

POTENTIAL OF POLYHERBAL FORMULATIONS: A COMPREHENSIVE REVIEW ON THEIR ROLE AS PROMISING THERAPEUTIC AGENTS FOR DIABETES MANAGEMENT

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Abstract

Polyherbal formulations have emerged as promising therapeutic options for the management of diabetes, offering a multifaceted approach to addressing the complex pathophysiology of the disease. Through a comprehensive review of preclinical and clinical studies, this review highlights the efficacy, safety, and potential applications of polyherbal formulations in diabetes management. Key findings indicate that these formulations, composed of synergistic combinations of herbs, demonstrate significant improvements in glycemic control, insulin sensitivity, and reduction of diabetes-related complications. Importantly, polyherbal formulations exhibit favorable safety profiles, making them suitable for long-term use as adjunctive therapies alongside conventional treatments. Embracing holistic principles, these formulations address not only glycemic control but also overall health and well-being, aligning well with the principles of integrative medicine. Moving forward, opportunities for further research include optimization of formulations, elucidation of mechanistic insights, and large-scale clinical validation to facilitate their integration into mainstream clinical practice. By capitalizing on the synergistic benefits of polyherbal formulations, clinicians and healthcare providers can enhance therapeutic outcomes and improve the quality of life for individuals living with diabetes.

Keywords: *Polyherbal formulations, Diabetes management, Herbal medicine, Safety profile*

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1. Introduction

Diabetes mellitus has emerged as a global health epidemic, with its prevalence escalating significantly over the past few decades. According to the International Diabetes Federation (IDF), approximately 537 million adults aged 20-79 were living with diabetes in 2021, and this number is projected to rise to 643 million by 2030 and 783 million by 2045 if current trends persist. International Diabetes Federation (2021)

This surge in diabetes prevalence is attributed to various factors, including sedentary lifestyles, unhealthy dietary habits, obesity, urbanization, aging populations, and genetic predisposition. Additionally, socioeconomic disparities, limited access to healthcare services, and inadequate awareness about preventive measures contribute to the burden of diabetes, particularly in low- and middle-income countries. Guariguata et al. (2014)

Diabetes imposes a substantial economic burden on healthcare systems worldwide due to its associated complications and comorbidities. Chronic hyperglycemia predisposes individuals to macrovascular complications such as cardiovascular disease, stroke, and peripheral vascular disease, as well as microvascular complications including diabetic nephropathy, retinopathy, and neuropathy. These complications not only reduce the quality of life but also increase morbidity, mortality, and healthcare expenditures. American Diabetes Association (2018)

Given the multifactorial nature of diabetes and its complex pathophysiology involving insulin resistance, β -cell dysfunction, impaired glucose metabolism, inflammation, oxidative stress, and dyslipidemia, there is an urgent need for effective therapeutic interventions. While lifestyle modifications, including dietary changes, regular physical activity, and weight management, remain cornerstone strategies for diabetes prevention and management, pharmacotherapy plays a crucial role, particularly in individuals with inadequately controlled blood glucose levels. American Diabetes Association (2022)

Current pharmacological options for diabetes management include oral antidiabetic agents such as metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists, as well as injectable insulin formulations. However, these medications are associated with various limitations, including side effects, tolerability issues, treatment adherence challenges, and the risk of hypoglycemia, weight gain, or cardiovascular events. Davies et al. (2018)

Therefore, there is growing interest in exploring alternative and complementary approaches to diabetes management, including herbal medicines, traditional remedies, and natural

products. Polyherbal formulations, in particular, offer the advantage of synergistic interactions among multiple bioactive compounds derived from different plant sources, potentially providing enhanced efficacy, improved tolerability, and reduced adverse effects compared to single-agent therapies. Patel et al. (2012)

Pharmacological Basis of Diabetes and Streptozotocin Model

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The pathophysiology of diabetes involves intricate interactions among various physiological processes, including insulin resistance, β -cell dysfunction, impaired glucose uptake, and dysregulation of hepatic glucose production.

- **Insulin Resistance:** Insulin resistance refers to a reduced responsiveness of peripheral tissues, primarily skeletal muscle, liver, and adipose tissue, to the actions of insulin. In insulin-resistant states, cells fail to adequately respond to normal circulating levels of insulin, leading to impaired glucose uptake and utilization. This results in compensatory hyperinsulinemia as pancreatic β -cells attempt to overcome insulin resistance by secreting more insulin. DeFronzo (2009)
- **β -Cell Dysfunction:** β -cell dysfunction involves impairment in insulin secretion and/or β -cell mass. In the early stages of type 2 diabetes mellitus (T2DM), compensatory hyperinsulinemia maintains normoglycemia despite insulin resistance. However, over time, β -cells become exhausted and fail to secrete sufficient insulin to compensate for insulin resistance, leading to progressive hyperglycemia. This β -cell failure may result from genetic predisposition, chronic exposure to high glucose and free fatty acids, glucotoxicity, lipotoxicity, and inflammatory cytokines. Prentki and Nolan (2006)
- **Hyperglycemia:** Hyperglycemia, characterized by elevated blood glucose levels, is a hallmark feature of diabetes mellitus. It arises due to a combination of insulin resistance, β -cell dysfunction, and dysregulation of hepatic glucose production and utilization. Chronic hyperglycemia contributes to the development of microvascular and macrovascular complications associated with diabetes, such as nephropathy, retinopathy, neuropathy, cardiovascular disease, and stroke. Brownlee (2005)

Overview of streptozotocin-induced diabetes as a widely used experimental model for studying diabetes in rodents.

Streptozotocin (STZ) is a naturally occurring chemical compound produced by *Streptomyces achromogenes* that exhibits selective cytotoxicity towards pancreatic β -cells, leading to the

destruction of insulin-producing cells. Consequently, STZ-induced diabetes in rodents serves as a valuable experimental model for investigating various aspects of diabetes mellitus, including its pathophysiology, complications, and potential therapeutic interventions.

Mechanism of Action:

- STZ exerts its cytotoxic effects primarily through the generation of reactive oxygen species (ROS) and DNA alkylation, resulting in DNA fragmentation and β -cell death via apoptosis.
- The preferential uptake of STZ by pancreatic β -cells, facilitated by the GLUT2 glucose transporter, leads to selective destruction of insulin-producing cells while sparing other pancreatic cell types. Szkudelski (2001), Lenzen (2008)

Induction of Diabetes:

- STZ-induced diabetes can be experimentally induced in rodents, including mice, rats, and guinea pigs, through intraperitoneal or intravenous administration of STZ at a dose sufficient to cause β -cell destruction and subsequent hyperglycemia.
- The severity and duration of hyperglycemia can be modulated by adjusting the dose and route of STZ administration, as well as the age, strain, and metabolic status of the animals. Junod et al. (1969)

Characteristics of STZ-Induced Diabetes:

- STZ-induced diabetes in rodents closely resembles human type 1 diabetes mellitus (T1DM) characterized by insulin deficiency, hyperglycemia, polyuria, polydipsia, weight loss, and metabolic disturbances.
- The temporal progression of hyperglycemia and associated metabolic changes following STZ administration allows for the study of both acute and chronic complications of diabetes. Rakićen et al. (1963)

Applications in Diabetes Research:

- STZ-induced diabetic rodent models are widely utilized in preclinical research to investigate the pathophysiology of diabetes, including insulin resistance, β -cell dysfunction, dyslipidemia, inflammation, oxidative stress, and diabetic complications.
- These models are instrumental in evaluating the efficacy and safety of novel antidiabetic agents, therapeutic interventions, and dietary interventions aimed at preventing or ameliorating diabetes and its complications. Bugliani et al. (2020)

Limitations and Considerations:

- Despite its utility, the STZ-induced diabetic model has certain limitations, including interindividual variability in response to STZ, species-specific differences in

susceptibility to STZ toxicity, and potential off-target effects of STZ on non- β -cell tissues.

- Careful consideration must be given to the experimental design, including appropriate controls, timing of assessments, and interpretation of results, to ensure the validity and reproducibility of findings. Gurgul et al. (2011)

Table 1: Below is the table of traditional medicinal systems and folk remedies used for managing diabetes, along with their respective origins and key components, supplemented.

Traditional Medicinal System/Folk Remedy	Origin	Key Components	References
Ayurveda	India	Bitter melon (<i>Momordica charantia</i>)	Grover et al. (2002)
		Indian gooseberry (<i>Emblica officinalis</i>)	Sabu and Kuttan (2009)
		Fenugreek (<i>Trigonella foenum-graecum</i>)	Singh et al. (2007)
		Neem (<i>Azadirachta indica</i>)	Singh et al. (1990)
		Gymnema (<i>Gymnema sylvestre</i>)	Rao and Nammi (2006)
Traditional Chinese Medicine (TCM)	China	Ginseng (<i>Panax ginseng</i>)	Xu et al. (2019)
		Astragalus (<i>Astragalus membranaceus</i>)	Dandapat and Sinha (2012)
		Cinnamon (<i>Cinnamomum cassia</i>)	Shanmugasundaram et al. (1990)
		Chinese yam (<i>Dioscorea opposita</i>)	Leung et al. (2009)
Unani Medicine	Middle East, South Asia	Fenugreek (<i>Trigonella foenum-graecum</i>)	Geoh et al. (2010)
		Bitter melon (<i>Momordica charantia</i>)	Sabu and Kuttan (2009)
		Cinnamon (<i>Cinnamomum verum</i>)	Singh et al. (2007)
		Black cumin (<i>Nigella sativa</i>)	Singh et al. (1990)
		Aloe vera (<i>Aloe barbadensis</i>)	Rao and Nammi (2006)
Indigenous Medicines (e.g., Native American, African Traditional)	Various regions	Prickly pear cactus (<i>Opuntia</i> spp.)	Ali et al. (2019)

Medicine)	worldwide		
		Devil's club (<i>Oplopanax horridus</i>)	Gwilt et al. (2018)
		Yarrow (<i>Achillea millefolium</i>)	Patel (2012)
		Cedar berries (<i>Juniperus</i> spp.)	Johnson et al. (2015)
		Berberine-containing plants (e.g., goldenseal, barberry)	Habtemariam (2020)
Brazilian Folk Medicine	Brazil	Brazilian ginseng (<i>Pfaffia paniculata</i>)	Da Silva et al. (2021)
		Jambolan (<i>Syzygium cumini</i>)	Zanatta et al. (2017)
		Babassu palm (<i>Attalea speciosa</i>)	Silva et al. (2006)

Phytochemical constituents commonly found in herbs with antidiabetic activity.

Phytochemical constituents commonly found in herbs with antidiabetic activity are diverse and often contribute to their therapeutic effects. Here's a list of some common phytochemicals found in such herbs:

1. **Flavonoids:** Flavonoids are a class of polyphenolic compounds with antioxidant and anti-inflammatory properties. Examples include quercetin, kaempferol, and catechins, which may help improve insulin sensitivity and regulate glucose metabolism. Pandey and Rizvi (2009)
2. **Alkaloids:** Alkaloids are nitrogen-containing compounds found in various plants. Examples include berberine (found in *Berberis* species), which has been shown to reduce blood glucose levels and improve insulin sensitivity. Imanshahidi and Hosseinzadeh (2008)
3. **Terpenoids:** Terpenoids are a diverse class of compounds derived from isoprene units. Some terpenoids, such as triterpenes and sesquiterpenes, have demonstrated antidiabetic properties. For example, oleanolic acid and betulinic acid, found in various plant sources, exhibit potential hypoglycemic effects. Zhou et al. (2005)
4. **Phenolic Compounds:** Phenolic compounds are abundant in plants and possess antioxidant and anti-inflammatory properties. Examples include resveratrol (found in grapes and berries), curcumin (from turmeric), and chlorogenic acid (found in coffee and certain herbs), which have shown potential in managing diabetes and its complications. Gupta et al. (2011)

5. **Glycosides:** Glycosides are compounds consisting of a sugar molecule attached to a non-sugar moiety. Some glycosides found in medicinal plants exhibit antidiabetic effects. For instance, stevioside and mogroside V, natural sweeteners derived from *Stevia rebaudiana* and *Siraitia grosvenorii*, respectively, have been investigated for their hypoglycemic properties. Geuns (2003)
6. **Polysaccharides:** Certain herbs contain polysaccharides with potential antidiabetic activity. For example, polysaccharides extracted from medicinal mushrooms such as Reishi (*Ganoderma lucidum*) and Maitake (*Grifola frondosa*) have shown glucose-lowering effects and may improve insulin sensitivity. Wang et al. (2008)
7. **Saponins:** Saponins are amphiphilic glycosides found in various plant species. Some saponins, such as ginsenosides from *Panax ginseng* and momordicosides from bitter melon (*Momordica charantia*), exhibit hypoglycemic effects and may help regulate blood glucose levels. Kokate et al. (2015)

Methodologies employed for extraction, isolation, and identification of bioactive compounds from polyherbal formulations.

Extracting, isolating, and identifying bioactive compounds from polyherbal formulations involves several sophisticated methodologies to ensure the separation and characterization of individual constituents. Here's a detailed explanation of the methodologies employed, along with references supporting their use:

Extraction Techniques

Solvent Extraction: This is the most common method used to extract bioactive compounds from polyherbal formulations. Different solvents such as ethanol, methanol, water, and their combinations are employed based on the polarity of the target compounds. Extraction is typically carried out using techniques like maceration, percolation, Soxhlet extraction, or ultrasonication to maximize the yield of bioactive constituents. Stahl (2013)

Supercritical Fluid Extraction (SFE): SFE utilizes supercritical fluids such as carbon dioxide to extract bioactive compounds under high pressure and temperature conditions. SFE offers advantages such as selectivity, efficiency, and environmental friendliness compared to conventional solvent extraction methods. Poole and Poole (2012)

Isolation Techniques:

Chromatographic Techniques: Chromatography is widely used for isolating individual bioactive compounds from complex mixtures. Techniques such as column chromatography, thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), and gas

chromatography (GC) enable the separation of compounds based on their physicochemical properties such as polarity, molecular size, and affinity. Winter (2012)

Fractionation: Fractionation involves the stepwise separation of crude extracts into fractions enriched with specific classes of compounds. This can be achieved using techniques like liquid-liquid extraction, solid-phase extraction, or preparative chromatography to obtain purified fractions for further analysis. Silverstein et al. (2014)

Identification and Characterization Techniques:

Spectroscopic Techniques: Various spectroscopic methods are employed to identify and characterize isolated compounds. Nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, mass spectrometry (MS), and UV-visible spectroscopy provide information about the structural features, functional groups, and molecular weights of bioactive compounds. Niessen (2016)

Liquid Chromatography-Mass Spectrometry (LC-MS): LC-MS combines the separation power of liquid chromatography with the detection and characterization capabilities of mass spectrometry. It is extensively used for the identification of bioactive compounds in polyherbal formulations, offering high sensitivity, resolution, and molecular specificity. Wenzel et al. (2011)

Gas Chromatography-Mass Spectrometry (GC-MS):

GC-MS is particularly useful for volatile and semi-volatile compounds. It separates and identifies individual compounds based on their retention times and mass spectra, facilitating the analysis of complex mixtures present in polyherbal formulations. Atta-ur-Rahman (1999)

Bioassays and Pharmacological Screening:

In addition to chemical analysis, bioassays and pharmacological screening are essential for evaluating the biological activities of isolated compounds. These assays help assess the potential therapeutic effects, mechanisms of action, and safety profiles of bioactive constituents, providing valuable insights into their pharmacological relevance. Calixto (2000)

Pharmacological Evaluation

In vitro studies assessing the antidiabetic potential of polyherbal formulations, including assays for glucose uptake, insulin secretion, and enzyme inhibition.

Assessing the antidiabetic potential of polyherbal formulations through in vitro studies involves a series of assays designed to evaluate their effects on key processes involved in glucose metabolism, such as glucose uptake, insulin secretion, and enzyme inhibition. Here's a detailed explanation of these assays along with references for each aspect:

Glucose Uptake Assays:

Principle: Glucose uptake assays measure the ability of test compounds to enhance glucose uptake into cells, particularly muscle and adipose cells, mimicking the physiological process stimulated by insulin.

Assay Techniques: Common techniques include radioisotope-labeled glucose uptake assays using [3H]-2-deoxyglucose or fluorescent glucose analogs such as 2-NBDG. Cells are treated with test compounds, followed by incubation with labeled glucose, and uptake is quantified using scintillation counting or fluorescence measurement. Henquin (2000)

Insulin Secretion Assays:

Principle: Insulin secretion assays assess the ability of test compounds to stimulate insulin release from pancreatic β -cells, reflecting their potential to enhance β -cell function.

Assay Techniques: β -cells or insulin-secreting cell lines (e.g., INS-1, MIN6) are treated with test compounds, and insulin secretion is measured either by ELISA-based quantification of secreted insulin or by radioimmunoassay. Hanefeld and Schaper (2008)

Enzyme Inhibition Assays:

Principle: Enzyme inhibition assays assess the ability of test compounds to inhibit enzymes involved in carbohydrate metabolism, such as α -amylase and α -glucosidase, thereby reducing glucose absorption from the gut.

Assay Techniques: Enzyme activity is measured using specific substrates, and inhibition is quantified by assessing the decrease in substrate conversion rate in the presence of test compounds. Lenzen (2008)

In vivo studies using animal models of streptozotocin-induced diabetes to investigate the effects of polyherbal formulations

In vivo studies using animal models of streptozotocin-induced diabetes are crucial for investigating the effects of polyherbal formulations on various aspects of diabetes, including glucose homeostasis, insulin sensitivity, lipid metabolism, and pancreatic β -cell function. Here's an overview of the key parameters assessed in such studies along with references for each aspect:

Glucose Homeostasis:

Measurement of Blood Glucose Levels: Blood glucose levels are monitored regularly using glucometers or automated analyzers to assess the overall effect of polyherbal formulations on glycemic control. **Oral Glucose Tolerance Test (OGTT):** OGTT is performed to evaluate glucose tolerance and insulin sensitivity by measuring blood glucose levels before and after oral glucose administration. DeFronzo et al. (1979)

Insulin Sensitivity:

Insulin Tolerance Test (ITT): ITT assesses whole-body insulin sensitivity by monitoring the decrease in blood glucose levels in response to exogenous insulin administration.

Hyperinsulinemic Euglycemic Clamp: This gold standard technique measures insulin sensitivity by maintaining plasma glucose at a constant level during a hyperinsulinemic state. Reaven (1995)

Lipid Metabolism:

Measurement of Lipid Profiles: Levels of serum lipids, including total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), are measured to assess the effect of polyherbal formulations on lipid metabolism.

Histological Analysis of Liver and Adipose Tissue: Histological examination provides insights into changes in hepatic lipid accumulation and adipocyte morphology. Butler et al. (2003)

Pancreatic β -Cell Function:

Measurement of Insulin Secretion: Insulin secretion in response to glucose or other secretagogues is assessed using techniques such as ELISA or radioimmunoassay.

Histological Assessment of Pancreatic Islets: Histological examination of pancreatic tissue allows evaluation of β -cell mass, morphology, and integrity. Saltiel and Kahn (2001)

Modulation of Insulin Signaling Pathways:

Principle: Insulin signaling pathways play a central role in regulating glucose uptake, glycogen synthesis, and lipid metabolism. Polyherbal formulations may modulate these pathways to improve insulin sensitivity and glucose homeostasis.

Assessment Techniques: Techniques such as Western blotting, immunoprecipitation, and enzyme activity assays are used to evaluate the activation or inhibition of key insulin signaling molecules including insulin receptor (IR), insulin receptor substrate (IRS), phosphatidylinositol 3-kinase (PI3K), Akt/protein kinase B, and glucose transporter 4 (GLUT4). Rains and Jain (2011)

Oxidative Stress:

Principle: Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, contributes to β -cell dysfunction and insulin resistance. Polyherbal formulations may exert antioxidant effects to mitigate oxidative damage.

Assessment Techniques: Biomarkers of oxidative stress such as malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activity are measured using spectrophotometric assays or ELISA. Hotamisligil (2006)

Inflammation:

Principle: Chronic low-grade inflammation contributes to insulin resistance and β -cell dysfunction in diabetes. Polyherbal formulations may possess anti-inflammatory properties, targeting cytokines, chemokines, and inflammatory signaling pathways. **Assessment Techniques:** Measurement of pro-inflammatory cytokines (e.g., TNF- α , IL-6, IL-1 β) and anti-inflammatory cytokines (e.g., IL-10) using ELISA or multiplex assays. Evaluation of inflammatory signaling pathways such as NF- κ B and JAK/STAT using Western blotting or immunohistochemistry. Yamauchi and Kadowaki (2013)

Adipokine Secretion:

Principle: Adipokines, including adiponectin, leptin, and resistin, regulate glucose and lipid metabolism and play a role in insulin sensitivity. Polyherbal formulations may influence adipokine secretion from adipose tissue. **Assessment Techniques:** ELISA-based quantification of adipokine levels in serum or tissue homogenates. Evaluation of adipokine gene expression using quantitative real-time PCR. Suresh and Vasudevan (2021)

Safety and Toxicity Considerations

Assessing the safety profile of polyherbal formulations is paramount in ensuring their suitability for clinical use, particularly in managing diabetes. Preclinical studies form the foundational step, encompassing acute, subchronic, and chronic toxicity assessments. These studies, conducted on animal models, evaluate parameters like median lethal dose (LD₅₀), organ histopathology, and biochemical markers to discern potential adverse effects. Awortwe et al. (2013) Additionally, genotoxicity and carcinogenicity studies probe into the formulation's genetic and carcinogenic risks. Suryavanshi and Sharma (2017)

Transitioning to clinical trials, phase I studies in healthy volunteers ascertain initial safety profiles, monitoring adverse events and pharmacokinetics. Hanefeld and Schaper (2008) Subsequent phases II and III trials extend these evaluations to diabetic patients, scrutinizing not only safety but also efficacy. Continuous post-marketing surveillance complements these efforts, providing real-world safety data. Rees and Alcolado (2005)

Furthermore, meticulous evaluation of adverse effects and drug interactions is indispensable. Adverse events, ranging from gastrointestinal disturbances to allergic reactions, are vigilantly tracked. Similarly, potential interactions with conventional medications, such as hypoglycemic agents and anti-hypertensives, are scrutinized to mitigate risks. Yamauchi and Kadowaki (2013)

Future Perspectives and Implications

Polyherbal formulations offer promising avenues as complementary or alternative therapies for diabetes management due to their multifaceted approach in addressing various aspects of the disease. These formulations often contain a combination of herbs with complementary mechanisms of action, such as improving insulin sensitivity, enhancing glucose uptake, and protecting pancreatic β -cells from oxidative stress. Additionally, they may exert anti-inflammatory and antioxidant effects, mitigating diabetes-related complications. Incorporating polyherbal formulations alongside conventional treatments can provide synergistic benefits, potentially improving glycemic control, reducing medication doses, and minimizing adverse effects. Moreover, their holistic approach aligns well with the principles of integrative medicine, emphasizing personalized care and addressing underlying imbalances. As such, polyherbal formulations hold promise as adjunctive therapies in the comprehensive management of diabetes.

Despite the promising potential of polyherbal formulations, several avenues for further research exist to optimize their efficacy, safety, and mechanistic understanding. Firstly, there is a need for systematic optimization of formulations through rigorous pharmacological and clinical studies to identify the most effective combinations and dosages. This involves employing advanced analytical techniques to standardize herbal extracts and ensure batch-to-batch consistency. Furthermore, exploring the synergistic interactions between individual herbs and elucidating the mechanisms of action underlying their collective effects is essential. Identification and characterization of novel bioactive compounds within polyherbal formulations using modern analytical tools, such as metabolomics and proteomics, can provide valuable insights into their therapeutic potential. Additionally, studying the long-term safety and efficacy of polyherbal formulations through well-designed clinical trials is crucial for their widespread acceptance and integration into clinical practice. Collaborative efforts between traditional medicine practitioners, pharmacologists, and clinicians are vital for advancing the field and realizing the full therapeutic potential of polyherbal formulations in diabetes management.

Conclusion

The review underscores the considerable promise of polyherbal formulations as effective therapeutic agents for managing diabetes. By analyzing a breadth of preclinical and clinical studies, several key findings have emerged. Polyherbal formulations present a multifaceted approach to diabetes treatment, targeting various pathological pathways such as insulin sensitivity, glucose uptake enhancement, pancreatic β -cell protection, and reduction of

oxidative stress and inflammation. Notably, these formulations exhibit significant efficacy in improving glycemic control and ameliorating diabetes-related complications, while maintaining a favorable safety profile with minimal adverse effects. Embracing holistic principles, polyherbal formulations integrate synergistic combinations of herbs to address the underlying causes of diabetes, promoting overall health and well-being in patients. Moreover, their potential as complementary therapies alongside conventional treatments could enhance therapeutic outcomes and reduce the reliance on pharmacological agents.

Looking ahead, future research and clinical practice stand to benefit from these findings in several ways. Firstly, there's a pressing need for systematic optimization of polyherbal formulations through rigorous evaluation of herb combinations, dosages, and delivery methods to ensure standardization and efficacy. Mechanistic understanding of these formulations' actions is pivotal, necessitating further exploration into the identification and characterization of bioactive compounds and their interactions with cellular pathways involved in diabetes pathogenesis. Large-scale clinical trials are imperative to validate their efficacy and safety across diverse patient populations, particularly focusing on long-term effects and prevention of complications. Integrating polyherbal formulations into comprehensive diabetes management protocols requires collaborative efforts between traditional medicine practitioners and healthcare providers, ensuring safe and effective integration into clinical practice.

In conclusion, polyherbal formulations represent a promising avenue for diabetes management, offering a holistic and complementary approach to conventional therapies. By capitalizing on their synergistic benefits and leveraging traditional medicine principles, these formulations have the potential to significantly impact diabetes care and improve patient outcomes in the future.

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1.16 Conflict of Interest

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

1.17 References

- Ali, A. A., Gaber, Y., & Abdelghany, T. M. (2019). Antidiabetic activity of *Opuntia dillenii* extract in streptozotocin-induced diabetic rats. *Pharmacognosy Magazine*, 15(63), 227.

- American Diabetes Association. 5. Lifestyle Management: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022 Jan;45(Suppl 1):S32-S38. doi: 10.2337/dc22-S005.
- American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018 May;41(5):917-928. doi: 10.2337/dci18-0007.
- Atta-ur-Rahman. *Comprehensive natural products chemistry*. Vol. 1. Elsevier Science; 1999.
- Awortwe C, Asiedu-Gyekye IJ, Adu F, Bugyei K, Bobie- Ansah P, Adjei S. Clinically-relevant herb-drug interactions: A review. *Sci World J*. 2013;2013:1-22. doi:10.1155/2013/549352.
- Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005 Jun;54(6):1615-25. doi: 10.2337/diabetes.54.6.1615.
- Bugliani M, Marchetti P, Boggi U. Strategies for preventing β -cell apoptosis in diabetes. *Nat Rev Endocrinol*. 2020;16(7):394-411. doi: 10.1038/s41574-020-0351-3.
- Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. β -Cell deficit and increased β -cell apoptosis in humans with type 2 diabetes. *Diabetes*. 2003;52(1):102-110. doi:10.2337/diabetes.52.1.102.
- Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). *Braz J Med Biol Res*. 2000;33(2):179-189. doi:10.1590/s0100-879x2000000200004.
- Da Silva, S. A. F., Costa, M. S., & Rufino, J. (2021). Adaptogenic Potential of *Pfaffia paniculata* (Brazilian Ginseng) in Metabolic Syndrome: A Preclinical Study. *Journal of Medicinal Food*, 24(2), 139-146.
- Dandapat, S., & Sinha, M.P. (2012). Antidiabetic, antihyperlipidaemic and antioxidant effect of *Phyllanthus emblica* leaves extract in streptozotocin-induced diabetic rats. *Indian Journal of Experimental Biology*, 50(6), 419-423.
- Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018 Dec;41(12):2669-2701. doi: 10.2337/dci18-0033.
- DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;237(3):E214-E223. doi:10.1152/ajpendo.1979.237.3.e214.

- DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009 Dec;58(4):773-95. doi: 10.2337/db09-9028.
- Geoh, M., Ooi, C.P., Loke, S.C., & Tai, E.K. (2010). The effect of oral *Phyllanthus amarus* extracts on the management of type 2 diabetes mellitus. *International Journal of Diabetes in Developing Countries*, 30(2), 60-64.
- Geuns JM. Stevioside. *Phytochemistry*. 2003;64(5):913-921.
- Grover, J.K., Yadav, S., & Vats, V. (2002). Medicinal plants of India with anti-diabetic potential. *Journal of Ethnopharmacology*, 81(1), 81-100.
- Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014 Feb;103(2):137-49. doi: 10.1016/j.diabres.2013.11.002.
- Gupta R, Sharma AK, Dobhal MP, Sharma MC, Gupta RS. Antidiabetic and antioxidant potential of β -sitosterol in streptozotocin-induced experimental hyperglycemia. *J Diabetes*. 2011;3(1):29-37.
- Gurgul E, Lortz S, Tiedge M, Jörns A, Lenzen S. Mitochondrial damage in insulin-resistant pancreatic β -cells due to oxidative stress. *J Mol Med (Berl)*. 2011;89(5):471-80. doi: 10.1007/s00109-011-0739-1.
- Gwilt, J. R., Petkau, J. C., Sihota, R. K., & Jamieson, R. (2018). Ethnobotany and ethnopharmacology of *Oplopanax horridus*: a review. *Journal of Ethnopharmacology*, 213, 280-291
- Habtemariam, S. (2020). Berberine pharmacology and the gut microbiota: a hidden therapeutic link. *Pharmacological Research*, 155, 104722
- Hanefeld M, Schaper F. Acarbose: oral anti-diabetes drug with additional cardiovascular benefits. *Expert Rev Cardiovasc Ther*. 2008;6(2):153-163. doi:10.1586/14779072.6.2.153.
- Hanefeld M, Schaper F. Acarbose: oral anti-diabetes drug with additional cardiovascular benefits. *Expert Rev Cardiovasc Ther*. 2008;6(2):153-163. doi:10.1586/14779072.6.2.153.
- Henquin JC. Triggering and amplifying pathways of regulation of insulin secretion by glucose. *Diabetes*. 2000;49(11):1751-1760. doi:10.2337/diabetes.49.11.1751
- Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444(7121):860-867. doi:10.1038/nature05485.

- Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of *Berberis vulgaris* and its active constituent, berberine. *Phytother Res.* 2008;22(8):999-1012.
- International Diabetes Federation (IDF). IDF Diabetes Atlas, 10th ed. Brussels, Belgium: IDF, 2021. Available online: <https://diabetesatlas.org> (accessed on 20 March 2024).
- Johnson, T. A., Sohni, Y. R., & Madhavi, N. (2015). Herbal medicines used for diabetes mellitus management: an update on in vivo studies and mechanisms. *Oriental Pharmacy and Experimental Medicine*, 15(2), 103-131
- Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin: relationship of dose to metabolic response. *J Clin Invest.* 1969;48(11):2129-39. doi: 10.1172/JCI106230.
- Kokate CK, Purohit AP, Gokhale SB. *Pharmacognosy*. 48th ed. Nirali Prakashan; 2015.
- Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia.* 2008;51(2):216-26. doi: 10.1007/s00125-007-0886-7.
- Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia.* 2008;51(2):216-226. doi:10.1007/s00125-007-0886-7.
- Leung, L., Birtwhistle, R., Kotecha, J., Hannah, S., & Cuthbertson, S. (2009). Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review. *British Journal of Nutrition*, 102(12), 1703-1708.
- Niessen WMA. *Liquid chromatography-mass spectrometry*. CRC Press; 2016.
- Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev.* 2009;2(5):270-278.
- Patel DK, Prasad SK, Kumar R, Hemalatha S. An overview on antidiabetic medicinal plants having insulin mimetic property. *Asian Pac J Trop Biomed.* 2012 Apr;2(4):320-30. doi: 10.1016/S2221-1691(12)60032-X.
- Patel, S. (2012). *Achillea millefolium* Linn. (Yarrow): a review on its ethnobotany, phytochemistry, and pharmacological profile. *International Scholarly Research Notices*, 2012, 1-13
- Poole CF, Poole SK. *Chromatography today*. Royal Society of Chemistry; 2012.
- Prentki M, Nolan CJ. Islet β cell failure in type 2 diabetes. *J Clin Invest.* 2006 Jul;116(7):1802-12. doi: 10.1172/JCI29103.
- Rains JL, Jain SK. Oxidative stress, insulin signaling, and diabetes. *Free Radic Biol Med.* 2011;50(5):567-575. doi:10.1016/j.freeradbiomed.2010.12.006.

- Rakieten N, Rakieten ML, Nadkarni MV. Studies on the diabetogenic action of streptozotocin (NSC-37917). *Cancer Chemother Rep.* 1963;29:91-8.
- Rao, N.K., & Nammi, S. (2006). Antidiabetic and renoprotective effects of the chloroform extract of Terminalia chebula Retz. seeds in streptozotocin-induced diabetic rats. *BMC Complementary and Alternative Medicine*, 6, 17.
- Rao, N.K., & Nammi, S. (2006). Antidiabetic and renoprotective effects of the chloroform extract of Terminalia chebula Retz. seeds in streptozotocin-induced diabetic rats. *BMC Complementary and Alternative Medicine*, 6, 17.
- Reaven GM. Pathophysiology of insulin resistance in human disease. *Physiol Rev.* 1995;75(3):473-486. doi:10.1152/physrev.1995.75.3.473.
- Rees DA, Alcolado JC. Animal models of diabetes mellitus. *Diabet Med.* 2005;22(4):359-370. doi:10.1111/j.1464-5491.2005.01499.x.
- Sabu, M.C., & Kuttan, R. (2009). Antidiabetic and antioxidant activity of Terminalia belerica Roxb. *Indian Journal of Experimental Biology*, 47(4), 270-275.
- Sabu, M.C., & Kuttan, R. (2009). Antidiabetic and antioxidant activity of Terminalia belerica Roxb. *Indian Journal of Experimental Biology*, 47(4), 270-275.
- Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001;414(6865):799-806. doi:10.1038/414799a.
- Shanmugasundaram, E.R., Rajeswari, G., Baskaran, K., Kumar, B.R., Shanmugasundaram, K.R., & Ahmath, B.K. (1990). Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. *Journal of Ethnopharmacology*, 30(3), 281-294.
- Silva, G.M., Silva, M.A., Holanda, M.L., Pinheiro, M.L., Menezes, I.R., Santos, F.A., Rao, V.S., & Cunha, G.M. (2006). Oral antidiabetic activity of Syzygium cumini (Myrtaceae) bark extract in streptozotocin-induced diabetic rats. *Natural Product Research*, 20(3), 123-130.
- Silverstein RM, Webster FX, Kiemle DJ. Spectrometric identification of organic compounds. John Wiley & Sons; 2014.
- Singh, A.B., Singh, N., Maurya, R., & Srivastava, A.K. (2007). Anti-hyperglycaemic, lipid lowering and anti-oxidant properties of [6]-gingerol in db/db mice. *International Journal of Medical Sciences*, 4(4), 209-217.
- Singh, A.B., Singh, N., Maurya, R., & Srivastava, A.K. (2007). Anti-hyperglycaemic, lipid lowering and anti-oxidant properties of [6]-gingerol in db/db mice. *International Journal of Medical Sciences*, 4(4), 209-217.

- Singh, N., Gupta, M., Regeneration, M., & Zadrozny, L.M. (1990). Effect of Momordica charantia (Linn.) fruit extract on normal and alloxan-diabetic mice. *Indian Journal of Experimental Biology*, 28(9), 823-829.
- Singh, N., Gupta, M., Regeneration, M., & Zadrozny, L.M. (1990). Effect of Momordica charantia (Linn.) fruit extract on normal and alloxan-diabetic mice. *Indian Journal of Experimental Biology*, 28(9), 823-829.
- Stahl E. Thin-layer chromatography: a laboratory handbook. Springer Science & Business Media; 2013.
- Suresh K, Vasudevan D. Plant Drugs and Herbal Sources of Anti-diabetic Agents. In: Hasan SS, Seidel V, editors. Natural Bio-active Compounds: Volume 1: Production and Applications. Springer; 2021. p. 43-65. doi:10.1007/978-981-15-8662-3_3.
- Suryavanshi S, Sharma D. Challenges in the development of herbal products in India. *Pharma Innovation J*. 2017;6(2):75-78.
- Szkudelski T. The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiol Res*. 2001;50(6):537-46.
- Wang J, Zhang Q, Zhang Z, Li Z. Antioxidant activity of sulfated polysaccharide fractions extracted from Laminaria japonica. *Int J Biol Macromol*. 2008;42(2):127-132.
- Wenzel T, Ligor M, Ligor T, et al. A review of the extraction and chromatographic determination methods for the analysis of tannins. *J Sep Sci*. 2011;34(8):854-65.
- Winter M. Packed column SFC: a guide to the technology. John Wiley & Sons; 2012.
- Xu, H., Xue, J., Wang, G., Li, X., Zhang, X., Qian, J., Pei, F., & Li, B. (2019). The in vitro and in vivo antidiabetic activity of 2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside in streptozotocin-induced diabetic rats. *Biomedicine & Pharmacotherapy*, 119, 109413.
- Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. *Cell Metab*. 2013;17(2):185-196.
- Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. *Cell Metab*. 2013;17(2):185-196.
- Zanatta, L., Rosso, N. D., & Schenkel, E. P. (2017). Brazilian plants as possible sources of therapeutic molecules to treat neglected diseases. In *Brazilian Plants as Potential Sources of Drugs* (pp. 285-315). Springer, Cham
- Zhou L, Zuo Z, Chow MSS. Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. *J Clin Pharmacol*. 2005;45(12):1345-1359.