STM JOURNALS

Nano Trends:
A Journal of Nanotechnology and Its Applications

ISSN: 0973-418X
Volume 26, Issue 1, 2024
January—April
DOI (Journal): 10.37591/NTs

https://journals.stmjournals.com/nts

Review NTs

Novel Nanotherapeutics for the Management of Diabetes

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Abstract

Diabetes is a severe chronic disorder with hyperglycemia, either due to dysfunctional pancreas (type I) or due to malfunctioned glucose utilizing entities like: liver, straight muscle or adipocytes (type II). type 1 or insulin-dependent/Juvenile diabetes and type 2 diabetes mellitus (DM) or non-insulin-dependent/adult-onset diabetes are the two broad classifications of diabetes. In case of type 1 diabetes injectable insulin is the major form of medication given and in case of type 2 DM, α-glucosidase inhibitors, insulin sensitizers, SGLT2, insulin secretagogues, biguanides, amylin antagonists, incretin mimetics, and inhibitors are majorly used. Monotherapy and combination therapies are the preferred therapies to manage type 2 diabetes nowadays. Conventional antidiabetic drugs majorly lack cost effectiveness and have side effects and so the world is now again shifting towards using traditional medications based on natural products. Traditional drugs also have many complexities such as: low bioavailability, small shelf life and non-targetability. To address such issues in both the cases of modern-day medicine or natural products-based medicines: nanotechnology-based drug delivery systems are being devised. The present review introduces the basics of diabetes and discusses nanotechnology-based drug delivery for diabetic patients, majorly for natural products-based antidiabetic.

Keywords: Diabetes, nano-therapeutics, nanotechnology, phytotherapeutics

INTRODUCTION

Diabetes is a metabolic disorder that evolves gradually if the pancreatic β-cells inadequately produce insulin or when the cells stop utilizing the produced insulin (hormone) effectively [1]. Chronically elevated blood glucose levels are a defining characteristic of diabetes. Diabetes is still incurable, and its management aids in controlling the condition. Given that diabetes is incurable, its management incurs significant costs. Owing to the advantages associated with herbal products, which include approachability, safety, economic efficiency, and promising properties against diabetes, herbal medications are increasingly utilized by individuals seeking to enhance their quality of life in diabetic conditions. Many phyto-remedies featured in herbal monographs of the World Health Organization (WHO) endorse this practice [2].

There have been many efforts to optimize the antidiabetic potential of herbal medications, and numerous studies have been conducted in recent years focusing on oral medication delivery. As natural products are mostly associated with low bioavailability and stability, efforts have been made

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Received Date: July 03, 2024
Accepted Date: July 26, 2024
Published Date: July 31, 2024

Citation: Rachana R., Khushi Sharma. Novel Nanotherapeutics for the Management of Diabetes. Nano Trends: A Journal of Nanotechnology and Its Applications. 2024; 26(1): 46–67p.

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to enhance their efficacy and bioavailability by designing formulations of nanometer-sized particles; others have explored the green synthesis of antidiabetic metal nanoparticles utilizing herbal extracts, where plant extracts/herbal molecules serve as capping, stabilizing, and reducing factors in this process, leveraging their high reducing potential to increase the biological activity of the nanomaterials [3].

Numerous earlier studies have reported various potential applications of nanotechnology in the development of novel treatments for diabetes [4]. Nanotechnology is now being used to attain extreme efficiency of herbal products, and in addition, the use of this technology makes drugs more cost-effective [5]. Drug delivery based on nanotechnology systems mostly consists of greater biological and physicochemical characteristics and has been shown to interact with biological molecules in a better way owing to its higher conductivity and large surface area. Additionally, controlled release at the target site inside the body can be achieved using nanocarriers [6]. The present article reviews the research that took place on nano-preparations for natural antidiabetic therapeutics, their usage, and understanding of their enhanced therapeutic potential, emphasizing their pros and cons for clinical applications.

OVERVIEW

Diabetes mellitus represents a multifaceted chronic disorder marked by heightened glucose concentrations in the body, a condition known as hyperglycemia [7]. Insufficient insulin secretion from pancreatic cells primarily contributes to elevated glucose levels. Insulin (a hormone) accountable for regulating blood glucose concentrations, is crucial in this process. This disorder can be symbolized as impairment of insulin action, secretion, or insulin resistance throughout the body. Insulin resistance is a state in which cells exhibit diminished responsiveness to insulin, thereby causing elevated blood glucose levels. This phenomenon is commonly observed in individuals who initially use insulin injections to deal with diabetes mellitus type 2 [8]. Diabetes can be categorized into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM), depending on its pathogenesis.

Classification of Diabetes

Insulin-dependent Diabetes (IDD) (Diabetes Type 1)

Type 1 diabetes mellitus typically arises because pancreatic β-cells undergo destruction due to an autoimmune disorder, which results in limited or no insulin (peptide hormone) synthesis. Substantial evidence has suggested that maintaining normal blood glucose levels can mitigate the risk of diabetes-related complications. However, hypoglycemia poses a challenge in attaining close-to-normal blood glucose levels in individuals with T1DM. Those with diabetes who are unaware of their hypoglycemic state are particularly at risk, impeding their ability to achieve the requisite glycemic control [9].

Non-insulin-dependent Diabetes (NIDD) (Diabetes Type 2)

In type 2 diabetes, there is a persistent chemical reaction condition distinguished by elevated sugar levels generally recognized as hyperglycemia due to conditions such as insulin resistance (IR) and inappropriate secretion. In this type of diabetes, pancreatic cells either produce insufficient insulin or are unable to utilize insulin efficiently, causing glucose to accumulate in the bloodstream [10].

Gestational Diabetes

During the initial stages of conception, fasting and postprandial glucose levels typically remain below normal glucose levels. However, as pregnancy progresses to the third trimester, the blood glucose levels tend to increase. When blood glucose levels reach diabetic levels during pregnancy, the condition is generally considered as GDM [11]. This accounts for nearly 90% of all the cases of diabetic individuals and related issues occurring during pregnancy. The prevalence of GDM varies significantly depending on the population studied, with incidence rates ranging from 1% to 14% in all pregnancies [12]. The causes of GDM are associated with the following risk factors: age, obesity, large newborn pregnancies, and previous instances of impaired glucose tolerance or GDM. Additionally, individuals with a past of GDM would be at higher exposure to getting T2DM further in existence. Therefore, consistent and

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lifelong testing and screening for every form of liver disease and glucose level impairment is strongly suggested for such individuals to verify early detection of T2DM [13].

CLAMPDOWN OF PHYTOMEDICINE

Herbal formulations have been used since ancient times to manage several illnesses including diabetes. Numerous strategies have been implemented to guarantee the effective inclusion of phytochemicals in plant extract medication delivery for diabetes treatment. Research on various plant secondary metabolites, which are occasionally employed in pure form or as extracts, has illustrated their impact on the management of diabetes. They have also been demonstrated to have preventative or ameliorative effects on related problems [14]. For instance, lutein can prevent ocular neuropathy, quercetin can protect against cardiovascular disease and retinopathy, and naringenin can prevent liver damage [15]. Most of these medications are orally administered. Their rapid fluctuations in metabolization patterns, nonspecific distribution to organs, less permeability, fast metabolization, lower absorption, low solubility in water, various ecological conditions, and high elimination still prevent their clinical use as therapeutic agents for diabetes [16]. Therefore, a substantial amount of medication is needed to achieve the desired therapeutic effect, which results in giving rise to side effects. In addition, owing to the presence of numerous components, certain drugs may interfere with each other. In addition, there are insufficient comprehensive deadliness research studies available for long-term use. Numerous plant-derived active compounds have been reported to exhibit poor bioavailability; however, this limitation has been mitigated through diverse nanoparticle formulations [1]. Examples of nanocarrier-mediated antidiabetic treatment modalities include metallic nanoparticles, solid-lipid nanoparticles (SLNs), polymeric nanoparticles, niosomes, nano emulsions, and liposomes. Hydrogels are utilized to release bioactive compounds for the treatment of a variety of chronic illnesses, including diabetic wounds. They may be created using cutting-edge methods that adjust to various conditions, including temperature and pH, and have high water content. The present article reports and discusses the use of herbal extract-derived nanocarriers for diabetes treatment [17].

NANOTECHNOLOGY

Nanoparticles, or nanoformulations, encompass a dimension range of 1–1000 nanometers and exhibit a significantly increased ratio of surface area to volume. This characteristic, together with their fabrication and composition methods, has a profound influence on their physicochemical properties and morphology [18]. Notably, nanoparticles have immense potential in the biological field, particularly in drug delivery systems. Their unique physicochemical properties, which are often absent in bulk materials, endow them with novel functionalities and enhanced performance compared with conventional therapeutic approaches.

In stimuli-responsive nanoparticles and nanofabricated devices, nanostructured lipid carriers have been observed to perform better than traditional drug delivery methods in terms of stability, biological availability, efficiency, biodistribution, and controlled drug release [19]. Moreover, adding ligands to nanocarriers improves their targeting power and shields the medications they contain from breaking down [20]. The impressive efficacy of nanostructured drug delivery systems has piqued scientists' curiosity about creating innovative drug formulations to treat a range of illnesses such as cancer, inflammatory conditions, cardiovascular illnesses, infectious diseases, and metabolic syndromes such as diabetes mellitus. The use of nanocarrier-assembled nanoparticles improves the penetration of drugs to specific targets, extends the duration of hypoglycemic results, and reduces the possibility of adverse effects [21].

Nanotechnology with Natural Compounds

Various therapeutic compounds from natural reservoirs, such as plant phenolics and flavonoids, have been reported to have antidiabetic properties. Several substances from these categories have shown strong antidiabetic effects *in vitro*; however, there is a discrepancy between their real effects in living creatures when investigated *in vivo*, limiting their therapeutic utility in clinical applications [19]. There

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are several possible causes for their inefficiency *in vivo*, including limited bioavailability, elevated P-glycoprotein (P-gp)-mediated efflux, rapid metabolism, and poor water solubility. Various formulation techniques, including solid dispersions, micronization (comminuted), hydrotrophy, and suspension systems (lipid-based) have been developed to enhance the therapeutic benefits of these substances against diabetes. However, compared to other formulation techniques, nanocarrier-based drug delivery approaches have shown promise for delivering antidiabetic substances that exist naturally but have subpar pharmacological qualities [22].

Nanotechnology for Antidiabetic Drugs

Several types of therapeutic delivery systems have been developed for use as antidiabetic drugs. These sophisticated drug delivery systems have the potential to augment the effectiveness, safety, and patient adherence to antidiabetic drugs for the treatment of T2DM. Nano-herbal formulations designed for T2DM depend on the category or type of nanomaterial used in the formulation, such as organic molecules (lipids and polymers) and inorganic materials (silver and gold nanoparticles) [23].

The combination of polymer science and nanotechnology has led to new developments in the field of drug delivery. Several polymeric nanostructured materials (PNMs) have been used for multiple purposes, such as diagnosis, drug delivery, and treatment of diseases. Polymeric nanoparticles can be any kind of nanoparticles, especially nanocapsules and nanospheres. Many water-soluble and insoluble drugs and natural compounds have been boosted using polymeric nanoparticles for specific targets by enhancing their safety, biocompatibility, and bioavailability.

Similarly, lipid-based nanoparticulate systems have also garnered significant interest owing to their advantageous characteristics, including cost-effective production, versatility in accommodating both hydrophilic and lipophilic drugs with high encapsulation efficiency, and the ability to achieve controlled drug release. These characteristics translate to enhanced bioavailability and broaden potential administration routes, including oral, intravenous, intramuscular, and pulmonary delivery [24]. In the case of metal nanoparticles, which are made using natural extracts/molecules for reducing metals, the metal or metal oxide that constitutes their inorganic portion serves as a transporter of phytoconstituents, amplifying their antidiabetic activity and fostering a synergistic effect. Presently, this green synthesis approach has been explored by the majority of researchers to supply both phytochemicals and metallic elements that are affixed to the target site [25].

Some case studies on nanoformulations based on polymers, lipids, and metal/metal oxides are discussed below.

Nanoparticles Using Polymers

Nanoformulations based on polymers possess diameters ranging between 10 and 1000 nanometers; and provide a robust platform for the provision of bioactive compounds. Polymeric nanoparticles have been shown to improve the efficacy of drugs for the treatment of diabetes. The fabrication of these nanoparticles utilizes biocompatible and biodegradable polymers, enabling the precise regulation of the release and transport of natural components. Polysaccharides including the chitosan and alginate (natural polymers), poly(L-lactic acid), poly(lactic-co-glycolic acid), polyvinyl alcohol, polyethylene glycol (PEG), (synthetic polymers) which ones are synthetic are commonly used in the development of polymer-based nanomaterials [26]. Based on the morphological attributes of the polymers employed, nanoformulations based on polymers can manifest as nanospheres or nanocapsules. Nanocapsules consist of polymeric membranes wherein a lipid core is enveloped in it, where natural substances could either be surface assimilation onto the membrane form of polymers or contained inside the lipid core. Conversely, spherical nanoparticles (nano spheres) are made of an entire framework consisting of polymers in which bioactive chemicals are stored or absorbed [27]. Few case studies employing polymeric nanoparticles for better treatment of diabetes mellitus type 2 by researchers have been discussed as follows.

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Anderson et al. (2003) investigated fractions of *Eucalyptus tereticornis* (Et), which were enriched in triterpenes (TFs), for their potential in managing type 2 diabetes (T2D) associated with obesity. Intraperitoneal administration of TFs in a diet-induced obesity mouse model demonstrated efficacy, whereas oral delivery was ineffective [28]. To overcome this limitation and facilitate effective oral administration, a polymeric nanoformulation has been developed. To achieve this purpose poly (lactic-co-glycolic acid) (PLGA) nanoparticles were employed for TF encapsulation. Extensive characterization of PLGA nanoparticles was conducted. Furthermore, *in vitro* release kinetics were evaluated using a simulated human gastrointestinal (GI) model, and *in vivo* metabolic marker assessment was performed for diet-induced obesity (DIO). Notably, the nanoformulation exhibited an 80% release of TFs within the first 6 h *in vitro*, with a 75% release observed *in vivo*. Additionally, treatment with the nanoformulation resulted in reduced blood sugar levels and body weight and enhanced insulin resilience in the DIO mouse model. These findings support the development of novel nanotherapeutic strategies utilizing natural components, such as Et-derived TFs for T2D management [29].

Mukhopadhyay et al. (2018) investigated pH-responsive polymeric nanoparticles for quercetin encapsulation. The nanoparticles were composed of alginate and succinyl chitosan, both of which exhibited pH sensitivity owing to carboxyl groups. Studies performed *in vitro* and *in vivo* illustrated the unique pH-triggered release profile of quercetin from spherical nanoparticles. Compared to free quercetin, both core-shell nanoparticle formulations displayed notable advancements in hypoglycemic effects and glucose tolerance in the streptozotocin-induced diabetic rat model. Importantly, nanoparticles exhibited no *in vivo* toxicity [30].

Nanoformulations Using Lipids

Lipids constitute a heterogeneous class of organic compounds characterized by their hydrophobic nature, making them insoluble in aqueous solvents but soluble in nonpolar solvents, such as chloroform or ether. Phospholipids are amphiphilic. Several types of nanoforms can be obtained from lipids or phospholipids, such as liposomes, Nanoemulsions, niosomes, and phytosomes. Lipid-based nanocarriers are a class of nanoparticle formulations designed to encapsulate therapeutic agents within a lipid matrix. These excipients, recognized as GRAS (generally regarded as safe) by the FDA, can be employed with or without surfactants to optimize the physicochemical properties [31].

Notably, nanoparticle formulations utilizing lipid-based carriers hold promise for improving the bioavailability of plant-derived antidiabetic medications. These carriers effectively encapsulate the drugs, masking any undesirable flavors while facilitating controlled drug release or potentially enabling target-specific delivery relevant to diabetes management, such as the pancreas or liver [32]. Lipid-based nanoformulations can be further categorized into two main classes: vesicular carriers, liposomes, and non-vesicular carriers, including lipid nanoparticles.

Lipid Nanocarriers Based on Vesicular System

Vesicular nanocarriers based on lipids contain an active medication enclosed in a vesicular structure composed of an oily shell encircling an aqueous phase. Lipophilic agents are found in the oily moiety, whereas hydrophilic agents are present in the aqueous portion. The vesicular delivery method involves liposomes, niosomes, and phytophospholipid (phytosomes), which have been used for the release of herbal medications with antidiabetic properties [33].

Liposomes

Liposomes are tiny vesicles with a spherical morphology that can be derived from natural and non-toxic phospholipids and cholesterol [34]. Many studies have explored the potential of liposomes to enhance the therapeutic potential of antidiabetic drugs. Gauttam and Kalia in 2019, encapsulated lyophilized hydroalcoholic extracts with antidiabetic properties of herbs, namely, *Withania somnifera, Trigonella foenum-graecum,* and *Momordica charantia,* in a ratio 2:2:1, achieved an encapsulation

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efficiency of about 66.9%, into liposomal form (phosphatidylcholine and cholesterol (8:2) vesicle system). Subsequently, the antidiabetic potential of these formulations was evaluated in diabetic rats receiving the treatments once a day for 21 days and compared with a freely marketed polyherbal formulation [34]. The study revealed that liposomal encapsulation enhanced the antidiabetic potential, with the dose of 500 mg/kg exhibiting more notable effectiveness p less than <0.05 in comparison to the 1000 mg/kg of the free polyherbal formulation.

Liposomes can be prepared from both natural and synthetic PLs. Liposomes are being explored to address the shortcomings of various drug molecules such as metformin. They were shown to enhance metformin uptake by Deng et al. (2019) as metformin remains the cornerstone therapy for type 2 diabetes mellitus (T2DM). However, its limitations include gastrointestinal (GI) discomfort, low oral bioavailability, and rapid elimination. Hyodeoxycholic acid (HDCA), a cholesterol-like molecule with glucose-regulating properties, was co-encapsulated to potentially synergize it with metformin, which was further shown to reduce blood glucose levels. Thin-film hydration was employed to synthesize liposomes with various HDCA: metformin ratios (HDCA: ME-(2:1), (1:1), and (0.5:1)). The formulations resulted in observable reductions in fasting blood glucose concentrations, enhanced glucose tolerance, hepatic protection, and modulation of oxidative stress markers. Interestingly, the HDCA: ME-(1:1) variant displayed the most potent activity, surpassing that of metformin alone. These findings suggest that the synergistic action of HDCA and metformin co-encapsulated within liposomes holds promise as a superior therapeutic strategy for T2DM management [35].

In another study, Jose et al. developed liposomes employing an ethanol-water extract of *Pterocarpus marsupium* (EE 82.7%). They conducted trials with diabetic rats to assess the effect on blood glucose levels, administering an oral dosage of 50 mg/100 g of the body weight routinely for seven days. Results showed that while *Pterocarpus marsupium* liposomes reduced blood glucose concentrations to about 113.1 mg/dL, and the crude extract of the plant decreased blood sugar concentrations of about 390.1 mg/dL (control) to 280.8 mg/dL. In conclusion, the formulated liposome formulation exhibited superior efficacy compared to the standard extract derived from *Pterocarpus marsupium* [36].

Phytosomes

These are currently discovered nanoscale delivery systems and can be derived from standardized herbal extracts (such as methanolic extract of peels of pomegranate, berberine, etc.) and phospholipids [31]. In a study by Barani et al (2021) the interaction between the polar head groups containing polyphenolic components and phospholipids (phosphatidylcholine, etc.) or the standardized herbal extracts (berberine, curcumin, pomegranate peel methanolic extract, etc.) results in the recently developed nanoparticulate systems known as phytosomes. Studies have shown that phytosomes enhance the bioactivity of phytoconstituents and botanical extracts by augmenting their absorption. Rats were administered berberine in the configuration of berberine-phytosome (with an encapsulation efficiency of 85%, administered at a single dose of approximately 50 mg/kg) [37]. In contrast to the conventional oral incorporation of berberine, the formulation exhibited a threefold increase in oral bioavailability and enhanced glucose metabolism [37].

One of the pharmacokinetic investigations was conducted by Riva et al. (2019) for oral administration of quercetin-phytosomes (quercetin and sunflower lecithin in a 1:1 weight ratio along with about a fifth part of food-grade excipients that are added to improve the physical state of the product and to standardize it to an HPLC-measured total quercetin content of approximately 40%). Phytosomes consist of plant-derived phospholipids and flavonoids, in which quercetin is encapsulated by phospholipids. Oral administration of 500 mg quercetin to human volunteers demonstrated a notable increase in quercetin plasma concentrations, up to 20 times greater than that achieved with free quercetin (encapsulation efficiency data not provided). Additionally, no significant side effects were observed [38].

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In another study by Rathee et al. (2017), employing a methanolic extract derived from fruits of *Momordica balsamina, Citrullus colocynthis* (L.), *Momordica dioica* phytosomes were created (prepared with combined polyherbal extract and phospholipid in weight/weight ratio) with EE 92.1±5.1% [39]. Following routine administration for approximately 15 days, the researchers assessed the antidiabetic efficacy of the polyherbal phytosomal formulation compared to that of free methanolic extract in rats. The reduction in the fasting blood glucose concentrations was more prominent with the dosage of 100 mg/kg per day phytosomal polyherbal formulation treatment (decreasing from 276 to 148 mg/dL) than with the dosage of 250 mg/kg/day of free methanolic mixed extract of all the bioactive compounds utilized for the experiment (range: 271–176 mg/dL). 92% of the formulation had a sustained release in 12 hours, according to *an in vitro* investigation [39].

Niosomes

Niosomes are surfactant vesicles that self-assemble from cholesterol and nonionic surfactants in the aqueous phase to form a bilayer structure [31]. In a study, noisome prepared (Span 60 and cholesterol 1:1 mol)) with lycopene (pure extract derived from tomatoes (*Lycopersicum esculentus*) when fed with orally route to a diabetic rat model for a total of about 14 days (200 mg/kg/day), with EE 62.8%, was shown to be more efficacious than free lycopene [40].

Using this, blood glucose concentration was reduced up to 91.6 mg/dL and 100.5 mg/dL, individually, contrary to the reference/control (260.3 mg/dL). Furthermore, while free lycopene lowered about 161.4 mg/dL of the cholesterol levels compared with the reference/control group's with 242.4 mg/dL, lycopene niosomes exhibited prolonged release, improved stability of lycopene over an extended duration, and decreased the overall cholesterol levels to about 108.5 mg/dL [40].

In a different investigation, Kamble et al. (2013) synthesized niosomes (nonionic surfactant and cholesterol) (designed by utilizing Span™ 40, which provided the steric stability of vesicles of 229.5 nm size range) filled with *Gymnema sylvestre* extract that had an 85.3% EE. According to an *in vitro* investigation, the phytocompounds gradually released (77.4% in less than 24 h) [36]. In comparison to the non-encapsulated extract with an area under the curve 0–2 h value of 80.5, the formulation (administered at 400 mg/kg) notably decreased blood glucose concentrations in diabetic rat models during an oral glucose tolerance test (OGTT). Niosomes demonstrated superior antihyperglycemic effects compared to the free extract [41].

Transfersomes

Transfersomes are lipid-based vesicular nanocarrier delivery systems designed in such a way that they consist of at least one inner aqueous compartment enclosed by a lipid bilayer, which is the activator of the edge [42]. These are specially designed to deliver drugs to biological membranes.

Chauhan et al. (2016) designed a transfersomes based nanoformulation of glimepiride utilizing sodium deoxycholate and phosphatidylcholine, which were converted into protransfersomes gels. With Franz diffusion, analysis of skin permeation was done the skin of pig ears for duration of 24 h and (5.129 ± 1.24 μg/cm^2/h) value of protransfersomal gel flux observed which persisted much superior than the drug suspensions having 0.430 μg/cm^2/h value. This gel nanoformulation was optimized and showed stability for approximately 3 months. Pharmacokinetic analysis indicates significant drug release in comparison to a conventional transdermal patch [43].

Abdallah and his colleagues fabricated transfersomal gel by Rotary Flask Evaporator Sonication technique, components include phospholipids, Sorbitan mono-oleate (Span 80; edge activator) encapsulating silymarin to enhance characteristics of silymarin. The transfersomal nanoformulation was done using 3-factor and 3-level Box Behnken design exploiting three autonomous and two dependent variables (sonication time, surfactant concentration, and phospholipid concentration) and *in vitro* release of drug and EE, respectively. The hydrogen ion concentration of the gel was identified 7.05,

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attained 55.35 mm diffusibility and 6.27 Pa viscosities were found eventually. The transfersomal gel showed 92.41 μg/cm^2/h flux which was comparatively greater compared to the suspension of silymarin. When compared with the oral formulation of the silymarin suspension and silymarin gel, a significant decrease in glucose concentrations was observed *in vivo* [44].

Non-vesicular Lipid Nanocarriers

Non-vesicular lipid nanocarriers are utilized for various medical applications, such as antimicrobial activity, gene transfer, and bioimaging, because they are versatile in nature. In addition, they can be incorporated through various routes, such as topical, intravenous, and oral, owing to their highly compatible nature. Numerous plant-derived compounds have been encapsulated in these delivery systems by various research groups. These non-vesicular nanocarriers include, nanostructured lipid nanocarriers, nanoemulsion, and solid-lipid nanoparticles (SNEDDS), as described below.

Solid-Lipid Nanoparticles

Solid-lipid nanoparticles are aqueous colloidal dispersions stabilized by nonionic emulsifiers. They primarily consist of solid lipids that maintain their solid state at ambient temperature [45].

SLNs transporters for the weakly soluble antidiabetic phytocompound berberine were prepared as previously described. Xue et al. in 2013, with EE 58% and 4.2% loading capacity (LC). When SLNs were compared with the exact amount of berberine given in the mice model, at a concentration of 100 mg/kg the bioavailability of berberine was found to be enhanced dramatically. In a different trial, mice were orally administered 10 mg/kg of myricetin daily. Incorporation of berberine in SLNs (made up of Tween 80 and Span 20 with a ratio of 1: 1), with encapsulation efficiency of 56.2% and it proceeded in a noteworthy downfall in blood sugar concentrations, indistinguishable to mice receiving 200 mg/kg of the metformin dose [46].

Nanostructured Lipid Carriers

The development of NLC or nanostructured lipid carriers represents a second generation of SLNs. This advancement involves the integration of small quantities of oils or room-temperature liquid lipids into the matrix, thereby causing rearrangement of its structural composition. The most common methods for preparing these materials are the microemulsion technique and high-pressure homogenization [47].

Recently, Palmer et al. (2016) developed baicalin-loaded nanostructured lipid carriers using Precirol, serving as a solid-lipid component, and Miglyol, functioning as a liquid lipid component with EE 85.29%. They administered it to a rat model orally at a dosage of 200 mg/kg [42]. Compared to administration free baicalin alone, the formulation exhibited prolonged baicalin release and led to a remarkable reduction in blood glucose concentrations by approximately 27%, as well as decreased levels of total cholesterol, and, glycosylated hemoglobin, total triglycerides [48].

In another study, Liu et al. (2014) reported sustained quercetin drug release in mice model during a biodistribution investigation of NLC containing quercetin (encapsulation efficiency of 89.3%) *in vivo*. They noted an enhancement in bioavailability (relative availability) of quercetin in the liver, kidney, and lung tissue. compared with administration of an integrated solution of quercetin [49].

Nanoemulsion

Nanoemulsions are fine water-in-oil (w/o) and oil-in-water (o/w) dispersions of two immiscible fluids [24]. Droplets of nano sizes ranging from tens to hundreds of nm are kinetically stable [50]. The goal of creating nanoemulsions is to boost the bioavailability of active herbal components or phytocompounds with limited solubility.

For example, the α-eleostearic acid (which contains about 50% bitter gourd oil) encased in nanoemulsion (bioactive lipid-conjugated linolenic acid (CLnA)), administered orally for 28 days daily.

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Consequently, lowered blood glucose concentration was observed with free α-eleostearic acid, and enhanced stability was observed at the end of the 12-week storage period of [51].

In another study, diabetic mice received 400 mg/kg body weight of *Abelmoschus esculentus*, aqueous extract of the nanoemulsion, orally for approximately 14 days. The findings revealed that while the free extract decreased the blood sugar concentrations up to 39.32%, the extract-loaded nanoemulsions achieved a higher reduction (52.05%) [52].

In a study, Javadi et al. (2021) prepared an oil-in-water nanoemulsion (O/W NE) using cumin essential oil and herbal extract of fenugreek and nettle by utilizing Span 80 and Tween 80 surfactants. L6 cell lines were used to determine glucose absorption, and cultured mouse pancreatic β-cells (RIN-5) were used to determine insulin secretion in the prepared formulation. The characterization of samples was done by SEM, TEM to determine the morphology and DLS to determine the zeta potential and size distribution. A stability study (30/90 days) was conducted using viscosity. These findings provide evidence for the use of nanoemulsions as herbal medicines against diabetes, as it was found to be a very simple and cost-effective method [53].

SNEDDS

Self-nano-emulsifying drug delivery systems (SNEDDS) are pharmaceutical formulations that are distinguished by their ability to spontaneously form nano-sized emulsions when introduced into aqueous environments, facilitating enhanced solubility, stability, and bioavailability of drugs. They contain approximately 30–60% of the drug, less than 20% of the weight of co-surfactants, oils, or co-solvents, structurally resembling nanoemulsions. They were prepared in the absence of water. The natural formation of aqueous media generates thin nanoemulsions of oil-in-water emulsion containing nanodroplets smaller than 200 nm [54].

Garg et al. (2017) investigated the dissolution of polypeptides in SNEDDSs. It was found that polypeptide-k was released in 15 min in SNEDDS whereas, only 18.42% of the polypeptide-k was released in one hour with the free drug [47]. SNEDDSs exhibited a 5.4-fold increase in the dissolution rate. In a parallel study, polypeptide-k in SNEDDSs administered to diabetic rats at a dose of about 800 mg/kg daily for about 28 days, a reduction in glycemia to a lesser amount than 100 mg/dL was experienced. Conversely, rats administered the same dose of free medication maintained glycemia slightly higher than 250 mg/dL, indistinguishable from that of the control (reference) group [54].

In a study by Khursheed et al. (2022), it was shown that the oral administration of 250 mg/kg curcumin SNEDDSs to the rats, a remarkable improvement in maximum blood levels and AUC of 1632.1% and 7411.1%, respectively, was observed while performing bioavailability assessment. The developed formulation was able to normalize the levels of blood glucose, lipids, antioxidant biomarkers, and tissue architecture of the pancreas and liver in streptozotocin-induced diabetic rats compared with their native forms [55].

In another study, Balata et al. (2016) created resveratrol SNEDDSs (of olive oil, Tween 80, and propylene glycol in the ratio 200:266.7:533.3, in mg) and demonstrated that their dissolution efficiency (94%) was greater than pure resveratrol (42%). There was a potential improvement in the oral bioavailability of resveratrol compared with that of unprocessed drugs. No significant difference was found between low (10 mg) and high (20 mg) doses of resveratrol SNEDDS in reducing blood glucose and body weight in STZ-induced diabetic rats, suggesting the high efficiency of resveratrol SNEDDS [56].

Another study was conducted to analyze the efficacy of SNEDDS, using the aqueous extract of the leaf of *Centella asiatica* (L.) for reducing the fasting blood glucose concentration in the zebrafish in

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alloxan-induced diabetes. Zebrafish were treated by submerging them in solutions containing 25 mg/2 L metformin, 100 mg/2 L, or 200 mg/2 L SNEDDS [48]. It was observed that metformin decreased blood glucose levels by 65.5%, 100 mg/2 L SNEDDS by 69.9%, and 200 mg/2 L SNEDDS by 72.2% [57].

Metal Nanoparticle

Nano-sized particles which are composed of either metallic elements or metal oxides, created from glucose-regulating phytochemicals are known as green-synthesized antidiabetic nanoparticles [58]. In such cases, the herbal extract solution is usually combined with a metal precursor that includes metallic salt preparations. Currently, there is considerable scientific interest in their possible applications in diabetes [58]. The phytochemicals associated with inorganic-based nanoformulations provide promising advantages, including the ability to penetrate deeper organs and enter the systemic circulation. Furthermore, the constituents synthesized through green methods can influence the biological efficacy of nanoparticles certain inorganic elements, like, Pa, Ni, Ti, Mo, Au, Pt, Vn, Mn, Fe, Zn, Cu, Mg, Ag, Cr, Ce, Se and W (tungsten) etc., have shown *in vitro* and *in vivo* properties which are beneficial for treating the diabetes [51]. These mechanisms also include their role as cofactors in enzymes and their ability to increase the levels of antioxidant enzymes, glucose utilization, and insulin sensitivity [59]. Compared to metals or plant products alone, nanoparticles produced through green synthesis have demonstrated enhanced antidiabetic efficacy, as nanoparticles are produced chemically or physically. However, very few researchers have examined *in vivo* and *in vitro* efficacy in comparison to their counterparts [60]. A few studies on the green synthesis of nanoparticles are discussed below.

Silver Nanoparticles

*S*ilver nanoparticles (AgNPs) through environmentally friendly methods and methods utilizing herbal extracts is being widely observed. This synthesis typically involves the reaction of herbal extracts with silver salts. Various silver salts have been used to prepare AgNPs, such as cerargyrite chlorargyrite hormone, silver Argentous chloride, silver chloride (AgCl), silver iodide (AgI), silver bromide (AgBr), and silver sulfide (Ag2S). Silver nitrate (AgNO3) is the most commonly used salt because of its high solubility, which facilitates efficient nanoparticle formation. They are also known to demonstrate notable antidiabetic effects *in vitro* and *in vivo* conditions [61].

In a study by Balan et al. (2016), the antidiabetic efficacy of AgNPs made with *Lonicera japonica* leaf extract was demonstrated [62]. The nanoparticles significantly inhibited digestive enzymes that break down carbohydrates. They were also found to be revocable non-competitive inhibitors of two important diabetes-related enzymes, α-glucosidase and α-amylase.

Likewise, the extracts of the *Allium cepa* AgNPs were produced and examined under controlled laboratory conditions (*in vitro)*, demonstrating notable reductions in the capacity to scavenge free radicals and inhibition of the enzymes that break down carbohydrates (α-amylase and α-glucosidase), which are equivalent to that of acarbose [63]. In another study, research conducted on diabetic rats utilizing silver nanoparticles produced from stem extract of *Musa paradisiaca* showed promising effects against diabetes by reducing blood sugar and glycosylated hemoglobin concentrations *in vivo* [64]. Similar effects have been observed with extract-AgNPs derived from *Zingiber officinales* and AgNPs synthesized using *Solanum nigrum* leaf extract [64].

Silver nanoparticles synthesized utilizing the leaf extract of *Ficus palmata* had shown antidiabetic activity inhibiting α-amylases and α-glucosidase to a much higher extent. The inhibition percentage of the nanoparticles increased with the range of the synthesized Ag nanoparticles. However, the IC_{50} values of the formulated AgNPs were less than that of the standard reference compound (acarbose, 18.5μg/mL) [65].

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Artificially Synthesized Zinc Nanoparticles

In a study conducted by Kazempour et al in 2021 demonstrated preparation of zinc oxide nanoparticles using Zn $(NO_3)_2$ (zinc nitrate) solution and the leaf extract of *Eryngium billardieri* which led diabetic rats' blood glucose levels to decrease and their insulin levels to rise noticeably. In addition, rats administered insulin plus *Eryngium billardieri* leaf extract had lower cholesterol than rats administered green-synthesis ZnO [66].

Another study utilizing seed extracts derived from *Silybum marianum L.* yielded comparable findings. *Azadirachta indica, Moringa oleifera, and Hibiscus rosa-sinensis, as Tamarindus indica, Hibiscus subdariffa, and Murraya koenigii* contain antidiabetic properties which are used to synthesize zinc oxide nanoparticles. These plants exhibit remarkably potent antidiabetic effects [67].

Kitture et al. (2015) used *Red sandalwood* natural extract (RSW) as an active and effective agent against diabetes in association with Zinc oxide nanoparticles for α-glucosidase and α-amylase inhibition assays were performed using extracts from the small intestine and pancreas of mice. A much higher inhibition was observed by the zinc oxide nanoparticle conjugate, contrary to the conjugated ZnO-RSW, which showed remarkably higher efficiency in inhibiting the porcine pancreatic α-amylase and was markedly more protective against crude murine pancreatic glucosidase as compared to either of its sole components (RSW and ZnO NPs). Specifically, the ZnO-RSW conjugate showed 61.93% inhibition in glucosidase activity, on the contrary, ZnO nanoparticles and RSW alone showed the inhibition levels of 21.48% and 5.90%, respectively [68].

Green-synthesized Nanoparticles of Selenium

In another study, Adibian et al. (2022) showed that the green-synthesized selenium nanoparticles by the combination of sodium selenite salt or selenious acid utilizing plant extracts *Rosmarinus officinalis, Ceropegia bulbosa Roxb.* The synthesized nanoparticles exhibited antidiabetic characteristics [69].

Selenium nanoparticles synthesized using a green method by Fan et al. (2020) involving selenium acid and extracts from *Hibiscus sabdariffa* leaves demonstrated antidiabetic effects when studies were conducted *in vivo* and they also increased resistance to oxidative stress [70].

In a different study, ethanolic extracts of *Pueraria lobata* and mulberry leaves were used to create SeNPs. They demonstrated appropriate stability and gradual release of medication in the simulated digestive fluid. Both normal and diabetic rats exhibited remarkable hypoglycemia following oral treatment. Pancreatic function is enhanced by reduced oxidative stress [71], and studies have shown that adipocytes use glucose efficiently.

Selenium nanoparticles produced from *Catathelasma ventricosum* polysaccharides exhibited significantly greater antidiabetic effects than chemically synthesized selenium nanoparticles in streptozotocin-induced diabetic male mice [72].

Artificially Synthesized Gold Nanoparticles

Various phytochemicals have been used to interact with gold ions derived from precursors, such as sodium tetrachloroaurate (III) dihydrate, auric chloride (AuCl3), and chloroauric acid (HAuCl4), to create green-synthesized gold nanoparticles [73].

In a study of Badeggi et al (2020), the procyanidin fractions of dimers and trimers (F1 and F2) from the *Leucosidea sericea* total extract (LSTE) were utilized as their chemical composition. *LSTE* and procyanidin fractions (F1 and F2) were used to create AuNPs [74]. F1 fraction contains a mixture of procyanidin dimers and trimers, whereas F2 fraction contains four major procyanidin dimers. The stability study and zeta potential measurements indicated the stability of the particles. Strong α-amylase inhibitory activity was shown by LSTE, F1, F2, and their corresponding AuNPs. The F1 fraction

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exhibited the highest IC50 value (1.88 µg/mL) whereas F2 fraction exhibited strong α-glucosidase activity (4.5 µg/mL). Also, they exhibited higher antioxidant (1834.0±4.7 µM AAE/g and 1521.9±3.0 µM TE/g, respectively) activity. This shows that these fractions were efficacious in forming bioactive and biostable AuNPs. In addition, they can enhance the activities of natural products, which in turn assists in smart delivery in biological applications [74].

In an i*n vivo* test with an alloxan-induced diabetic rat model, gold nanoparticles made from *Cassia auriculata* with a concentration of 0.5 mg/kg of the body weight were administered. The nanoparticle formation with the green methods showed remarkable reductions in blood glucose, triglyceride, and cholesterol levels (with a p-value of less than 0.001) [75].

In another study, Opris et al. (2015) [74, 75] used an extract from *Sambucus nigra L.* to produce gold nanoparticles, and they examined the antidiabetic benefits of these nanoparticles in rats that were administered streptozotocin to induce diabetes. Over 14 days, singular doses were orally administered, comprising 15 mg/kg body weight of an extract and 0.3 mg/kg body weight of artificially synthesized Au nanoparticles (AuNPs). This regimen resulted in a higher mitigation of oxidative stress, markers of inflammation, and blood glucose concentrations compared to the extract alone. There were no toxicological indications that were notably absent. This study demonstrated that lower doses of artificially produced AuNPs may be more efficacious in managing diabetes owing to their increased antioxidant defenses, suppression of metalloproteinase activity, and mitigation of liver tissue inflammation [76].

Additional Manufactured Inorganic Nanoparticles (Green Synthesis)

Green palladium nanoparticles are mostly made from precursors of palladium ions such as palladium acetate. In such reactions between the herbal extract and precursor, the natural compounds serve as bioreductors to assist in the development of these nanoparticles [77]. Hazarika et al. (2019) reported the inhibitory action of α-glucosidase on Pd nanoparticles derived from *Zanthoxylum armatum* fruit extract [77].

Similarly, Nickel ion precursors for nickel oxide nanoparticles were prepared from nickel chloride hexahydrate and nickel nitrate hexahydrate ($NiCl_2 \cdot 6H_2O$). Shwetha et al (2021) were used to produce nanoparticles composed of nickel oxide by taking extracts of leaf of *Areca catechu* and nickel nitrate hexahydrate. The formation of nanoparticles using eco-friendly methods demonstrated appropriate *in vitro* α-amylase inhibitory efficacy [78].

The nanoparticles and their therapeutic potentials described above are summarized in Tables 1 and 2, respectively [79].

CHALLENGES IN NANOTECHNOLOGY

In addition to the benefits of using nanotechnology in medicinal sciences, the safety of nanoparticles, their biocompatibility, and their specificity are still in a challenging mode with emerging nanocarriers for drug delivery. Numerous nanotechnology-based products face regulatory challenges because of the shortage of standardized testing and safety assessment methods that are very specific to nanoparticles. However, a proper set of guidelines for approval and nanomedicine commercialization is lacking in many respects. Large-scale production of nanoparticles and nanomedicines is quite low because of their complex manufacturing process, which in turn has negative effects on their widespread availability and affordability.

Nanoparticles with degradation characteristics over time consequently affect their efficacy and stability, and it is crucial to maintain their stability during storage to retain their therapeutic properties. Although nanocarriers have the potential for targeted drug delivery, the specific targeting of some nanomedicines to diseased cells or tissues remains a challenge. In addition, the biodistribution and clearance mechanisms of nanoparticles in the body are crucial for optimizing their therapeutic efficacy.

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Table 1. Illustrations of effects of recent phytocompounds loaded in lipid Nanocarriers *in vivo* and *in vitro*.

Nanoparticles	Active compound	Base compound	Model	Advantages	References
Polymeric nanoformulations	*Eucalyptus teretericonis*	Poly (lactic-co-glycolic acid) (PLGA)	DIO induced mouse model	Enhanced insulin resilience, reduced blood sugar levels, body weight	[28, 29]
	Quercetin	Alginate and succinyl chitosan	*in vivo* (STZ-induced diabetic model)	Elevated levels of hypoglycemic activity	[30]
	Seed oil of *Phoenix dactylifera*	Eudragit RS100	α-glucosidase and α-amylase *In vitro* analysis	Suppression of both enzymes observed	[78]
	Fennel (*Foeniculum vulgare* Mill. essential oil)	Tween 20 and propylene glycol	Diabetic rats (STZ-induced)	Increased hypoglycemic activity and prevent weight loss	[78]
Liposomes	*Withania somnifera, Trigonella foenum-graecum,* and *Momordica charantia*	Phosphatidylcholine and cholesterol	*In vivo* (Wistar rats)	Increased hypoglycemic activity	[34]
	Pterocarpus marsupium	Ethanol and water	*In vivo* (Alloxan-induced diabetic rats)	Reduced blood glucose levels by 70%	[36]
	Betanin	Ethanol	STZ-induced diabetic rats	Reduced anti-hyperlipidemic activity and oxidative stress	[80]
	Liquiritin	Isopropyl myristate (IPM), cholesterol and lecithin. Vanillylacetone (98% purity) and sodium cholate	STZ-induced diabetic rats	Increased hypoglycemic activity	[81]
Phytosomes	Methanolic extract of peels of berberine, pomegranate, circumin	Phospholipids and polyphenolic components	*In vivo*	Increased in oral bioavailability and enhanced glucose metabolism	[37]
	Quercetin	Phospholipids	*Human volunteers*	Increase in quercetin plasma concentrations	[38]
	Extracts derived from fruits of *Citrullus colocynthis (L.) Momordica balsamina* and *Momordica dioica*	Phospholipids	*In vitro and in vivo* (Swiss albino rats)	Increased antidiabetic efficacy with 100mg/kg/day of phytosomes	[39]
Niosomes	Lycopene	Span 60 and cholesterol	Streptozotocin-Nicotinamide-induced diabetic rats	Reduced glucose concentrations	[40]

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	Gymnema sylvestre (Gudmar) extract	Nonionic surfactant and cholesterol	Diabetic rats (Alloxan-induced)	Elevated hypoglycemic action	[41]
Transfersomes	Silymarin	Span 80 and phospholipids	*In vivo*	Decrease in blood glucose concentrations	[44]
	Glimepiride	Sodium deoxycholate and Phosphatidylcholine	*Skin of pig ears*	Remarkable drug release	[43]
Solid-Lipid NPs	Berberine	Tween 20 and Span 80	Adult male rat	Increased hypoglycemic activity and prevent weight loss possibilities	[46]
	Mycritin	Tween 80 and many more components	Nicotinamide and STZ-induced rats	Elevated levels of hypoglycemic activity and showed programmed cell death effects	[82]
Nanostructured based Lipid Carriers	Baicalin	Precirol and Miglyol	STZ-induced diabetic rats	Increased hypoglycemic activity	[48]
	Quercetin	Glycerol monostearate	In vivo	Enhancement in bioavailability of quercetin	[49]
Nanoemulsions	Resveratrol		Nicotinamide and STZ-induced rats	Increased hypoglycemic activity and prevent weight loss	[83]
	α-eleostearic acid (contains about 50% bitter gourd oil)	Conjugated linolenic acid	Alloxan-induced diabetic rats	lowered blood glucose concentration	[51]
	Extract of *Abelmoschus esculentus*	Ethanol	Alloxan-induced diabetic rats	Increased antidiabetic efficacy by enhanced penetration of active compounds	[52]
	Cumin essential oil and Extract of Fenugreek and nettle	Span 80 and Tween 80	*In vitro (*RIN-5 and the L6*)*	Less cytotoxicity, higher stability with antidiabetic properties	[53]
SNEDDS	polypeptide-k	Oleoyl polyoxyl-6 glycerides, Tween 80, and diethylene glycol monoethyl ether	STZ-induced diabetic rats	Exhibited antidiabetic activity	[54]
	Curcumin	Labrafil M1944CS®, Capmul MCM®, Tween-80® and Transcutol P®	STZ-induced diabetic rats	Normalized levels of blood glucose, lipids, antioxidants, etc.	[55]
	Resveratrol	Olive oil, tween 80, propylene glycol	STZ-induced diabetic rats	Potential improvement in oral bioavailability	[56]

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Table 2. Illustrations of effects of recent phytocompounds loaded in Inorganic metal nanocarriers *in vivo* and *in vitro.*

Nanoparticles	Active compound	Base compound	Model	Advantages	References
AgNPs	*Ficus palmate*	$AgNO_3$, zinc acetate, and sodium hydroxide	*In vitro* analysis	Suppression by IC_{50} by Ag NPs of α-glucosidase and α-amylase	[65]
	Leaf extract of *Lonicera japonica*	DPPH, p-nitrophenyl-α-D-glucopyranoside (PNPG)	α-glucosidase and α-amylase	Notable antidiabetic activity against the key enzymes of diabetes	[62]
	Extract of *Allium cepa*	Silver nitrate solution	α-glucosidase and α-amylase	Remarkable reductions in enzymes that break down carbohydrates	[63]
	Stem extract of *Musa paradisiaca*	AgNO3 solution	Male albino rats Sprague–Dawley strain	Reduced blood sugar and glycosylated hemoglobin level	[64]
	Zingiber officinales	Silver nitrate solution	Wistar albino rats	Enhanced hypoglycemic effects	[64]
(ZnO) Zinc oxide	*A. catechu*	Zn(NO3)2·6H2O (Oxidizer)	Assay of (Glucose uptake)	Yeast cell treated with zinc oxide nanoparticles demonstrated reduction in uptake ultimately contributes to antidiabetes	[84]
	RSW	Zinc acetate solution, ethanol, KOH	*In vitro* analysis *(*α-glucosidase and α-amylase)	Suppression of 61.93% showed by conjugation of ZnO-RSW	[68]
	Seed extract of Silybum marianum L	Zinc nitrate (Zn (NO3)2·6H2O) and sodium hydroxide (NaOH)	*In vivo* antidiabetic (Alloxan-induced Wistar rats)	Reduction in fasting blood glucose concentration	[67]
	Leaf extract of *Eryngium billardieri*	Zinc (II) nitrate, ethyl alcohol, and sodium hydroxide	*In vivo* (Alloxan-induced diabetic rats)	Reduced fasting blood glucose levels	[66]
	Aqueous leaf extracts of *Azadirachta indica, Hibiscus rosa-sinensis, Murraya koenigii, Moringa oleifera, and Tamarindus indica*	Zinc nitrate hexahydrate and sodium hydroxide	*In vitro (*α-amylase and α-glucosidase)	Increased antioxidant activity, inhibitory activity of α-amylase and α-glucosidase	[67]
Selenium nanoparticles	Herbal extract of *Rosmarinus officinalis, Ceropegia bulbosa Roxb*	Combination of sodium selenite salt or selenious acid	*In vivo*	Possess antidiabetic activity	[69]
	Aqueous leaf extracts of *Hibiscus sabdariffa*	Selenious acid (H_2SeO_3)	*In vivo* (streptozotocin-induced	Elevated antioxidant enzyme activities	[70]

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			diabetic Wistar rats)		
	Ethanolic extract of Mulberry leaf and *Pueraria lobata*	PLGA–PEG, DOTAP and Poloxamer188	*In vivo*	Reduced blood glucose concentrations with remarkable hypoglycemic effects	[71]
	polysaccharides solution of *Catathelasma ventricosum*	*Catathelasma ventricosum* polysaccharides (CVPs), Sodium selenite	Streptozotocin-induced rats (STZ)	Increased antidiabetic activity observed	[72]
Gold nanoparticles	*Whole extract of L. sericea*	Methanol (HPLC grade), ethanol, ethyl acetate and hexane	α-amylase (*In vitro*)	Exhibited highest IC_{50} value	[74]
	Cassia auriculata	Propanoic acid 2-(3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl) (PAT)	*Alloxan-induced diabetic rats*	Remarkable reductions in blood glucose, triglycerides and cholesterol levels	[75]
	Sambucus nigra L.	Hydrogen tetrachloroaurate solution	Streptozotocin-induced rats (STZ)	Suppression of metalloproteinase activity, mitigation of liver tissue inflammation	[76]
Palladium oxide nanoparticles (PdONPs)	*Zanthoxylum armatum fruit aqueous extract*	rGO Nano sheets	Inhibition assay	Magnificent enzyme inhibition with IC_{50} = 0.0218 ± 0.01 µg/mL	[77]
Nickel oxide nanoparticles (NiONPs)	*Areca catechu leaf extract*	Nickel nitrate hexahydrate Ni $(NO_3)_2 6H_2O$)	α-amylase inhibition assay	Possess higher inhibition of enzymes	[78]

FUTURE PERSPECTIVE

To the best of our knowledge, nanotechnology presents significant prospects for diagnosis and medicine, fulfilling the challenges of specificity, bioavailability, safety, and scalability. Further research should focus on developing herbal formulations to eliminate the toxicity of inorganic nanoformulations for treating diabetes and any particular disease. This will improve the overall scenario of the negative effects of harmful drugs in the body. In addition, after *in vitro and in vivo*, trials must be conducted on human mimics to check the efficacy of the drug. This will lead to research in a new way and will excite researchers to work more on it after achieving success.

CONCLUSION

It is clear from the above discussion that botanical remedies, particularly those utilized in economically disadvantaged regions for addressing medical conditions such as diabetes, offer promising potential owing to their diverse bioactive compounds. However, challenges persist regarding suboptimal bioavailability and safety profiles, particularly in chronic disease management. Developments in nanotherapeutics have proven highly beneficial and approachable as they hold good potential in the treatment of diabetes, as they have various advantages such as fewer side effects, targeted drug delivery, and enhanced bioavailability.

Nanoscience and nanotechnology have experienced rapid advancement, expanding their applications across various fields. Nanotechnology has found widespread use, particularly in the medical and health sciences. In medical science, the utilization of formulations having nanosizes represents a significant breakthrough in therapeutic delivery systems compared with traditional approaches. By enhancing the

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biopharmaceutical characteristics, target specificity, and pharmacodynamic profiles of medicines, this breakthrough increases their clinical efficacy. Different types of drug nanoparticles are assembled in/on nanocarriers, including metallic nanoparticles, dendrimers, polymeric nanoparticles, niosomes, nanomicelles, and liposomes.

Efforts are underway to enhance therapeutic outcomes through nanoformulations, such as niosomes, liposomes, and transfersomes, which show promising encapsulation efficiency. Green-synthesized inorganic nanoparticles also present a novel avenue for enhancing antidiabetic activity. Comprehensive *in vivo* experimentation and safety assessments are essential for realizing the clinical potential of these botanical remedies and nanoformulations.

Acknowledgement

I would like to thank Jaypee Institute of Information Technology, Noida, for providing us with all the basic facilities and infrastructure for carrying out this theoretical project.

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