



NANOPARTICLE-MEDIATED DELIVERY OF HERBAL BIOACTIVES IN DIABETES MANAGEMENT: A CRITICAL REVIEW OF NANOCARRIER SYSTEMS, MECHANISMS, AND TRANSLATIONAL CHALLENGES

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ABSTRACT

Persistent hyperglycemia is a hallmark of diabetes mellitus, a chronic metabolic condition that has serious long-term consequences such as retinopathy, neuropathy, nephropathy, and cardiovascular disorders. Conventional pharmacotherapies are still the mainstay of managing diabetes, but their clinical efficacy is frequently constrained by side effects, low patient compliance, and an incapacity to address the multifactorial character of the condition. Because of their multi-target pharmacological activities, antioxidant qualities, and generally good safety profiles, herbal medications have emerged as intriguing therapeutic alternatives. However, poor water solubility, low bioavailability, fast metabolism, and physicochemical instability greatly impede the practical translation of herbal bioactive substances. Recently, nanoparticle-mediated drug delivery systems have drawn a lot of interest as a cutting-edge strategy to get around these restrictions. By increasing solubility, preventing degradation, permitting controlled and sustained release, and enabling targeted distribution, these nanoscale carriers improve the pharmacokinetic and pharmacodynamic performance of phytoconstituents. With a focus on their function in the treatment of diabetes, this study offers a thorough and critical assessment of the main nanocarrier systems, such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanoemulsions. Additionally, the molecular processes that underlie the antidiabetic effect of nanoparticles are reviewed, including the activation of AMP-activated protein kinase (AMPK), the increase of insulin sensitivity, the reduction of oxidative stress, and the enhancement of glucose absorption through GLUT4 translocation. In order to determine the best systems based on therapeutic efficacy, safety, and scalability, a comparative study of nanocarrier platforms is provided. Even with promising preclinical results, there are still a number of obstacles to overcome, such as possible toxicity, a lack of uniformity, limitations in large-scale manufacturing, and regulatory uncertainty. The integration of green nanotechnology, formulation design driven by artificial intelligence, and well-structured clinical trials are just a few of the future prospects that are outlined in this study along with important research needs. All things considered, herbal medication delivery systems based on nanoparticles offer a revolutionary approach with substantial potential to raise the effectiveness and safety of diabetes treatments.

Key words:

Diabetes mellitus, Herbal medicine, Nanoparticle drug delivery, Phytoconstituents, Bioavailability enhancement, AMPK signaling pathway, Targeted drug delivery, Nano-herbal formulations

1. INTRODUCTION

A major burden on healthcare systems around the world, diabetes mellitus is a fast-expanding global health concern [1]. The IDF projects that the prevalence of diabetes will rise dramatically over the next few decades, especially in developing nations. Persistent hyperglycemia brought on by decreased insulin production, insulin resistance, or a combination of the two is the hallmark of this long-term

metabolic disease. Diabetes is often divided into Type 1 and Type 2 diabetes based on its etiology, with Type 2 diabetes making up the majority of cases worldwide. Neuropathy, nephropathy, retinopathy, and cardiovascular illnesses are among the worst long-term sequelae that are strongly linked to prolonged hyperglycemia. These conditions greatly increase morbidity and mortality [2-4].

Metformin, sulfonylureas, and insulin therapy are examples of conventional pharmaceutical interventions that continue to be the principal approaches for managing diabetes. However, side effects include hypoglycemia, gastrointestinal issues, weight gain, and decreased patient compliance are frequently linked to these medications. Furthermore, the majority of traditional treatments fail to address the complex, multivariate nature of diabetes by focusing on a single pathway. Due to these restrictions, there is a growing interest in alternative treatment methods, especially herbal remedies, which include anti-inflammatory and antioxidant qualities in addition to multi-target modes of action [5-6].

Through the regulation of several metabolic pathways, herbal bioactive substances derived from medicinal plants like *Momordica charantia*, *Gymnema sylvestre*, *Curcuma longa*, and *Berberis aristata* have shown encouraging antidiabetic potential. These phytoconstituents can lower oxidative stress, control glucose metabolism, increase insulin secretion, and improve insulin sensitivity. Despite

these benefits, poor water solubility, low bioavailability, fast metabolism, and instability under physiological conditions limit the therapeutic use of herbal medicines [7-8].

Drug delivery methods based on nanotechnology have become a viable way to get around these restrictions and improve the therapeutic effectiveness of herbal substances in recent years. Improved drug solubility, protection from degradation, regulated and prolonged release, and targeted delivery to particular tissues are all made possible by nanocarriers, which are usually between 1 and 1000 nm in size. The pharmacokinetic and pharmacodynamic profiles of herbal bioactives are greatly enhanced by these characteristics [9]. The goal of this review is to present a thorough and critical analysis of herbal medication delivery systems based on nanoparticles for the treatment of diabetes. It focuses on how nanocarriers are categorized, how they work, and how they can improve the therapeutic potential of herbal medications.

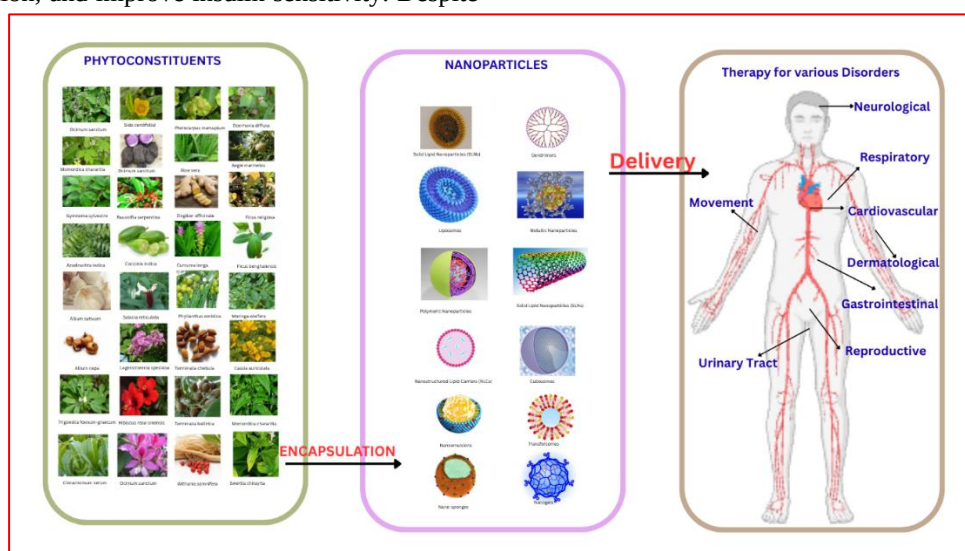


Figure 1: Schematic Representation of Herbal Bioactives Encapsulation into Nanocarriers and Their Targeted Drug Delivery Mechanism

Despite these benefits, adverse pharmacokinetic characteristics, such as low bioavailability and poor water solubility, sometimes restrict the use of herbal medications [10]. To get over these restrictions and improve the therapeutic efficiency of herbal bioactive components, drug delivery methods based on nanotechnology have become a viable approach in recent years [11-14].

2. HERBAL DRUGS IN DIABETES MANAGEMENT

Because of their multi-target pharmacological activities and generally good safety profiles, herbal medications have attracted a lot of interest in the treatment of diabetes

mellitus. Phytoconstituents provide a more thorough and all-encompassing approach to diabetes treatment by modulating several biochemical pathways, in contrast to traditional antidiabetic medications that usually work on a single molecular target. These strategies include protecting pancreatic β -cells, reducing oxidative stress, inhibiting enzymes that break down carbohydrates, increasing insulin production, and improving insulin sensitivity [15-16]. Preclinical and clinical research has shown that a number of medicinal plants have significant antidiabetic potential. *Momordica charantia* (bitter melon), *Gymnema sylvestre*, *Curcuma longa* (turmeric), and *Berberis aristata* are the most well-researched and frequently reported of these.

These plants' bioactive components, which include charantin, gymnemic acids, curcumin, and berberine, are essential for controlling glucose homeostasis and enhancing metabolic processes [17].

For instance, *Momordica charantia* has been shown to enhance peripheral glucose uptake and suppress hepatic gluconeogenesis, thereby contributing to improved glycemic control. *Gymnema sylvestre* exhibits unique properties, including stimulation of insulin secretion and potential regeneration of pancreatic β -cells, along with a reduction in intestinal glucose absorption. *Curcuma longa*, primarily through its active component curcumin, demonstrates strong antioxidant and anti-inflammatory activities, which are essential for mitigating insulin resistance and chronic inflammation associated with diabetes. Similarly, berberine derived from *Berberis aristata* has gained considerable attention due to its ability to activate the AMP-activated protein kinase (AMPK) pathway, a key regulator of cellular energy homeostasis.

Notably, berberine has shown effects comparable to conventional antidiabetic drugs such as metformin in certain studies [18-19].

Despite these encouraging pharmacological characteristics, there is still very little clinical use of herbal medications. Poor water solubility, low oral bioavailability, fast metabolism, and instability under physiological circumstances are some of the main obstacles. These restrictions prevent their extensive clinical use by reducing systemic availability and producing variable treatment results [20]. Therefore, even while herbal remedies offer a solid basis for the creation of innovative antidiabetic treatments, sophisticated drug delivery techniques are necessary to fully fulfill their therapeutic potential. By improving the solubility, stability, bioavailability, and targeted administration of herbal bioactive substances, nanoparticle-based delivery systems have emerged as a viable strategy to get over these obstacles [21].

Table 1. Key Antidiabetic Herbal Drugs with Mechanisms of Action (Selected High-Evidence Plants)
Table: Antidiabetic Medicinal Plants and Their Mechanisms (APA 7A Style)

Plant (Scientific Name)	Key Constituent	Mechanism of Action	Reference
<i>Momordica charantia</i>	Charantin	Enhances insulin secretion, $\uparrow$ glucose uptake	[22]
<i>Gymnema sylvestre</i>	Gymnemic acids	β -cell regeneration, $\downarrow$ glucose absorption	[23]
<i>Curcuma longa</i>	Curcumin	Anti-inflammatory, $\uparrow$ insulin sensitivity	[24]
<i>Berberis aristata</i>	Berberine	AMPK activation, $\downarrow$ insulin resistance	[25]
<i>Trigonella foenum-graecum</i>	4-hydroxyisoleucine	Stimulates insulin release	[26]
<i>Cinnamomum verum</i>	Cinnamaldehyde	$\uparrow$ insulin receptor activity	[27]
<i>Azadirachta indica</i>	Nimbidin	Antioxidant, improves glucose tolerance	[28]
<i>Allium sativum</i>	Allicin	$\uparrow$ insulin secretion, antioxidant	[29]
<i>Phyllanthus emblica</i>	Vitamin C	Reduces oxidative stress	[30]
<i>Nigella sativa</i>	Thymoquinone	β -cell protection, antioxidant	[31]

3. LIMITATIONS OF HERBAL DRUG THERAPY

Due to a number of physicochemical and pharmacokinetic limitations, the clinical usefulness of herbal medicines is still severely restricted, despite their enormous therapeutic potential and extensive usage in the treatment of diabetes mellitus. The effectiveness, consistency, and translational potential of herbal bioactive substances are significantly impacted by these constraints [32-33]. The poor aqueous solubility of herbal medicines is one of their main problems. Curcumin, quercetin, and resveratrol are just a few of the many phytoconstituents that are naturally hydrophobic. After oral administration, their absorption and systemic availability are greatly reduced due to their poor solubility, which limits their dissolution in gastrointestinal fluids [34-37]. Low oral bioavailability is a significant obstacle to the therapeutic success of herbal drugs in addition to solubility-related problems [38-40].

This restriction results from substantial first-pass metabolism in the liver, ineffective gastrointestinal absorption, and low membrane permeability. As a result, only a small fraction of the administered dose reaches systemic circulation in its active form, leading to suboptimal therapeutic outcomes [41-42].

The instability of herbal bioactive chemicals in physiological and environmental settings is another important issue [43-44]. According to Yadav et al. (2011), many phytochemicals are extremely susceptible to changes in pH, temperature, light exposure, and enzymatic breakdown. For example, curcumin is known to degrade quickly in alkaline environments, and intestinal and hepatic enzymes rapidly metabolize a number of polyphenols, reducing their pharmacological effectiveness [45]. Herbal compounds also have a short biological half-life due to their quick metabolism and excretion, which

makes frequent doses necessary to maintain therapeutic medication levels. This decreases long-term treatment efficacy in addition to decreasing patient compliance. Furthermore, irregular pharmacokinetic profiles and unpredictable therapeutic responses result from variations in phytochemical content brought about by variations in plant species, geographic origin, harvesting conditions, and extraction methods [46].

When taken as a whole, these restrictions seriously impede the clinical application and general acceptance of herbal remedies in contemporary pharmacology. Therefore, sophisticated medication delivery methods that can successfully handle these issues are desperately needed. By increasing solubility, boosting bioavailability, preventing degradation, and facilitating the controlled and targeted delivery of herbal bioactive compounds, nanoparticle-based drug delivery systems present a promising solution in this regard [47-49].

4. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

By increasing the solubility, stability, bioavailability, and targeted administration of herbal bioactive components, nanocarrier-based drug delivery systems significantly improve their therapeutic efficacy. Numerous nanocarriers have been created, but their appropriateness for antidiabetic applications depends on a number of variables, such as the drug's physicochemical characteristics, the route of administration, release kinetics, and biocompatibility [50]. Polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), and nanoemulsions are the most studied and often used nanocarrier systems for the delivery of herbal medications in the treatment of diabetes. In terms of regulated medication release, better absorption, and increased therapeutic efficacy, these systems provide clear benefits. Because they offer structural stability and defense against enzymatic degradation, polymeric nanoparticles are very useful for attaining regulated and prolonged drug release. On the other hand, because of their special phospholipid bilayer structure, liposomes are extremely adaptable vesicular structures that can encapsulate both hydrophilic and lipophilic substances. They can therefore be used to provide a variety of herbal bioactives [51].

Because of their superior biocompatibility, capacity for regulated release, and enhanced stability of encapsulated chemicals, solid lipid nanoparticles (SLNs) have attracted a lot of interest. They are especially well suited for chronic illnesses like diabetes mellitus because of their solid lipid core, which protects labile phytoconstituents and improves

oral bioavailability. Similarly, because of their enormous surface area and nanoscale droplet size, nanoemulsions greatly increase the solubility and absorption of hydrophobic substances.

On the other hand, despite their scientific potential, advanced nanocarrier systems like dendrimers, carbon nanotubes, and quantum dots are now constrained by issues with toxicity, high manufacturing costs, difficult synthesis processes, and regulatory obstacles. As a result, their use in the treatment of diabetes is still mostly experimental [52]. Overall, because of their good safety profile, scalability, and efficiency in increasing the bioavailability of hydrophobic herbal substances, lipid-based nanocarriers—such as SLNs and nanoemulsions—show great translational promise. Polymeric systems are still very useful, nonetheless, for applications involving regulated and prolonged drug administration. Therefore, a balanced assessment of efficacy, safety, and practical feasibility should be the foundation for choosing an acceptable nanocarrier [53].

4.2 Types of Nanocarriers

By increasing the solubility, stability, bioavailability, and targeted delivery of herbal medications, nanocarrier systems significantly contribute to their increased therapeutic efficacy. Despite the fact that many different types of nanocarriers have been created, not all of them are equally appropriate for use in antidiabetic applications. The physicochemical characteristics of the medication, the mode of administration, and the intended release profile all influence the choice of nanocarrier [54]. The most researched and commonly used technologies for the delivery of herbal drugs include polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), and nanoemulsions. These technologies provide clear benefits in terms of improved absorption, biocompatibility, and regulated release [55].

While liposomes offer exceptional versatility by encasing both hydrophilic and lipophilic molecules, polymeric nanoparticles are especially useful for prolonged medication release and protection against degradation. Because of their solid lipid core, SLNs provide better stability and controlled release, whereas nanoemulsions greatly increase the solubility and absorption of hydrophobic phytoconstituents [56]. On the other hand, despite their promise, sophisticated systems like dendrimers, carbon nanotubes, and quantum dots are still constrained by issues with toxicity, high production costs, and regulatory obstacles. Therefore, rather than depending on extremely complicated systems, the main focus of current research is on optimizing ordinary nanocarriers.

Table 2. Major Nanocarrier Systems in Herbal Drug Delivery: Features and Relevance in Diabetes Management

Nanocarrier System	Key Features	Herbal Example	Clinical Relevance	Reference
Polymeric Nanoparticles	Sustained release, high stability	Curcumin (<i>Curcuma longa</i>)	Ideal for chronic therapy	[57]
Liposomes	Encapsulate hydrophilic & lipophilic drugs	Resveratrol (<i>Vitis vinifera</i>)	Versatile and biocompatible	[58]
Solid Lipid Nanoparticles (SLNs)	Controlled release, lipid core stability	Berberine (<i>Berberis aristata</i>)	Improved bioavailability	[59]
Nanostructured Lipid Carriers (NLCs)	Higher drug loading than SLNs	Curcumin	Enhanced delivery efficiency	[60]
Nanoemulsions	Improved solubility & absorption	Quercetin (<i>Allium cepa</i>)	Rapid onset of action	[61]
Polymeric Micelles	Solubilize hydrophobic drugs	Curcumin	Suitable for poorly soluble drugs	[62]
Dendrimers	Targeted delivery via surface groups	Quercetin	Experimental stage	[63]
Nanogels	Swelling-controlled release	Berberine	Controlled drug release	[64]
Phytosomes	Drug-phospholipid complex	Silymarin	Enhanced absorption	[65]
Niosomes	Stable vesicular system	Quercetin	Alternative to liposomes	[66]

Although many other types of nanocarriers have been investigated, lipid-based systems (SLNs, NLCs, nanoemulsions) have demonstrated better results in the treatment of diabetes because they can increase the bioavailability of hydrophobic phytoconstituents. However, polymeric systems offer greater control over the kinetics of drug release, which makes them appropriate for long-term treatment. However, because of toxicity issues, difficult manufacturing processes, and regulatory

obstacles, the clinical application of sophisticated nanocarriers like dendrimers and quantum dots is still restricted. As a result, biocompatible, biodegradable, and scalable nanocarrier systems are becoming more popular in study.

4.3 Polymeric Nanoparticles

Polymeric nanoparticles provide sustained drug release and improved stability.

Table 3. Types of Polymeric Nanoparticles with Mechanisms of Drug Release

Type of Polymeric Nanoparticle	Mechanism of Drug Release	Example Herbal Drug (Scientific Name)	Reference (APA Style)
Nanospheres	Drug release via diffusion and polymer degradation	Curcumin (<i>Curcuma longa</i>)	[67]
Nanocapsules	Drug diffusion through polymeric shell	Berberine (<i>Berberis aristata</i>)	[68]
Polymeric Micelles	Drug release via micelle dissociation and diffusion	Curcumin (<i>Curcuma longa</i>)	[69]
Dendrimers	Surface-bound drug release and bond cleavage	Quercetin (<i>Psidium guajava</i>)	[70]
Nanogels	Swelling-controlled drug release	Berberine (<i>Berberis aristata</i>)	[71]
Polymersomes	Drug diffusion across polymeric membrane	Resveratrol (<i>Vitis vinifera</i>)	[72]

Polyplexes	Controlled drug dissociation from complex	Neem extract (<i>Azadirachta indica</i>)	[73]
PEGylated Nanoparticles	Prolonged circulation with slow drug release (stealth effect)	Curcumin (<i>Curcuma longa</i>)	[74]
Chitosan Nanoparticles	Enzymatic degradation-mediated drug release	Alkaloids (<i>Tinospora cordifolia</i>)	[75]
Albumin Nanoparticles	Enzymatic degradation and controlled release	Polyphenols (<i>Camellia sinensis</i>)	[76]

4.4 Liposomes

Liposomes are among the most extensively studied and widely utilized nanocarrier systems in drug delivery owing to their remarkable biocompatibility and structural versatility. They are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core.

This distinctive architecture enables the encapsulation of both hydrophilic drugs within the aqueous core and lipophilic drugs within the lipid bilayer, thereby making them highly suitable for delivering a diverse range of pharmaceutical and herbal compounds [77-79].

Table 4. Types of Liposomes with Mechanisms and Herbal Drug Applications

Type of Liposome	Mechanism / Features	Example Herbal Drug (Scientific Name)	Reference (APA Style)
Conventional Liposomes	Passive encapsulation within lipid bilayer or aqueous core	Resveratrol (<i>Vitis vinifera</i>)	[80]
Stealth Liposomes	Reduced opsonization and prolonged systemic circulation	Curcumin (<i>Curcuma longa</i>)	[81]
Targeted Liposomes	Receptor-mediated targeted drug delivery	Berberine (<i>Berberis aristata</i>)	[82]
Cationic Liposomes	Electrostatic interaction with negatively charged cell membranes	DNA/herbal extracts (<i>Azadirachta indica</i>)	[83]
pH-sensitive Liposomes	Triggered drug release in acidic microenvironment	Curcumin (<i>Curcuma longa</i>)	[84]
Thermosensitive Liposomes	Temperature-induced drug release	Resveratrol (<i>Vitis vinifera</i>)	[85]
Immunoliposomes	Antigen-specific targeting and enhanced selectivity	Polyphenols (<i>Camellia sinensis</i>)	[86]
Multilamellar Vesicles (MLVs)	Sustained and slow drug release	Quercetin (<i>Allium cepa</i>)	[87]
Small Unilamellar Vesicles (SUVs)	Rapid absorption and improved bioavailability	Curcumin (<i>Curcuma longa</i>)	[88]
Large Unilamellar Vesicles (LUVs)	High drug encapsulation efficiency	Berberine (<i>Berberis aristata</i>)	[89]

4.5 Solid Lipid Nanoparticles (SLNs)

Because they may enable regulated drug release and improve the stability of encapsulated molecules, solid lipid nanoparticles (SLNs), an advanced class of lipid-based nanocarriers, have garnered a lot of interest in drug delivery. Triglycerides, fatty acids, and waxes are

examples of physiologically compatible solid lipids that make up these systems. These lipids stay solid at both room temperature and body temperature. The medication is integrated into the solid lipid matrix, which protects it from chemical deterioration and permits controlled and prolonged release [90-93].

Table 5. Types of Solid Lipid Nanoparticles (SLNs) with Mechanisms and Herbal Applications

Type of SLN Model	Structure / Drug Distribution	Mechanism / Features	Example Herbal Drug (Scientific Name)	Reference (APA Style)
Homogeneous Matrix Model	Drug uniformly dispersed within solid lipid core	Controlled release via slow diffusion from lipid matrix	Curcumin (<i>Curcuma longa</i>)	[94]
Drug-enriched Shell Model	Drug concentrated in outer lipid shell	Initial burst release followed by sustained release	Quercetin (<i>Allium cepa</i>)	[95]
Drug-enriched Core Model	Drug localized in central core region	Controlled diffusion from core to surface	Berberine (<i>Berberis aristata</i>)	[96]
PEGylated SLNs	PEG-coated lipid nanoparticles	Reduced RES uptake and prolonged circulation time	Curcumin (<i>Curcuma longa</i>)	[97]
Targeted SLNs	Ligand-conjugated surface	Receptor-mediated targeted delivery	Berberine (<i>Berberis aristata</i>)	[98]
Cationic SLNs	Positively charged lipid systems	Enhanced interaction with negatively charged cell membranes	Herbal extracts (<i>Azadirachta indica</i>)	[99]

4.6 Nanoemulsions

Advanced colloidal drug delivery systems known as nanoemulsions are made up of nanoscale droplets (usually 20–200 nm) distributed in water-in-oil (W/O) or oil-in-water (O/W) systems. Surfactants and co-surfactants stabilize these formulations by lowering interfacial tension

and preventing droplet coalescence. Nanoemulsions significantly improve the solubility and absorption of poorly water-soluble medications, especially hydrophobic herbal medicinal components, due to their incredibly small droplet size and vast surface area [100].

Table 6. Types of Nanoemulsions with Characteristics and Herbal Drug Applications

Type of Nanoemulsion	Mechanism / Features	Example Herbal Drug (Scientific Name)	Reference (APA Style)
Oil-in-Water (O/W) Nanoemulsion	Improves solubility of lipophilic drugs and enhances oral absorption	Curcumin (<i>Curcuma longa</i>)	[101]
Water-in-Oil (W/O) Nanoemulsion	Protects drug from degradation and improves stability	Aloe extract (<i>Aloe vera</i>)	[102]
Bicontinuous Nanoemulsion	Enables delivery of both hydrophilic and lipophilic drugs	Berberine (<i>Berberis aristata</i>)	[103]
Self-Emulsifying Nanoemulsion (SNE)	Enhances bioavailability via spontaneous GI emulsification	Quercetin (<i>Allium cepa</i>)	[104]
Microemulsion-Based Nanoemulsion	Improves drug dissolution and permeability	Resveratrol (<i>Vitis vinifera</i>)	[105]
Pickering Nanoemulsion	Stabilized by solid particles; improved stability and reduced toxicity	Herbal polyphenols (<i>Camellia sinensis</i>)	[106]
High-Energy Nanoemulsion	Produces uniform droplet size via mechanical energy (e.g., homogenization)	Curcumin (<i>Curcuma longa</i>)	[107]
Low-Energy Nanoemulsion	Controlled droplet formation via phase inversion or self-assembly	Berberine (<i>Berberis aristata</i>)	[108]

5. MECHANISM OF NANOPARTICLE ACTION IN DIABETES

Through a variety of interrelated pharmacokinetic and molecular mechanisms, drug delivery methods based on nanoparticles improve the therapeutic efficacy of herbal bioactive substances. In addition to increasing the effectiveness of medication delivery, these devices actively alter important biochemical pathways related to insulin signaling, glucose homeostasis, and metabolic control. The improvement of intestinal absorption is one of the main mechanisms. Nanoparticles greatly boost the permeability and dissolving rate of weakly soluble phytoconstituents because of their huge surface area and nanoscale size. In comparison to traditional formulations, this promotes better transport across the intestinal epithelium via both transcellular and paracellular pathways, leading to increased systemic bioavailability [109]. Targeted distribution to pancreatic β -cells is another crucial strategy. By interacting with particular cellular receptors, surface-functionalized nanoparticles can facilitate receptor-mediated uptake and preferential accumulation in pancreatic tissues. This tailored strategy improves treatment precision and lowers systemic toxicity by increasing insulin secretion while decreasing off-target effect [110]. Additionally, nanoparticles are essential for preventing oxidative stress and apoptosis in pancreatic β -cells. Although many herbal bioactive substances have potent antioxidant qualities, their efficacy is frequently undermined by instability and quick breakdown.

At the molecular level, nanoparticle-mediated delivery systems significantly influence key signaling pathways associated with glucose metabolism. In particular,

activation of the AMP-activated protein kinase (AMPK) pathway has been widely reported in nanoformulations of herbal compounds such as curcumin and berberine. AMPK acts as a central energy sensor, and its activation enhances glucose uptake, promotes fatty acid oxidation, and improves overall metabolic balance. Additionally, nanoparticles facilitate GLUT4 translocation in peripheral tissues such as skeletal muscle and adipose tissue, thereby increasing cellular glucose uptake and improving glycemic control [78]. Additionally, by modifying inflammatory pathways, nanoparticle systems enhance insulin sensitivity. Insulin resistance is largely caused by chronic low-grade inflammation, which is mainly mediated by pro-inflammatory cytokines including $\text{TNF-}\alpha$ and IL-6. By lowering the expression of these cytokines, anti-inflammatory phytoconstituents delivered via nanoparticles improve metabolic function and restore insulin responsiveness [65]. The capacity of nanoparticle-based systems to deliver regulated and prolonged medication release is another important benefit. By lowering the frequency of doses and limiting blood glucose variations, this guarantees the maintenance of therapeutic medication concentrations over an extended period. For the long-term treatment of chronic conditions like diabetes mellitus, such sustained release characteristics are especially advantageous [56]. Overall, a synergistic combination of improved pharmacokinetics, targeted administration, bioactive compound protection, and regulation of important molecular pathways results in the antidiabetic efficacy of nanoparticle-based herbal drug delivery systems. When compared to traditional herbal formulations, these integrated processes work together to improve therapeutic effects.

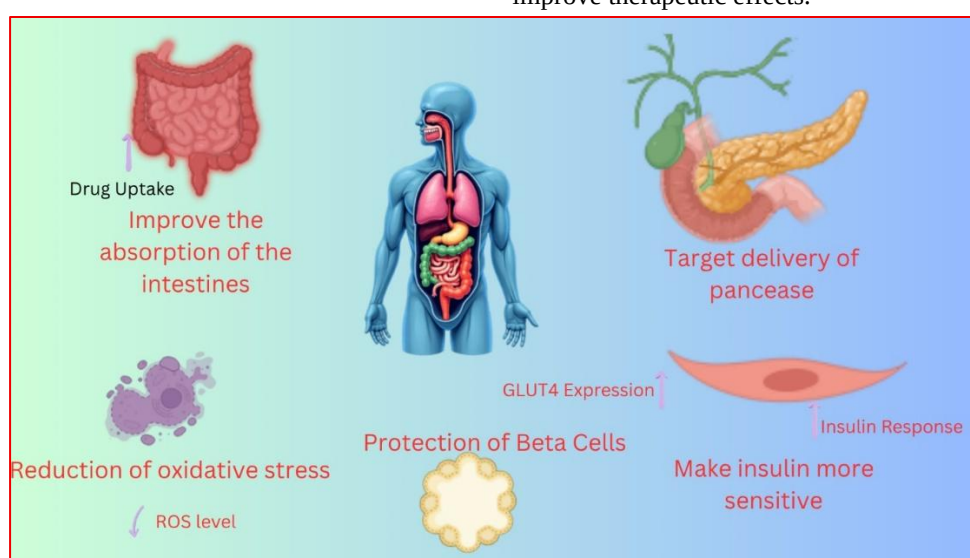


Figure 2: Mechanistic Overview of Antidiabetic Action Showing Enhanced Intestinal Absorption, Pancreatic Targeting, Oxidative Stress Reduction, and Improved Insulin Sensitivity

The multi-level mechanisms of nanoparticle-mediated antidiabetic action, such as improved intestinal absorption, targeted pancreatic delivery, decreased oxidative stress, activation of AMP-activated protein kinase (AMPK) signaling, and increased insulin sensitivity, are depicted schematically. When compared to traditional herbal preparations, these combined benefits result in better glycaemic management [34].

6. Recent Advances in Nanoparticle-Based Herbal Drug Delivery

The therapeutic potential of phytoconstituents in the treatment of diabetes has been greatly increased by recent developments in nanoparticle-based herbal drug delivery systems. As nanotechnology continues to advance, new formulation techniques have been created to get around the inherent drawbacks of herbal bioactive chemicals, improving their stability, potency, and targeted delivery. The therapeutic potential of phytoconstituents in the treatment of diabetes has been greatly increased by recent developments in nanoparticle-based herbal drug delivery systems. As nanotechnology continues to advance, new formulation techniques have been created to get around the inherent drawbacks of herbal bioactive chemicals, improving their stability, potency, and targeted delivery. Similar to this, berberine-based nanoformulations have drawn a lot of interest because of their capacity to overcome obstacles such as significant first-pass metabolism and low intestinal absorption. Berberine's systemic availability and therapeutic efficacy are greatly increased when it is encapsulated into nanocarriers. Strong antidiabetic effects have been shown by these formulations, especially through improved lipid metabolism and AMPK signaling regulation [35]. The creation of green-synthesized nanoparticles, which use plant extracts as stabilizing and reducing agents, is another significant accomplishment. This environmentally friendly method lowers potential toxicity, improves biocompatibility, and uses less hazardous chemicals. Additionally, phytochemicals on the surface of these nanoparticles may have additional therapeutic benefits, enhancing antidiabetic efficacy in a synergistic way [69]. Furthermore, combination-based nanoparticle systems have shown promise as a diabetic treatment approach. These systems allow for the co-administration of traditional antidiabetic medications and herbal bioactive substances, producing synergistic therapeutic effects. These strategies have been demonstrated to improve medication efficacy, lower necessary dosages, decrease side effects, and maybe postpone the development of drug resistance [45]. Additionally, the precision of nanoparticle systems has been greatly enhanced by developments in

surface functionalization and targeted distribution. By specifically targeting particular tissues, including insulin-responsive tissues or pancreatic β -cells, ligand-conjugated nanoparticles can improve treatment outcomes while lowering off-target effects [40]. All things considered, these recent advancements show a distinct move toward nanoparticle-based delivery systems that are more effective, focused, and sustainable. It is anticipated that advancements in multidisciplinary research and ongoing formulation strategy innovation would hasten the clinical translation of nano-herbal therapies in the treatment of diabetes.

7. Challenges and Future Perspectives

Although nanoparticle-based herbal drug delivery systems show great promise, a number of crucial issues need to be resolved in order to enable their successful clinical translation. The toxicity and long-term safety of nanocarriers are among the main issues. Despite the fact that many nanomaterials are made to be biocompatible, thorough in vivo and clinical testing is necessary due to their accumulation in tissues and possible harmful effects [109].

The absence of standardization in herbal preparations is another significant drawback. Inconsistent therapeutic results result from variations in phytochemical composition caused by variations in plant sources, geographic conditions, and extraction techniques. Reproducibility and quality control in nano-herbal formulations are severely hampered by this variability. Furthermore, manufacturing limitations and scalability continue to be major obstacles to commercialization. Large-scale manufacturing is challenging because the creation of nanoparticle systems frequently entails complicated procedures, significant prices, and strict quality criteria. It is especially difficult to guarantee long-term stability and batch-to-batch consistency [110]. The clinical implementation of these technologies is further complicated by regulatory concerns. The processes of safety assessment, efficacy validation, and approval are made problematic by the lack of clear regulatory rules for nano-herbal compositions. Therefore, it is crucial to harmonize international regulatory systems. Furthermore, well-designed clinical trials assessing the safety and effectiveness of herbal medicines based on nanoparticles in humans are scarce. There is a big gap between experimental research and clinical application, as the majority of studies are still restricted to in vitro and preclinical models. Future studies should concentrate on creating tailored, non-toxic, biodegradable nanocarriers with better pharmacokinetic characteristics. By combining modern drug design techniques, machine learning (ML),

and artificial intelligence (AI), formulation tactics can be further optimized and biological interactions can be predicted with more accuracy. Furthermore, interdisciplinary cooperation and a focus on green nanotechnology will be essential in hastening the shift from lab research to clinical application.

8. Conclusion

By successfully resolving the inherent drawbacks of traditional herbal medicines, nanoparticle-based herbal medication delivery systems mark a substantial progress in the field of diabetes control. Solubility, stability, bioavailability, and targeted distribution have been significantly improved when bioactive phytoconstituents are combined with sophisticated nanocarrier systems, such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanoemulsions. These nanoscale delivery platforms not only enhance pharmacokinetic and pharmacodynamic performance but also facilitate the modulation of key molecular pathways involved in glucose metabolism, such as AMP-activated protein kinase (AMPK) activation, GLUT4 translocation, reduction of oxidative stress, and improvement of insulin sensitivity. Therefore, when compared to traditional methods, nanoparticle-mediated herbal formulations provide better therapeutic potential, especially for the treatment of complicated and multifactorial conditions like diabetes mellitus. Despite these encouraging advancements, a number of obstacles still stand in the way of their extensive clinical use. Concerns about long-term toxicity, inconsistent herbal formulations, the scalability of nanoparticle production, and regulatory ambiguities continue to be major issues. Additionally, a substantial gap between experimental research and practical treatment implementation is highlighted by the scarcity of well-designed clinical trials. Future research should focus on the development of biocompatible, biodegradable, and targeted nanocarriers with optimized pharmacokinetic profiles. In addition, the integration of advanced technologies such as artificial intelligence and machine learning for formulation design, along with the adoption of green synthesis approaches, may further enhance the safety, efficiency, and sustainability of nano-herbal drug delivery systems.

In conclusion, nanoparticle-mediated delivery of herbal bioactives holds immense promise as a next-generation therapeutic strategy for diabetes management. With continued advancements in nanotechnology, improved regulatory frameworks, and robust clinical validation, these systems have the potential to bridge the gap between traditional medicine and modern pharmacotherapy,

ultimately leading to more effective, safe, and patient-centric treatment options.

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