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DEVELOPMENT OF A POLYHERBAL FORMULATION WITH ANTIOXIDANT AND HYPOGLYCEMIC PROPERTIES FOR DIABETES MANAGEMENT

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Abstract:

Persistent hyperglycemia, insulin resistance, increasing β-cell dysfunction, and problems brought on by oxidative stress are the hallmarks of diabetes mellitus, a chronic metabolic disease. Despite the availability of a number of synthetic antidiabetic medications, their long-term usage is frequently restricted by side effects and insufficient defense against oxidative damage. Derived from traditional medical systems, polyherbal preparations create synergistic hypoglycemic, antioxidant, and anti-inflammatory benefits by combining many therapeutic plants with complimentary processes. In addition to highlighting medicinal plants with proven antidiabetic potential and examining the role of oxidative stress in diabetes, this review also covers the scientific justification, creation, standardization, and assessment of polyherbal formulations. The available clinical evidence, safety, toxicity, herb-drug interactions, regulatory obstacles, and prospects for incorporating polyherbal formulations into conventional diabetic treatment are all rigorously examined.

Keywords:

Diabetes mellitus; Polyherbal formulation; Antioxidant activity; Hypoglycemic activity; Oxidative stress; Medicinal plants; Antidiabetic therapy

1. Introduction

Chronic hyperglycemia brought on by decreased insulin production, insulin resistance, or both is a hallmark of diabetes mellitus, a multifactorial metabolic disease. The International Diabetes Federation estimates that 537 million adults worldwide had diabetes in 2021; by 2030, that number is expected to increase to 643 million, with type 2 diabetes mellitus making up about 90% of cases (International Diabetes Federation, 2021). Reactive oxygen species (ROS) are produced in excess by persistent hyperglycemia, which causes oxidative stress, low-grade inflammation, endothelial dysfunction, and gradual cellular damage. Both macrovascular problems like cardiovascular disease and microvascular problems like nephropathy, neuropathy, and retinopathy are caused by these pathophysiological pathways (Giacco & Brownlee, 2010).

Although there are many classes of synthetic antidiabetic drugs available, such as biguanides, sulfonylureas, DPP-4 inhibitors, and SGLT2 inhibitors, long-term treatment is frequently constrained by side effects like hypoglycemia, gastrointestinal problems, weight gain, and insufficient defense against complications caused by oxidative stress. Furthermore, the complicated and progressive character of diabetes, which involves numerous interrelated molecular pathways, may not be adequately addressed by monotherapy focusing on a single metabolic pathway (DeFronzo et al., 2015). Due to these restrictions, interest in complementary and alternative therapy strategies that can simultaneously modulate several targets has increased.

Because they contain a variety of bioactive phytochemicals, such as flavonoids, phenolic acids, alkaloids, saponins, and terpenoids, medicinal plants have long been utilized in traditional medical systems to control diabetes. By increasing insulin secretion, increasing insulin sensitivity, inhibiting enzymes that break down carbohydrates, modifying glucose transporters, and reducing oxidative stress and inflammation, these substances have antidiabetic effects (Mukherjee et al., 2006). A key component of Ayurveda is the polyherbal formulation approach, which is based on synergism—the combination of herbs having complimentary pharmacological activities to maximize therapeutic efficacy while reducing toxicity. Therefore, a promising multitargeted strategy for all-encompassing diabetes control is represented by polyherbal formulations with combination hypoglycemic and antioxidant qualities. The development and assessment of polyherbal formulations, their safety and clinical evidence, the

pharmacological justification of antidiabetic medicinal plants, the role of oxidative stress in diabetes, and future prospects for their integration into standard diabetes care are all critically examined in this review.

2. Diabetes Mellitus: Pathophysiology and Therapeutic Targets

2.1 Classification of diabetes (Type 1, Type 2, Gestational)

Hyperglycemia brought on by decreased insulin secretion, action, or both is a hallmark of diabetes mellitus, a chronic metabolic disease. The American Diabetes Association and the World Health Organization describe it as type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (American Diabetes Association, 2024; World Health Organization, 2019).

While most cases of diabetes are caused by T2DM, which is characterized by insulin resistance and relative insulin deficit, T1DM is caused by autoimmune death of pancreatic β-cells, resulting in absolute insulin deficiency (Atkinson et al., 2014; DeFronzo et al., 2015). GDM, or glucose intolerance initially identified during pregnancy, is linked to a higher chance of developing type 2 diabetes in the future for both the mother and the unborn child (Plows et al., 2018). These different categories highlight important therapeutic goals include lowering oxidative stress, maintaining β-cell function, and improving insulin sensitivity.

2.2 Role of Insulin Resistance and β-Cell Dysfunction

Type 2 diabetes mellitus is primarily caused by insulin resistance and pancreatic β-cell malfunction. Initially, compensatory hyperinsulinemia is caused by decreased insulin responsiveness in peripheral tissues, which reduces glucose absorption and increases hepatic glucose output. However, long-term metabolic stress causes β-cell malfunction, fatigue, and apoptosis, which leads to persistent hyperglycemia (DeFronzo et al., 2015; Prentki & Nolan, 2006). The necessity for treatments that improve insulin sensitivity while maintaining β-cell function is highlighted by the fact that this process is made worse by glucotoxicity, lipotoxicity, and oxidative stress, resulting in a vicious cycle of growing insulin resistance and β-cell failure (Weir & Bonner-Weir, 2004).

2.3 Oxidative Stress, Inflammation, and Metabolic Dysregulation

The pathophysiology of diabetes and its consequences is significantly influenced by oxidative stress. Through glucose autoxidation, mitochondrial dysfunction, and the activation of the polyol and hexosamine pathways, chronic hyperglycemia increases the production of reactive oxygen species (ROS). Insulin resistance and β-cell dysfunction are caused by oxidative damage to lipids, proteins, and DNA, which results from an imbalance between ROS generation and antioxidant defenses (Brownlee, 2005; Evans et al., 2002).

Insulin signaling pathways are further disrupted by low-grade chronic inflammation, which is characterized by increased pro-inflammatory cytokines such TNF-α, IL-6, and CRP. These pathways are crucial targets for antioxidant-based therapeutic approaches because oxidative stress, inflammation, and metabolic dysregulation interact to hasten the onset of hyperglycemia and exacerbate diabetic consequences (Hotamisligil, 2006).

2.4 Key Molecular Targets for Hypoglycemic and Antioxidant Therapy

Carbohydrate-digesting enzymes (α-amylase and α-glucosidase), insulin signaling regulators like AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPARs), and glucose transporters (GLUT4) involved in cellular glucose uptake are among the molecular targets essential to successful hypoglycemic and antioxidant therapy in diabetes (Zhang et al., 2009; Hardie, 2014). Glycemic management and insulin sensitivity are enhanced by altering these pathways. The goal of antioxidant methods is to reduce the production of reactive oxygen species while boosting natural defense mechanisms including glutathione peroxidase, catalase, and superoxide dismutase. Flavonoid, phenolic, and alkaloid-rich polyherbal formulations can concurrently reduce inflammation, oxidative stress, and hyperglycemia, offering a multitargeted strategy for all-encompassing diabetes care (Maritim et al., 2003; Alam et al., 2013).

3. Role of Oxidative Stress in Diabetes and Its Complications

3.1 Sources of Reactive Oxygen Species (ROS) in Diabetes

One of the main causes of increased reactive oxygen species (ROS) production in diabetes is chronic hyperglycemia. Superoxide overproduction results from increased mitochondrial electron transport chain activity caused by elevated glucose levels, and ROS generation is further amplified by activation of pathways like polyol flux, protein kinase C (PKC), advanced

glycation end-product (AGE) formation, and glucose autoxidation (Brownlee, 2005; Evans et al., 2002). Because of their intrinsic low antioxidant capacity, pancreatic β-cells are especially susceptible to oxidative injury.

3.2 Antioxidant Defense Mechanisms

In addition to non-enzymatic antioxidants like glutathione, vitamins C and E, and polyphenols, the body's antioxidant defense system also consists of enzymatic antioxidants like superoxide dismutase, catalase, and glutathione peroxidase. Persistent oxidative stress overwhelms these defense mechanisms in diabetes, leading to decreased insulin signaling and cellular damage (Maritim et al., 2003). Therefore, improving antioxidant capacity is a crucial therapeutic approach to reduce oxidative damage linked to diabetes.

3.3 Link Between Oxidative Stress and Diabetic Complications

The development of both microvascular and macrovascular diabetic problems is united by oxidative stress. Excess ROS contributes to progressive tissue damage in several organs by triggering inflammatory pathways, endothelial dysfunction, and cellular death (Brownlee, 2005).

3.3.1 Diabetic Neuropathy

Oxidative stress impairs blood flow and causes neuronal death in peripheral nerves in diabetic neuropathy. Nerve conduction problems and sensory loss are caused by ROS-mediated activation of inflammatory cascades and mitochondrial dysfunction (Vincent et al., 2011).

3.3.2 Diabetic Nephropathy

By encouraging glomerular hypertrophy, mesangial enlargement, and extracellular matrix buildup, oxidative stress hastens the development of diabetic nephropathy. Renal fibrosis and loss of kidney function are caused by ROS-induced activation of inflammatory mediators and transforming growth factor-β (TGF-β) (Forbes & Cooper, 2013).

3.3.3 Diabetic Retinopathy

Oxidative stress increases vascular permeability, damages microvascular integrity, and encourages retinal cell death in the retina. In diabetic retinopathy, mitochondrial ROS and AGE buildup are major causes of retinal neurovascular injury (Kowluru & Chan, 2007).

3.3.4 Cardiovascular Complications

Because it causes endothelial dysfunction, lipid peroxidation, and atherosclerosis, oxidative stress plays a key role in the development of cardiovascular problems in diabetes. Chronic inflammation and decreased nitric oxide bioavailability worsen vascular damage and raise the risk of stroke and coronary artery disease (Giacco & Brownlee, 2010).

4. Herbal Medicines in Diabetes Management

4.1 Historical and Traditional Use of Medicinal Plants

Long before the development of contemporary pharmacology, medicinal herbs were essential to the treatment of diabetes. Ayurveda, Traditional Chinese Medicine (TCM), Unani, and Siddha are examples of traditional medicinal systems that describe illnesses similar to diabetes (such as Madhumeha in Ayurveda) and provide plant-based treatments to manage excessive thirst, urination, and metabolic imbalance. Gymnema sylvestre, Momordica charantia, Trigonella foenum-graecum, and Syzygium cumini are examples of plants that have been widely utilized in traditional formulations and are still essential to ethnomedicine in Asia and Africa (Grover et al., 2002; Modak et al., 2007). The identification of bioactive phytoconstituents has been greatly aided by ethnopharmacological evidence, which has also given contemporary antidiabetic medication development a logical foundation.

4.2 Advantages of Herbal Therapy over Synthetic Drugs

Compared to traditional synthetic antidiabetic medications, herbal therapies have a number of advantages, especially when it comes to managing chronic illnesses. They frequently have multitargeted effects, influencing oxidative stress, inflammation, lipid homeostasis, and glucose metabolism all at once. In diabetes, a multifactorial condition involving intricate metabolic abnormalities, this pleiotropic aspect is particularly advantageous. Furthermore, when administered properly, herbal drugs are typically linked to greater long-term tolerability,

fewer side effects, and increased patient compliance (Patwardhan, 2005; Modak et al., 2007). Their therapeutic effectiveness is further enhanced by the presence of natural anti-inflammatory and antioxidant substances, which lower the risk of problems related to diabetes.

4.3 Challenges and Limitations of Herbal Medicines

Herbal remedies have therapeutic potential, but there are a number of drawbacks that prevent them from being widely used in clinical settings. Efficacy and reproducibility may be impacted by variations in phytochemical composition brought on by variations in plant species, geographic origin, harvesting circumstances, and extraction techniques. Their integration into evidence-based therapy is further hampered by a lack of standardization, inadequate dose optimization, and a dearth of large-scale clinical trials. Furthermore, strict quality control and regulatory frameworks are required due to concerns about adulteration, contamination, and herb-drug interactions (Ekor, 2014; Heinrich et al., 2020).

4.4 Mechanisms of Antidiabetic Action of Medicinal Plants

Through a variety of complimentary mechanisms, medicinal plants target underlying pathophysiological processes as well as glycemic control to produce antidiabetic benefits.

4.4.1 Insulin Secretion and Sensitization

By improving pancreatic β-cell activity or shielding β-cells from oxidative damage, a number of plant-derived substances increase insulin output. Others decrease peripheral insulin resistance and alter insulin receptor signaling pathways to increase insulin sensitivity. Flavonoids, terpenoids, and alkaloids are examples of phytochemicals that have been shown to improve insulin action and maintain β-cell integrity (Prabhakar & Doble, 2011).

4.4.2 Inhibition of Carbohydrate-Digesting Enzymes

One well-known way that medicinal plants lower postprandial hyperglycemia is by inhibiting intestinal α-amylase and α-glucosidase. Similar to synthetic enzyme inhibitors but with fewer gastrointestinal adverse effects, a variety of plant extracts and isolated phytoconstituents slow the digestion of carbohydrates and the absorption of glucose (Tundis et al., 2010).

4.4.3 Glucose Uptake Enhancement

By encouraging GLUT4 translocation in skeletal muscle and adipose tissue, some medicinal herbs improve peripheral glucose absorption. Insulin resistance can be decreased by enhancing glucose utilization and energy homeostasis through the activation of AMP-activated protein kinase (AMPK) and associated metabolic pathways (Zhang et al., 2009).

4.4.4 Antioxidant and Anti-inflammatory Effects

Insulin resistance and consequences from diabetes are largely caused by oxidative damage and persistent low-grade inflammation. Polyphenols, flavonoids, and phenolic acids found in medicinal plants improve endogenous antioxidant defenses, scavenge reactive oxygen species, and inhibit pro-inflammatory mediators including TNF-α and IL-6. These benefits shield tissues from the harm caused by diabetes and increase insulin sensitivity (Maritim et al., 2003; Giacco & Brownlee, 2010).

5. Concept of Polyherbal Formulation

5.1 Principle of Polyherbalism and Synergism

Traditional medical systems, especially Ayurveda, which emphasizes combining several medicinal plants to achieve increased therapeutic efficacy and less toxicity, are the foundation of the notion of polyherbalism. This idea states that each herb in a formulation works in concert with the others to provide a stronger pharmacological impact than if they were administered separately. Bioactive phytoconstituents can work in concert to improve bioavailability, efficacy, and safety through additive, potentiating, or complementing effects (Patwardhan et al., 2005; Wagner, 2011). Due to the multifactorial character of diabetes, which includes inflammation, oxidative stress, insulin resistance, and hyperglycemia, polyherbal formulations are particularly pertinent.

5.2 Scientific Basis of Herb–Herb Interactions

Modern pharmacology and systems biology are increasingly being used to explain herb-herb interactions in polyherbal compositions. Improved therapeutic results may result from the action of many phytochemicals on different molecular targets. For example, whereas one herb may increase insulin secretion, another may enhance insulin sensitivity or provide antioxidant defense. By improving the absorption, distribution, or metabolic stability of active ingredients,

these interactions may also have an impact on pharmacokinetics (Williamson, 2001; Wagner & Ulrich-Merzenich, 2009).

5.3 Advantages of Polyherbal Formulations in Diabetes

When it comes to managing diabetes, polyherbal formulations have several advantages than monoherbal or synthetic medicines. They simultaneously target a variety of disease processes, including oxidative stress, inflammation, dyslipidemia, and altered glucose metabolism. Individual herbs are appropriate for long-term usage when used in lower doses that retain efficacy while lowering the risk of toxicity (Patwardhan, 2005; Parasuraman et al., 2014).

5.4 Traditional Polyherbal Formulations Used in Diabetes

Ayurveda and other medical systems have used a number of traditional polyherbal mixtures to treat diabetes. In both experimental and clinical investigations, traditional formulations like Ayush-82, Triphala, and Nishamalaki (Curcuma longa and Emblica officinalis) have shown antidiabetic, antioxidant, and lipid-lowering benefits (Modak et al., 2007; Parasuraman et al., 2014).

6. Medicinal Plants with Antioxidant and Hypoglycemic Properties

6.1 Gymnema sylvestre

One of the most researched medicinal herbs with antidiabetic properties is *Gymnema sylvestre*. Its bioactive components, especially gymnemic acids, are known to promote insulin production by regenerating pancreatic β-cells and inhibit intestinal glucose absorption. *G. sylvestre* treatment has been shown to significantly lower fasting blood glucose and HbA1c levels in both experimental and clinical investigations. Furthermore, its antioxidant activity contributes to long-term glycemic control by shielding β-cells from oxidative stress-induced damage (Shanmugasundaram et al., 1990; Persaud et al., 1999).

6.2 Momordica charantia

Compounds like vicine, polypeptide-p, and charantin are responsible for the strong hypoglycemia effects of *Momordica charantia*, or bitter melon. These components promote insulin secretion, improve peripheral glucose consumption, and prevent gluconeogenesis. By scavenging free radicals and lowering lipid peroxidation, the plant also exhibits potent

antioxidant qualities, enhancing insulin sensitivity and averting problems associated with diabetes (Joseph & Jini, 2013; Grover & Yadav, 2004).

6.3 Trigonella foenum-graecum

The alkaloid trigonelline, saponins, and soluble fiber found in fenugreek seeds all work together to increase insulin sensitivity and postpone the absorption of glucose. In particular, the amino acid 4-hydroxyisoleucine increases insulin secretion that is dependent on glucose. Additionally, fenugreek has antioxidant properties that improve lipid metabolism in diabetes circumstances and lower oxidative stress indicators (Basch et al., 2003; Hannan et al., 2007).

6.4 Tinospora cordifolia

In Ayurveda, *Tinospora cordifolia* is frequently used to treat metabolic conditions. Its bioactive substances, including as alkaloids and diterpenoid lactones, increase glucose absorption and insulin sensitivity to produce hypoglycemic effects. The plant has strong immunomodulatory and antioxidant qualities that lower inflammation and oxidative stress linked to diabetes and its consequences (Saha & Ghosh, 2012; Stanely Mainzen Prince & Menon, 2003).

6.5 Syzygium cumini

Because Syzygium cumini (Jamun) seeds can reduce α-glucosidase activity and regulate insulin production, they have long been used to treat diabetes. The plant, which is high in flavonoids, anthocyanins, and ellagic acid, has potent antioxidant properties that improve glycemic control in experimental models and shield pancreatic tissue from oxidative damage (Ayyanar & Subash-Babu, 2012).

6.6 Curcuma longa

Curcuma longa's main polyphenol, curcumin, improves insulin sensitivity, activates AMPK, and suppresses inflammatory pathways to show notable antidiabetic benefits. Its potent antioxidant properties slow the development of diabetes complications and lessen ROS-mediated β-cell dysfunction. Curcumin's function as a supplementary agent in the treatment of diabetes is supported by both preclinical and clinical research (Aggarwal & Harikumar, 2009; Panahi et al., 2017).

6.7 Withania somnifera

Ashwagandha, or *Withania somnifera,* has antidiabetic effects mainly due to its adaptogenic, antioxidant, and anti-inflammatory qualities. While antioxidant activity guards against oxidative damage in diabetic tissues, withanolides enhance insulin sensitivity and lower stress-induced hyperglycemia. It is an important part of polyherbal antidiabetic formulations due to its multitarget effects (Singh et al., 2011).

6.8 Other Promising Antidiabetic Herbs

Through various processes, a number of additional medicinal plants, such as Azadirachta indica, Emblica officinalis, Ocimum sanctum, Pterocarpus marsupium, and Allium sativum, have shown hypoglycemic and antioxidant properties. These plants support their inclusion in polyherbal formulations for all-encompassing diabetes care because they increase glucose metabolism, boost antioxidant defenses, and reduce inflammation (Grover et al., 2002; Modak et al., 2007).

Table 1. Key medicinal plants with antioxidant and hypoglycemic activities relevant to polyherbal diabetes management

Medicinal plant	Part used	Major bioactive constituents	Antidiabetic mechanisms	Antioxidant activity	Evidence type
Gymnema sylvestre	Leaves	Gymnemic acids	β-cell regeneration, insulin secretion	Free radical scavenging	In vitro, in vivo
Momordica charantia	Fruit	Charantin, polypeptide-p	Glucose uptake, enzyme inhibition	Lipid peroxidation inhibition	In vivo, clinical
Trigonella foenum-graecum	Seeds	Trigonelline, saponins	Insulin sensitization	ROS scavenging	In vivo
Curcuma longa	Rhizome	Curcumin	Anti-inflammatory, insulin sensitivity	Strong antioxidant	In vitro, in vivo
Syzygium cumini	Seeds	Anthocyanins	Enzyme inhibition	Reduces oxidative stress	In vivo

7. Development of Polyherbal Formulation

7.1 Selection Criteria of Medicinal Plants

A crucial step that integrates ethnopharmacological understanding with contemporary pharmacological validation is the selection of medicinal plants for polyherbal compositions. Plants are selected according to their safety profile, potential for complementary or synergistic effects, and established antidiabetic, antioxidant, and anti-inflammatory properties. For instance, the two main causes of diabetic problems, hyperglycemia and oxidative stress, can be addressed by mixing insulinotropic herbs (Gymnema sylvestre) with antioxidant-rich plants (Curcuma longa). To guarantee that the combination offers optimum performance without unfavorable interactions, bioavailability, dose compatibility, and chemical stability of the plant extracts are also taken into account (Patwardhan et al., 2005; Parasuraman et al., 2014).

7.2 Collection, Authentication, and Processing of Plant Materials

To guarantee repeatable quality, medicinal plants should be gathered in accordance with good agriculture and collection methods (GACP). To avoid adulteration, accurate botanical identification using microscopic, molecular, and morphological methods is crucial. In order to retain active phytoconstituents, post-harvest processing entails cleaning, regulated low-temperature drying or shade drying, and then pulverization into coarse or fine powders. These procedures guarantee consistent particle size for reliable extraction efficiency while lowering microbiological contamination. For substances that are susceptible to oxidation or heat, certain formulations also use defatting or pre-extraction procedures (World Health Organization, 2007; Mukherjee, 2019).

7.3 Extraction Methods and Standardization

The polarity and stability of bioactive substances are taken into consideration while selecting extraction techniques. Maceration, percolation, and Soxhlet extraction are examples of conventional procedures; ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and supercritical fluid extraction are examples of contemporary approaches. Determining the total phenolic content, flavonoid content, and quantitative measurement of marker chemicals are all part of standardization, which is essential to guaranteeing batch-to-batch uniformity. The polyherbal extracts are fingerprinted using chromatographic methods

such as HPTLC, HPLC, and GC–MS, which are utilized as quality control instruments for repeatability and regulatory compliance (Kunle et al., 2012; Mukherjee, 2019).

7.4 Formulation Strategies (Powder, Tablet, Capsule, Liquid)

To improve patient compliance and therapeutic efficacy, polyherbal formulations can be created in a variety of dose forms. Although powder formulations are straightforward and retain phytochemicals, they could taste bad. Accurate dosage, improved stability, and controlled release characteristics are offered by tablets and capsules. In pediatric or elderly populations, liquid extracts or syrups are frequently favored due to their quick absorption. To preserve phytochemical stability, solubility, and bioavailability, excipient selection (binders, diluents, and disintegrants) is improved. To enhance the solubility, absorption, and controlled release of bioactive substances, novel delivery methods including microencapsulation and nanoformulations are also being investigated more and more (Aulton & Taylor, 2018; Mukherjee, 2019).

7.5 Quality Control Parameters

The safety, effectiveness, and repeatability of polyherbal compositions are guaranteed by quality control. Microbial load determination, physicochemical analysis (moisture content, ash value, extractive value), and organoleptic evaluation (color, odor, taste) are some of the parameters. Marker-based standardization, which uses HPLC or HPTLC to quantify recognized bioactive chemicals (such as gymnemic acid, curcumin, and trigonelline), is used in modern quality control. Pesticide residue screening and heavy metal analysis (lead, arsenic, and cadmium) guarantee food safety. In order to comply with national and international regulatory norms, these actions are essential (Kunle et al., 2012; Mukherjee, 2019).

7.6 Stability Studies

Stability studies evaluate how the formulation's physical, chemical, and pharmacological characteristics are affected by environmental elements such light, humidity, and temperature. To ascertain shelf life and ideal storage conditions, accelerated stability experiments (e.g., 40°C ± 2°C, 75% ± 5% RH for 6 months) and long-term stability studies are carried out in accordance with ICH Q1A(R2) criteria. Appearance, pH, moisture content, bioactive content, and in vitro pharmacological activity are important factors that are tracked. Because several

phytochemicals may interact to impact potency and safety, stability is especially crucial for polyherbal formulations (ICH, 2003; Mukherjee, 2019).

8. Evaluation of Antioxidant Activity

A major factor in the development, course, and consequences of diabetes is oxidative stress. Several phytochemicals with strong antioxidant properties, including polyphenols, flavonoids, terpenoids, and alkaloids, are frequently found in polyherbal preparations. In vitro chemical tests, cellular research, in vivo animal or human investigations, and indicators of oxidative stress are all used to assess antioxidant function.

8.1 In Vitro Antioxidant Assays

In vitro tests are quick, economical, and appropriate for preliminary screening of formulations or extracts. They evaluate the phytochemicals' power to reduce, scavenge free radicals, and chelate metals.

8.1.1 DPPH Assay

The DPPH (2,2-diphenyl-1-picrylhydrazyl) assay evaluates antioxidants' ability to neutralize the stable DPPH radical by donating hydrogen or electrons. Radical scavenging activity is indicated by a decrease in absorbance at 517 nm, which can be measured as IC_{50} (the concentration needed to scavenge 50% of DPPH radicals). For instance, Gymnema sylvestre had high scavenging activity at comparable concentrations, and Curcuma longa extract demonstrated IC_{50} values of 35–50 µg/mL, indicating the efficacy of polyherbal combinations (Brand-Williams et al., 1995; Aggarwal & Harikumar, 2009).

8.1.2 ABTS Assay

When antioxidants neutralize the $ABTS^{+}$ radical cations produced during the ABTS experiment, the absorbance at 734 nm decreases. This test is perfect for complicated polyherbal extracts that contain several phytochemical classes since it may be used with both hydrophilic and lipophilic chemicals. Trolox equivalent antioxidant capacity (TEAC) is typically used to express ABTS results. For example, high TEAC values indicate synergistic antioxidant benefits in polyherbal mixes comprising Syzygium cumini, Momordica charantia, and Trigonella foenum-graecum (Re et al., 1999; Joseph & Jini, 2013).

8.1.3 FRAP Assay

The ability of antioxidants to decrease the Fe^{3+}–TPTZ combination to Fe^{2+}, generating a blue complex detected at 593 nm, is assessed by the FRAP (Ferric Reducing Antioxidant Power) experiment. This test enhances radical scavenging tests and sheds light on electron-donating capacity. Strong FRAP activity is often seen in polyherbal extracts high in polyphenols and flavonoids, which is correlated with in vivo protection against oxidative stress in diabetes animals (Benzie & Strain, 1996).

8.2 In Vivo Antioxidant Evaluation

In vivo models validate the biological relevance of antioxidant activity. Common models include:

- Streptozotocin (STZ)-induced diabetic rats: Mimics type 1 diabetes by destroying pancreatic β-cells.
- Alloxan-induced diabetic rats: Another model of β-cell toxicity and hyperglycemia.

Parameters measured include:

- Enzymatic antioxidants: Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx).
- Non-enzymatic antioxidants: Reduced glutathione (GSH), vitamin C, vitamin E.
- Lipid peroxidation markers: Malondialdehyde (MDA).

Research has demonstrated that in diabetic rats, polyherbal formulations containing Curcuma longa, Gymnema sylvestre, and Tinospora cordifolia dramatically increase antioxidant status, lower MDA, and restore SOD, CAT, and GPx levels (Maritim et al., 2003; Saha & Ghosh, 2012). These findings show how multi-plant compositions work in concert to combat oxidative stress.

8.3 Biomarkers of Oxidative Stress

Biomarkers indicating DNA, protein, and lipid oxidation as well as reactive nitrogen species are used to measure oxidative stress in diabetes:

- **Malondialdehyde (MDA):** Indicates lipid peroxidation and membrane damage.
- **Protein carbonyl content:** Reflects oxidative damage to proteins**.**
- **8-Hydroxy-2'-deoxyguanosine (8-OHdG):** Marker of oxidative DNA damage.
- **Nitric oxide (NO) and peroxynitrite ($ONOO^-$):** Reflect reactive nitrogen species-mediated stress.

A thorough evaluation of the protective effects of polyherbal formulations against oxidative stress caused by diabetes can be obtained by monitoring these indicators in conjunction with enzymatic and non-enzymatic antioxidant levels (Giacco & Brownlee, 2010; Vincent et al., 2011).

8.4 Correlation of In Vitro and In Vivo Results

Antioxidant activity in vivo and in vitro correlations aid in the prediction of clinical efficacy. In animal models, enhanced enzymatic antioxidant defense and decreased oxidative damage are frequently correlated with high in vitro radical scavenging capacity. The synergistic potential of numerous phytochemicals is shown by the fact that polyherbal formulations often show higher antioxidant activity than individual plant extracts (Joseph & Jini, 2013).

9. Evaluation of Hypoglycemic and Antidiabetic Activity

To determine the therapeutic potential of polyherbal formulations meant for diabetes control, assessment of hypoglycemic and antidiabetic activities is crucial. In vitro enzyme inhibition tests, in vivo animal models, glycemic and metabolic parameter assessment, and mechanistic studies are all part of this study. Because polyherbal formulations can target several glucose homeostasis pathways at once, they are especially effective.

9.1 In Vitro Antidiabetic Assays

In vitro tests are frequently employed as first screening methods to evaluate the antidiabetic efficacy of polyherbal mixtures and plant extracts. The main goal of these tests is to suppress the enzymes that break down carbohydrates, which are crucial for postprandial hyperglycemia.

9.1.1 α-Amylase and α-Glucosidase Inhibition

Two essential enzymes that break down complex carbs into absorbable glucose units are α-amylase and α-glucosidase. Inhibiting these enzymes lowers postprandial blood glucose levels by delaying the absorption of glucose and the digestion of carbohydrates. Significant inhibitory action against both enzymes has been shown by polyherbal formulations high in flavonoids, tannins, and phenolic acids; these formulations are frequently on par with conventional medications like acarbose. Strong α-glucosidase inhibition is demonstrated by herbs such as Momordica charantia, Trigonella foenum-graecum, and Syzygium cumini, which supports their use in managing postprandial hyperglycemia (Krentz & Bailey, 2005; Tundis et al., 2010).

9.2 In Vivo Animal Models of Diabetes

The systemic antidiabetic activity of polyherbal preparations is revealed by in vivo research. Alloxan-induced, streptozotocin (STZ)-induced, and high-fat diet-induced type 2 diabetic models in rodents are frequently employed in experiments. While high-fat diet models imitate insulin resistance linked to type 2 diabetes, STZ specifically destroys pancreatic β-cells, simulating insulin-deficient diabetes. Polyherbal preparations considerably lower fasting blood glucose levels, increase insulin sensitivity, and improve glucose tolerance in these animals, according to numerous research (Srinivasan et al., 2005; Pari & Umamaheswari, 2000).

9.3 Effect on Blood Glucose, HbA1c, and Lipid Profile

Prolonged hyperglycemia raises the risk of complications from diabetes, dyslipidemia, and elevated glycated hemoglobin (HbA1c). It has been demonstrated that polyherbal formulations considerably lower HbA1c, lower fasting and postprandial blood glucose levels, and improve lipid markers such total cholesterol, triglycerides, LDL, and HDL levels. Since diabetes is frequently linked to an increased risk of cardiovascular disease, improving the lipid profile is very crucial. Improved insulin action, decreased hepatic lipid production, and increased lipid metabolism are the reasons for the hypolipidemic impact of polyherbal formulations (Sharma et al., 2011; DeFronzo et al., 2015).

9.4 Mechanistic Insights into Hypoglycemic Action

Polyherbal preparations provide hypoglycemic effects through a variety of complementing mechanisms, such as inhibition of hepatic gluconeogenesis, protection and regeneration of

pancreatic β-cells, augmentation of peripheral glucose uptake, and stimulation of insulin secretion. Furthermore, anti-inflammatory and antioxidant qualities lessen insulin resistance and β-cell damage brought on by oxidative stress. While Curcuma longa and Tinospora cordifolia enhance insulin sensitivity by modifying oxidative stress and inflammatory pathways, herbs like Gymnema sylvestre encourage β-cell regeneration. The improved effectiveness of polyherbal formulations over single-herb or monotherapy approaches can be explained by this multitargeted approach (DeFronzo et al., 2015; Maritim et al., 2003).

Table 2. Common in vitro and in vivo methods used for evaluation of antioxidant and antidiabetic activity

Category	Method / Parameter	What it evaluates	Relevance to diabetes
In vitro antioxidant	DPPH assay	Free radical scavenging	Oxidative stress reduction
In vitro antioxidant	ABTS, FRAP	Reducing power	Antioxidant capacity
In vitro antidiabetic	α-amylase inhibition	Carbohydrate digestion	Postprandial glucose control
In vitro antidiabetic	α-glucosidase inhibition	Glucose absorption	Glycemic regulation
In vivo	STZ-induced diabetic rats	β-cell dysfunction	Type 1/T2DM models
Biomarkers	Blood glucose, HbA1c	Glycemic control	Disease progression
Oxidative markers	MDA, SOD, CAT, GPx	Oxidative damage	Complications prevention

10. Safety, Toxicity, and Herb–Drug Interactions

For polyherbal antidiabetic formulations to be clinically accepted, safety evaluation is a crucial prerequisite. Despite the widespread belief that medicinal plants are fundamentally safe, there may be safety issues associated with improper combinations, chronic use, or concomitant administration with synthetic medications. Consequently, it is crucial to conduct comprehensive toxicity studies, evaluate interactions, and adhere to regulations.

10.1 Acute and Sub-Chronic Toxicity Studies

In accordance with OECD recommendations, acute and sub-chronic toxicity studies are frequently carried out in rats to evaluate the safety profile of herbal and polyherbal preparations. While sub-chronic studies (28–90 days) analyze effects on body weight, organ weights, hematological, biochemical, and histopathological parameters, acute toxicity studies assess mortality and behavioral alterations after a single high dose. When appropriately made and standardized, the majority of reported polyherbal antidiabetic formulations have demonstrated no notable toxicity at therapeutic levels, demonstrating their relative safety (OECD, 2008; Parasuraman et al., 2014).

10.2 Safety Concerns in Long-Term Use

Concerns about phytochemical bioaccumulation, pesticide or heavy metal contamination, and active ingredient variability may arise from long-term usage of polyherbal formulations. Liver and kidney function may potentially be impacted by long-term intake without appropriate standardization. Thus, long-term safety evaluation, pharmacovigilance, and biochemical marker monitoring are crucial, especially for diabetes patients who frequently need lifetime treatment (Mukherjee, 2019).

10.3 Potential Herb–Drug Interactions

Herb-drug interactions are a significant safety concern, particularly for people on traditional antidiabetic drugs. Drug bioavailability and efficacy may be altered by specific herbs that either increase or decrease drug-metabolizing enzymes such cytochrome P450. For instance, combining insulin or sulfonylureas with hypoglycemic medicines may make hypoglycemia more likely. To guarantee the safe co-administration of polyherbal formulations with conventional medicines, it is therefore essential to comprehend pharmacokinetic and pharmacodynamic interactions (Izzo et al., 2016).

10.4 Regulatory Considerations

Polyherbal formulations' regulatory approval varies around the world and is based on proof of their effectiveness, safety, and quality. Standardization, quality assurance, and clinical validation of herbal products are priorities for organizations like the FDA, WHO, and AYUSH. In order to enable market authorization and integration into healthcare systems, it is becoming

more and more necessary to adhere to Good Manufacturing Practices (GMP) and submit toxicological and clinical data (WHO, 2004).

11. Clinical Evidence Supporting Polyherbal Antidiabetic Formulations

Important proof of the effectiveness and safety of polyherbal formulations in the treatment of diabetes comes from clinical research. Although the quality of the data varies, a number of conventional formulations have advanced from laboratory examination to human trials.

11.1 Human Clinical Trials

Small- to medium-sized clinical trials have assessed several polyherbal antidiabetic formulations, mostly in individuals with type 2 diabetes mellitus. Over the course of eight weeks to six months, these studies have evaluated outcomes such fasting blood glucose, postprandial glucose, and HbA1c. Significant glycemic improvement above baseline readings is reported in numerous trials (Patel et al., 2012; Chauhan et al., 2015).

11.2 Efficacy Outcomes

Clinical results frequently show improvements in the lipid profile and decreases in fasting blood glucose, postprandial glucose, and HbA1c. When used as adjuvant therapy, certain formulations have demonstrated efficacy comparable to that of conventional oral hypoglycemic medications. These advantages, which include insulin sensitization, enzyme inhibition, and antioxidant effects, are ascribed to the polyherbal formulations' multitargeted action (Bhattacharya et al., 2014).

11.3 Safety and Tolerability

Good tolerance and little side effects are reported in the majority of clinical investigations, especially when formulations are used at approved dosages. The most frequently reported moderate side effect is intestinal pain. Significantly, severe hypoglycemia episodes are uncommon, indicating that, with appropriate monitoring, polyherbal formulations may provide a safer substitute or supplement to traditional medication (Chauhan et al., 2015).

11.4 Limitations of Existing Clinical Studies

Many clinical studies suffer from limited sample sizes, short durations, poor blinding, and lack of randomization despite encouraging results. Reproducibility is further hampered by variations in formulation composition and the lack of uniform outcome measurements. These drawbacks emphasize the necessity of carefully planned, extensive randomized controlled studies in order to provide conclusive clinical efficacy (Patwardhan et al., 2005).

12. Challenges and Future Perspectives

12.1 Standardization and Reproducibility Issues

Batch-to-batch variability resulting from variations in plant sources, harvesting conditions, and extraction techniques is one of the main obstacles in the development of polyherbal formulations. Reproducibility and regulatory acceptance are hampered by the absence of validated biomarkers and marker-based standards (Mukherjee, 2019).

12.2 Scientific Validation of Traditional Claims

Even if traditional knowledge offers useful leads, many statements are still not sufficiently supported by contemporary scientific techniques. To convert conventional formulations into evidence-based treatments, pharmacological, toxicological, and molecular research must be integrated (Patwardhan et al., 2005).

12.3 Need for Well-Designed Clinical Trials

Randomized, double-blind, placebo-controlled clinical studies with standardized formulations and clinically significant objectives like HbA1c and long-term complication risk must be the main focus of future research. For polyherbal antidiabetic treatments to be accepted globally, such research is essential (Bhattacharya et al., 2014).

12.4 Integration of Polyherbal Formulations into Mainstream Diabetes Care

Polyherbal preparations have the potential to supplement traditional antidiabetic therapy as interest in integrative medicine grows. Strong scientific proof, regulatory approval, physician awareness, and patient education will be necessary for their successful incorporation into

mainstream care, guaranteeing their safe and efficient usage in conjunction with contemporary medication.

13. Conclusion

Although traditional antidiabetic medications are effective, their long-term use is frequently restricted by side effects and single-target mechanisms. Diabetes mellitus is a multifactorial metabolic disorder in which hyperglycemia, oxidative stress, inflammation, and insulin resistance collectively drive disease progression and complications. By combining medicinal plants with complementary hypoglycemic, antioxidant, and anti-inflammatory properties, polyherbal formulations provide a logical, multitargeted therapeutic approach that improves glucose homeostasis, increases insulin sensitivity, protects pancreatic β-cells, and reduces tissue damage caused by oxidative stress. The effectiveness and relative safety of well-designed polyherbal antidiabetic formulations are supported by evidence from in vitro assays, in vivo experimental models, and emerging clinical studies; however, issues with standardization, reproducibility, regulatory acceptance, and the absence of large-scale, well-controlled clinical trials still exist. To enable the incorporation of polyherbal formulations into mainstream diabetes therapy as efficient, secure, and reasonably priced long-term therapeutic choices, these constraints must be addressed through strict quality control, mechanistic validation, and solid clinical research.

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15. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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