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Polyherbal Formulations as Emerging Therapeutics for Diabetes Mellitus: Mechanistic and Clinical Perspectives

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Abstract: *Diabetes mellitus is a chronic metabolic disorder affecting over 537 million adults globally and the number is projected to rise up to 643 million by 2030 and 783 million by 2045. To control the outrage of this disease many synthetic medications are available in market. Along with control over the symptoms of diabetes, these drugs often come with adverse side effects which is major concern. most of the synthetic drugs often targets limited pathways for managing disease progression, on the other medical plants offer rich source of phytoconstituents with active antidiabetic bioactivity like flavonoids, alkaloids, terpenoids, saponins and phenolic compounds. These compounds interact with multiple targets involved in diabetes pathophysiology. This review systematically examines the antidiabetic bioactivity, their mechanism and targets of individual medicinal plants along with the polyherbal formulations. Polyherbal formulation is a traditional concept well documented in classical Ayurvedic texts, it a combination of two or more than two medicinal herbs enhancing their bioactivity by working synergistically by targeting multiple pathways, complementary mechanism like antioxidant, anti-inflammatory, alpha- glucosidase and alpha amylase inhibition, insulin sanitization, slowing carbohydrate metabolism, beta cell protection and regeneration. Though here are already enlisted polyherbal formulations for diabetes control, but having certain key clinical challenges including lack of standardization, quality control, regulatory control, limited preclinical and clinical human trials. This review concludes that the polyherbal formulations is promising alternative for conventional drug with some research and clinical validations.*

Keywords: Diabetes Mellitus, Polyherbal Formulation, Phytoconstituents, Antidiabetic Activity, Synergistic Activity, Medicinal Plants, Postprandial Hyperglycemia.

I. INTRODUCTION

Diabetes is chronic, progressive disorder emerged as a major challenge for 21st century due to its prevalence has increased in number worldwide very significantly over decades putting pressure on healthcare system. The condition arises by persistent hyperglycemia resulting from dysfunction in insulin secretion or its action or both. According to International Diabetes Federation (IDF), approximately 537 million adults are currently living with diabetes globally. The number is projected to increase 643 million adults by 2030 and 783 million by 2045. The growing number of cases has become a significant burden on global healthcare system.[2] [9]. Diabetes mellitus is mainly classified into two types: Type 1 diabetes and Type 2 diabetes. T1 diabetes also referred as insulin dependent or juvenile diabetes, is a chronic autoimmune disorder in which immune system mediated destruction of insulin secreting pancreatic β cells resulting in low or no production of insulin. Without insulin, glucose cannot enter cell efficiently as a result gets accumulated in bloodstream causing hyperglycemic conditionT2 diabetes registers majority of its cases worldwide and it is strongly connected to lifestyle, obesity and genetic factors. [4] Type 2 diabetes cause due to several reasons like

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improper metabolism of glucose, impaired insulin secretion and progressive insulin resistance. One of the major issues for diabetes is postprandial hyperglycemia (PPHG). This is a condition where blood glucose level remains persistently high after consuming meal, which when kept unmanaged for long term causes complications like nephropathy, neuropathy, retinopathy, cardiovascular diseases. [1] Rising number of cases has drawn attention towards medicinal pharmacological research and drug development. several synthetic drugs are available in market each targeting different pathways and mechanism to control the disease. Common class of drugs like Biguanides, glinides, alpha-glucosidase inhibitors, SGLT2- inhibitors, thiazolidineidiones, DPP-4, Sulfonylureas etc. [10][11]. These therapies are effective at controlling the hyperglycemia and symptoms rather than focusing on pathophysiology of disease, targeting multiple pathways of disease progression. Many of the synthetic drugs often cause side effects like weight gain, hepatic failure, gastrointestinal issues. The financial burden of these therapies also remains a concern [3]. Additionally prolonged exposure gradually reduces the efficacy of these therapeutics, leading to progressive dosage adjustment [4]. These challenges or limitations contribute majorly to think about plant-based medicine as an alternative [8]. Medicinal plants showing anti-diabetic activity contains diverse array of phytoconstituents - flavonoids, alkaloids, terpenoids, saponins, carotenoids etc. These medicinal herbs are often used for their higher efficacy, low adverse effect and comparatively lower cost. In recent times there has been significant growth in usage of herbal medicine for treatment of diabetes [12]. An important concept in traditional medicine is polyherbal formulation, where combination of two or more than two medicinal plants to increase the therapeutic benefits documented in classical Ayurvedic texts such as Sharangadhar Samhita. The antidiabetic activity of individual plants relatively well characterized in the literature, but there synergistic or combined activities still remain less explored [8][13]. This review aims to address that gap by systematically examining the existing literature on polyherbal formulation used in managing diabetes mellitus, focusing on their phytochemical composition, their mechanism of action and their synergistic activity.

II. SEARCH METHODOLOGY

A structural literature search was carried out across major databases related to polyherbal formulation and their antidiabetic potential, such as PubMed, Scopus, Web of Science, Springer, Nature and Google scholar. The search was carried out in between March 2026 and May 2026. The literature was performed using keywords like “polyherbal formulations”, “diabetes mellitus”, “herbal therapeutics”, “antidiabetic medicinal plants”, “phytoconstituents”, “alpha amylase and alpha glucosidase inhibition”. Boolean operators (AND, OR, NOT) were used to refine the search strategy.

Inclusion criteria:

- Peer-reviewed articles
- Review and research papers
- In vitro, in vivo, and clinical studies
- English-language publications

Exclusion criteria:

- Duplicate records
- Conference abstracts
- Non-English articles
- Studies lacking relevant experimental evidence

III. PATHOPHYSIOLOGY OF DIABETES

Diabetes mellitus is characterized by hyperglycemia an abnormal condition where blood glucose level remains persistently high. Under physiological conditions insulin secreted from pancreatic β cell helps glucose enter cell through insulin dependent GLUT4 transporter protein present on the membrane of skeletal muscle and adipose tissues [14]. Glucose serves as primary energy substrate for most of the tissues.

In Type 1 diabetes autoimmune destruction of β cells leads to absolute insulin deficiency. Without insulin, GLUT4 remains inactive and glucose cannot enter muscle or adipose tissue, accumulating in bloodstream [21-22]. In Type 2 diabetes the primary cause is insulin resistance, a state where targeted tissues like skeletal muscle, adipose tissues and liver become progressively less sensitive towards insulin signaling [15]. This is closely associated with inflammation, metabolic dysfunction, obesity driven by unhealthy lifestyle. To compensate the higher insulin demand by the body the β cells get overstimulated, gradually begins to fall in production. By the time of diagnosis of disease most of the people have already lost major proportion of β cell mass and function [28].

Diabetes induces many irregularities and a cascade of metabolic dysregulation in body throughout disease progression - pancreatic β cell dysfunction, reduced insulin secretion and sensitivity, insulin resistance, decreased glucose uptake, persistent hyperglycemia, increased generation of reactive oxygen species causing more oxidative stress and chronic inflammation [16]. Among many irregularities Postprandial hyperglycemic (PPHG) is one of core cause of disease as it is detectable at very early stage. This condition arises due to loss of first phase insulin secretion by β cells, improper utilization of glucose and reduced peripheral insulin sensitivity [25]. At enzymatic level, alpha glucosidase and alpha amylase enzymes in small intestine plays key role in PPHG by how rapidly they breakdown complete carbohydrates to absorbable monosaccharides. Inhibiting these enzymes provides a solid control over PPHG [25-27]. Synthetic drugs mainly focus single pathway or limited pathways to get control over the symptoms. That's why polyherbal formulation offers wide range of therapeutics by working synergistically across multiple targets.[8].

Current Synthetic Antidiabetic Drugs: Classes, Mechanism and Drawbacks

Drug Class	Example	Mechanism	Key Side Effects
Biguanides	Metformin	Activates AMPK → reduces hepatic glucose output	Gastrointestinal disorders, Vitamin B12 deficiency
Alpha-Glucosidase inhibitors	Acarbose	Delays carbohydrate digestion → blunts PPHG	Gastrointestinal disorders, transaminases
SGLT2-I	Empagliflozin Dapagliflozin Canagliflozin	Blocks renal glucose reabsorption → increases urinary glucose excretion, Reduction in Body weight	Diabetic ketoacidosis, Genital infection, Urinary tract infection, Bones fracture prone
DPP-4 Inhibitors	Sitagliptin	Inhibits DPP-4 → increases incretin levels → stimulates insulin	Nasopharyngitis, joint pain
Thiazolidinediones	Pioglitazone	PPAR-γ agonist → improves insulin sensitivity	Weight gain, fluid retention, hepatotoxicity
Sulfonylureas	Glimepiride Gliclazide Glibenclamide	Stimulates insulin secretion from β cells	Hypoglycemia, weight gain
Glinides	Repaglinide, Nateglinide	Short-acting insulin secretagogues	Hypoglycemia, Headache, Respiratory tract Infection.

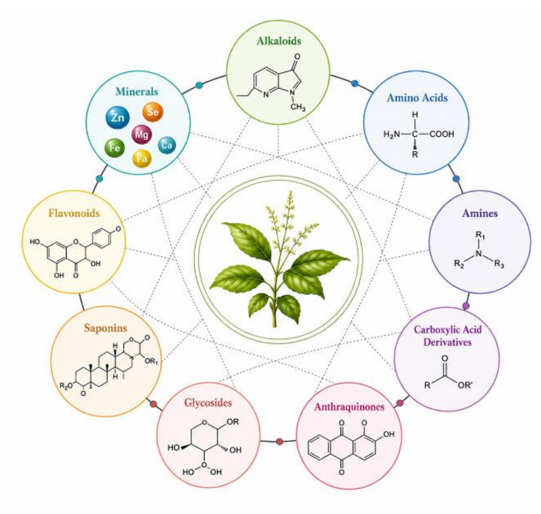
Taken together, the existing classes of synthetic antidiabetic drugs offers wide and valuable therapeutics for hyperglycemia. But each class while offering benefits comes with adverse effects. Most of drugs target one or two pathways, leaving broader cascade of metabolic irregularities behind.

IV. ANTIDIABETIC PHYTOCONSTITUENTS: CLASSES AND MECHANISMS OF ACTION

Medicinal plants with phytoconstituents shows antidiabetic activity. These phytoconstituents interact with multiple biological targets in human body, often working as antagonist, agonist complimenting the action of synthetic drugs while contributing with anti-oxidant and anti-inflammatory effects. [31]

Flavonoids:

Flavonoids are the class of secondary metabolites composed of polyphenolic compounds distributed wide across the



plant kingdom. Along with other important medicinal effects, in reference with diabetes flavonoids shows antidiabetic effects with several mechanisms:

Activation of AMPK leading to enhanced GLUT4-mediated glucose uptake in muscle cells; [31] inhibition of alpha-glucosidase and alpha-amylase to reduce PPHG;[43] reduction of oxidative stress through free radical scavenging; and downregulation of pro-inflammatory cytokines such as TNF-α and IL-6 that worsen insulin resistance. Prominent antidiabetic flavonoids include quercetin, kaempferol, rutin, naringenin, and luteolin [47].

Alkaloids:

Alkaloids, class of secondary metabolite composed of nitrogen containing compounds with wide range of pharmacological activities. The well know antidiabetic activity is by activating AMPK and it inhibits mitochondrial complex I, resulting in effects that close to metformin [45]. Other important antidiabetic alkaloids include trigonelline in fenugreek (stimulates insulin secretion) and vincamine in Catharanthus roseus (hypoglycemic) [47].

Terpenoids:

Terpenoids are large and structurally diverse class of secondary metabolites. In context of antidiabetic activity triterpenoids such as oleanolic acid, lupeol, and ursolic acid have demonstrated the ability to enhance insulin sensitivity, activate PPAR-γ, and protect pancreatic β cells from oxidative damage [45]. Curcumin, a diterpenoidrelated polyphenol from Curcuma longa, activates PPAR-γ, inhibits NF-κB-mediated inflammation, and improves insulin receptor signaling [44, 45].

Saponins:

Saponins are glycosidic compounds having hydrophilic and lipophilic properties. In diabetes, their antidiabetic actions include inhibition of intestinal glucose absorption, stimulation of insulin secretion, and improvement of lipid profiles and hypoglycemic effects [43, 47].

Tannins and Phenolic Compounds:

Tannins class of secondary metabolites exert antidiabetic effects primarily through inhibition of alpha-amylase and alpha-glucosidase, by reducing the rate of carbohydrate digestion. They also show anti-oxidant activity [43]. Phenolic compounds present in several fruits and coffee also inhibit intestinal glucose transporter via SGLT-1 working complementary [47].

Carotenoids:

Carotenoids are primarily known for their anti-oxidant activity enriched with pro-vitamin A activity, which has been highlighted research literature for their role in reducing diabetic complications. Β carotene and lycopene reduce oxidative stress which helps for damage recovery caused from persistent hyperglycemic effect [45].

Antidiabetic Herbs in Indian Traditional Medicine:

Having the major classes of antidiabetic phytoconstituents and their molecular mechanisms it is easy to evaluate the medicinal plants on the basis of their rich sources phytoconstituents. The following table represents well documented medicinal plants with high antidiabetic activity highlighting their key bioactive compounds, their mechanism of action and their therapeutic outcomes. These plants provide solid base for scientific foundation for polyherbal formulation to target diabetes mellitus.

Antidiabetic Mechanism of action Medicinal herbs Insulin secretion:

- Insulin sensitization
- Inhibition of carbohydrate metabolizing enzymes
- Regeneration of beta cell
- Antioxidant and anti-inflammatory
- Lipid metabolism regulation

Medicinal herbs with their phytoconstituents, mechanism and outcomes

Medicinal Plant	Phytochemicals	Mechanism	Result
Ocimum sanctum (Holy Basil)	Eugenol, ursolic acid, flavonoids	Antioxidant and anti-inflammatory; enhances insulin secretion	Improves insulin sensitivity, reduces oxidative stress, protects pancreatic β cells from damage
Cinnamomum verum (Cinnamon)	Cinnamaldehyde, eugenol, proanthocyanidins, flavonoids	Enhance insulin receptor sensitivity; inhibits alpha-amylase and alpha-glucosidase enzymes	Improves insulin signaling, slows glucose uptake, reduces postprandial blood glucose
Curcuma longa (Turmeric)	Curcumin, curcuminoids	Antioxidant and anti-	Reduces oxidative

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		inflammatory; activates PPAR-γ pathway	stress, protects β cells, improves glycemic and inflammation control
Allium sativum (Garlic)	Allicin, diallyl disulfide	Enhances insulin secretion; antioxidant activity; improves lipid metabolism	Improves lipid profiles, reduces fasting blood glucose levels
Moringa oleifera (Moringa)	Glucosinolates, flavonoids, polyphenols, isothiocyanates	Enhances insulin secretion, improves insulin sensitivity, inhibits intestinal glucose absorption	Prevents postprandial blood glucose spike, improves overall glycemic control
Zingiber officinale (Ginger)	Gingerol, shogaol, paradol	Improves insulin sensitivity; reduces oxidative stress and inflammation; enhances GLUT4-mediated glucose uptake	Enhances glucose uptake into cells, improves glycemic control
Syzygium cumini (Jamun)	Jamboline, anthocyanins, ellagic acid	Antioxidant and anti-inflammatory; insulin-mimetic activity; inhibits alpha-glucosidase	Reduces blood glucose and lipid levels, decreases oxidative stress
Momordica charantia (Bitter Gourd)	Charantin, momordicin, polypeptide-p (plant insulin)	Inhibits alpha-glucosidase; stimulates insulin secretion from pancreatic β cells	Hypoglycemic effect; increases insulin secretion; reduces fasting and postprandial glucose
Gymnema sylvestre (Gurmar)	Gymnemic acids, gurmarin	Blocks intestinal glucose absorption; stimulates insulin secretion; promotes β cell regeneration	Enhances insulin secretion, regenerates β cells, reduces intestinal glucose absorption
Trigonella foenum-graecum (Fenugreek / Methi)	4-Hydroxyisoleucine, soluble fibre (galactomannan), saponins	Delays gastric emptying and glucose absorption; stimulates insulin secretion	Increases insulin sensitivity, delays carbohydrate absorption, reduces postprandial glucose
Tinospora cordifolia (Giloy / Guduchi)	Berberine, tinosporin, palmatine, tinosporide	Antioxidant; enhances insulin secretion; inhibits alpha-glucosidase	Reduces oxidative stress, improves β cell function, protective effects on pancreatic tissues
Azadirachta indica (Neem)	Nimbolide, quercetin, flavonoids	Increases glucose uptake in peripheral	Lowers blood glucose, reduces oxidative

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		tissues; improves glycogenesis; antioxidant activity	damage, improves hepatic glucose metabolism
Aloe vera	Aloe-emodin, anthraquinones, acemannan	Antioxidant and anti-inflammatory; stimulates insulin secretion from β cells	Increases insulin sensitivity, decreases ROS generation, reduces pro-inflammatory cytokines
Coriandrum sativum (Coriander)	Linalool, flavonoids, terpinene	Stimulates insulin secretion from β cells; increases peripheral glucose uptake	Reduces fasting blood glucose; improves insulin release in a dose-dependent manner
Allium cepa (Onion)	Quercetin, allyl propyl disulphide, flavonoids	Inhibits alpha-glucosidase and alpha-amylase; stimulates insulin release	Reduces postprandial glucose levels, improves insulin secretion
Aegle marmelos (Bael)	Marmelosin, coumarins, alkaloids	B cell protection; antioxidant activity; improves glucose tolerance via pancreatic regeneration	Restores β cell function, reduces blood glucose, improves glucose tolerance
Withania somnifera (Ashwagandha)	Withanolides, withaferin A	Lowers cortisol levels, reducing stress-induced insulin resistance; antioxidant and anti-inflammatory	Reduces stress-induced hyperglycemia, improves insulin sensitivity, lowers fasting glucose
Emblica officinalis (Amla)	Emblicanin A and B, gallic acid, vitamin C	Antioxidant; inhibits alpha-glucosidase; protects β cells from oxidative damage	Lowers postprandial glucose, regenerates β cells, reduces HbA1c levels

V. MARKETED ANTIDIABETIC POLYHERBAL FORMULATIONS:

BGR-34 (AIMIL/CSIR-NBRI & CIMAP):

This was claimed to India's first ayurvedic antidiabetic formulation awarded by CSIR.

Ingredients:

Rubia cordifolia (Manjeestha),
Trigonella foenum-graecum (Fenugreek), Berberis aristata (Daruharidra), Tinospora cordifolia (Guduchi), Pterocarpus marsupium (Vijaysar), Gymnema sylvestre (Gurmar),

Mechanism: it acts on pancreatic functions, antioxidant role and improves carbohydrate metabolism [8]

D-400 / Diabecon (Himalaya):

Ingredients:

Includes Gymnema sylvestre, Pterocarpus marsupium, Shilajit, Commiphora mukul, Azadirachta indica.

Mechanism: Enhance insulin secretion, delays glucose absorption and supports beta cell health [8-24]

Madhumeha Kusumakar Ras (Classical Ayurveda):
Ingredians: Gold bhasma, silver bhasma, and herbs like Asparagus racemosus**.** [8].

IME-9 (CCRUM/Multani Pharmaceuticals):
Ingredients: Pterocarpus marsupium, Gymnema sylvestre, Syzygium cumini, Momordica charantia, and others.
Mechanism: It supports glycemic control and pancreatic regeneration. [8].

Ayush-82 (CCRAS, Ministry of AYUSH):
Ingredients: Gymnema sylvestre, Pterocarpus marsupium, Momordica charantia, Syzygium cumini.
Mechanism: Hypoglycemic effect, reduction in fasting glucose [8].

Challenges and Limitations in Polyherbal Formulation.

Despite promising pharmacological evidences as we reviewed above the transition of polyherbal formulation from traditional drug to preclinical trials has many challenges. Putting light on the challenges and limitations strengthens the scientific bases rather weakens them. Below are the top challenges which should be addressed.

Lack of Standardization and dose determination:

One of the most important things about the medication is dosage. In polyherbal formulated drug, the concentration of active phytoconstituents in extracts varies depending upon the plants source, extraction method and batch to batch consistency. Due to lack of consistency and varying concentration the establishing of effective dosage is difficult. [58-59]

Clinical Evidences:

Majority of polyherbal drugs are studied have been conducted using in vitro and in vivo studies, there is still not sufficient data on human trials as it involves years of progression metabolic dysfunctions [51-52].

Quality control:

Bioavailability of phytoconstituents, risk of adulteration, contamination as they get affected by changing environments. Also, misidentification of plants may lead to compromise quality of the herbal drug. [8]

Regulatory issues:

In India and globally there are many problems for herbal medicines, face regulatory hurdles for classifications, safety and marketing [8].

Herb-Drug Interaction:

Several plants constituents are often known to modulate the normal functioning body proteins. These interactions are rarely addressed in polyherbal clinical studies.

Long term safety:

Less data on long term usage of herbal medicine, need to know particular combinations with their long-term effects.

VI. FUTURE DIRECTIONS

Future research should be focused on establishing well clinical and preclinical trials to ensure the safety and efficacy of the herbal drug. Major problem of standardization of extractions methods, quality control and dosage should be strengthened to maintain constancy in phytoconstituents for better outcomes of drugs. Further mechanistic study should be studied well, also the synergistic interactions among combinations of different medicinal herbs need to be studied with reference to their targets. Along with all of these pharmacokinetics investigations, stronger regulatory frameworks and public awareness regarding evidence-based use of herbal therapeutics contributing towards better development on integration of polyherbal formulations for diabetes management.

VII. CONCLUSION

Diabetes mellitus remains one of the most challenging chronic diseases and burden on global healthcare. This complex metabolic disorder involves multiple interconnected pathways including abnormal insulin secretion, insulin resistance, β cell dysfunction, oxidative stress, inflammation and glucose metabolism these abnormalities demand therapeutic strategies not just control over the symptoms but the overall progression of disease. Although conventional synthetic medicine has significantly brought control over disease but the long-term therapy often associated with adverse effects and economic burdens. Medicinal plants and their bioactive compounds provide promising alternative for conventional drugs. Indias traditional medicinal heritage provides rich sources for managing disease by herbal formulations. Many plants with active phytoconstituents like flavonoids, alkaloids, saponins, phenolic compounds, terpenoids are capable of targeting more than one pathway to control disease. Polyherbal formulations with synergistic interactions among phytoconstituents provides much more benefits than single medicinal herb. However, there are still many things to be fully known, challenges related to standardization, clinical trials, regulatory framework and long-term effects limits the applications. Future study should be focused on research and development of safe and effective polyherbal formulation for diabetes management.

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