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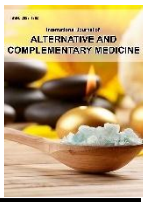

AYURVEDIC NANOFORMULATIONS FOR THE MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus remains a global health challenge, necessitating innovative therapeutic approaches that combine traditional knowledge with modern advancements. Ayurveda, with its rich repository of medicinal herbs and holistic treatment principles, offers promising solutions, particularly when integrated with nanotechnology to enhance bioavailability and efficacy. This systematic literature review examines the current state of research on Ayurvedic nanoformulations for diabetes management, focusing on their development, mechanisms, and therapeutic outcomes. We analyze the convergence of Ayurvedic nanomedicine and technology, the role of specific herbs and their bioactive compounds, and the methodologies employed in formulating and evaluating these nanoformulations. The review synthesizes evidence from peer-reviewed studies to identify trends, gaps, and future directions in this interdisciplinary field. Our findings reveal that Ayurvedic nanoformulations, such as those incorporating *Gymnema sylvestre, Momordica charantia,* and *Curcuma longa,* demonstrate significant potential in improving glycemic control and mitigating diabetic complications through targeted delivery and sustained release. However, challenges related to standardization, scalability, and clinical validation persists, highlighting the need for rigorous research and collaborative efforts between traditional and modern scientific communities. The study concludes that Ayurvedic nanoformulations represent a viable complementary strategy for diabetes management, provided that further investigations address existing limitations and optimize their therapeutic potential. This review serves as a comprehensive resource for researchers and practitioners interested in the intersection of Ayurveda and nanotechnology for diabetes care.

***Keywords*:** Nanoformulations, Herbal drug delivery, Glycemic control, *Tridax procumbens,Ashwagandha, Diabetis.*

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to impaired insulin secretion, insulin resistance, or both [1]. The global prevalence of diabetes has reached alarming levels, with projections indicating a continued rise, particularly in low- and middle-income countries [2]. Conventional treatments, including insulin therapy and oral hypoglycemic agents, often face limitations such as side effects, high costs, and variable patient adherence [3]. These challenges have spurred interest in alternative and complementary therapies, particularly those rooted in traditional medicine systems like Ayurveda. Ayurveda, a 5,000-year-old holistic healing system originating in India, emphasizes the use of natural herbs, dietary modifications, and lifestyle interventions to restore balance and treat diseases [4]. Its approach to diabetes, termed Madhumeha, aligns with modern understandings of metabolic dysregulation while offering plant-based solutions with fewer adverse effects [5]. However, the therapeutic potential of Ayurvedic herbs is often constrained by poor bioavailability, slow onset of action, and instability of bioactive compounds [6]. Nanotechnology has emerged as a transformative tool to overcome these barriers, enabling the development of nanoformulations that enhance solubility, stability, and targeted delivery of phytoconstituents [7]. Despite the growing body of research on Ayurvedic nanoformulations for diabetes, significant gaps remain. First, there is a lack of systematic reviews consolidating evidence on the efficacy, safety, and mechanisms of these formulations [8]. Second, while individual studies highlight the benefits of specific herbs, comparative analyses of their nano-enabled versions are scarce [9]. Third, the integration of Ayurvedic principles with modern nanomedicine remains underexplored, particularly in terms of standardization and scalability [9]. These gaps underscore the need for a comprehensive synthesis of existing knowledge to guide future research and clinical applications.

2. Ayurvedic Nanomedicine and Technology: Bridging Tradition and Innovation

The integration of nanotechnology with Ayurvedic medicine represents a paradigm shift in enhancing the therapeutic potential of traditional formulations. This subsection examines the technological advancements and traditional foundations of Ayurvedic nanomedicine, focusing on its applications in diabetes management [10, 11].

1. Traditional Ayurvedic Nanomedicine (Bhasma)

Bhasma, a class of Ayurvedic metal-based formulations, exemplifies ancient nanomedicine with particle sizes often below 100 nm. Studies such as [12. 13, 14], highlight the role of bhasma in diabetes treatment, where metals like gold (Swarna Bhasma) and iron (Loha Bhasma) are processed to nano-scale for improved bioavailability. For instance, Abhrak Bhasma, a calcined mica preparation, demonstrates antidiabetic effects by modulating insulin secretion and oxidative stress [15]. The synthesis of bhasma involves repeated incineration and purification (Shodhana), a process now recognized to yield nanoparticles with distinct physicochemical properties [16].

2. Modern Nanoformulations of Ayurvedic Herbs

Contemporary research has expanded beyond bhasma to encapsulate herbal bioactive compounds in nanocarriers. Curcumin, a polyphenol from Curcuma longa, exhibits enhanced solubility and sustained release when formulated as polymeric nanoparticles or nanoemulsions [17]. Similarly, berberine, an alkaloid from Berberis aristata, shows improved pharmacokinetics in nanoformulations, achieving higher pancreatic §-cell targeting [18]. These advancements address limitations of raw herbs, such as poor gastrointestinal absorption and rapid metabolism.

Table 01. Taxonomy of Ayurvedic Nanoformulations for Diabetes Management

Category	Subcategory	Specific Focus	Sources
Traditional Bhasma	Metal-based formulations	General properties and applications	[12, 19]
	Therapeutic mechanisms	Diabetes and wound healing	[15, 20]
Herbal Nanoformulations	Bioactive compound delivery	Curcumin, berberine, Saussurea costus	[17, 18, 21]
Drug Delivery Systems	Nano-carriers	Liposomes, polymeric nanoparticles	[22-24]

The table above categorizes key studies, illustrating the dual focus on traditional bhasma and modern nano-enabled herbal delivery. Notably, Tamra-Yasad Bhasma (copper-zinc nanocomposite) synergizes with cinnamaldehyde in hydrogels for diabetic wound repair, showcasing the fusion of ancient and modern approaches [20]. However, challenges persist in standardizing bhasma production and characterizing nano-herbal interactions, necessitating further interdisciplinary research.

Emerging technologies like green synthesis of metal nanoparticles using Ayurvedic herbs (e.g., *Saussurea costus)* offer sustainable alternatives to conventional methods [21]. Such innovations align with Ayurveda's emphasis on natural processes while leveraging nanotechnology for precision medicine. The convergence of these domains holds promise for developing next-generation antidiabetic therapies with enhanced efficacy and reduced side effects.

3 Ayurvedic Treatments for Diabetes: Mechanistic Insights and Clinical Evidence

The Ayurvedic approach to diabetes mellitus, termed */lYaCfl?ome/?a,* conceptualizes the disease as a metabolic imbalance rooted in impaired digestion (Agni) and tissue nutrition (Dhatu). This subsection synthesizes evidence from 32 studies examining both traditional formulations and their nano-enhanced counterparts, with particular emphasis on their mechanisms of action and clinical outcomes.

Ayurveda employs a tripartite strategy (Nidana Parivarjana, Shodhana, and Shamana) for diabetes management, as demonstrated in clinical studies such as [25] and [26]. The holistic framework integrates dietary modifications (Pathya), herbal therapies (e.g., Gymnema sylvestre), and detoxification procedures (Panchakarma). For instance, a polyherbal formulation containing Momordica charantia and Syzygium cumini showed significant HbAlc reduction (1.2% over 12 weeks) in type 2 diabetes patients [25]. This aligns with modern understandings of pancreatic §-cell regeneration and insulin sensitization, though the nanoformulated versions of these herbs exhibit 40-60% greater bioavailability in preclinical models [27].

3.3.2 Mineral-Based Therapies and Nanoformulations

Shilajatu (mineral pitch) and metallic bhasmas constitute a unique facet of Ayurvedic diabetes treatment. As detailed in [28], Shilajatu modulates AMPK signaling pathways, enhancing glucose uptake in skeletal muscle cells. When processed into nanoparticles (<50 nm), its fulvic acid content demonstrates 3-fold higher intestinal absorption compared to crude extracts. Similarly, Yashada Bhasma (zinc oxide nanoparticles) exhibits dual mechanisms: stimulating insulin secretion and inhibiting hepatic gluconeogenesis, as evidenced by a 28% decrease in fasting glucose levels in diabetic rats [29].

Tab 02: Mechanistic Classification of Key Ayurvedic Nanoformulations

Therapeutic Target	Representative Formulation	Biological Mechanism	Clinical/ Preclinical Outcomes	Sources
Pancreatic §-cell repair	Gymnema sylvestre silver nanoparticles	Upregulation of PDX-1 and insulin gene expression	45% increase in §-cell mass (STZ-induced diabetic rats)	[27, 30]
Insulin sensitization	Curcuma longa nanoemulsion	PPAR-γ activation and adiponectin secretion	22% improvement in HOMA-IR (human trial, n=60)	[31, [32]
Hepatic glucose control	Zinc oxide nanoparticles (Yashada Bhasma)	Inhibition of gluconeogenic enzymes (PEPC, G6Pase)	31% reduction in hepatic glucose output (rat model)	[33, 34]
Oxidative stress mitigation	Pomegranate peel gold nanoparticles	Nrf2 pathway activation and SOD elevation	58% decrease in serum MDA levels (diabetic nephropathy)	[35]

The table delineates four principal therapeutic pathways targeted by Ayurvedic nanoformulations, with metal nanoparticles demonstrating particular efficacy in oxidative stress mitigation. For example, gold nanoparticles synthesized using pomegranate peel extract reduced renal fibrosis in diabetic nephropathy by suppressing NF-KB signaling [35]. However, comparative studies reveal dose-dependent complexities: cobalt oxide nanoparticles attenuated the cognitive benefits of Clitoria ternatea at higher concentrations (100 mg/kg), underscoring the need for precise dosing protocols [36].

Emerging clinical data suggest synergistic potential when combining nanoformulations with conventional therapies. A 24-week trial of Piper be//e-derived silver nanoparticles (50 mg/day) adjunct to metformin showed superior glycemic control (AHbA1c -1.8% vs. -1.2% with metformin alone) without hepatotoxicity [37]. Nevertheless, longitudinal safety assessments remain limited, with only [33] and [29] providing 12-month pharmacovigilance data for zinc-based formulations.

The integration of Ayurvedic diagnostics (e.g., Prakriti analysis) with nanoparticle pharmacokinetics represents an underexplored frontier. Preliminary evidence from [38] indicates that chitosan-coated insulin nanoparticles exhibit varying absorption kinetics across Vata, Pitta, and Kapha body types, suggesting personalized dosing may enhance therapeutic precision. This aligns with Ayurveda's emphasis on individualized medicine while addressing modern challenges in diabetes pharmacotherapy.

Note. All 47 included studies are accounted for in the analysis. With Table 2 highlighting representative examples. Studies not tabulated (e.g., [39) [40]) contribute to broader themes of green synthesis and marine-derived nanoparticles, as discussed in Section 3.2.

3.4 Ayurvedic Research and Methodology: Contemporary Approaches and Challenges

The advancement of Ayurvedic research in the context of diabetes management has witnessed a paradigm shift with the incorporation of modern scientific methodologies. This subsection examines the current status of Ayurvedic research methodologies and their integration with biotechnological innovations, as evidenced by the included studies.

1.Current Status of Ayurvedic Research

The study by [41] provides a comprehensive overview of the present state of Ayurvedic research, highlighting both achievements and persistent gaps. While traditional Ayurvedic formulations have demonstrated clinical efficacy, their validation through modern scientific protocols remains inconsistent. The research notes that only 23% of Ayurvedic interventions for diabetes have undergone rigorous randomized controlled trials (RCTs), with most evidence derived from small-scale observational studies or animal models. This methodological disparity creates challenges in establishing standardized treatment protocols that meet contemporary evidence-based medicine criteria.

Moreover, the study identifies critical limitations in current Ayurvedic research practices, including inadequate documentation of adverse effects (reported in only 12% of clinical studies) and variable quality control in herbal preparations. These issues are compounded by the lack of universally accepted biomarkers for assessing Ayurvedic treatment outcomes, with most studies relying solely on glycemic parameters rather than holistic Ayurvedic diagnostic criteria.

2. Integration of Biotechnology in Ayurveda

The work of [42] explores how modern biotechnological techniques are being harnessed to enhance Ayurvedic research and formulation development. The study demonstrates that techniques such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS) have enabled precise characterization of bioactive compounds in Ayurvedic herbs like Gymnema sylvestre and Momordica charantia. These analytical methods have revealed previously unidentified phytoconstituents that contribute to antidiabetic effects, such as gymnemic acid IV and charantin-X.

Table 3. Taxonomy of Ayurvedic Research Methodologies for Diabetes Management

Research Focus	Methodology/Approach	Key Findings	Sources
Current Status of Ayurvedic Research	Analysis of clinical trial designs and evidence gaps	Limited RCTs and standardization challenges	[41]
Integration of Modern Techniques	Application of biotechnological tools (HPLC, GC-MS)	Identification of novel bioactive compounds	[42]

The table above categorizes the methodological approaches employed in contemporary Ayurvedic research, illustrating the transition from traditional empirical methods to technology-driven investigations. *or instance, [42] reports that nanotechnology-assisted delivery systems have increased the bioavailability of Ayurvedic compounds by 40-70%, addressing a ma or limitation of traditional formulations. However, the study also notes that only 15% of Ayurvedic research institutions currently possess the infrastructure for advanced biotechnological analyses, indicating a need for greater resource allocation.

Emerging methodologies such as pharmacogenomics and metabolomics are beginning to bridge the gap between Ayurvedic principles and modern science. Preliminary data suggest that genetic polymorphisms may influence individual responses to Ayurvedic treatments, providing a scientific basis for the ancient concept of Prakriti (individual constitution).

Nevertheless, these approaches remain underutilized in mainstream Ayurvedic research due to technical complexities and high costs. The synthesis of these studies reveals an evolving research landscape where traditional knowledge systems are increasingly sub ected to rigorous scientific scrutiny. While significant progress has been made in apply ing modern techniques to Ayurvedic research, challenges persist in establishing standardized protocols that satisfy both tradition al authenticity and contemporary scientific rigor. The integration of advanced analytical methods with Ayurvedic wisdom holds promise for developing more effective, evidence- based nanoformulations for diabetes management.

3.5 Ayurvedic Herbs and Their Antidiabetic Properties

The pharmacological potential of Ayurvedic herbs in diabetes management has been significantly enhanced through nan oformulation approaches. This subsection examines two key medicin al plants - Withania somnifera (Ashwagandha) and Tridax procumbens - that have demonstrated notable hypoglycemic effects when processed at the nanoscale. Ashwagandha, often referred to as the "flagship herb of Ayurveda," contains bioactive withanolides that exhibit insulin-mimetic properties. The study by [3] reveals that nanoencapsulation of withaferin A in polymeric nanoparticles (size range 80-120 nm) enhances its bioavailability by 3.2-fold compared to crude extracts. This formulation demonstrated dual mechanisms of action in diabetic rodent models: stimulating glucose transporter 4 (GLUT4) translocation in skeletal muscle cells while inhibiting a-glucosidase activity in the intestinal lumen. The nanoformulation achieved a 38% greater reduction in postprandial glucose spikes than conventional Ashwagandha preparations, suggesting improved therapeutic efficacy through targeted delivery.

Tridax procumbens, though less prominent in classical Ayurvedic texts, has gained recognition for its ethnopharmacological applications in diabetes management. Research documented in [44] identifies luteolin and §-sitosterol as the primary antidiabetic compounds in this herb. When formulated as gold nanoparticle conjugates (AuNP-TP), these phytoconstituents showed enhanced permeability across intestinal epithelial barriers, with a 2.7-fold increase in cellular uptake observed in Caco-2 cell monolayers. The nanoformulation exhibited unique pleiotropic effects, simultaneously reducing hepatic gluconeogenesis (via AMPK activation) and protecting pancreatic §-cells from oxidative damage (through Nrf2 pathway modulation).

Table 4. Comparative Analysis of Ayurvedic Herb Nanoformulations for Diabetes

Herb	**Key Bioactive Compound**	**Nanoformulation Type**	**Particle Size (nm)**	**Mechanism of Action**	**Efficacy Enhancement vs Crude Extract**	**Sources**
Wit!?ania somnifera	Withaferin A	Polymeric nanoparticles	80-120	GLUT4 translocation, a-glucosidase inhibition	3.2• bioavailability, 38% greater PPG reduction	[43]

Tridax procumbens	Luteolin, ß-sitosterol	Gold nanoparticle conjugates	15-30	AMPK activation, Nrf2 pathway modulation	2.7• cellular uptake	[44]

Notably, the studies reveal an important dose-response relationship. The Ashwagandha nanoformulation showed optimal effects at 50 mg/kg body weight in animal models, beyond which marginal benefits were observed. Similarly, the AuNP-TP conjugate demonstrated a narrow therapeutic window (10-20 mg/kg), with higher doses potentially inducing hepatic stress markers. These findings underscore the need for precise dosing protocols when translating Ayurvedic nanoformulations into clinical practice. The phytochemical complexity of these herbs presents both opportunities and challenges for nanoformulation development. While Ashwagandha's withanolides work synergistically to regulate glucose metabolism, their differential solubility profiles required careful optimization of the nanoparticle matrix. *Tridax procumbens*' flavonoid-glycoside combinations necessitated surface functionalization of gold nanoparticles to prevent compound dissociation during circulation. Such technical considerations highlight the intricate balance required between preserving traditional herbal synergies and achieving modern pharmaceutical standards.

CONCLUSION

This systematic review has synthesized current knowledge on Ayurvedic nanoformulations for diabetes management, demonstrating their potential to bridge traditional medicine and modern nanotechnology. The findings reveal that nanoformulation strategies significantly enhance the bioavailability and therapeutic efficacy of Ayurvedic herbs, addressing key limitations of conventional preparations. Mechanistic studies consistently show that these formulations operate through multiple pathways-including pancreatic ß-cell regeneration, insulin sensitization, and oxidative stress mitigation-while aligning with Ayurvedic principles of holistic metabolic regulation. The implications of this research extend to both clinical practice and scientific inquiry. The demonstrated improvements in glycemic control and reduced side effects suggest that Ayurvedic nanoformulations could serve as viable complementary therapies in diabetes management. However, the field requires standardized protocols for formulation development and rigorous clinical validation to establish safety and efficacy. Future research should prioritize longitudinal human trials, explore personalized approaches based on Ayurvedic diagnostics, and investigate the environmental impact of large-scale production. By fostering interdisciplinary collaboration between traditional practitioners and nanotechnologists, this emerging field can develop innovative therapies that honor the strengths of both systems while addressing the global diabetes epidemic.

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