Nanomaterials Drug Delivery System in Herbal Formulation For Antidiabetic Activity: A Review

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Abstract
Diabetes, a chronic metabolic disorder, results in high blood glucose levels due to insufficient insulin production or ineffective insulin utilization. Management entails lifestyle changes, exercise, and medication adherence. Monitoring blood sugar levels, healthy eating, and medication are crucial for controlling diabetes and preventing complications. The illness, currently incurable, necessitates management strategies for regulation. Medical treatments are expensive and require long-term adherence, leading many, especially those from low-income nations, to resort to herbal remedies. However, phytocompounds, though promising, often suffer from limited bioavailability due to poor solubility, permeability, or rapid elimination. Plant nanomedicines offer a promising avenue to address these challenges and alleviate the financial strain on disadvantaged populations. Encapsulated treatments using plant extracts or antidiabetic chemicals at the nanoscale have shown promising results. Our study aims to provide a thorough examination of lipid- and inorganic-based nanoparticulate delivery systems combined with plant extracts or phytocompounds for diabetes management Our analysis will highlight both the advantages and limitations of these systems for future clinical application. Examined studies revealed that nanoparticulate formulations displayed strong antidiabetic effects at lower doses compared to individual plant extracts or phytocompounds. Additionally, nanoparticulate systems have effectively addressed the issue of low bioavailability in herbal medications, showing promise for enhanced therapeutic outcomes.

Keywords: Oral delivery; Antidiabetic phytocompounds; Lipid-based nanoparticles; inorganic nanoparticles

1. INTRODUCTION

Herbal pharmaceuticals are administered to treat diabetes using herbal-based antidiabetic medication delivery systems. Diabetes is a chronic metabolic disease that develops when the body is unable to use the insulin that the pancreas does make efficiently, or when it fails to create enough of it.[1,2] It is characterized by a continuous rise in blood glucose levels. Diabetes is still regarded as an incurable illness as of right now. The management carefully considers the benefits and drawbacks of medication in order to help regulate the state.[3,4] Diabetes management is expensive as there is no cure for the condition. Currently, low- and middle-income nations account for 90% of the population with undiagnosed diabetes. Because of the benefits herbal treatments provide—easy accessibility, safety, affordability, and amazing promise for curing diabetes—they use them to improve their quality of life.[5,6] The World Health Organization (WHO) has included various herbal treatments in their monographs on certain plants in an effort to encourage this behaviour. Consequently, Extensive research has been conducted recently to improve the antidiabetic effectiveness of herbal medications. The delivery of medications orally is the focus of current study.[7,8] Some people make formulations with nanoparticles in an attempt to increase the phytocompounds' bioavailability or antidiabetic effect. Plant extracts are useful because of their strong reduction potential in the environmentally friendly synthesis of antidiabetic metal nanoparticles.[9,10] Together with their biological action, they serve as agents that reduce, cap, and stabilize these nanoparticles. To fully understand how these formulations can improve the efficacy considering the use of herbal medications for treating diabetes, it is crucial to examine the existing literature. that currently exists on their use and the increased therapeutic advantages they have provided. This article will provide a thorough examination of the use of plant extracts or phytocompounds in conjunction methods to treat diabetes. We shall highlight these systems' advantages and disadvantages for possible clinical application.[11,12]

2. Diabetes: Its Significance and Management

Diabetes is typified by consistently high blood glucose levels, which lead to Heightened production of free radicals and reduced antioxidant ability. This finally results in a number of side effects, including nephropathy, neuropathy, diabetic foot, cardiovascular disease, and retinopathy. It is a serious worldwide health concern that causes many deaths and has a steadily rising incidence rate.[13,14] Juvenile-onset diabetes, also referred to as type 1 diabetes mellitus, is a medical condition characterized by inadequate or lacking insulin secretion by the pancreatic β-cells. The illness is brought on by viral or genetic factors that lead to the autoimmune

destruction of β-cells. This kind of diabetes is more common in children and adolescents, while it can appear at any age.[15,16] The hallmark of type 2 diabetes, commonly referred to as noninsulin-dependent diabetes, is a reduced ability of cells to use insulin. It impacts about 90% of people with diabetes and is linked to genetic inheritance, being overweight, and lifestyle choices. Less than 5% of cases are of gestational diabetes, which develops during pregnancy and is linked to hormonal swings. High thirst, frequent urination, excessive appetite, fatigue, inexplicable impairment are common signs of diabetes.[17,18] Giving patients with type 1 diabetes exogenous insulin is the mainstay of treatment. Furthermore, it is recommended that these individuals exercise, have a healthy diet, and routinely check their blood glucose levels.[19,20] The primary way that the hormone glucagon affects the liver is by encouraging glycogenolysis. For individuals diagnosed with type 2 diabetes, it is advised that they utilize strategies including consistent exercise, a low-carb diet, and medication therapy afterward. Several kinds of oral hypoglycemic medications are used to treat type 2 diabetes. Biguanides as the initial therapy, sulfonylureas, sodium-glucosidase cotransporter (SGLT2) inhibitors. The treatment of gestational diabetes is based on dietary and lifestyle changes; if these methods don't work, insulin injections can be used. In addition therapies, there are alternative medications made from plants. Because herbal remedies contain phytocompounds with hypoglycemic and antioxidant properties, such as flavonoids, and polyphenols they are employed in herbal therapy.[21,22]

3. Herbal-Based Anti-Diabetic Drugs

Herbal remedies come from traditional medicine, a collection of established practices, knowledge and opinions grounded in comprehensible or illogical cultural notions. These medications are used in the diagnosis, treatment, and prevention of both mental and physical illnesses. These customs are transmitted from one generation to the next via accumulated prior experiences, insights, and knowledge, or via a spiritual bond with ancestors. Numerous techniques, including the use of minerals, plants are used in traditional medicine to treat patients. The main tool for treating illnesses among these techniques is the use of medicinal herbs. Different plant parts can be used to make phytocompounds. These plant components can be utilized as crude or refined extracts or as raw dietary supplements.[23,24] Various sections of a single plant may exhibit distinct characteristics concentrations of active phytochemicals. Regarding Ficus capensis, the concentration of flavonoids in the leaves is higher than that of the roots, while the concentration of tannins in the roots is higher than that of the leaves. Mangifera indica is a well-known species whose leaves are used to cure many different diseases, including diabetes. Throughout human history, plants have been vital to human survival because they provide food, shelter, medicine, and nutrition for animals. All countries make extensive use of medicinal plants, and research from the WHO indicates approximately 80% of people in impoverished nations depend on plants for their primary healthcare. This is applicable to all people who live in Asia and Africa. Because medicinal herbs are common in rural regions and have little side effects, herbal medicines are the primary means of treating diabetes. Partially relieving the expensive burden of conventional medications is traditional medicine.[25,26]

Phytomedicines, or treatments made from plants, have been demonstrated in many research investigations to have positive effects on type 1 and type 2 diabetes. These mechanisms include blocking intestinal α glucosidase and pancreatic α amylase, which inhibits the absorption of glucose from the intestine; restoring β cell function; encouraging insulin secretion and expression; decreasing insulin resistance; improving glucose utilization; preventing the production of glucose by liver cells; controlling the metabolism of carbohydrates and fats; inhibiting the enzyme dipeptylpeptidase-4; and raising the activity of antioxidant enzymes.[27,28]

Herbal treatments are used to cure diabetes and improve patients' general well-being when paired with a healthy lifestyle. Many of their antidiabetic properties have attracted the attention of researchers, who are now writing articles on them. Additionally, they gave a thorough explanation of how the separated phytocompounds present in these plants may have antidiabetic effects. Some compounds in the class of commonly used plant-derived chemicals are not as bioavailable as they may be. The mixture contains the following types of compounds: terpenic, nitrogenous, phenolic and miscellaneous.[29,30]

3.1 Phenolic Materials

3.1.1 Cercetin

Numerous plants, including fennel, buckwheat tea, apples, onions, tomatoes, berries, and citrus fruits, contain quercetin, a polyphenolic component. Studies have shown that it is involved in a variety of antidiabetic activities, improvement of glucose levels. It also has potent anti-inflammatory and antioxidant qualities. Additionally, it protects the cardiovascular system, fights cancer, ulcers, allergies, and acts as a preventive measure against retinopathy. Rats with type 2 diabetes, a 400 mg oral dosage of quercetin reduced postprandial hyperglycemia and inhibited α-glucosidase activity. A recent meta-analysis of people with metabolic diseases discovered that quercetin, at doses more than 500 mg/day, can significantly lower plasma glucose levels after more than eight weeks. Consequently, the dosage and duration of a treatment have a significant impact on its effectiveness. Quercetin is approved for use in humans based on safety tolerance tests conducted at doses up to 2000 mg/day. But due to its poor solubility, only 2% to 6.7% of It is assimilated by the gastrointestinal tract following oral consumption. In 0.7–7.0 hours, it likewise reaches its plasmatic peak.[31,32]

3.1.2 Curcumin

Curcumin is the name of the main naturally occurring curcuminoid found in turmeric. It originates from the roots of plant whose medicinal properties have garnered a lot of interest due to their anti-inflammatory, antioxidant, and antihyperglycemic properties. Traditional Chinese and Ayurvedic medicine have long utilized curcuma longa. Multiple studies have demonstrated that curcumin enhances global antioxidant power of diabetic patients, reduces hyperglycemia. It increases the enzyme adenosine monophosphate-activated protein kinase (AMPK) and inhibits the activities of glucose 6-phosphatase (G6Pase). In clinical research with type 2 diabetes who were overweight or obese were given 300 mg of curcumin orally every day for three months. Compared to the baseline, there was a documented 18% reduction in glucose levels and an 11% decrease in glycosylated hemoglobin. Curcumin has been deemed safe by the Food and Drug Administration (FDA); a daily dose of up to 8 g is recommended without concern. Curcumin is safe to recognize and has a range of physiological effects, but due to limited digestive absorption, the oral bioavailability is low, around 1%, which leads to excretion. This limitation hinders its effectiveness in therapy.[33,34]

Figure 1. Curcumin

3.1.3 Naringenin

Citrus fruits have significant quantities of naringenin, a polyphenol or more precisely a flavonoid, with grapefruits and oranges having the highest concentrations. These pharmacological properties, which include hepatoprotective and antioxidant effects, are explained. Naringenin was administered orally to rats with type 2 diabetes at doses of 25, 50, and 100 mg/kg daily for a period of 28 days in a study conducted by Sharma et al. Adiponectin and β-cell function were shown to rise along with significant reductions in TNF-α, IL-6, dyslipidemia, hyperinsulinemia, hyperglycemia, and insulin resistance. It was found that these effects varied with dosage. Conversely, naringenin has low intestinal absorption, limited water solubility in organic solvents like alcohol. As a result, it has a low bioavailability and quick elimination when given orally. When given orally at a daily dosage of 500 mg/kg body weight in Beagle dogs for six months, the study revealed that it was safe. Additionally, it has been shown that adults can safely take 900 mg orally once.[35,36]

Figure 2. Naringenin

3.1.4 Resveratrol

Resveratrol is a naturally occurring polyphenolic molecule that belongs to the stil benoid class. It may be extracted from a wide range of plants. Resveratrol has been shown to have strong anti-oxidant and anti-diabetic effects. α-amylase and α-glucosidase activity are reduced, glucose uptake and storage are increased, and insulin sensitivity is improved. Because antioxidant enzymes are antioxidants, increasing their activity prevents apoptosis and dysfunction of pancreatic β-cells.Consequently, based on an analysis of research trials on the impact of resveratrol on individuals with type 2 diabetes who have hyperglycemia. Despite its powerful effects,

low bioavailability (less than 1%), low light and heat stability, and poor stability provide serious challenges to clinical usage.[37,38]

Figure 3. Resveratrol

3.1.5 Ferulic Acid

Ferulic acid is a phenolic compound found in a variety of commonly eaten foods. The substance in question is well-recognized for its powerful antioxidant and antidiabetic characteristics. Ferulic acid has been shown to suppress α glucosidase, enhance insulin sensitivity in cells, and boost insulin secretion. In a clinical study, hyperlipidemic subjects were given a daily oral dose of 1000 mg ferulic acid. The study lasted six weeks. These results demonstrated the potential benefits of ferulic acid for hyperlipidemic diabetic individuals. The LD50 of ferulic acid in male and female rats was determined, demonstrating its incredibly low toxicity. Several nations, including Japan, acknowledge it as an antioxidant and add it to food products. On the other hand, ferulic acid offers beneficial antidiabetic, antioxidant, and antihyperlipidemic properties. Additionally, it undergoes a substantial first-stage transit metabolism, and the metabolites it produces are swiftly excreted in urine.[39,40]

Figure 4. Ferulic acid

3.1.6 Myricetin

A naturally occurring polyphenolic compound, myricetin is mostly found in plants belonging to the Myricaceae family as well as other families such as Pinaceae, Polygonaceae, Anacardiaceae, and Berries. Fruits, wine, and teas also contain it. It is added to beverages by the United States and the Food and Agricultural Organization (FAO). The FEMA states that it is safe. Its antidiabetic qualities were demonstrated by both in vitro and in vivo studies. Using an oral myricetin dose of 3 mg every 12 hours for two days decreased blood glucose levels in a diabetic mouse model by 50% when compared to the control group, according to a different study by Ong and Khoo. However, when given orally, myricetin is weakly soluble. [41,42]

Figure 5. Myricetin

3.1.7 Liquiritin

Plants belonging to the Glycyrrhiza species are used to extract liquidritin, a phytocompound with anti-diabetic properties. Liquiritin has been shown to enhance lipid metabolism, reduce insulin resistance, improve levels of antioxidant enzymes like SOD1 and SOD2, decrease levels of inflammatory factors. It was found that rats had a surprisingly low peak plasma concentration of liquiritin, measuring 39.5 ± 7.8 ng h/mL.[43,44]

Figure 6. Liquiritin

3.1.8 Baicalin

The medicinal plant Scutellaria baicalensis yields a flavonoid known as baicalin, which is used to treat inflammatory disorders in addition to other maladies. Its major flavonoid, baicalin, is assumed to be the cause of its ability to control the proinflammatory response. It has been found to have anti-inflammatory, antioxidant, and antidiabetic effects by engaging the AMPK signaling cascade and activating GLUT-4 and insulin receptor substrate-1 (IRS-1). Furthermore, it has been demonstrated to inhibit α-glucosidase and the lipopolysaccharide (LPS)-induced generation of TNF-α, IL-6, and other chemicals. Wang et al. investigated the impact in mice by intragastrically administering 4 mg/kg of baicalin daily to streptozocin-induced diabetic pregnant mice. Baicalin treatment resulted in a substantial decrease in glycemia after three weeks, as compared to the diabetic controls. As a result, despite its action, baicalin has poor bioavailability (approximately 3%) and poor absorption.[45,46]

Figure 7. Baicalin

3.2 Nitrogen Substances

3.2.1. Berberine

Berberines is an alkaloid that belongs to the isoquinone group. It has been utilized for treating a range of ailments, including diabetes. Berberine has been shown in studies to reduce plasma lipids, glycated haemoglobin, total cholesterol, fasting blood glucose, and postprandial blood glucose. Berberine has the ability to hypoglycemia in a number of ways. Thirty newly diagnosed type 2 diabetics were given a 12-week oral regimen consisting of 500 mg of metformin or 500 mg of berberine every 12 hours in a study published by

Shende et al. Berberine has a low bioavailability and is excreted in high quantities as a result of insufficient absorption.[47,48]

Figure 8. Berberines

3.2.2. Betanin

The main sources of betalain, a reddish-violet pigment that is soluble in water. The United States and the EFSA have both approved bethanin. FDA is a natural colorant with antioxidant and antidiabetic qualities. It triggers the AMPK pathway and reduces nuclear factor-κB mRNA expression. Because of its betanin, demonstrated antidiabetic, antioxidant, and anti-inflammatory qualities, beetroot has long been used to treat diabetes. Yanardag et al. found that diabetic rats saw a 50% reduction in blood glucose levels when administered oral Beta vulgaris Administer at a dosage of 2 grams per kilogram once daily. Moreover, in another trial, a 40% reduction in blood glucose levels was noted. without any weight loss or liver impairment following administering the identical dosage to diabetic rats. But a human study found that after oral administration, its bioavailability was incredibly low, implying that it is mainly lost during digestion.[49,50]

Figure 9. Betanin

3.3 Terpenic Compounds

3.3.1. Glycyrrhizin

Roots of certain Glycyrrhiza species, like Glycyrrhiza glabra, Glycyrrhiza uralensis, and Glycyrrhiza inflata, provide glycyrrhizin, a triterpenoid saponin. Its taste is nearly thirty times sweeter than that of saccharose, and it doesn't cause blood sugar to rise. Glycyrrhizin has long been utilized in herbal treatment because of its various advantages, including its capacity to lower blood sugar and function as an antioxidant. Despite being highly soluble, glycyrrhizin is only partially and only little absorbed when taken orally, which makes it minimally bioavailable. Wang et al. reported that its oral bioavailability was 4% and that of its active metabolite, glycyrrhizic acid, which results from hydrolysis, was around 14.2%. Baltina et al. discovered that rats administered oral glycyrrhizic acid administered dosage 100 mg/kg experienced a 35.5% drop pertaining to blood glucose levels after two hours.[51,52]

Figure 10. Glycyrrhizin

3.3.2. Gymnemic Acids

Gymnemic acids are glycosides of triterpenes that are obtained from the leaf extracts of *Gymnema sylvestre*. Based on in vivo studies, gymnemic acids have been found to reduce blood glucose levels in individuals with type 2 diabetes, protect β cells from oxidative stress, and enhance insulin release by enhancing the permeability of beta cells' membranes. These activities have been confirmed through specific clinical experiments using extracts from *Gymnema sylvestre*. As per a study carried out by Khare et al., individuals with diabetes were administered a dosage of 2 grams of aqueous extract three times daily for a duration of 15 days. As a result, there was a decrease in both the levels of hyperglycemia generated by oral intake for two hours and the fasting blood glucose levels. However, there have been reports indicating that these substances have a remarkably low ability to be absorbed by the mouth, a limited ability to dissolve in fats, and a low solubility in water. Based on the limited clinical data now accessible, it appears that high doses of *Gymnema sylvestre* extracts could provide a potential risk. Therefore, the widespread use of these characteristics in therapeutic settings is limited.[53,54]

Figure 11. Gymnema sylvestre

3.3.3. Thymogenic acid

Thymoquinone, an oily and volatile substance obtained from Nigella sativa seeds, has been utilized for a considerable time in both medicinal and culinary fields due to its numerous advantageous characteristics. Some of its qualities include anti-inflammatory, hypolipidemic, antioxidant, antidiabetic, and anticancer effects. Evidence demonstrates that it reduces fasting insulin levels, improves insulin sensitivity and glucose tolerance, decreases hepatic glucose production, and reduces blood glucose and oxidative stress in a rat model. A clinical trial was conducted to evaluate the effects of Nigella sativa seed powder in capsule form, namely thymoquinone-assisted glycemia management, on persons with uncontrolled type 2 diabetes. The reductions were compared to the initial level of 195.95 mg/dL. Additionally, the treatment led to a decrease of 1.52% in glycated hemoglobin. The glycemic indicators also shown significant reductions, as indicated by the study conducted by Najmi et al. Thomas et al. conducted a clinical trial on healthy individuals and found that Nigella

sativa oil, which contains 5% thymoquinone, is safe for daily use at a dosage of 200 mg/kg for a period of 90 days. Nevertheless, thymo-quinone demonstrates poor water solubility, significant lipophilicity, restricted absorption, quick elimination, low bioavailability, and vulnerability to degradation. When administered orally, it is quickly removed since it binds to serum proteins more than 99%.[55,56]

Figure 12. Nigella sativa

3.3.4. Lutein

Lutein is a carotenoid phytochemical that is abundant in zeaxanthin. It is used to treat diabetes-related problems, such as diabetic retinopathy, due to its potent capability to eliminate reactive oxygen and its beneficial antioxidant qualities. Evidence demonstrates that it can decrease oxidative harm to the retina and mitigate the impact of elevated blood glucose on the immune system. It has obtained FDA approval and is classified as GRAS. Based on a study carried out by Katyal et al., lutein has been found to be highly efficient in preventing and halting the development of diabetic nephropathy. Administering a daily dosage of 1.5 mg/kg orally for a period of 4 weeks led to a notable blood reduction sugar levels and a rise in presence of antioxidants. Although lutein possesses notable properties, it has low solubility in water and is not easily absorbed when ingested orally, which presents challenges with obtaining a Physiologically impactful quantity from Sources of food.[57,58]

Figure 13. Lutein

3.3.5. Gamma-Oryzanol

Rice oil is mainly composed of γ-Oryzanol. According to the FDA, γ-Oryzanol is considered safe and has been found to have antioxidant benefits that could potentially aid in the prevention of diabetes. Consuming brown rice is widely recognized as an effective measure to prevent postprandial hyperglycemia. Kozuka et al.'s in vivo research demonstrates that γ-oryzanol improves blood sugar levels, stimulates the release of insulin. Orally administering γ-Oryzanol at a dosage of 3.2 mg per gram of body weight resulted in a significant decrease in beta cell apoptosis with a rise in beta cell activity. Conversely, γ-oryzanol exhibits limited bioavailability and is characterized by poor solubility.[59,60]

Figure 14. Gamma-Oryzanol

3.4 Miscellaneous

3.4.1 Bitter Gourd Seed Oil Polypeptide-k

Momordica charantia yields polypeptide-k and seed oil. Many countries have relied on this plant for food and medicinal. Momordica charantia fruit extracts increase AMPK, which aids glucose absorption, making it a popular anti-diabetic herb. Approximately half of the seed oil contains α-eleostearic acid, which has anti-inflammatory and antioxidant properties. In vitro, polypeptide-K and seed oil dramatically reduce blood glucose levels by affecting peripheral tissues and blocking α-glucosidase and α-amylase. Polypeptide-k is also called a phytoinsulin since it resembles insulin. Lok et al. found that 2.0 mg polypeptide K soft buns lowered blood sugar in 18 healthy people. Two hours after oral dosing, blood glucose dropped 0.9 mmol/L. Polypeptide-k and bitter gourd seed oil are poorly soluble and absorbed in the gut, limiting bioavailability. To get therapeutic advantages, a correct form is essential. Our expertise of safety studies is limited despite their extensive usage in traditional medicine.[61,62]

Figure 15. Momordica charantia

3.4.2. Sage Oil

For millennia, various countries have utilized Salvia officinalis oil to address a range of health issues, including diabetes. Salvia officinalis metabolites contain diterpenes and polyphenols, which may explain its antidiabetic properties. Elseweidy et al. found that Salvia officinalis oil reduced high blood sugar and was antibacterial, antioxidant, and anti-inflammatory. Sage oil was administered IV into diabetic rats with low zinc levels at 0.042 mg/kg body weight for eight weeks. Results showed that the drug significantly decreased blood glucose to 94.17 mg/dL. However, the zinc-deficient control group had much higher serum glucose (547 mg/dL). According to a sage oil toxicity research, dosages above 0.5 g/kg can damage the nervous system and cause convulsions. Sage oil is resulting in limited solubility.[63,64]

Figure 16. Sage Oil

4. Nano-formulation for Antidiabetic Phytochemical Limitations

Several refined or partially pure plant secondary metabolites have been found to manage diabetes. Their ability to prevent or reduce problems has also been established. Lutein and quercetin can reduce visual neuropathy, retinal, and cardiovascular disease. Naringenin may reduce liver damage similarly. These medications are mostly used orally. These substances' limited ability to dissolve in water, be absorbed by the body, penetrate tissues, reach systemic circulation, resist metabolism, remain stable throughout the gastrointestinal tract or in varying environmental conditions, distribute specifically to organs, and avoid rapid elimination hinders their use as diabetes treatments. To achieve therapeutic effects, a large amount must be consumed. These items may have Drug-drug interactions because of their many constituents absence of long-term toxicity studies. To overcome the low bioavailability of some plant active chemicals, alternative nanoparticle compositions have been used.[65,66]

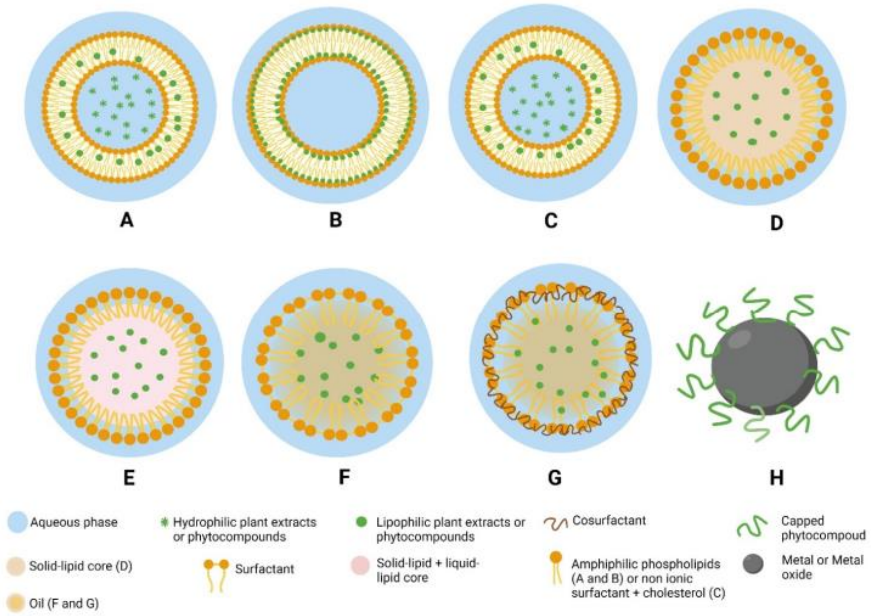


Figure 17. Present lipid and inorganic nanoparticle delivery methods are being examined for their effectiveness in delivering antidiabetic herbal medications

5. Antidiabetic herbal medicines using lipid- and inorganic-based nano-formulations

Nano-formulations are colloidal nanoparticle dispersions from 1 to 1000 nm. Nanoparticles have a large ratio of surface area to volume ratio and their appearance and behaviour rely on their constituents and manufacturing processes. Medication transfer is one of its many uses. Since they offer unique properties not found in bulk material, they are highly appreciated. They help medicinal chemicals penetrate biological barriers and boost bioavailability. Scientists are creating nanoparticle compositions with antidiabetic plant components to expand their application.[67,68]

Nanoparticle-based herbal medicines have better targeted efficacy, bioavailability, toxicity, and biocompatibility than larger ones. Below are lipid-based and inorganic nanocarrier formulations being tested for diabetic treatment. Antidiabetic phytocompound or crude plant extract lipid-based nanoparticle compositions.

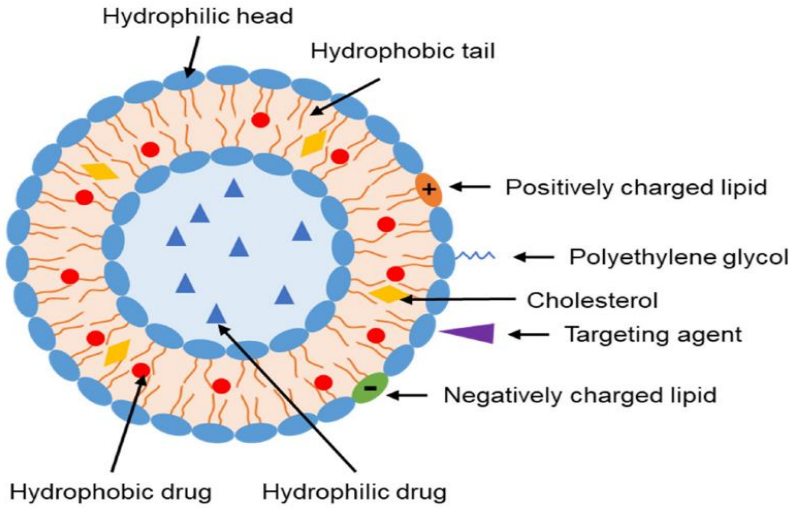
Nanoparticles suspended or dissolved in lipidic excipients form lipid-based nanocarriers for medications. These formulations may contain surfactants. The FDA approves their excipients as safe. The affordable price, ability to contain hydrophilic and lipophilic substances, high encapsulation efficiency, controlled drug release, production efficiency different formulations, enhanced drug bioavailability, and suitability for oral, intravenous, intramuscular, and pulmonary administration are some of these benefits. Mostly, lipid-based nanoparticle compositions boost the bioavailability of plant-based diabetic medicines. These formulations can protect the drug from plant extraction by enclosing it, concealing disagreeable tastes, controlling release and effectively transferring the active ingredient to specific tissues, compares the effects of lipid-based nanoparticulate carriers loaded with plant-derived antidiabetic medicines to unloaded carriers in vivo. Lipid-based nanoparticulate formulations with phytocompounds or plant extracts with antidiabetic effects is able to separate Vesicular and non-vesicular lipid carriers.[69,70]

5.1 Vesicular lipid nanocarriers for antidiabetic phytocompounds or plant extracts

Drug delivery method called vesicular lipid nanocarriers encloses an active medicament in an oily shell enclosing an aqueous phase. The watery section contains hydrophilic compounds, while the oily portion contains lipophilic medications. Liposomes, phytosomes, and niosomes, among other vesicular delivery routes, have been explored for transporting anti-diabetic herbal medicines.[71,72]

5.1.1 Liposomes

Liposomes are small lipid bilayer spherical vesicles. Liposomes are stable lipid bilayers with water cores. Amphiphilic phospholipids with hydrophilic heads and hydrophobic tails dominate the envelope. The lipid bilayer and watery core of cells contain hydrophobic and hydrophilic molecules, respectively. Their composition resembles cell membranes, helping drugs penetrate cells. Studies show that carriers improve the efficacy, availability, and stability of isolated phytocompounds and plant extracts. Amjadi et al. generated betanin-containing liposomes with 26.78% LC and 80.35% EE. Betanin-loaded liposomes were given to diabetic rats daily at 20 mg/kg. In vitro investigations showed liposomes increased betanin stability and antioxidant activity. Comparing betanin loading versus free betanin, tissue analysis showed the former was safer. Wang et al. found similar benefits in rats using liquiritin-loaded liposomes. The 8.8-fold increase in oral bioavailability over free liquiritin exhibited hypoglycemic and antioxidant effects. Gauttam and Kalia et al, encapsulated freeze-dried hydroalcoholic extracts of *Withania somnifera*, *Trigonella foenum-graecum*, and *Mordica charantia* in liposomes. Use of these plants was 2:2:1. The encapsulation method achieved 66.9% EE. The rats received the formulations daily for 21 days. The study found that liposome encapsulation boosted antidiabetic effectiveness. A daily dose of 50 mg per 100 g body weight was given for seven days. The trial found that Pterocarpus marsupium crude extract decreased blood glucose. Thus, Pterocarpus marsupium liposomal formulation outperformed standard extract. Complexing plant extracts with phospholipids creates phytosomes, which transport medication.[73,74]



5.1.2 Phytosomes

Recent nanoscale structures called phytosomes contain polar head sections of phospholipids like phosphatidylcholine and polyphenolic compounds or standardized plant extracts. Phytosomes promote biological activity by improving phytocompound or plant extract absorption. Berberine-phytosomes (EE 85%) were given to rats at 50 mg/kg all at once. The formulation boosted berberine oral bioavailability by threefold, improving glucose metabolism more effectively than normal oral dosing. Riva et al. showed that oral distribution of 500 mg quercetin-phytosomes to human volunteers dramatically increased plasma levels of quercetin. Free quercetin increased the rise by 20 times (exact enhancement factor not provided). When subjects were tested,

no negative effects were found. They compared their methanolic extract to a free one on rats for antidiabetic properties. Daily extracts were administered for 15 days. A lab investigation found 92% of the combination released in 12 hours.[75,76]

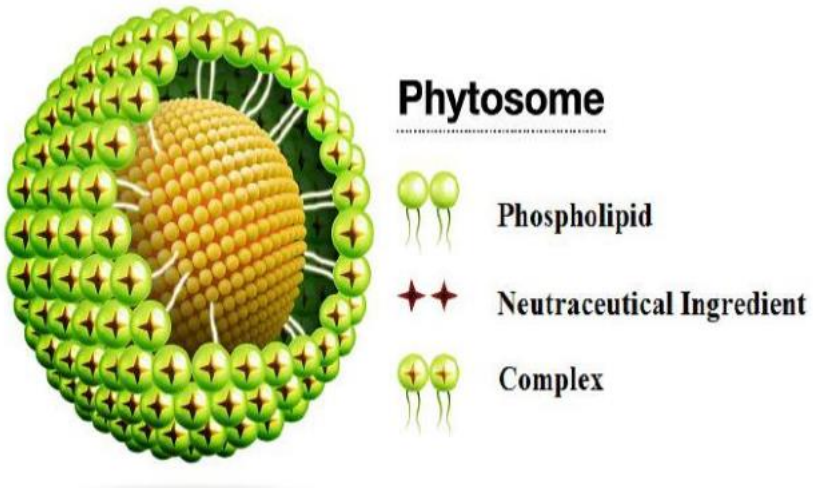


Figure 18. phytosomes

5.1.3 Niosomes

Niosomes are bilayer surfactant vesicles. Cholesterol and nonionic surfactants self-assemble in water to produce these structures. Lycopene niosomes (with an encapsulation effectiveness of 62.8%) developed by PK et al. in 2017 were more effective than free lycopene when given orally to diabetic rats at 200 mg/kg per day for 14 days. Compared to the control group, blood glucose levels dropped to 91.6 and 100.5 mg/dL. Free lycopene also lowered cholesterol to 161.4 mg/dL, compared to 242.4 mg/dL in the control group. Lycopene niosomes released lycopene longer, increased stability, and lowered cholesterol to 108.5 mg/dL. Kamble et al. developed 85.3%-encapsulated Gymnema sylvestre niosomes in another investigation. In vitro, 77.4% of phytocompounds were released in less than 24 hours.[77,78]

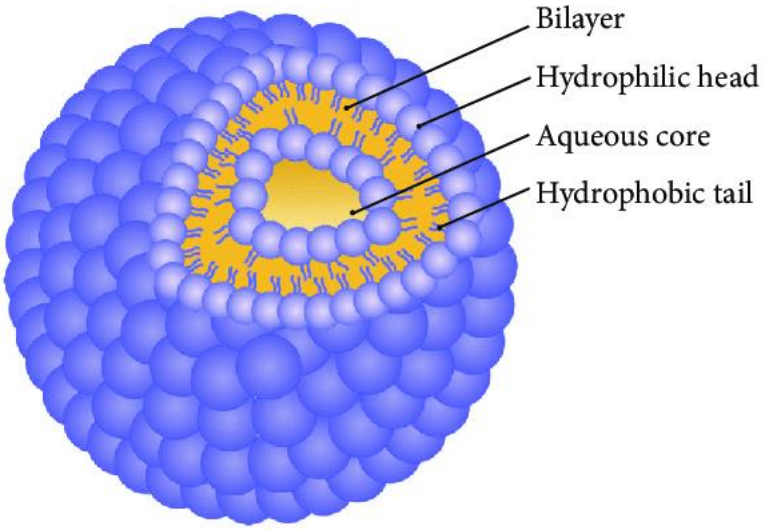


Figure 19. Niosomes

5.2. SLNs are non-vesicular lipid nanocarriers for phytocompounds or plant extracts.

Aqueous colloidal systems stabilized by non-ionic emulsifiers and composed of solid lipids at ambient conditions are solid lipid nanoparticles. Transporters for poorly soluble anti-diabetic phytocompounds are used with solid lipid nanoparticles. The oral administration of the formulation at 100 mg/kg enhanced berberine bioavailability compared to free berberine. In another investigation, mice received 10 mg/kg of myricetin orally using solid lipid nanoparticles (SLNs) with 56.2% EE and 5.62% LC. Thus, blood glucose levels dropped significantly, as in rats given 200 mg/kg metformin.[79,80]

5.2.1 NLCs use for Antidiabetic of plant extracts or phytocompounds

Nanostructured lipid carriers, solid lipid nanoparticles, are made by adding small amounts of room-temperature liquid lipids (oils) to the matrix to change its structure. The most common preparation methods are

microemulsion and high-pressure homogenization. Using baicalin-containing nanostructured lipid carriers, Shi et al. achieved 85.29% encapsulation. Oral carriers were given to rats at 200 mg/kg. The formulation released baicalin longer than baicalin alone and reduced blood glucose by 27%. A mouse biodistribution investigation by Liu et al. found that nanostructured lipid carriers loaded with quercetin released the chemical sustainably.[81,82]

5.2.2 SNEDDSs and nano-emulsions.

Nano-emulsions (NEs) use surfactants to evenly disperse nanosized oil droplets in water. The kinetically stable droplets have tens to hundreds of nano-meter sizes. Nano-emulsions improve phytocompound or poorly soluble active herbal medication bioavailability. Nano-emulsion-enclosed herbal diabetic therapies are more stable, effective at lowering glucose levels, and absorbed better. To illustrate, diabetic rats received α-eleostearic acid (0.5 and 1%) in nano-emulsions (NEs), containing 50% of bitter gourd oil, daily for 28 days. Substituting NEs for free α-eleostearic acid significantly reduced blood glucose levels. After a 12-week storage period, α-eleostearic acid in nano-emulsions showed increased stability. In another study, diabetic mice received 400 mg/kg body weight of Abelmoschus esculentus ethanolic extract nano-emulsion orally for 14 days. The free extract reduced blood glucose by 39.32%, while extract-loaded NEs reduced it by 52.05%.[83,84] They are waterless. In water, they spontaneously form oil-in-water nano-emulsions with nanodroplets smaller than 200 nm. Its composition makes SNEDDS nanoparticulate carriers that improve lipophilic medication stability and bioavailability. Garg et al. put polypeptide-k into SNEDDSs and investigated its dissolution. The study found that SNEDDS released polypeptide-k faster than the free medicine. The free drug released 18.42% of polypeptide-k in an hour, but SNEDDS released the entire amount in 15 minutes. SNEDDSs increased disintegration by 5.4. In the same study, 800 mg/kg polypeptide-k in SNEDDSs lowered diabetes rats' blood sugar to < 100 mg/dL for 28 days. The rats who got the same dose of drug unbound had glycemia levels slightly above 250 mg/dL, similar to the control group. Rayanta et al. gave rats 250 mg/kg oral curcumin SNEDDSs. The bioavailability analysis showed a 1632.1% rise in blood maximum concentration and a 7411.1% increase in area under the curve. Khursheed et al. observed that curcumin and quercetin in SNEDDS increased their bio-availabilities by 50.2-fold and 5.6-fold, respectively.[85,86] For antidiabetic therapy, Jumaryatno et al. investigated the stability of SNEDDSs made from *Ipomoea reptans* ethanolic leaf extract. There was no phase separation or particle size change. Hayati et al. tested SNEDDS, an ethanolic *Centella asiatica* (L.) leaf extract, on zebrafish fasting blood glucose levels. Indonesians treat diabetes with *Centella asiatica*. No other extract resembled the free extract. The author used Ipomoea reptans ethanolic extract-SNEDDSs with similar findings.[87,88]

5.3 Inorganic nanoparticle formulations for Antidiabetic Phytocompounds or Plant Extracts

Metal or metal oxide nanoparticles produced through green synthesis are created using antidiabetic plant components. Using plant-based bioactive molecules to reduce metal ions creates green treatments. Mixing the plant extract solution with metal precursor salt preparation is typical. Metallic ions are reduced and encapsulated by phytochemicals to generate metal or metal oxide nanoparticles. After collection, they are dehydrated. Recent interest has focused on their diabetic treatment potential. The inorganic component of phytoconstituents, such as a metal or metal oxide, improves and synergizes their antidiabetic actions. The new green synthesis method produces phytochemicals and metallic elements. Thus, phytochemicals in inorganic-based nanoformulations of herbal products can better permeate internal organs and reach the systemic circulation. Additionally, green nanoparticles' biological activity might be affected by their components. In vitro and in vivo tests have indicated antidiabetic properties for several inorganic elements. They do this by increasing antioxidant enzymes, glucose intake, and insulin sensitivity. Biologically manufactured nanoparticles, including green synthesis, are more effective at treating diabetes than metal, plant, chemical, or physical nanoparticles. However, few studies have compared their efficacy in real organisms (in vivo) and lab settings (in vitro) to their larger equivalents.[89,90]

5.3.1 Silver nanoparticles Made using green synthesis methods

Plant extracts and silver salts are used to manufacture green AgNPs. Silver nitrate (AgNO3) is more soluble than sparingly soluble silver salts, hence it releases silver ions faster during synthesis. An water-based leaf extract of Lonicera japonica produced silver nanoparticles (AgNPs) with antidiabetic effects, according to Balan et al. Lab tests showed that the produced nanoparticles significantly suppress carbohydrate-breaking digestive enzymes. In the lab, researchers made and tested Allium cepa extract-AgNPs. Studies indicate a considerable decrease in the ability to eliminate damaging free radicals and break down carbs (α-glucosidase and α-amylase), similar to acarbose. Silver nanoparticles produced from Musa paradisiaca stem extract lower blood glucose. Both Zingiber officinales extract and Solanum nigrum leaf extract-AgNPs have similar effects.[91,92]

5.3.2 Synthesized Zinc Oxide Nanoparticles

When producing zinc oxide nanoparticles with plant extracts, (Zn (NO3)2.6H2O), (Zn (OOCCH3)2), or (ZnSO4) are often used. Zinc is essential for animal cells and helps regulate diabetes. Zinc dramatically lowers glycated haemoglobin. Alpha glucosidase and alpha amylase are inhibited, although hepatocytes and lipid metabolism are increased. Insulin production, storage, and release increase while proinflammatory cytokines decrease.

Kazempour et al. observed that phytocompounds in zinc oxide nanoparticles made from zinc nitrate solution and Eryngium billardieri leaf extract markedly decreased blood glucose and elevated insulin levels in diabetic mice. Green-synthesised ZnO decreased cholesterol levels in rats compared to insulin and Eryngium billardieri leaf extract. A different research project involving Silybum marianum L. seed extract found similar results. Anti-diabetic plants include *Tamarindus indica*, *Hibiscus subdariffa, Murraya koenigii*, *Azadirachta indica,* and *Hibiscus rosa-sinensis* help make zinc oxide nanoparticles. These herbs have powerful anti-diabetic effects.[93,94]

5.3.3 Synthesized Selenium Nanoparticles

In a green synthesis procedure, plant extracts are combined with Na_2SeO_3 or H_2SeO_3 to make selenium nanoparticles. Their diabetes-treating properties are evident. Fan et al. synthesized SeNPs from selenium acid and Hibiscus sabdariffa leaf extract. These SeNPs protected against oxidative stress and diabetes in vivo. In another study, researchers synthesized SeNPs from Pueraria lobata and mulberry leaf ethanolic extracts. The medicine's stability and regulated release in simulated digestive fluid were shown. Non-diabetic and diabetic rats showed significant hypoglycemic effects following oral treatment. Selenium nanoparticles made from Catathelasma ventricosum polysaccharides demonstrated better antidiabetic effect than chemically synthesized in diabetic male mice.[95,96]

5.3.4 Gold Nanoparticle Production

In a green synthesis technique, plant extracts with phytochemicals react with gold ions from a precursor like HAuCl4, AuCl3, or HAuCl4 to form gold nanoparticles. Venkatachalam and colleagues produced gold nanoparticles from Cassia auriculata and gave them to Diabetic rats were administered alloxan at 0.5 mg/kg body weight. Nanoparticles made utilizing green technologies dramatically reduced blood glucose, cholesterol, and triglycerides. They subsequently examined how these nanoparticles affected streptozocin-induced diabetes in rats. This treatment reduced hyperglycemia-related oxidative stress, inflammatory markers, and blood glucose more than the extract. No toxicity was detected. In liver tissue, green-synthesized gold nanoparticles increased antioxidant defense, decreased metalloproteinase activity, and reduced inflammation. Thus, they may treat diabetes at low doses. Another study used Fritillaria cirrhosa aqueous extract to synthesize gold nanoparticles. In diabetic mice, the mixture lowered blood indicators (AST, ALT, and ALP) to normal levels and prevented diabetes than in diabetic rats. The antidiabetic properties of gold nanoparticles synthesized utilizing environmentally safe methods.[97,98]

5.3.5 Synthesized Iron Nanoparticles

Plant extracts are used to bioreduce Fe(II) or Fe(III) salts like FeSO4, FeCl3 6H2O, Fe(NO3)3.9H2O, and Fe(C5H8O2)3) to produce iron nanoparticles (Fe2O3) and (Fe3O4). Iron nanoparticles made from Fe2O3 and Fe3O4 are produced. Iron nanoparticles synthesized using ecologically safe technologies are being tested for antidiabetic benefits. Methanolic extracts from different plant extract helped synthesize iron nanoparticles. At a concentration of 250 µg/mL, radical-scavenging activity decreased by 74.5% and α-amylase activity decreased by 70.5%. FeNPs made utilizing green technologies have excellent antioxidant and antidiabetic characteristics, making them a promising hyperglycemia treatment. In another study, Bano et al. found that green-made iron nanoparticles showed a 50% α-amylase inhibition effect.[99,100]

5.3.6 Copper Nanoparticles Synthesize

Environmentally Friendly Copper Nanoparticle Production Synthesis involves merging materials or ideas to create something new or cohesive. Copper compounds like CuCl2, Cu(CH3COO)2, CuSO4, and Cu(NO3)2 can react with phytoconstituents in plant extracts to form environmentally benign copper nanoparticles. Research suggests that copper nanoparticles made using green synthesis can treat diabetes by suppressing α-amylase, α-glucosidase, and antioxidants. Low-concentration copper nanoparticles have been found to treat diabetes in lab studies and real creatures.[101,102]

6. Future Perspectives

Nanocarriers have garnered increasing attention in the realm of medicine. Patient adherence is essential for achieving treatment objectives in diabetes management, a condition often demanding ongoing and extended attention. Nanocarriers have been discovered to enhance patient adherence and therapeutic effectiveness by offering several pathways for delivery, masking unpleasant Flavors, optimizing the controlled release of medications, enhancing the active ingredient stability, and enhancing the objective selectivity. Therefore, the investigation of nanocarriers as antidiabetic drugs has witnessed a surge in recent years. Vegetable-derived active ingredients have been receiving increased attention as a result of the diverse adverse effects associated with modern antidiabetic medications. They have the potential to produce comparable outcomes as contemporary medications, albeit with a reduced incidence of adverse reactions. The majority of research on nanocarriers containing plant-based antidiabetic active agents has been concentrated on polymeric nanoparticles. In addition, the process of increasing the size and producing a large quantity of polymeric

nanocarriers is significantly simpler compared to liposomes or niosomes. Polymeric nanocarriers demonstrate superior stability compared to other types of nanocarriers.[103,104]

Regarding the study results, certain antidiabetic medicines exhibited hypoglycaemic properties and the capacity to alleviate complications associated with elevated blood glucose levels. Betanin and curcumin, both active antidiabetic drugs, shown the capacity to mitigate oxidative damage induced by hyperglycaemia. The pancreatic tissue exhibits a diminished capacity to counteract oxidative stress, rendering it more susceptible to injury and subsequent impairment of pancreatic beta cells. The enhancement of pharmacokinetic and therapeutic efficacy of natural product based active agents capable of carrying them.[105,106]

Continuing research suggests that nanocarrier technology has the potential to provide significant biomedical opportunities and difficulties. In addition, numerous plant-derived antidiabetic compounds exhibit other biological characteristics, including antioxidant and antihyperlipidemic effects. Hence, these nanocarriers have the capacity to be utilized alongside therapies for various other ailments. Nevertheless, the available data from current trials remain insufficient to forward the research to the next stage, particularly in terms of the long-term therapeutic efficacy, the potential for adverse effects over extended treatment, and the durability of the formulations. Therefore, further investigation is necessary to fully exploit the capabilities of plant-based antidiabetic nano-formulations. A novel modified metallic nanoparticle, with an optimal size range of 150-250 nm, could be employed for diabetes therapy due to its enhanced trapping capabilities and reduced toxicity profile. The utilization of nanocarriers to deliver plant-derived antidiabetic medications has created novel avenues for diabetes treatment.[107,108]

7. CONCLUSION

Low-income countries use herbal remedies to treat several diseases, including diabetes, according to research. Multiple studies have shown the pros and downsides of traditional medicine's plant-derived diabetes treatments. Plant extracts produced by varied medicinal plants around the world have multiple benefits, including antidiabetic action. The main drawback is the poor oral bioavailability of many active phytocompounds. The low solubility or permeability and fast elimination are typically to blame. Despite their use in healthcare and as food, therapeutic plant compounds for chronic illnesses. Long-term phytocompound consumption is needed to treat chronic diseases. However, the dangers of this therapy strategy remain unknown. Solutions are being developed to solve limits and difficulties to provide more effective formulations that need less intake. These documented continuing methods demonstrated encapsulating botanical goods (either crude extracts or isolated chemicals) in nano formulations (by encapsulating them within, though, or attaching them to the nanocarrier) significantly improves their diabetes treatment efficacy. They can transport large amounts of medications. A modest dose of medication delivered by lipid nanocarriers increases activity, according to studies. Since lipid carrier components are GRAS, these investigations focused on activity and dose rather than safety. However, this must be considered when planning a clinical implementation. Green-synthesized inorganic nanoparticles contain phytochemicals and metallic components that restore glycemic homeostasis. The phytochemical amounts were not measured, but the antidiabetic impact was substantially larger at low dosages than inorganic nanoparticles made without green approaches. However, these trials provided minimal safety data. Most biosynthesized inorganic nanoparticles have been generated using crude extracts, with only a few studies exploring the antidiabetic properties of green nanoparticles derived from isolated phytocompounds. Many of these studies lack in vivo testing to evaluate their efficacy and safety profiles. Zinc oxide nanoparticles (ZnONPs) are special because they are GRAS and used in food. Zinc is a good option for therapeutic use in diabetes treatment due to in vivo studies. However, more verification is needed. These models mostly show type 1 diabetes. We advocate using natural diet diabetic animal models to imitate type 2 diabetes's hyperglycemia and insulin resistance. This method will improve study analysis and interpretation.

The research suggests employing nanoparticles to deliver plant-based compounds as an alternative diabetes treatment, especially in low-income nations.

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