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Anti-diabetic Potential of Traditional Herbal Drugs in Polyherbal Formulation–A Review

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ABSTRACT

Background: Diabetes mellitus, characterized by hyperglycemic symptoms, has emerged as a major global health challenge. The disease's severity is compounded by both micro- and macrovascular complications associated with hyperglycemia, leading to significant morbidity. Current conventional anti-diabetic medications, while widely prescribed, often demonstrate high failure rates and are associated with adverse pathological effects.

Purpose: This paper aims to evaluate the potential of polyherbal formulations in the treatment of diabetes mellitus, addressing the need for alternative therapeutic approaches with enhanced efficacy and reduced side effects.

Methods: The study examines various natural extracts and their constituents derived from medicinal plants, focusing on their hypoglycemic properties. Special attention is given to polyherbal formulations, which combine multiple herbs to potentially enhance therapeutic efficacy while reducing individual herb concentrations and associated adverse effects.

Results: While numerous herbal medications have been developed for diabetes mellitus treatment, the review identifies a significant gap in scientific validation and medical proof of their efficacy. Polyherbal formulations show promise in enhancing therapeutic action while minimizing adverse events through reduced concentrations of individual herbs.

Conclusion: The investigation highlights the potential of polyherbal formulations as an alternative approach to diabetes management. However, there is a crucial need for rigorous scientific validation and clinical trials to establish their efficacy and safety profiles before widespread implementation in diabetes treatment protocols.

1. Introduction

Humanity may benefit much from plants. Many of them are only exclusively for medical functions. According to the World Health Organization (WHO) (Sofowora *et al.*, 2013). "A medicinal plant is a plant that, in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for chemopharmaceutical semi-synthesis." Pharmaceutical businesses are in high demand for the active compounds found in such plants (David *et al.*, 2015).

Hyperglycemia, caused by inadequate insulin production, insulin action, or both, abnormally elevated blood sugar, altered metabolism of carbs, protein, and lipids, and a higher risk of vascular consequences are all characteristics of diabetes mellitus (DM), a systemic metabolic disease (Aranaz *et al.*, 2023; Khan *et al.*, 2014). Hyperglycemia is brought on by decreased skeletal muscle glucose absorption, decreased glycogen synthesis, and unchecked hepatic glucose production (Kelkar *et al.*, 2019). It has been shown that chronic hyperglycemia is associated with dysfunction as well as failure of vital organs such as the

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blood vessels, kidneys,brain, nerves, nerves, eyes, and heart (Sharma *et al.*, 2021).

The long-established health issues linked to DM are widely recognized and persist to cause a major challenge for the numerous peoples affected by this condition (Arokiasamy *et al.*, 2021). With the decline in mortality rates from the vascular disease, which once accounted for over 50% of deaths in people with diabetes, cancer and cognitive impairment have now emerged as the primary reasos for deaths in certain countries for individuals with diabetes (Tomic *et al.*, 2022). WHO defines DM as a chronic metabolic disorder that occurs when the body cannot efficiently utilize the secretion of insulin from the pancreas or when it fails to produce sufficient insulin. DM is an increasingly significant public health issue in developed countries (Amutha & Aishwarya, 2010). A hormone called insulin controls blood sugar. Common characteristics of chronic hyperglycemia are present, along with alterations in the metabolism of carbohydrates, proteins, and fats leading to hyperlipidemia, hyperaminoacidemia, and hypoinsulinemia (Sarkar *et al.*, 2021). Diabetes is the cause of various pathological processes, including the autoimmune damage of the pancreatic beta cells, which leads to inadequate insulin production and conditions that cause insulin resistance. DM, or 'Madhumeham,' has been recognized for centuries as a condition associated with sweetness (Gowri, 2013; Panari & Vegunarani, 2016). Protein, fat, and carbohydrate metabolism is aberrant when insulin does not act on target tissues. The primary cause of insulin shortage may result from insufficient insulin production or declined tissue responses to insulin at various points within the complex hormonal action pathways. Due to the presence of decreased insulin secretion and action in the same patient, the fundamental cause of the hyperglycemia sometimes becomes ambiguous. Impaired vision, polyphagia, weight loss, polyuria, tachycardia, polydipsia, hypotension, and wasting are symptoms of hyperglycemia. While uncontrolled diabetes produces varying grades of ketoacidosis and hyperosmolar (nonketotic hyperglycemic) coma, chronic diabetes also has the potential to hinder development and increase susceptibility to certaidiseases (Sharma *et al.*, 2023). In diabetic patients, long-term complications may involve retinopathy, potentially leading to vision lss; nephropathy, which can result in kidney failure; peripheral neuropathy, increasing the likelihood of Charcot joints, foot ulcers, and amputations; and autonomic neuropathy, which may cause symptoms affecting the gastrointestinal, cardiovascular, and sexual systems and genitourinary as well as infertility. Additionally, cardiovascular, cerebrovascular, atherosclerotic, peripheral, and arterial disorders are more common in these people (Boon *et al.*, 2006; Lodhi, 2021; Ramachandran, 2014).

The current diabetes treatments involve hormone therapy (insulin) or the use of glucose-lowering medications, including thiazolidinediones, sulfonylureas, biguanides, and alpha-glucosidase inhibitors. Unfortunately, these treatments are not able to lower the risk of cardiovascular disease, retinopathy, nephropathy, and other delayed diabetes consequences. Currently available treatment options in modern medicine have several adverse effects (Preethi, 2013; Nagpal *et al.,* 2023). Historically, many plants have been believed to possess antihyperglycmic properties because of their ability to restore pancreatic tissue function by boosting insulin production, inhibiting glucose absorption through the intestinal wall or aiding metabolites in insulin-dependent processes (Malviya *et al.*, 2010; Pandeya *et al.*, 2010).

2. Polyherbal Formulations

In comparison to their synthetic competitors, herbal remedies and their formulation are typically thought to be the least hazardous and devoid of adverse effects. Traditional medicine from plant extracts has proved to be more affordable, clinically effective, and have relatively fewer adverse effects than modern drugs (Beula *et al.*, 2023). Natural remedies from medicinal plants are considered to be effective and safe alternative treatments for various diseases. Drug formulation in Ayurveda is based on two principles: Use as a single drug and use of more than one drug in a single dosage form is known as polyherbal formulation (Karole *et al.*, 2019). *Sarangdhar Samhita* the literature of Ayurveda, gives the suggestion of polyherbalism to attain better beneficial effectiveness and lesser adverse effects (Mukherjee *et al.*, 2018). Polyherbal formulations are utilized worldwide because of their medicinal and therapeutic benefits in various diseases (Jahan & Singh, 2022). It is also known as polyherbal therapy or herb-herb combination. When multiple herbs or herbs with minerals in precise proportions can create formulations that offer stronger therapeutic effects while reducing the harmful side effects (Brahma *et al.*, 2024). They are thought to have greater and longer therapeutic potential than a single herb, making them more beneficial for the control of diabetes. Polyherbal formulations are employed globally due to their health-promoting and therapeutic applications (Mamatha *et al.*, 2020).

2.1. Concept and Rationale of Polyherbal Formulations

Conventional medicine systems like Ayurveda, Traditional Chinese Medicine, and Unani embrace a holistic approach that often involves combining multiple herbs. This practice forms the foundation of polyherbal formulations

(Singh *et al.*, 2013). Individual plants often contain multiple phytochemicals. When several plants and herbs are combined, their various components can work together synergistically, enhancing the overall medicinal effect (Meena *et al.*, 2009). This comprehensive method might offer improved safety and tolerability compared to alternative approaches. Comparative/meta-analysis of data from multiple studies suggests that polyherbal formulareducing bloode more efficient than control treatments in reducing blood glucose levels after fasting (Suvarna *et al.*, 2021a).

The rationale behind the use of polyherbal formulations lies in the inherent complexity of herbal medicines and the synergistic interactions among their phytochemical constituents. Ayurvedic literature suggests that combining multiple ingredients can amplify desired therapeutic effects while simultaneously reducing the adverse effects (Katiyar *et al.*, 2015).

2.2. Polyherbal Formulations for Diabetes

Numerous plants have been shown to be efficient in treating a variety of systemic diseases in coveinsulin-dependent andstems. DM, encompassing both T1DM insulin-dependent and T2DM non-insulin-dependent, is a prevalent and significant metabolic disorder worldwide. Ancient literature contains extensive documentation of the polyhedral formulation notion. Numerous plants have been studied for their potential benefits in both T1DM and T2DM, with findings published in many scientific journals (Pandeya *et al.*, 2010). Traditional herbal remedies have been utilized worldwide to treat DM (Suvarna *et al.*, 2021b). Numerous herbs andherb combinations are believed to treat and manage diabetes, additionally without causing side effects. Prevention is better than cure and is less expensive (Choudhary & Chaudhary, 2015). Therefore, it was intended for the current study to investigate how polyherbal formulations are used to treat DM. (Bastin *et al.*, 2011; Dahake *et al.*, 2009; Dhanabal *et al.*, 2006; Divya & Ilavenil, 2012; Fugh-Berman, 2000; Herman *et al.*, 2006; Ismail, 2009). Thus, in the current study, efforts have been undertaken to scientifically validate the antihyperglycemic effects of herbal medicines, which are thought to be special formulations that aid in the holistic control of blood sugar and issues associated with diabetes. Several medicinal plants having anti-diabetic properties are tabulated in Table 1. Figure 1 shows various herbs used in polyherbal formulations for DM.

Table 1: Some Important Herbs Possessing Potential Anti-Diabetic Activity are Utilized in Polyherbal Formulations

Sr. No.	Common Name	Botanical Name	Mechanism of Action (Activities)	Dose	References
1.	Gudmar Leaf	*Gymnema sylvestre*	Its mechanism of action is by inhibiting the glucose absorption in the intestine through the saponin fraction of the herb.	500-1000 mg/day	(Ayyanar *et al.*, 2008; Di Fabio *et al.*, 2014; Srivastava *et al.*, 2012)
2.	Vijayasar wood	*Pterocarpus marsupium*	It may reduce blood sugar levels by safegaurding and regenerating insulin-producing cells. Numerous animal studies have demonstrated its ability to reverse damage to beta cell (insulin-producing cells) and restore normal insulin levels, as well as inhibit aldose reductase activity.	200 mg/kg/day	(Dhanabal *et al.*, 2006; Xu *et al.*, 2018)
3.	Jamun Seed	*Syzygium cumini*	The excessive production of ROS having a key role in the development Diabetes. Consequently, neutralization of ROS by Jamun appears a key mechanisms in Diabetes management. (Molecular level reduction in glucose level may be associated with Jamun's having capacity to triggers the PPARα, PPARγ, and AKT which subssequently downregulate the expression of Foxo-1, PGC1α, Scid 1, ACC1, SREPB1c, endoplasmic reticulum protein retention receptor (KEDL), and GPR98 leading to decreased activities of G6Pase, ADA, 5'NTase, PEPCK, and Fas)	1000 mg/kg	(Chhetri *et al.*, 2005; Srivastava *et al.*, 2013; Tripathi & Kohli, 2014)

4.	Karela Seeds	*Momordica charantia*	The potential mechanisms by which M. charantia and its different extracts and compounds include lowering blood sugar levels, by inhibiting key enzymes involved in gluconeogenesis, activating crucial enzymes in the HMP , and preserving both the structure and function of β cells.	150 mg/kg/ day	(Baby Joseph & Jini, 2011; Joseph & Jini, 2013; Liu, *et al.*, 2021)
5.	Neem Leaf	*Azadirachta indica*	Hypoglycemic and β-cell regeneration	250 mg/kg/ day	(Khosla *et al.*, n.d.; McCalla *et al.*, 2016)
6.	Vinca Leaf	*Vinca rosea*	Hypoglycemic	500 mg/kg/ day	(Ahmed *et al.*, 2010; Singh *et al.*, 2001)
7.	Tulsi Leaf	*Ocimum sanctum*	Antidiabetic effects by inhibiting hepatic glucose release and the carbohydrate metabolizing enzymes.	300 mg–1000 mg/day	(Husain *et al.*, 2015; Hussain *et al.*, 2001; Patil *et al.*, 2011)
8.	Fenugreek (Methi) Seeds	*Trigonella foenum-graecum*	By reguating insulin secreation from the pancreatic β-cells. Additionally, a clinical study indicatd that fenugreek's antidiabetic effect was due to its ability to enhance insulin sensitivity.	100 mg/kg/ day	(Kumar *et al.*, 2012; Xue *et al.*, 2007)
9.	Cinnamon	*Cinnamomum verum*	Hypoglycemic effect by reducing the activity of intestinal enzymes, which impacts glucose absorption and in turn, decrease postprandial blood glucose levels.	200-1200 mg/ kg/day	(Crawford, 2009; Li *et al.*, 2013; Mang *et al.*, 2006; Rao & Gan, 2014)
10.	Guava Leaf	*Psidium guajava*	Anti-hyperglycemic and anti-hyperlipidemic by Inhibition of Alpha-glucosidase	400-1000 mg/ kg/day	(Huang *et al.*, 2011)
11.	Mango Leaf	*Mangifera indica*	Hypoglycemic effect by inhibiting starch-digesting enzyme, enhancing glucose adsorption and uptake capacity, suppressing nitric acid production, and neutralizing free radicals.	250 mg/kg/ day	(Ganogpichayagrai *et al.*, 2017; Gondi *et al.*, 2015)
12.	Insulin Plant Leaf	*Costus igneus*	Antihyperglycemic, hypoglycemic, and hypolipidemic	250 mg/kg/ day	(Bavarva & Narasimhacharya, 2008; Eliza *et al.*, 2009)
13.	Aloe	*Aloe barbadensis*	Insulinotropic effects, contributing directly or indirectly to insulin secretion in a synergistic way.	300 mg/kg/ day	(Huseini *et al.*, 2012; Kim *et al.*, 2009)
14.	Green Tea	*Camellia sinensis*	Prevents adipocyte proliferation and differentiation, enhances cellular defenses against oxidative stress, and inhibits SGLT1.	100-200 mg/ kg/day	(Abeywickrama *et al.*, 2011; Ankolekar *et al.*, 2011)
15.	Jalkumbhi	*Eichhornia*	Lowers plasma glucose level	400 mg/kg/ day	(Bhavsar *et al.*, 2020; Raju *et al.*, 2021)
16.	Vansh Lochan	*Bambusa arunadinacea*	Lowers plasma glucose level	100-300 mg/ kg/day	(Gaikwad & More, 2015)
17.	Jaiphal	*Myristica fragrans*	It enhances the lipid per oxidation and insulin metabolism.	500 mg/kg/ day	(Abourashed & El-Alfy, 2016)
18.	Javitri	*Myristica fragrans*	By reducing hepatic glucose production by decreasing both glyconeogenesis and glycogenolysis.	500 mg/kg/ day	(Abourashed & El-Alfy, 2016)
19.	Choti Elaichi	*Elettaria cardamomum*	It helps to regulate and lowers blood glucose in diabetes patients by enhancing insulin sensitivity and decreasing hepatic glucose production.	250 mg/kg/ day	(Ahmed *et al.*, 2017; Kazemi *et al.*, 2017)

20.	Alsi Seeds	*Linum usitatissimum*	Regulates the functioning of glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase and glutathione reductase in tissues.	200 mg/kg/day	(Gök *et al.*, 2016)
21.	Lady Finger	*Abelmoschus bammia*	By reducing carbohydrate metabolizing enzymes, increasing insulin sensitivity, regeneration of damaged β-cells, and enhances insulin production and release	100-300 mg/kg	(Mishra *et al.*, 2016; Sabitha *et al.*, 2011)

Figure 1: Various Herbs Used in Polyherbal Formulations for DM

3. Various Mechanism of Action of Polyherbal as Anti-diabetic effects

The antidiabetic properties of herbs depend upon a variety of mechanisms. The mechanism of action of herbal antidiabetics could be grouped as:

Blocking potassium channels in pancreatic β-cells and promoting cycl adenosine Adenosine monophosphate (AMP) as a cellular messenger (Jarald *et al.*, 2008), Stimulation of insulin release from pancreatic islet β-cels and/or slowing down the breakdown of insulin (Walia *et al.*, 2021), This leads to a reduction in the kidney's ability to reabsorb glucose from the urine back into the bloodstream (Bilal *et al.*, 2018), enhancing the glycogenesis and breakdown of glucose (glycolysis) in the liver (Lee *et al.*, 2012), enhancement of digestion along with a decrease in blood glucose as well as urea level, inhibition of β-galactocidase and α–glucocidase (Alam *et al.*, 2019), and an increase in both size and quantity of cells within the pancreatic islets of Langerhans (Anggraini *et al.*, 2021), shown in Figure 2.

4. Various Other Molecular Pathways by which Polyherbal Formulations Targeting Various Mechanisms in DM

4.1. Polyherb Formulations Act by Targeting the JNK Pathway Involved in DM

The enzyme c-Jun N-terminal kinase (JNK) promotes inflammation and is found throughout the body. Obesity, a condition characterized by mild but persistent inflammation, leads to increased levels of cytokines and free fatty acids. These substances can trigger JNK activity in multiple organ tissues. Active, it's thought to play a role in two major aspects of T2DM that are caused by obesity: the body's reduced response to insulin and the inability of the pancreas to secrete enough extra insulin to make up for this resistance. These two factors are central to the development of T2DM (Yung & Giacca, 2020). JNK-1 worsens oxidative stress, which in turn triggers cell death processes activated by stress. Additionally, JNK-1 promotes inflammation, impairs the function of insulin-producing β-cells in the pancreas, and causes these cells to release either insufficient amounts of insulin. It also triggers inflammation, disrupting the functioning of β-cells, which leads to insufficient release of insulin from β-cells (Mazzoli *et al.*, 2021). Studies have revealed that certain herbal formulations can suppress the activation of the JNK pathway, which is linked with the elevated blood bloodof ofhe LOFresion of this process, leading to a substantial decrease in damaging reactive oxygen species (ROS), which helps to protect the insulin-secreting β-cells in the pancreas (Aslam *et al.*, 2024).

4.2. Polyherbal Formulations Act by Targeting the Nrf-2/Keap1-Involved Pathway in DM

The balance of oxidation and reduction reactions in cells, known as redox homeostasis, is mainly controlled through changes in gene expression. This regulation happens both when cells are under stress and in normal conditions. The primary system responsible for managing this balance is the nuclear factor erythroid 2-related factor 2/kelch-like ECH-associated protein 1/antioxidant response element (Nrf2/Keap1/ARE) pathway, which responds to changes in the cellular environment by altering the activity of specific genes (Liu *et al.*, 2022). The Nrf2/Keap1/ARE pathway shows therapeutic potential by targeting the extensive oxidative stress involved in pancreatic injury, impaired insulin function and sensitivity, and the development of various diabetes-related complications (Ghareghomi *et al.*, 2021). While some research indicates that ROS can hinder insulin secretion by decreasing adenosine triphosphate (ATP) production (Thiruvengadam *et al.*, 2023). Additionally, evidence suggests that a lack of Nrf2 may exacerbate both type I and type II diabetes. The Nrf-2/Keap-1/ARE pathway has been recognized as a crucial anti-oxidant mechanism in the development and progression of DM pathogenesis (Chaudhary *et al.*, 2023). Studies using mice models lacking Nrf2 have shown unexpected effects, including lower blood glucose levels, improved insulin signaling, and reductions in both body fat and overall weight (Rahimi *et al.*, 2021). Diabetic rats administered polyherbal formulation showed a significant increase in Nrf-2 level while reduction in Keap-1 level. The finding indicated that polyherbal formulations exhibited dose-dependent antioxidant effects by promoting Nrf-2 nuclear translocation and reducing Keap-1 mRNA levels in pancreatic tissues of alloxan-induced diabetic rats (Aslam *et al.*, 2024).

4.3. Polyherbal Formulations Act by Targeting SGLT2 Inhibitors Involved in DM

Kidneys play a key function in maintaining glucose balance through various mechanisms, such as glucose utilization, gluconeogenesis, and reabsorption of glucose from the glomerular filtrate (Gerich, 2010). Glucose transport into renal tubular epithelial cells, facilitated by active cotransporters known as sodium-glucose cotransporters 2 (SGLT), these ATP-dependent proteins transport glucose against its concentration gradient while concurrently transporting Na+ down its concentration gradient (Glosse & Föller, 2018). Even though six distinct SGLT genes are in the human genome, only SGLT1 and SGLT2 have been thoroughly studied, with their functions in glucose transport being that SGLT1 is crucial for glucose transport in the intestine, while SGLT2 performs a similar function in the kidneys. (Vrhovac *et al.*, 2015). Most of the glucose that has been filtered is taken back into the blood through SGLT2. Investigations showed that the anti-diabetic effect and safety report of polyherbal formulations, which were further examined for their SGLT2 inhibitory activity through an *in-silico* approach, utilized the primary compounds from the herbs contained in polyherbal formulations (Kumar *et al.*, 2022).

4.4. Polyherbal Formulations Act by Targeting the IRS-PI3K-Akt-GLU Signaling Pathway Involved in DM.

Phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT) pathway plays an important function in regulating gluconeogenesis and glucose transport, making it essential for investigating glucose metabolism (Zhou *et al.*, 2024). Glucose transporter isoform 2 (GLUT2), a main variant of the GLUT family in the liver, which plays a critical function in controlling glucose uptake. The amount of glucose taken up is mainly determined by the concentration of glucose in the blood (Sooksawat *et al.*, 2024). Numerous research studies showed that the PI3K-AKT signaling pathway promotes glucose absorption through the movement of GLUT2 transporters to the cell's membrane surface in response to insulin signals (Xiao *et al.*, 2024). Studies demonstrated that the treatment with the polyherbal formulation significantly preserved the normal blood sugar levels, supported antioxidant defenses, improved fat metabolism indicators, protected liver structure, and prevented cellular changes in diabetic rats. Additionally, diabetic rats exhibited harmful effects on the mRNA expression of AMP-activated protein kinase (AMPK) and insulin receptor substrate (IRS)-PI3K-Akt-GLUT2 signaling, which were mitigated through Polyherbal formulation treatment (Haye *et al.*, 2022). Another study has also demonstrated that C-DM1 extract alleviated diabetes symptoms in mice that had been fed a high-fat diet for an extended period. This improvement was achieved by modulating IRS/PI3K/AKT and AMPK pathways in both pancreatic and liver tissues. These findings suggest that C-DM1 polyherbal formulation could potentially slow down or prevent the development of T2DM (Wang *et al.*, 2024).

4.5. Polyherbal Formulations Act by Targeting Oxidative Stress and the PKC Pathway Involved in DM.

Maintaining balance between the production and removal of free radical generation is crucial. Excessive generation of radicals can be damaging to the cells. If radical production significantly increases or their elimination decreases, oxidative stress within the cell occurs. Strong experimental and clinical evidence indicates that the production of reactive oxygen species (ROS) rises in both types of diabetes. Furthermore, the research also indicates that the beginning stages of diabetes are closely associated with an imbalance in the body's oxidative state known as oxidative stress (Matough *et al.*, 2012). The abnormalities caused by hyperglycemia are linked with disrupted nitric oxide (NO) metabolism, involving complex changes in NO production, degradation, and neutralization, which reduce NO bioavailability. Additionally, hyperglycemia-induced increases in diacylglycerol (DAG) contribute to the activation of protein kinase C (PKC) (Evcimen & King, 2007). Endothelial PKC activation in DM results in impaired endothelium-dependent vasodilation. Studies have shown that herbal formulations with glutathione demonstrate potent anti-diabetic properties by lowering the oxidative stress, which in turn prevents the activation of PKC (Sheethal *et al.*, 2023).

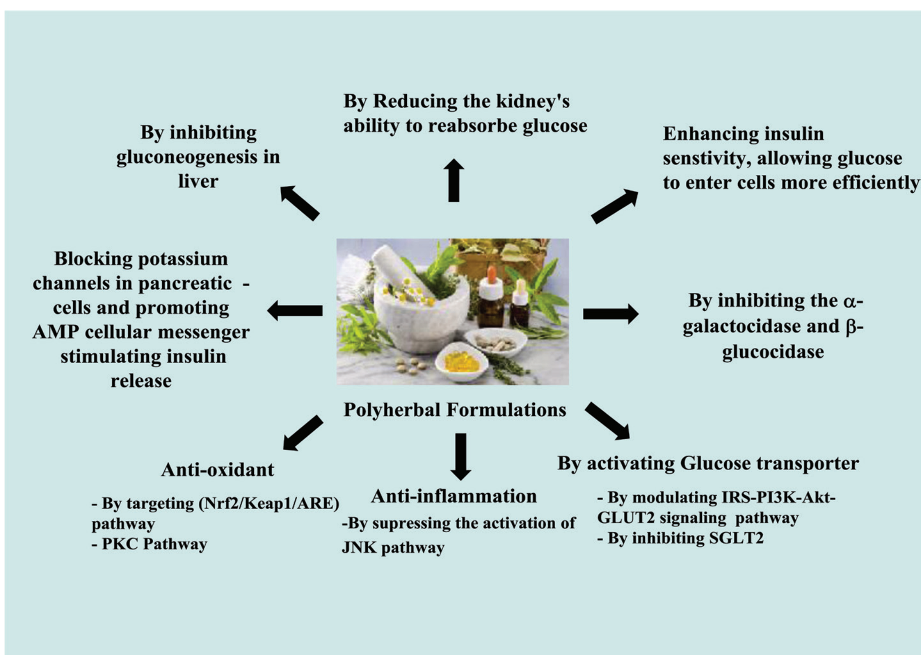

Figure 2: Polyherbal Formulations Showing Anti-Diabetic Effect by Various Mechanisms

5. Synergistic Therapeutic Actions of Polyherbal Formulations

Multiherbal preparations can work together more effectively than the single herbs due to several underlying mechanisms. These include influencing the same or different targets across various biological pathways, thereby boosting overall efficacy. They may also regulate receptors, enzymes, and transporters to enhance how well drugs are absorbed orally (Palla *et al.*, 2021). The combined effect of multiple chemical constituents, whether found in a single herb or a mixture of different herbs, can lead to synergistic effects (Sharma *et al.*, 2020). This type of polyherbal therapy is considered rational and more efficacious in multi-targeted diseases (Rajini & Muralidhara, 2023). The ability of multi-herb mixtures to both boost effectiveness and reduce adverse effects motivated our review of existing research on how well these combinations work against metabolic syndrome, a condition that is becoming more common worldwide (Sahib *et al.*, 2013). There are various preclinical and clinical studies that showed polyherbal formulations used for the management of diabetes are given below in Table 2 and Table 3.

Table 2: Preclinical Studies of Polyherbal Formulations Having Anti-Diabetic Properties

Sr. No.	Common Name	Composition of Ingredients	Mechanism of Action	Outcomes	References
1.	Diashis	*Holarrhena antidysenterica, Syzygium cumuni, Pongamia pinnata, Momordica charantia, Tinospora cordifolia, Asphultum Gymnema Sylvestre* and *Psoralea corylifolia*	Activates the secretion of insulin from β-cells	Diashis has no general toxic effect as body weights remain similar to those in the control and the 'Diashis'-treated groups. Moreover, there was no change in the activities of serum GOT and GPT in the PHF-treated group which also illustrates the nontoxic effect of 'Diashis.'	(Bera *et al.*, 2010)
2.	*Taraxacum officinale and Momordica charantia* (Polyherbal formulations)	*Taraxacum officinale and Momordica charantia*	Restore the partially damaged pancreatic β cells, supporting insulin secretion and improving glucose uptake	The polyherbal combination exerted improved antidiabetic properties; increased DPP-4, α-amylase, and α-glucosidase inhibition. The polyherbal combination tested in vivo on diabetic rats showed optimum blood glucose-lowering activity comparable to that of Glibenclamide and Metformin. Study also confirms that the polyherbal combination of T. officinale and M. charantia to be rich in various bioactive compounds, which exhibited antidiabetic properties. So, this natural PHF would serve as an alternative medication to treat T2DM with minimal or completely no side effects, unlike conventional drugs.	(Perumal *et al.*, 2022)
3.	Insuwin Forte	*Eugenia jambolana, Gymnema sylvestre, Trigonella foenum-graecum Tinospora cordifolia* and *Momordica charantia*	Enhance insulin receptor binding, increase GLUT-4 expression, slows carbohydrate digestion, protects against β-cell damage	Insuwin forte showed a superior hypoglycemic effect, improve glucose uptake by induced insulin releases, regularize lipid abnormality, better liver and kidney protection, and improve the islet of Langerhans in β-cell.	(Thangavel *et al.*, 2023)
4.	*Opuntia ficus-indica, Eclipta alba, Syzygium cumini, Coffea arabica* and *Rhus coriaria* (Polyherbal formulations)	*Opuntia ficus-indica, Eclipta alba, Syzygium cumini, Coffea arabica* and *Rhus coriaria*	Stimulate insulin secretion from β-cell and enhance insulin receptor binding	Treatment with PHF on diabetic rats induced through a high-fat diet and STZ displayed, there was a significant reduction in glucose levels, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and recovery weight loss.	(Hassan *et al.*, 2023)

5.	DB14201	*Aerva lanata* (plant with flower), *Ziziphus jujuba* (fruits with seeds), *Syzygium cumini* (fruits with seeds), *Curcuma longa.* (rhizomes), *Strychnos potatorum* (seeds), *Mangifera indica* (seed without cover), *Emblica officinalis Gaertn* (fruits), *Coscinium fenestratum (Goetgh.)* (stem with bark), *Terminalia chebula (Gaertn)* (fruits), *Biophytum sensitivum* (whole plant), *Vetiveria zizanioids* (roots), *Cyclea peltata* (rhizomes), *Salacia oblonga* (roots), *Centella asiatica* (whole plant), *Embelia tsjeriam-cottom* (seeds), *and Cyperus rotundus* (rhizomes)	Enhanced glucose uptake through the stimulation of insulin release by RIN-5f cells	The extract DB14201 demonstrated considerable increase in glucose uptake, inhibition of TNF-α and glucose co-stimulated glycerol release in 3T3-L1 adipocytes and inhibition of LPS stimulated IL-6 release in 3T3-L1 preadipocytes. It also showed increased insulin release in pancreatic β-cell.	(Pillai *et al.*, 2017)
6.	Panchvalkal	*Gymnema sylvestre, Momordica charantia, Eugenia jambolana, Tinospora cordifolia* and *Trigonella foenum-graecum*	Improve insulin sensitivity, Enhance glucose uptake in peripheral tissues	Panchvalkal modulates the expression of hexokinase, lactate dehydogenase and triphosphate isomerase genes involved in glycolysis and induces hypoglycemic effect. Thus antidiabetic attribute of Panchvalkal could be a promising resource to the communities in the prevention and treatment of T2DM.	(Singh *et al.*, 2022)
7.	Polyherbal formulation (FA1)	*Pterocarpus marsupium, Gymnema sylvestre, Trigonella foenum-graecum, Momordica charanita, Eugenia jambolana, Tinospora cordifolia, Swertia chirayita, Curcuma longa* and *Azadirachta indica*	Improve insulin sensitivity, Enhance glucose uptake in peripheral tissues	FA1(PFA) study demonstrated significant anti-diabetic effects by improving insulin sensitivity and through anti-oxidant properties. FA1 decreases blood glucose levels and improved glucose tolerance in diabetic rats. Study also demonstrated that FA1 may be a useful adjunct in the management of Diabetes particularly in improving glycemic control and insulin sensitivity.	(Mandoria *et al.*, 2021)

Table 3: Clinical Trials of Polyherbal Formulations having Anti-Diabetic Properties

Sr. No.	Identifier No.	Study Type	Interventions	Outcomes	Conditions
1.	NCT03884920	Observational	Both Diabetes Mellitus and Pre Diabetes groups were treated with Dietary Supplement: Polyherbal formulation Test candidates were administered per oral before / with meal in two divided doses	Fasting Glucose Tolerance (FGT) enhancement of fasting glucose tolerance (<100mg/dl), Glucose Tolerance (GT) enhancement of oral glucose tolerance (<140mg/dl) and HB-A1c improvement in glycated hemoglobin (HB-A1c) percentage <6% [Time Frame: six week]	Diabetes Mellitus and Pre Diabetes

2.	NCT02866539	Interventional	Polyherbal capsule coccinia, bougainvillea, catharanthus A unique combination of 3 herbs that lower blood sugars	Number of diabetes subjects achieving glycemic control a 0.5% reduction in baseline A1c and/or fasting plasma glucose below 125 mg/dl or 2 hour postprandial glucose <180 mg/dl and Number of pre-diabetes achieving euglycemic status measured as A1c < 5.7% and/or fasting plasma glucose <100mg/dl [Time Frame: 6 months]	Diabetes Mellitus

Table 4: Various Patents Of Polyherbal Formulations Having Antidiabetic Properties

Patent No.	Inventors	Title	Country Name	Filling date	Publication date	Outcomes
AU2021104048A4	Piyush Bhardwaj, Rishikesh Gupta, Pushpendra Kumar, RamNarayan Prajapati, Vijay Kumar Yadav and Vimal Kumar Yadav	A novel polyherbal extract having antidiabetic potential	Australia	2021-07-11	2021-09-09	Upon administration of ethanolic extract of polyherbal powder of leaves of Punica granatum, Beta vulgaris, and Azadirachta Indica, significant changes were recorded in blood glucose levels. The results obtained from the present study showed that the polyherbal powder of Punica granatum, Beta vulgaris, and Azadirachta indica had beneficial effects on lowering blood glucose levels. This polyherbal powder appears to be an attractive material for further studies, leading to possible drug development for diabetes.
DE202022100612U1	Mohd Nazam Ansari	Poly herbal formulation for diabetes	Germany	2022-02-03	2022-02-23	The polyherbal composition is in a dosage form. The dosage form includes, but is not limited to, tablets, soft capsules, hard capsules, pills, granules, powders, emulsions, suspensions, sprays, syrups, elixirs, and pellets. The formulation is effective in both type 1 and type 2 diabetes. The formulation may also be useful for lowering blood sugar levels and hyperlipidemia.

6. Commercially Available/ Marketed Polyherbal Formulations having Antidiabetic Properties

Table 5: Commercially Available Polyherbal Formulations having Antidiabetic Properties

Sr. No.	Common Name	Composition of Ingredients	Mechanism of Action	References
1.	Diabecon (Himalaya Drug Company), India	Bhuiavla (Phyllanthus amarus), Guggal (Commiphora wighti), Shilajeet (Asphaltum punja-bignum), Gurmar (Gymnema sylvestre), Indian kino (Pterocarpus marsupium), Licorice and sweet wood (Glycyrrhiza glabra), Jamun (Syzygium cumini), Punarnava (Boerhavia diffusa), Gorakhmundi (Sphaeranthus indicus), Giloy (Tinospora cordifolia), Tulsi (Ocimum sanctum), Chiretta (Swertia chirata), Gokharu (Tribulus terrestris), Gamhar (Gmelina arborea), Levant cotton (Gossypium herbaceum), Barberry (Berberis aristata), Aloe vera (Aloe Barbadenis), Triphala, Ampalaya (Momordica charantia), Black pepper (Piper Nigrum), Kanghi (Abutilon indicum),Vajra (Abhrak bhasma), Gurcha (Praval bhasma), Golden dock (Rumex maritimus), Bhang Bhasma (Vanga bhasma), Shatavari (Asparagus racemosus), Turmeric (Curcuma longa), and Trikatu	Improve insulin function by supporting pancreatic beta cell function	(Kapure *et al.*, 2019; Rayala *et al.*, 2024)
2.	Diasulin (Sami Labs Ltd.), India	Kundri (Coccinia indica), Ampalaya (Momordica charantia), Amla (Emblica officinalis), Gurmar (Gymnema sylvestre),Goatweed (Scoparia dulcis), Jambolan (Syzygium cumini), Methi (Trigonella foenum- graecum), Amrita and Guduchi (Tinospora cordifolia), Tarwar (Cassia auriculata), and Turmeric (Curcuma longa.)	Reducing glucose absorption in intestine and increasing insulin secretion from pancreas	(Mishra & Yadav, 2023; Saad *et al.*, 2022)
3.	Glyoherb	Mahamejva, Katuki (Picrorhiza kurrooa), Daruhaldi (Berberis aristata), Amala (Phyllanthus emblica), Chirayata (Swertia chirata), Karela (Momordica charantia), Indrajav (Holarrhena pubescens), Haridra (Curcuma longa), Gudmar (Gymnema sylvestre), Gokshur (Tribulus terretris), Jambu bij (Eugenia Jambolana), Methi (Trigonella foenum-graecum), Neem, Chandraprabha, Arogyavardhini, Bang Bhasma, Devdar, Nagarmotha (Cyperus scariosus), Haritaki (Terminalia chebula), Shuddha Shilajit, and Galo	Lowers serum cholesterol and triglyceride levels	(Kaur & Valecha, 2014)
4.	Diabeta Plus (Baidyanath Ayurved Bhawan Ltd.)	Gurmar (Gymnema sylves), Madagascar periwinkle (Catharanthus roseus), Vijayasar (Pterocarpus marsupium), Shilajit (Asphaltum), Karela (Momordica charantia), and Jamun (Syzygium cumini)	Stimulate insulin secretion, enhance insulin receptor binding, modulate key enzymes and hormones involved in glucose homeostasis	(Choudhury *et al.*, 2018)

7. Advantages of Polyherbal Formulations over Single-Herb Formulations

The existence of numerous active substances, when combined can create a synergistic effect that may not be achievable with a single compound (Rana, Badola, and Agarwal, n.d.). Polyherbal formulations, which consist of a diverse array of ingredients, target illness complications through various mechanisms, therby providing a comprehensive approach to disease treatment (Rajini & Muralidhara, 2023). These formulations are widely accepted across the globe due to their potency, affordability, easy availability, clinical efficacy, safety, high patient tolerance, making them particularly successful in managing chronic conditions (Anwar *et al*., 2022).

8. Conclusion

The most prevalent endocrine disorder, diabetes, affects around 100 million people globally. India, widely referred to as the world's diabetes capital, has seen a startling increase in the number of diabetes cases in the past ten years.

The invention of several pharmacological medications, including biguanides, thiazolidinediones, and insulin, is a result of advancements in contemporary medicine. The use of herbal medicine to treat the problems of Type I and Type II diabetes is widely acknowledged. In particular for the poor world, allopathic medication frequently has limitations in its efficacy, has a risk of side effects, and is frequently too expensive. Several plants have been used separately or in combinations to cure diabetes based on early research and scientific confirmation. Because these formulations are safe and non-toxic, their scientifically proven benefits could potentially be applied more broadly.

Abbreviations

ROS: (Reactive oxygen species), **PPAR:** (Peroxisome proliferator-activated receptor) **Foxo-1:** (Forkhead box O1), **AKT:** (Protein kinase B), **ACC1:** (Acetyl-CoA carboxylase 1), **PGC1α:** (PPAR-gamma coactivator 1 alpha), **SREPB1c:** (Sterol regulatory element-binding protein-1c), **ADA:** (Adenosine deaminase), **PEPCK:** (Phosphoenolpyruvate crboxykinase), **Fas:** (Fatty acid synthase), **HMP:** (Hexose monophosphate) and **SGLT1:** (Sodium-glucose cotransporter-1).

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Authorship Contribution

Conceptualization: Deepak Kajla. Data Analysis: Deepak Kajla; Writing of the manuscript: Suryakant Verma, Akhil Sharma, Ashi Mannan. Visualization: Suryakant Verma. Editing of the Manuscript: Suryakant Verma, Akhil Sharma, Ashi Mannan, Milind Sharad Pande, Ravinder Kumar Mehra, Manu Grover, Muhammad Tawhid. Critical Review of the article: Deepak Kajla; Supervision: Deepak Kajla. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Ethical Approvals

No ethical approvals were required for this study.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

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