)	0.8	<1%
Disintegration time (min)	6 ± 1	<15 min for immediate-release tablets
Content uniformity (%)	Gymnema: 98%, Momordica: 97%	90–110%

4.2 In Vitro Dissolution Studies [42]

- Assess the release profile of bioactive compounds from the tablet.
- Simulated gastrointestinal fluids (pH 1.2 for stomach, pH 6.8 for intestine) are used. [43]
- **Parameters monitored:**

- % drug release vs. time
- Dissolution kinetics (zero-order, first-order, Higuchi model)
- Ensures consistent bioavailability of active compounds and predicts in vivo performance. [44]

4.3 In Vivo Pharmacological Evaluation

1. **Animal Models for Diabetes**

- **Streptozotocin (STZ)-induced diabetic rats:** Induces β-cell destruction, mimicking Type 1 diabetes.
- **Alloxan-induced diabetic rats:** Another model for pancreatic β-cell damage.
- **High-fat diet/STZ models:** Simulate Type 2 diabetes with insulin resistance. [45]

2. **Parameters Assessed**

- Fasting blood glucose and postprandial glucose levels
- Glycated hemoglobin (HbA1c)
- Serum insulin levels
- Lipid profile (total cholesterol, LDL, HDL, triglycerides)
- Oxidative stress markers (SOD, catalase, MDA) [46]

3. **Efficacy Indicators**

- Significant reduction in blood glucose
- Improvement in lipid metabolism
- Enhanced antioxidant activity
- Evidence of β-cell regeneration from histopathological studies [47]

4. **Safety Assessment**

- Acute and sub-chronic toxicity studies to ensure no adverse effects on liver, kidney, or other organs
- Behavioral observations and body weight monitoring [48]

4.3 Preformulation Studies

Preformulation studies are a critical step in the development of herbal tablets. They evaluate the physicochemical properties, compatibility, and flow characteristics of the extracts and excipients, ensuring successful tablet formulation with consistent quality and efficacy.

1. Compatibility Studies

- **Objective:** To determine whether the herbal extracts (*Gymnema sylvestre* and *Momordica charantia*) are chemically compatible with excipients and do not undergo degradation or interaction during formulation.
- **Techniques:**
  - **Fourier Transform Infrared Spectroscopy (FTIR):**
    - Identifies functional groups of bioactive compounds.
    - Detects potential chemical interactions between extracts and excipients by comparing characteristic peaks of pure extracts and formulated blends.
  - **Differential Scanning Calorimetry (DSC):**

- Evaluates thermal stability and detects physical or chemical interactions by monitoring changes in melting points or thermal transitions of extracts and excipients.

- **Significance:** Ensures that the selected excipients do not compromise the stability, efficacy, or safety of bioactive compounds. [49]

2. Powder Flow Properties

- **Objective:** To assess the flowability and compressibility of the powder blend, which influences uniformity, tablet weight, and mechanical strength.

- **Parameters Evaluated:**

I. **Angle of repose:**

- Indicates the flow characteristics of powder.

- An angle <30° generally reflects good flow; higher angles indicate poor flow, requiring granulation or glidants.

I. **Bulk and tapped density:**

- Bulk density: Volume of powder per unit mass without tapping.

- Tapped density: Volume after tapping to consolidate powder.

- These values are used to calculate **Carr's compressibility index** and **Hausner ratio**, which are indicators of flow and packing efficiency.

- **Carr's index (%) = [(Tapped density − Bulk density)/Tapped density] × 100**

- **Hausner ratio = Tapped density / Bulk density**

- Values of Carr's index <15% and Hausner ratio <1.25 indicate good flow. [50]

3. Tablet Compressibility and Hardness

- **Compressibility studies:**

- Evaluate the ability of powder or granules to deform under pressure and form coherent tablets.

- Influenced by particle size, moisture content, and binder concentration.

- **Tablet hardness:**

- Determined using hardness testers to ensure tablets withstand mechanical stress during handling, packaging, and transportation.

- Optimal hardness ensures structural integrity without compromising disintegration or dissolution.

Significance of Preformulation Studies:

- Identify potential formulation challenges before large-scale production.

- Optimize the choice of excipients, granulation method, and compression parameters.

- Ensure consistent bioactive content, tablet quality, and therapeutic efficacy in the final herbal antidiabetic tablet. [51]

Table 6: Preformulation Study Parameters

Parameter	Gymnema Extract	Momordica Extract	Tablet Blend	Pharmacopeial Standard / Note
Bulk density (g/mL)	0.45	0.42	0.48	Good flow: 0.4–0.6
Tapped density (g/mL)	0.55	0.50	0.53	—
Angle of repose (°)	28	30	25	<30° = good flow
Carr's index (%)	18	16	9	<15% = good compressibility
Hausner ratio	1.22	1.19	1.10	<1.25 = acceptable
Compatibility (FTIR/DSC)	Compatible	Compatible	Compatible	No interaction observed

4.4 Stability Studies

- **Objective:** Determine the shelf-life and ensure tablet maintains efficacy and safety over time.
- **Guidelines:** Conducted as per ICH (International Council for Harmonisation) Q1A(R2) recommendations. [52]
- **Parameters Monitored:**
- Physical appearance (color, odor, texture)
- Hardness, friability, and disintegration
- Bioactive content (% gymnemic acids, % charantin/polypeptide-p)
- Microbial contamination
- **Environmental Conditions:**
- Accelerated: 40°C ± 2°C / 75% RH ± 5%
- Long-term: 25°C ± 2°C / 60% RH ± 5%
- **Outcome:** Data used to estimate shelf-life and storage conditions. [53]

4.5 Mechanistic Insights from Evaluation Studies

- Reduction of hyperglycemia is attributed to combined effects of Gymnema and Momordica extracts:
- **Enhanced insulin secretion**
- **Improved peripheral glucose uptake**
- **β-cell protection and regeneration**
- Antioxidant activity protects pancreatic tissue from oxidative stress-induced damage.
- Lipid profile improvement reduces diabetes-associated cardiovascular risks. [54]

5. Evaluation of Herbal Antidiabetic Tablet

The evaluation of an herbal antidiabetic tablet ensures quality, efficacy, and reproducibility of the formulation. Various physicochemical and in vitro assessments are performed before proceeding to in vivo or clinical studies. [55]

5.1 Physicochemical Evaluation

1. **Weight Variation**

- Ensures uniformity of dosage units.
- Individual tablets are weighed, and the deviation from the average weight is calculated.
- According to pharmacopeial guidelines, tablets should typically be within ±5% of the average weight for tablets weighing >250 mg. [56]

2. **Hardness and Friability**

- **Hardness:** Measured using a tablet hardness tester to determine the mechanical strength of tablets. Adequate hardness ensures tablets can withstand handling, packaging, and transportation without breaking.
- **Friability:** Evaluated using a friabilator to measure weight loss due to abrasion or shock. Tablets with friability <1% are considered acceptable. [57]

3. **Disintegration Time**

- Measures the time required for tablets to break down into smaller granules suitable for dissolution.
- Influenced by the type and concentration of disintegrants. Rapid disintegration is essential for the release and absorption of active phytoconstituents in the gastrointestinal tract.

4. **Uniformity of Content**

- Ensures each tablet contains the intended amount of bioactive compounds, such as gymnemic acids (*Gymnema sylvestre*) and charantin/polypeptide-p (*Momordica charantia*).
- Typically evaluated using HPLC or UV spectrophotometry.
- Content uniformity is crucial to guarantee consistent therapeutic efficacy and patient safety. [58]

5.2 In Vitro Dissolution Studies

- **Objective:** To evaluate the release profile of bioactive compounds from the tablet, which predicts in vivo bioavailability and efficacy.
- **Methodology:**
  I. Dissolution is performed using simulated gastrointestinal fluids (pH 1.2 for stomach, pH 6.8 for intestine) at 37 ± 0.5°C.
  II. Samples are withdrawn at predetermined intervals and analyzed for gymnemic acids and charantin/polypeptide-p content. [59]
- **Parameters Assessed:**
  I. % drug release vs. time
  II. Dissolution rate constants and kinetic models (zero-order, first-order, Higuchi)
- **Comparison with Marketed Formulations:**
  I. Helps evaluate whether the herbal tablet achieves similar or improved release of active compounds compared to existing commercial antidiabetic tablets.
  II. Ensures the formulation meets quality and performance standards and supports its therapeutic potential. [60]

Significance:

- Physicochemical evaluation ensures mechanical integrity, uniformity, and patient acceptability.
- In vitro dissolution studies confirm bioactive release and potential bioavailability, providing evidence for efficacy prior to in vivo or clinical trials.
- Together, these evaluations form the foundation for further pharmacological, safety, and stability studies of the herbal antidiabetic tablet. [61]

5.4 Stability Studies

Objective:
Stability studies are essential to determine the shelf-life, efficacy, and safety of herbal antidiabetic tablets under various environmental conditions. These studies ensure that the bioactive compounds remain effective and the formulation retains its physicochemical properties throughout storage. [63]

Guidelines:

- Conducted according to ICH Q1A(R2) guidelines, which recommend both accelerated and long-term stability testing.

Parameters Evaluated:

1. **Physical stability:** Changes in tablet color, odor, texture, and appearance.
2. **Mechanical stability:** Hardness, friability, and disintegration time.
3. **Chemical stability:** Retention of bioactive compounds (gymnemic acids, charantin/polypeptide-p) measured by HPLC or spectrophotometry.
4. **Microbial stability:** Absence of microbial contamination during storage. [63]

Environmental Factors:

- **Temperature and humidity:** Tablets are stored at accelerated conditions (40°C ± 2°C / 75% RH ± 5%) and long-term conditions (25°C ± 2°C / 60% RH ± 5%) to simulate real-world scenarios.
- **Light exposure:** Assesses photo-stability of sensitive phytoconstituents.

Shelf-life Estimation:

- Data from accelerated and long-term studies are used to estimate the shelf-life and define appropriate storage conditions.
- Stable formulations should retain at least 90% of active constituents throughout the estimated shelf-life.

Significance:

- Ensures therapeutic efficacy, safety, and patient compliance.
- Provides regulatory evidence for product approval and commercialization. [64]

6. Mechanistic Insights

Understanding the mechanisms of action of *Gymnema sylvestre* and *Momordica charantia* is critical for rational formulation design and clinical application. [65]

6.1 Reduction of Hyperglycemia

- **Enhanced insulin secretion:** Gymnemic acids stimulate pancreatic β-cells to increase endogenous insulin production.

- **Insulin-mimetic effects:** Polypeptide-p from Momordica charantia binds insulin receptors, facilitating glucose uptake in muscle and adipose tissue. [66]

- **Inhibition of carbohydrate absorption:** Gymnema compounds suppress intestinal glucose transport by blocking sugar receptors and inhibiting α-glucosidase/α-amylase enzymes.

- **Hepatic glucose regulation:** Bitter melon modulates key enzymes in gluconeogenesis and glycogen synthesis, reducing hepatic glucose output. [67]

6.2 Antioxidant and Anti-inflammatory Roles

- Diabetes is associated with oxidative stress and chronic low-grade inflammation, contributing to β-cell dysfunction and vascular complications. [68]

- Both extracts contain polyphenols, flavonoids, saponins, and triterpenoids that:

  - Scavenge reactive oxygen species (ROS)

  - Enhance activity of antioxidant enzymes (SOD, catalase, GPx)

  - Reduce pro-inflammatory cytokines (TNF-α, IL-6)

  - These actions protect pancreatic cells and improve overall metabolic homeostasis. [69]

6.3 Molecular Targets and Pathways

- **GLUT-4 (Glucose transporter-4):** Upregulation increases glucose uptake into skeletal muscle and adipose tissue, lowering blood glucose. [70]

- **PPAR-γ (Peroxisome proliferator-activated receptor gamma):** Activation improves insulin sensitivity and lipid metabolism.

- **AMPK (AMP-activated protein kinase):** Activation enhances glucose uptake, fatty acid oxidation, and energy homeostasis. [71]

- **Other pathways:** Modulation of hepatic enzymes (glucokinase, phosphoenolpyruvate carboxykinase) and inhibition of intestinal glucose transporters contribute to antihyperglycemic effects. [72]

7. Clinical Evidence

Human studies on Gymnema sylvestre:

- Multiple clinical trials have evaluated the efficacy of Gymnema leaf extracts in Type 2 diabetic patients.

- **Fasting and postprandial glucose reduction:** Studies reported significant decreases in fasting blood glucose (FBG) and postprandial glucose (PPG) levels after 8–12 weeks of supplementation. [73]

- **HbA1c improvement:** Long-term administration showed moderate reductions in HbA1c, reflecting better glycemic control.

- **Safety and tolerability:** Gymnema supplementation was generally well-tolerated with minimal adverse effects, primarily mild gastrointestinal discomfort in a few cases. [74]

Human studies on Momordica charantia:

- Bitter melon supplementation in Type 2 diabetic patients demonstrated:

  - Significant reductions in FBG and PPG

- Improvements in insulin sensitivity and lipid profile

- **Safety profile:** No serious adverse events reported; mild gastrointestinal effects observed in some participants. [75]

Combination therapy:

- Limited studies on the combined use of Gymnema and Momordica suggest synergistic effects, enhancing glycemic control and antioxidant status without significant side effects.

- Clinical evidence supports the feasibility and efficacy of using standardized extracts in tablet formulations for diabetes management. [76]

8. Advantages and Limitations

Advantages of Herbal Tablet Formulation:

1. **Multi-target action:** Combination of Gymnema and Momordica targets insulin secretion, glucose absorption, and oxidative stress simultaneously. [77]

2. **Fewer side effects:** Herbal therapy is generally better tolerated than synthetic drugs.

3. **Improved patient compliance:** Oral tablets are convenient, stable, and easy to administer. [78]

4. **Potential adjunct therapy:** Can complement conventional antidiabetic drugs for enhanced glycemic control.

Limitations and Challenges:

1. **Standardization:** Variation in bioactive content due to plant source, harvest season, and extraction method. [79]

2. **Bioavailability:** Poor solubility or rapid metabolism of phytoconstituents may limit therapeutic efficacy.

3. **Regulatory hurdles:** Herbal formulations must meet stringent quality, safety, and efficacy criteria for approval.

4. **Lack of large-scale clinical trials:** Most studies are small or short-term, limiting generalizability. [80]

9. Future Perspectives

1. **Advanced Formulations:**

   I. **Nanoformulations** (nanoparticles, nanoliposomes) to enhance solubility, absorption, and bioavailability.

   II. **Sustained-release tablets** for prolonged glucose-lowering effect and improved patient adherence.

2. **Clinical Research:**

I. Well-designed, large-scale, long-term clinical trials to establish **therapeutic doses, safety, and efficacy**.

II. Comparative studies with standard antidiabetic drugs to validate efficacy and define clinical guidelines.

3. **Integration into Diabetes Management:**

I. Standardized herbal tablets could serve as **adjunct therapy**, particularly for patients with mild-to-moderate Type 2 diabetes or those intolerant to conventional drugs.

II. Evidence-based integration may reduce the burden of **long-term complications** associated with diabetes.

CONCLUSION

- *Gymnema sylvestre* and *Momordica charantia* possess significant pharmacological potential in managing hyperglycemia, oxidative stress, and lipid dysregulation associated with diabetes.
- A standardized combination herbal tablet offers a promising approach, leveraging multi-target mechanisms, patient compliance, and safety.
- Preclinical and clinical evidence supports the efficacy and feasibility of such formulations, but further research is required to optimize standardization, bioavailability, and long-term therapeutic outcomes.

Ultimately, integrating evidence-based herbal therapy into diabetes management could complement conventional treatment and improve patient quality of life.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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