REVIEW ARTICLE

Phytonanoformulations as New Frontier in Effective Management of Diabetes Mellitus Type 2

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ABSTRACT

The chronic metabolic disease known as type 2 diabetes mellitus (T2DM) is typified by β-cell dysfunction, insulin resistance, and poor glucose metabolism. Despite the availability of pharmacological treatments, many patients experience inadequate glycemic control and adverse side effects. Recent developments in nanomedicine, especially the application of phytonanoparticles (PNPs), have demonstrated potential as a cutting-edge strategy for the treatment of type 2 diabetes. Phytonanoparticles are plant-based nanoparticles with special qualities like low toxicity, biocompatibility, and antioxidant activity that make them excellent options for treating diabetes. Phytonanoparticles exhibit several mechanisms of action that can address key aspects of T2DM. Their antioxidant and anti-inflammatory qualities aid in lowering oxidative stress, which is a major contributor to the etiology of type 2 diabetes. Additionally, PNPs may promote β-cell function, control glucose homeostasis, and improve insulin sensitivity. Additionally, phytonanoparticles can facilitate the targeted delivery of therapeutic agents, minimizing side effects and improving drug bioavailability. This review explores the synthesis, characterization, and therapeutic potential of phytonanoparticles in T2DM treatment. Various plant sources, such as *Curcuma longa* (turmeric), *Azadirachta indica* (neem), and *Allium sativum* (garlic), have been explored for their ability to produce nanoparticles with anti-diabetic properties. Furthermore, we discuss the mechanisms through which PNPs exert their beneficial effects, including modulation of inflammatory pathways, enhancement of insulin signaling, and reduction of hyperglycemia. Although research on PNPs in T2DM is still in its early stages, the results to date suggest that they hold significant potential as adjuncts to conventional treatments, offering a safer, more effective therapeutic option for managing T2DM. Phytonanoparticles represent a promising frontier in diabetes therapy, combining the power of plant-based compounds with nanotechnology to offer a multi-targeted approach to combat Type 2 diabetes mellitus.

Keywords: Diabetes type 2, natural products, phytochemicals, nanotechnology, bioavailability, and drug delivery.
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INTRODUCTION

Over 400 million individuals worldwide suffer from type 2 diabetes mellitus (T2DM), a global health emergency that is expected to continue to increase in the ensuing decades. A leading cause of morbidity and mortality, type 2 diabetes is characterized by insulin resistance, poor glucose metabolism, and β-cell dysfunction. It also contributes to consequences such renal failure, neuropathy, retinopathy, and cardiovascular disease. Currently available treatments include insulin therapy in more severe cases and oral hypoglycemic medications such metformin, sulfonylureas, and thiazolidinediones. But over time, these medications frequently lose their effectiveness and can cause negative side effects like weight gain, gastrointestinal issues, and an elevated risk of cardiovascular events.[1] This emphasizes the necessity of creative treatment approaches that go beyond blood glucose regulation. Nanomedicine has shown great promise in treating chronic illnesses, particularly type 2 diabetes, in recent years. In contrast to their bulk counterparts, nanoparticles—which are defined as objects ranging in size from 1 to 100 nanometers—display distinct physical, chemical, and biological characteristics. Nanoparticles are very appealing for drug delivery and therapeutic applications because of their characteristics, which include greater surface area, improved bioavailability, and the capacity to pass through biological barriers. Phytonanoparticles (PNPs), which are made from plant-based materials, have attracted a lot of attention among the various kinds of nanoparticles because of their low toxicity, biocompatibility, and potential to use the medicinal qualities of substances produced from plants. Plant extracts, phytochemicals, or biomolecules obtained from plants are used to create pytonanoparticles. These nanoparticles are excellent options for treating type 2 diabetes because of their many qualities, including anti-inflammatory, anti-diabetic, and antioxidant effects. PNPs can offer a safer and more effective substitute for traditional diabetic therapies by fusing the special benefits of nanotechnology with the natural medicinal effects of plants. Additionally, PNPs enable tailored drug delivery, which

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lessens the systemic adverse effects that conventional medications frequently cause. [2]

Mechanisms of Action of Phytonanoparticles in Type 2 Diabetes Mellitus

The pathogenesis of T2DM is multifaceted, involving genetic, environmental, and lifestyle factors that lead to insulin resistance, β-cell dysfunction, and impaired glucose homeostasis. Phytonanoparticles can exert beneficial effects through several mechanisms, addressing multiple aspects of the disease simultaneously. [3]

Antioxidant Activity and Reduction of Oxidative Stress

The onset and course of type 2 diabetes are significantly influenced by oxidative stress, which is caused by an imbalance between reactive oxygen species (ROS) and the body's antioxidant defense mechanism. Increased ROS levels are linked to inflammation, β-cell death, and insulin resistance. Flavonoids, phenolic acids, and terpenoids are among the several plant-derived substances that are utilized in PNP synthesis and are well-known for their strong antioxidant capabilities. PNPs can increase insulin sensitivity and lessen oxidative tissue damage by neutralizing ROS. For instance, PNPs made from turmeric, or Curcuma longa, which includes the potent antioxidant curcumin, have demonstrated potential in reducing oxidative stress and enhancing glucose metabolism. [4]

Anti-inflammatory Effects

Chronic low-grade inflammation is another hallmark of T2DM, contributing to insulin resistance and β-cell dysfunction. Phytochemicals such as polyphenols, alkaloids, and terpenes, which are commonly found in plants used for nanoparticle synthesis, possess anti-inflammatory properties. For instance, *Azadirachta indica* (neem), a plant traditionally used in Ayurvedic medicine, contains compounds that can inhibit the production of pro-inflammatory cytokines, thereby reducing inflammation and improving insulin action. PNPs derived from such plants may thus help to alleviate inflammation-related insulin resistance, providing an additional therapeutic approach in T2DM management. [5]

Enhancement of Insulin Sensitivity

Insulin resistance is a key factor in the development of T2DM. Many plant-based nanoparticles, such as those derived from *Allium sativum* (garlic), have been shown to enhance insulin sensitivity. These nanoparticles can influence various signaling pathways involved in glucose metabolism, such as the insulin receptor pathway and the AMPK (AMP-activated protein kinase) pathway. By activating these pathways, PNPs can improve cellular glucose uptake, enhance glycogen synthesis, and reduce hepatic glucose production, ultimately leading to better blood glucose control. [6]

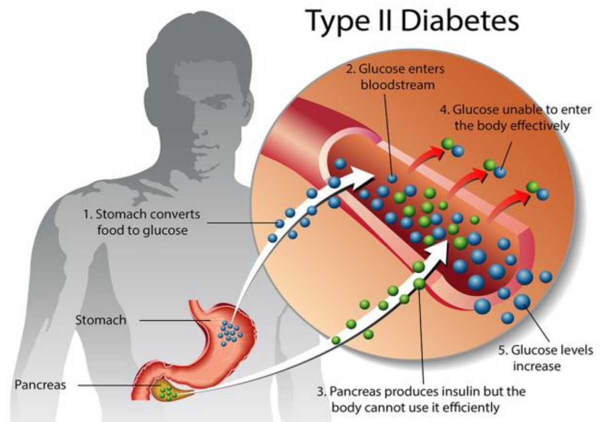

Figure 1: Type 2 Diabetes Insulin Resistance and Occurrence of Type 2 Diabetes [20]

Regulation of Glucose Metabolism and β-cell Protection

In T2DM, impaired insulin secretion from pancreatic β-cells is a critical factor contributing to hyperglycemia. Phytonanoparticles can exert protective effects on β-cells, promoting their survival and function. For example, studies have shown that PNPs derived from *Glycyrrhiza glabra* (licorice) or *Cinnamomum verum* (cinnamon) can stimulate insulin secretion and improve β-cell proliferation. Moreover, these nanoparticles may help to mitigate the toxic effects of elevated glucose levels on β-cells, reducing the risk of β-cell apoptosis and dysfunction. [7]

Targeted Drug Delivery

One of the key advantages of using phytonanoparticles in diabetes therapy is their ability to act as carriers for targeted drug delivery. Nanoparticles can be engineered to encapsulate therapeutic agents, such as insulin, glucagon-like peptide-1 (GLP-1) agonists, or metformin, and deliver them directly to specific tissues or organs. By targeting the pancreas or liver, for example, PNPs can enhance the bioavailability of these drugs while minimizing their systemic side effects. Additionally, the surface of PNPs can be functionalized with ligands that specifically bind to receptors on β-cells or insulin-sensitive tissues, further improving the precision and efficacy of treatment. [8]

Synthesis of Phytonanoparticles for Type 2 Diabetes Mellitus[9]

The synthesis of phytonanoparticles typically involves green synthesis methods, which utilize plant extracts or biomolecules to reduce metal ions or assemble nanoparticles. By using this eco-friendly method, hazardous chemicals and solvents that are frequently used in the production of traditional nanoparticles are avoided. A number of techniques have been investigated for PNP preparation, including:

Hydrothermal Synthesis

To create nanoparticles, plant extracts are heated in water. It is a straightforward, economical method that enables the creation of nanoparticles with precise size and shape.

The sol-gel process is a technique that uses plant extracts as reducing agents to turn metal salts into nanoparticles. High control over the nanoparticles' size and form is possible with this method.

Green Reduction of Metal Salts

This technique reduces the metal ions and creates nanoparticles by combining plant extracts with metal salts like gold chloride or silver nitrate. The plant extracts' phytochemicals serve as stabilizing and reducing agents.

Plants like *C. longa*, *A. sativum*, *Zingiber officinale* (ginger), *Camellia sinensis* (green tea), and *Moringa oleifera* are some of the commonly used sources for the synthesis of PNPs with potential anti-diabetic properties. These plant sources are rich in bioactive compounds such as flavonoids, polyphenols, alkaloids, and saponins, which are known to possess a wide range of therapeutic effects, including anti-diabetic activity.

CHALLENGES AND FUTURE DIRECTIONS

While the potential of phytonanoparticles in T2DM treatment is promising, there are several challenges that need to be addressed. First, the large-scale production of PNPs in a reproducible and cost-effective manner remains a significant hurdle. Second, comprehensive clinical trials are required to assess the long-term safety and effectiveness of PNPs in people. Additionally, issues such as nanoparticle stability, biodistribution, and potential toxicity must be addressed to ensure the safety of PNP-based therapies. [10]

Notwithstanding these obstacles, there are promising opportunities to enhance the treatment of type 2 diabetes in the developing field of phytonanoparticles. To improve the therapeutic efficacy and safety profile of PNPs, ongoing research is concentrated on refining their synthesis and functionalization. For people with type 2 diabetes, the combination of phytonanoparticles and conventional therapies may open the door to more individualized, efficient, and long-lasting therapy alternatives. One new and promising tactic in the fight against Type 2 diabetes mellitus is the use of phenylanoparticles. PNPs can provide numerous advantages in the treatment of type 2 diabetes by utilizing the medicinal qualities of substances obtained from plants and fusing them with the special powers of nanotechnology. These nanoparticles may enhance glucose metabolism, preserve β-cell function, and have anti-inflammatory, insulin-sensitizing, and antioxidant properties. With continued research and development, phytonanoparticles have the potential to revolutionize the treatment of T2DM, offering a safer, more effective alternative to conventional therapies. [11]

Complications of Type 2 Diabetes

If not properly managed, T2DM can lead to a wide range of complications, many of which can be severe or even life-threatening. Chronic high blood glucose levels damage various tissues and organs over time, leading to complications that affect the cardiovascular system, kidneys, eyes, and nerves. [12]

Cardiovascular Disease

Heart disease, stroke, and peripheral artery disease are among the cardiovascular disorders for which people with type 2 diabetes are more susceptible. Atherosclerosis is a condition where plaque accumulates in the arteries, narrowing them and raising the risk of heart attack and stroke. It is exacerbated by insulin resistance, high blood sugar, and abnormal lipid levels. [13]

Kidney Damage (Diabetic Nephropathy)

Diabetic nephropathy is caused by prolonged elevated blood glucose levels that harm the kidneys' filtration units and blood vessels. If left untreated, this illness can lead to renal failure, necessitating dialysis or, in extreme situations, a kidney transplant. [14]

Retinopathy

Diabetic retinopathy, which can result in blindness and vision impairment, is caused by high blood sugar levels damaging the tiny blood vessels in the eyes. It is among the main reasons why adults become blind. [15]

Neuropathy

People with type 2 diabetes may develop diabetic neuropathy, a form of nerve damage. Pain, tingling, numbness, and weakness are some of the symptoms that can result from high blood sugar damaging nerves, especially in the feet and legs. Amputations and foot ulcers may result in extreme situations. [16]

Infections and Poor Healing

Elevated glucose levels impair immune function, making individuals with T2DM more susceptible to infections, especially in the skin, urinary tract, and gums. Wounds and cuts may take longer to heal, which increases the risk of infection and complications. [17]

Skin Disorders

Diabetic individuals are more prone to skin infections, fungal infections, and conditions like diabetic dermopathy (light brown, scaly patches), which can occur due to poor circulation and impaired immune response. [18]

Cognitive Decline

Research suggests that people with long-term T2DM may experience an increased risk of cognitive decline and dementia. Chronic hyperglycemia can affect brain function, contributing to memory problems and an increased risk of Alzheimer's disease. [19]

CONCLUSION

Phytonanoparticles (PNPs) represent an exciting and innovative approach in the treatment and management of Type 2 diabetes mellitus (T2DM). The growing burden of T2DM, coupled with the limitations of current therapies, has fueled the search for alternative and complementary strategies that can address the underlying pathophysiology of the disease. Phytonanoparticles, derived from plant sources, offer unique advantages over traditional pharmaceutical formulations, including enhanced biocompatibility, low toxicity, and the ability to target multiple molecular pathways involved in the development of T2DM. The therapeutic potential of PNPs in T2DM is multifaceted. These nanoparticles exhibit significant antioxidant, anti-inflammatory, and insulin-sensitizing properties, all of which are crucial in combating the metabolic disturbances associated with T2DM. By reducing oxidative stress and inflammation, PNPs help mitigate insulin resistance and protect pancreatic β-cells from damage. Furthermore, the ability of PNPs to enhance insulin sensitivity, regulate glucose metabolism, and promote β-cell function makes them valuable adjuncts to conventional therapies. The targeted delivery of therapeutic agents through PNPs further improves their bioavailability and efficacy, potentially reducing side effects and optimizing treatment outcomes. Several plant-derived compounds, such as flavonoids, polyphenols, alkaloids, and terpenoids, have shown promising results in preclinical studies involving PNPs. Plants like *Curcuma longa* (turmeric), *Azadirachta indica* (neem), *Allium sativum* (garlic), and *Glycyrrhiza glabra* (licorice) have been explored for their anti-diabetic potential when incorporated into nanoparticle formulations. These compounds not only exhibit direct therapeutic effects but also enhance the stability and controlled release of bioactive molecules, which is crucial for sustained blood glucose regulation. The application of PNPs in the treatment of type 2 diabetes is still in its infancy, despite these encouraging findings. Optimizing PNPs' synthesis, size, and surface characteristics to optimize their therapeutic potential still presents challenges. Furthermore, in order to assess the long-term safety, effectiveness, and pharmacokinetics of PNPs in humans, comprehensive clinical trials are required. Nevertheless, the integration of nanotechnology with traditional plant-based medicine offers a promising frontier in diabetes care, potentially providing safer, more effective, and personalized treatment options for individuals with T2DM. In conclusion, phytonanoparticles hold great promise as a novel therapeutic strategy in managing Type 2 diabetes mellitus. By harnessing the power of plant-derived bioactive compounds and the unique advantages of nanotechnology, PNPs may revolutionize the way T2DM is treated, offering a multifaceted approach to managing this complex and prevalent condition. Continued research into PNPs will be key to unlocking their full potential and establishing them as a viable and effective alternative in diabetes management.

Conflicts of Interest
According to the writers, they have no conflicting interests.

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