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REVIEW ARTICLE

The Potential Role of Zinc Oxide Nanoparticles in the Treatment of Diabetes Mellitus: An Updated Review

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Abstract

Nanotechnology has made serious evolution in several scientific fields. Nanoparticles (NPs) are small-scale compounds having unique characters (at least 100 nm in one dimension). When materials are decreased to the nanoscale, their properties are typically modified, allowing them to act specifically with cell biomolecules. Therapeutic chemicals are loaded into NPs and transported to target cells. Metallic NPs, such as gold, silver, iron, Zn, and metal oxide NPs, have existed serious hurdles in the medical field and their usage in recent years. ZnO nanoparticles (ZnO NPs) have been revealed to show catalytic, electrical, photochemical, anticorrosive, photovoltaic, antifungal, antibacterial, and antiviral characters. ZnO NPs have been utilized in the biomedical field to yield biosensors for many ranges purposes, enhance diagnostics via imaging, regulate medication targeting, and to deliver gene therapy. Multiple studies on the anticancer, antidiabetic, and antibacterial activities of ZnO NPs yield promising scientific data for the treatment of each disease globally. Diabetes mellitus (DM) is a serious health issue that influences people worldwide. The majority of diabetes problems are caused by oxidative stress, which is followed by a decline in cellular zinc levels and zinc-dependent antioxidant enzymes. The pharmacological trials through which ZnO NPs reduce DM and diabetic sequelae are summarized in this review.

Keywords: Nanotechnology; Nanoparticles; Zinc; ZnO nanoparticles; Diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a metabolic illness known by excessive blood glucose. It is obtained by insufficient production of insulin or glucose produced via the pancreas that can`t be handled by the patient`s body. DM attacks a large number of people worldwide, and this number is rising. The World Health Organization (WHO) reported that DM ends the life of 1.5 million patients per year, and is considered one of the most reasons of death in most countries [1].

Polyuria, polydipsia, and polyphagia are regular symptoms of diabetic individuals with an increased level of blood sugar. To control and regulate DM, many medicines with multiple techniques of action and glucose-lowering activities must emerge [2]. Many studies have shown that trace metals have a role in glucose metabolism and have a relation to DM. Zinc, magnesium, and chromium have all been related to blood sugar control and are used in diabetic treatment [3].

Zinc initiates around 300 enzymes in the body and is essential in a variety of metabolic paths, like glucose metabolism. Zinc is also familiar with maintaining the conformation of insulin and is entered in insulin manufacture, storage, and secretion. Multiple zinc transporters in β-cells, such as transporter number 8, have essential character in insulin secretion in several studies [4]. Zinc can enhance insulin signaling via a variety of techniques, including enhancing the phosphorylation of the insulin receptor,

inducing phosphoinositide 3-kinase action, and inhibiting glycogen synthase kinase-3. Furthermore, this metal has been shown to improve the signs of DM complications such as nephropathy and cardiomyopathy [5].

As a result, the interaction between zinc, DM, and its complications, and symptoms is highly complex. Traditional drug delivery mechanisms have multiple drawbacks, as improper dosage, decreased potency, and decreased specificity for the target, which may lead to adverse side impacts in multiple organs [6].

Natural products may have the capability to overcome the limited uses of DM therapy. To overcome the limitations of medication pharmacokinetic, innovative drug delivery systems have been introduced as a viable option for treating multiple diseases and disorders. Insulin, and other sugar-lowering drugs and nutraceuticals, have been loaded into nanoparticles (NPs) as more proper, non-invasive, and safer alternative administration techniques [7].

Nanotechnology is the most common topic in modern scientific study. This technology can be utilized for multiple novel applications, as novel fabric chemicals, food processing, agricultural production, and sophisticated medicinal techniques. The production, characterization, and exploration of materials in the nanoscale range (1–100 nm) are known as nanotechnology. The used materials in this field are a result of their nanoscale size that shows novel and elevated physicochemical and biological characters, as well as distinct phenomena and functionalities [8].

NPs have bigger surface areas than macro-sized molecules because of their nanoscale size. At the atomic level, NPs also named controlled or modified particles. They have size-related properties that differ from bulk materials. NPs have larger structures due to their small size that allows them to be used in biosensors, nanomedicine, and bionanotechnology [9].

NPs and nanomaterials are seeing an increase in new uses, and working with nanomaterials has allowed for a far better understanding of biology [10]. As a result, there is the possibility of discovering new approaches to treat diseases that were previously difficult to focus on due to size constraints. Bio-functional NPs are being synthesized for medical specialty uses [11]. Previous studies have shown that Zinc oxide nanoparticles (ZnO NPs) are effective in treating diabetes and reducing its consequences. Herein, we described the summary of the recent advances of Zinc oxide (ZnO) and its NPs in medicine.

Biological activities of ZnO nanoparticles

Zinc is widely recognized as an essential trace element that can be found in most tissues of the body, as the brain, skin, bone, and muscles. Zinc has a role in the metabolic process of the body and has a critical contribution in protein and nucleic acid formation as a key component of numerous enzyme systems. Due to the ZnO NPs small size, zinc is rapidly liberated into the body. As a result, ZnO NPs are frequently utilized in food. Furthermore, the USA Food and Drug Administration (FDA) have classified ZnO as a safe chemical [12].

ZnO is found naturally in the earth's crust as the mineral zincite, but most of its commercial products are synthesized. In addition to fabrics and surfaces that contact with flesh, ZnO is harmless and compatible with human skin. In comparison with bulk ZnO, the elevation extent of nanoscale ZnO can enhance fabric products [13].

Due to its promising physical and chemical characters, ZnO NPs, which are considered as one of the metal NPs most essential, are widely used in multiple sectors. Firstly, ZnO NPs are entered in the rubber industry to give wear protection to rubber compounds, enhance the toughness, and provide antiaging characters. ZnO is increasingly entered in female care compounds, as body creams and sunblock, due to its powerful UV absorption ability [14].

ZnO NPs are increasingly being used in industrial items like rubber, paint, coatings and cosmetics. Because of ZnO NPs low toxicity and cost, they are considered one of the most important metal oxides used in several metabolic techniques over the last two decades. ZnO NPs have shown efficiency in anticancer [15] and antibacterial cure [16], diabetic management, anti-inflammation, wound remedial, and biomedical imaging [17]

due to their strong ability to control reactive oxygen species (ROS), liberate zinc parts and the promote death of cancer cells [18].

ZnO NPs induced cytotoxicity in HepG2 cancer cells by upregulating the internal release of zinc ions from cells, then increasing ROS production and inducing apoptosis. Furthermore, ZnO NPs attract phosphorylation of p53ser15 [19]. ZnO NPs induce cancer cell apoptosis in myoblastoma and are cytotoxic to myoblastoma cancer cells. In addition, they increased the protein (p53), the ratio of Bcl-2-associated X protein (Bax)/B-cell lymphoma 2(Bcl-2), and cysteine-aspartic proteases-3 (caspase-3) activity [20].

Antibacterial action might be inhibited by adding ZnO NPs in bacterial cells' outline layers or protoplasm, which may lead to bacterial cell membrane decomposition and membrane protein degradation, inducing bacteria death. Sarwar et al. [21] studied the impact of ZnO NPs on Vibrio cholerae for developing nanomedicine against cholera. ZnO NPs were more powerful at stopping the growth of the biotype of V. cholera, which was related to the formation of ROS. The bacterial membrane would be destroyed, permeabilization would elevate, and their shape would be seriously changed.

In 2020, the scientists used Azadirachta indica leaf extract to evaluate the antioxidant effect of ZnO NPs. The formed ZnO NPs demonstrated effective 1,1-diphenyl-2-picrylhydrazyl (DPPH)-2,2-diphenyl-1-picrylhydrazyl or DPPH radical scavenging and ferric reduction [22]. The antioxidant activity of ZnO NPs was also evaluated using Camellia sinensis leaf extract. In adipocytes, ZnO NPs revealed cytoprotective properties against H2O2-induced oxidative damage (3T3L1) [23].

Cho et al. [24] studied the cell proliferation and antibacterial activity of a polycaprolactone/nanohydroxyapatite scaffold coated with ZnO. They found the ZnO antibacterial and cell proliferation activities and documented that the scaffold with ZnO coating could be the most ideal bone-regenerating scaffold.

The antioxidant and anti-Alzheimer properties of ZnO NPs have been demonstrated. It was proved to have a modest inhibitory effect on the enzymes alpha-amylase and alpha-glucosidase. ZnO NPs showed anti-aging properties, as evidenced by their inhibitory activity against enzymes, pentosidine advanced glycation end products (AGEs) and vesperlysine AGEs. Furthermore, ZnO NPs were proved to have anti-inflammatory properties, by suppression the inflammatory enzymes secretory phospholipase A2 group IIA (sPLA2-IIA) and 15-lipoxygenase (15-LOX) [25].

The beneficial uses of ZnO NPs in livestock production and health industry

In vitro and in vivo, Wiegand et al. [26] studied the impact of ZnO in the controlling and regulating of Alzheimer's disease. When patients infected with Atopic dermatitis (AD) and covered their body with the ZnO fabric all night for several nights, there was a serious amelioration in skin itches and sleeping troubles. In a mouse model of Alzheimer's disease, ZnO NPs had better anti-inflammatory impacts than bulk ZnO by decreasing some cytokines. These findings revealed that tiny ZnO NPs had a serious impact on decreasing skin inflammation in AD animals [27].

When a zygote of zebrafish was subjected to 10–120 mg/L ZnO NPs for 4 days, it lowered the death of the zygote. The toxicity of ZnO NPs was studied in fresh zebrafish embryos that were incubated with 10, 30, 60, 90, and 120 mg/L ZnO, which increased the generation of ROS in zebrafish embryos and thereby initiated cellular apoptosis through the p53-mitochondria-caspase-mediated pathway [28].

When zebrafish embryos were subjected to ZnO NPs in comparison with ZnSO4, the genes related to inflammation only responded to ZnO NPs but not to ZnSO4 [29]. It was stated that the more time zebrafish embryos were subjected to other NPs, the more impairment on the growth and development of larvae was observed. In another study, when multiple carps were supplemented with ZnO NPs, it was proved that ZnO NPs had an impact on immunity and serum protein levels [30]. Moreover, feeding rainbrow trout on ZnO NPs for a period led to formation of the gills and intestine. Elimination of ZnO NPs from the liver, led to disturbance in the antioxidant defense mechanism [31].

A study evaluated the toxicity of ZnO NPs to goldfish in a water-sediment ecosystem using an elevated level of CO2 for 30 days. The result proved that the Zn present in ZnO NPs was the reason for increasing the CO2 concentration. In addition, ZnO NPs enhanced the ROS levels and changed the liver's and brain's regular metabolic mechanism [32].

While female Wistar rats were supplemented with ZnO NPs and ZnO (300 and 2000 mg/kg, respectively), significant changes in blood tests, and pathological areas in the liver, stomach, and renal tissues were detected [33]. In another experiment, while supplementation of ZnO NPs for a period of time to albino mice, no abnormalities were noticed in muscle and no neurological behaviors were recorded. However, long-term ZnO NPs supplementation induced a decrease in memory capabilities due to alteration in synaptic plasticity [34].

Supplementation of male mice with 50-500 mg/kg ZnO NPs induced low toxicity. While, supplementation with 5000 mg/kg of ZnO NPs induced alteration in the weight of the brain, lung, and pancreas. When ZnO NPs (300-600 mg/kg) were fed to male rats, it had negative impacts on cytokines and cytochrome C, liver enzymes [35].

The influence of ZnO NPs inhalation on the breath of male rats was evaluated. Administration of rats with nano-sized ZnO led to a decrease in ascorbate, formate, glycine and taurine levels and increased the levels of isoleucine and valine in the lung, because of the anti-oxidation impact and cell membrane integrity of ZnO NPs [36].

Wistar rats supplemented with ZnO NPs at different concentrations for a period suffered from an oxidative damage and decreased the catalase and superoxidase level in the cortex of the kidney [37]. In liver cells, oxidative and DNA damage have also been observed in male mice in another experiment when injected with ZnO NPs; the bone marrow was also reported to be affected [38].

In poultry [39], Zn NPs were proved to boost growth and feed efficiency. Furthermore, they induced animal immunity by decreasing the somatic cell count in a subclinical mastitic cow and enhanced the milk output after their administration in cows and sheep [40]. Hassan et al. [41] stated that addition of 8g/mL ZnO NPs to the tested medium stopped aflatoxigenic mould growth and aflatoxins formation. While adding 10g/mL of ZnO NPs to the tested medium stopped the ochratoxin A and fumonisin B1, which lead to mould growth and mycotoxins formation. However, ZnO NPs helped in stopping the production of harmful toxins as aflatoxin by Aspergillus flavus in the feed when NPs were administrated to it before.

ZnO NPs were administered to rabbits in comparison to curcumin. The biochemical analysis of rabbit serum revealed that aflatoxin B1 elevated nitric oxide (NO) and malondialdehyde (MDA) levels, while decreasing glutathione (GSH) levels and superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-PX) activities. Plasma total protein, albumin, and globulin showed a significant decrease. Aflatoxin B1 had a significant genotoxic impact on the liver and kidneys. Immune boosting impact of ZnO NPs or curcumin improved these modifications in aflatoxicated animals. The researchers found that adding ZnO NPs and curcumin to the diet has a hepatoprotective impact by scavenging the free radicals or increasing the antioxidant activity, which then detoxifies the free radicals [42].

Because of ZnO NPs strong antibacterial impact, they have gotten a lot of attention. ZnO NPs are also an essential trace mineral in poultry feed. In this way, giving ZnO NPs to poultry can boost growth and performance and act as a disease-controlling antibacterial factor. ZnO NPs were found to have effective antibacterial properties against poultry-associated foodborne pathogens, with Staphylococcus aureus (S. aureus) being the most vulnerable [43].

In broilers, suitable doses of ZnO NPs boost growth activity and antioxidative properties when compared to bulk ZnO food administration. So, growth performance, antioxidative capabilities, and feed cost in broiler feed are considered the ideal factors according to an experiment [44].

In another experiment, ZnO NPs decreased the broiler feed conversion ratios by a factor of two; induced Zn retention in the liver

independent of source or amount, and mitigated the deleterious impacts of heat stress by inducing the antioxidant effect and suppressing the lipid peroxidation. It was also proved that ZnO NPs reduced serum corticosterone levels during heat stress in chickens fed on 40 - 60 mg/kg ZnO NPs in comparison with one fed on 100 mg/kg; the relation between food and serum corticosterone levels has gotten a lot of attention [45].

The antibacterial activities of ZnO NPs

It was found that supplementing piglets' diets with ZnO NPs was more powerful than high diet supplemented with ZnO as it decreased diarrhea caused by Escherichia coli (E. coli) and Salmonella. So, ZnO NPs could be used as a feed antibiotic, and could be used instead of a high diet supplemented with ZnO levels [46]. However, the specific antimicrobial mechanism of ZnO NPs is not still familiar, and the most common antibacterial impact of ZnO NPs is related to a variety of processes, such as ion formation from the NPs' surface [47]. The ions will unit with electron donor groups on the bacterial cell surface, leading to damage of the cell membrane [48]. Furthermore, ZnO NPs' intrinsic physicochemical characters promoted the production of ROS, which led to oxidative damage and apoptosis [49].

Zinc supplementation improves the development of chickens [50] and Japanese quails [51]. Also, ZnO NPs increased the growth of broilers [52]. In an experiment studying the ZnO NPs' antibacterial efficacy against various bacterial agents that cause bovine mastitis, 24 milk samples were obtained from cows with mastitis in Egypt. The antibacterial properties of generated ZnO NPs at different doses were evaluated in vitro versus S. aureus, E. coli, and Klebsiella pneumoniae (K. pneumonia) recovered from afflicted cows' milk. For the treatment of bovine mastitis, ZnO NPs synthesized with starch as a covering factor could be very powerful and economical antibacterial factor versus S. aureus, E. coli, and K. pneumonia [53].

Dog bite wounds were frequently infected with a variety of bacteria from various sources that slowed healing and make them more resistant to antimicrobial therapy [54]. The animals were more susceptible to bacterial infection, which can lead to severe septicemia and mortality. According to reports, Pseudomonas aeruginosa or methicillin-resistant S. aureus (MRSA) were responsible for almost 75% of burn-related deaths. ZnO NPs and pancreatin (PK) had been proven to be powerful against MRSA, and can be utilized to resist infections caused by these bacteria [55].

Role of ZnO NPs in Diabetes mellitus

The progress of zinc-based agent would be valuable in the treatment of DM and its related complications as zinc administration have shown a powerful impact in several experiments [56]. Alkaladi et al. [57] evaluated the anti-diabetic impacts of ZnO NPs by promoting more production of insulin, and its receptors, and its effect on glucose metabolizing enzymes. Umrani and Paknikar [58] revealed the influence of ZnO NPs in decreasing blood glucose in diabetic rats.

Insulin resistance is a feature of type 2 DM. Zn plays both insulin-mimetic and antioxidant roles, and insufficiency of zinc has been related to insulin resistance. In insulin-stimulated glucose metabolisms, protein kinase B (Akt) signaling is very important. In several studies, Zn has been shown to activate Akt at which the insulin receptor (IR) signaling cascade is activated. When insulin is united with the extracellular subunits of IR, the s-subunits undergo conformational changes, resulting in autophosphorylation of many tyrosine residues. Phosphorylation of numerous intracellular substrates is achieved by activated IR (IRSs) [59]. Several signaling molecules that affect the phosphatidylinositol-3-kinase (PI3K)/ Akt pathways unite to phosphorylated IRSs, which act as docking proteins. Zn increases phosphorylation of tyrosine sites on several receptor protein tyrosine kinases (R-PTKs), including IR, insulin-like growth factor-1 receptors (IGF-1R), and epidermal growth factor receptor (EGFR). The PI3-K/Akt signaling pathway is activated by these R-PTKs, which leads to changes in glucose and lipid metabolism [60].

Akt is required for the phosphorylation of serine residues as well as the inhibition of glycogen synthase kinase 3 (GSK-3) during

insulin signaling. GSK-3 phosphorylation produced by Zn has also been linked to gluconeogenesis, a process that controls Zn's response to enhanced glycogen synthesis by up-regulating glycogen synthase and inhibiting gluconeogenesis [61].

ZnO NPs have been found in several experiments to decrease blood glucose levels in diabetics while administration of animals administrated by ZnO NPs (1–10 mg/kg/day) and dipeptidyl peptidase (DPP)–4 inhibitor(Vildagliptin) orally. The results revealed that diabetic rats administrated ZnO NPs had a decrease in blood glucose levels. Insulin and glucagon, two major pancreatic hormones, are responsible for controlling blood glucose homeostasis. They are essential in the development of DM. Oral administration of ZnO NPs for a month only or in combination with the vildagliptin decreased the diabetic rat's histological changes in the pancreas [62].

MicroRNA (miR)-103 and miR-143 are essential new regulators of type 2 DM. MiR-103 expression has been elevated in obese mice and diabetic rats. Animals treated with ZnO NPs at different doses for several weeks, either alone or in a mix with vildagliptin decreased the rise in MicroRNA levels [63].

In another study, administration of streptozotocin (STZ)-induced diabetic rats resulted in decreased the SOD activity by more than a half. In RIN-5F cells, ZnO NPs elevated the SOD activity and decreased the glutathione levels at doses up to 10 g/mL. In rat erythrocytes and pancreas, ZnO NPs decreased the STZ-induced SOD activity and restored the CAT activity [64].

Kitture et al. [65] utilized an extract of red sandalwood (RSW) conjugated with ZnO NPs as an efficient antidiabetic drug. The ZnO-RSW complex had a slightly higher percentage of inhibition versus pig α-amylase and was stronger against murine glucosidase than ZnO-RSW complex. The conjugated ZnO-RSW stopped β-glucosidase by 61.93%, meanwhile the unconjugated one stopped it by 21.48 - 5.90%.

The interaction of ZnO NPs with β cells of the pancreas was studied previously [66]. These cells engulfed ZnO by endocytosis, leading to the disassociation of NPs and release of zinc only. Increasing zinc parts inside the cells showed multiple essential impacts, which include increasing SOD and GSH levels, but no influence on ROS levels or cell death. When cells are liable to H2O2, ROS are produced, which leads to oxidative damage and subsequent cancer cell death. Therefore, pretreatment with ZnO particles protects the cells against H2O2-promote oxidative and cell death.

Nazarizadeh and Asri-Rezaie [67] evaluated the anti-diabetic impact and anti-oxidative influence of ZnO NPs with ZnSO4 and found that ZnO NPs had a better antidiabetic impact at higher doses. There was an effective decline in the level of blood glucose and an improvement in insulin. However, the increased level of MDA production and a significant decrease in serum total antioxidant capacity were all signs of serious oxidative stress, especially at a higher dosage.

By evaluating the C-reactive protein (CRP) and interleukins, hyperglycemia can increase the inflammatory state, which is related to the development of cardiovascular illnesses. To decrease diabetic problems, Hussein et al. [68] made up ZnO that could decrease MDA, rapid blood sugar, interleukin-1, CRP and asymmetric dimethylarginine levels and enhance nitric oxide.

ZnO NPs were evaluated in mice for their antidiabetic and oral glucose tolerance test (OGTT) characters in diabetic mice. The results revealed that ZnO NPs decreased blood glucose levels by 39.79 %, while a complex of ZnO NPs and insulin decreased blood glucose levels by 38.78 % and insulin by 48.60 %. ZnO NPs (8 and 14 mg/kg body weight) reduced the level of blood glucose by 25.13 and 29.15 %, respectively, in the hypoglycemic experiment [69].

In 2021, a study found that 10 mg/kg ZnO NPs and 50 mg/kg curcumin NPs on a high-fat diet /STZ-induced hepatic and pancreatic pathology in type 2 DM were more effective as anti-diabetic agents than traditional anti-diabetic medicine, metformin. The activation of the PI3K/AKT signaling pathway in the hepatic tissue helps in the drop of serum glucose and insulin levels. Therefore, ZnO NPs decreased inflammation, oxidative stress, and insulin resistance by upregulation of AKT,

inhibition of the mitogen-activated protein kinase (MAPK) pathways, and decrease of liver structural damage [70].

Diamicron and ZnO NPs proved to have a synergistic power in diabetic treatment. ZnO NPs, together with the traditional antidiabetic medication, diamicron, showed promising anti-diabetic medicines since they both restore cell function and structure. ZnO NPs supplementation may slow the progression of diabetes type 2 in people who are pre-diabetic [71]. While curcumin NPs / ZnO NPs revealed that they had the most powerful antidiabetic activity compared to rats supplied with Diamicron, with significant reductions in blood glucose, raised insulin levels, and controlled glucose transporter 2 (GLUT2) and glycerol kinase (GK) genes [72]. Synergistic interactions between ZnO NPs and other drugs such as vildagliptin and thiamine have also been demonstrated in the experimental DM [73].

Long-term organ deterioration induced by a range of pathogenic conditions causes diabetic complications. As previously stated, Zn is a crucial cofactor for a variety of enzymes, transcriptional factors, and metalloproteins. Under hyperglycemic conditions, Zn shortage may cause these enzymes or proteins to malfunction, eventually resulting in cell and organ damage, which presents as chronic diabetes problems. Zn supplementation protects against diabetic cardiomyopathy [74]. Furthermore, administration of ZnO NPs and l-carnitine had a protective effect; it preserves the ovarian function by increasing sex hormones levels and antioxidant activity and decreasing lipid peroxidation in diabetic rats [75].

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. It is one of the most familiar consequences of DM. Through the interaction of autophagy and nuclear factor erythroid 2–related factor 2 (Nrf2)/ thioredoxin-interacting protein (TXNIP)/ NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome signaling, ZnO NPs could be a viable drug for delaying the course of DN [76].

ZnO NPs improved diabetic complications; B-type natriuretic peptide (BNP) is indicated for heart failure produced by the cardiac tissue. In diabetic rats, supplementation with ZnO NPs at different doses for two months decreased BNP levels and similarly enhanced the histopathological characters of heart muscle. An elevated concentration of ZnO NPs, on the other hand, was dangerous to heart tissue [77].

Advanced oxidation protein products (AOPPs) are formed in those who have kidney or cardiac diseases. In STZ induced diabetic rats, ZnO NPs lowered the increase in plasma AOPPs. Plasma paraoxonase is shared in the protection of LDL against oxidation. Supplementation of ZnO NPs for a month could help to stop the loss of plasma paraoxonase activity in mice [78].

For sperm generation and preservation, glucose metabolism was essential. Because DM affected sperm function, motility, and quality, the prevalence of subfertility in diabetic males was major. In diabetic men, oxidative stress can induce decreased fertility. The level of SOD, CAT, GSH-Px, and glutathione reductase was decreased by more than 50% in diabetic rats' testicular tissue. In addition, GSH levels were declined to 30% and MDA levels were improved fivefold. Orally, supplementation of ZnO NPs for 30 days stopped these effects [79].

DM can also influence testosterone production, an androgen formed in the testis that stimulates spermatogenesis. In diabetic rats, the count and motility of sperms, and serum testosterone levels were also evaluated. The diabetic group's histological abnormalities suggested spermatogenesis impairment. The characters of the seminiferous epithelium and interstitium were restored by ZnO NPs. ZnO NPs might also re-establish the count of primordial spermatocytes, spermotogonia cells, and Sertoli cells, which have a supporting and nutritional role, according to immunohistochemistry evaluations [80].

DNA methylation of germ cell-specific genes is important to manage and control spermatogenesis and male productivity [81]. In diabetic groups, the cells of testis with DNA methylation were not prevalent. The DNA-methylated cells were increased in number by ZnO NPs. Nuclear respiratory factor 1 (NRF1) and sirtuin 1 (SIRT1) have been studied to evaluate DNA methylation. As a result, ZnO

NPs might control DNA methylation by stimulating NRF1 and SIRT1 [82].

Diabetic retinopathy (DRP) is a type of retinal illness induced by DM and characterized by vascular leakage, vascular growth, and retinal ischemia. By inducing STZ in DRP, ZnO NPs corrected changes in insulin and glucose levels, HbA1c, retina thickness, oxidative/antioxidative markers, and inflammatory mediators. The results of histological analysis of retinal tissues backed up and confirmed these findings, demonstrating that conventional ZnO NPs could be a better treatment for DRP [83].

In another study, ZnONPs were proved to reduce the kidney damage in a diabetic rat model of nephropathy by increasing renal function, decreasing renal fibrosis, oxidative stress, inflammation, and aberrant angiogenesis, and delaying podocyte injury development [84]. Table 1 illustrated the potential role of ZnO NPs in experimental animals.

Table 1. Ameliorative influence of ZnO NPs in experimental animals

Animals	Concentration	Duration	Effects	References
Adult male Wister rats	10-30 mg/kg	30 days	In the STZ-induced diabetes group, ZnO NPs had a stronger anti-diabetic impact by lowering AST, ALT, and blood glucose levels, increasing insulin levels, and improving IR, GluT2, and glucokinase (GCK) expression levels.	[85]
Zebrafish embryos	100 mg/Kg	24 h	ZnONPs have a critical role in lowering blood glucose levels in hyperglycemic induced zebrafish.	[86]
Female albino mice	0.1and 0.5 mg/Kg	20 days	ZnO NPs only or with thiamine enhanced DM treatment.	[87]
Male Wistar rats	100 and 200 mg/ kg	One month	ZnO NPs and Ag NPs had a more powerful anti-hyperglycemic influence.	[88]
HepG2, L6, 3T3L1 and RIN5f cell lines	1, 3, 10, 30 and 100 µg/mL	2 days	Powerful anti-diabetic influence of ZnO NPs via enhanced insulin activity, glucose uptake, a decline in hepatic glucose output, decreased lipolysis, and improved pancreatic beta cell mass.	[89]
Old male Wistar rats	10–100 mg/kg	6 h	ZnO NPs cause a hyperglycemic reaction in diabetic and healthy rats in the short-term administration.	[90]
Male albino mice	120 mg/kg	28 days	Oxidative stress indices and ROS were significantly decreased, indicating that the ZnO NPs had inhibitory effects on hyperglycemic secondary consequences.	[91]
Adult Wistar rats RIN5f and HepG2 cells	1, 3 and 10 mg/kg 0.1, 1, 10, 100 and 1000 µg/mL	One month 72 h	Improvement of glucose tolerance and insulin, and decrease in non-esterified fatty acids, and triglycerides through ZnO NPs supplementation.	[58]
Male Wistar rats	1, 3 and 10 mg/Kg	10 days	ZnO NPs have a synergistic influence on the treatment of DM type-2.	[62]
Wistar rats	10 mg/Kg	One month	ZnO NPs have a protective impact on the pancreas.	[67]
Male albino rats	10 mg/ Kg	One month	Ameliorative impact of ZnO NPs against the complications of DM.	[68]
Male Wistar rats	10 mg/Kg	One month	The protective impact of ZnO NPs against testicular diabetic complications.	[80]

Future perspectives and conclusions

It is vital to find a therapy for DM, as the disease's predominance on a global scale continues to rise. Many materials, including ZnO NPs, are now being evaluated for biological applications and disease-modifying medicines because of advances in nanotechnology. According to previous studies, ZnO NPs can be used to treat a variety of DM symptoms. As a result, ZnO NPs appear to be a promising anti-diabetic drug that merits additional research, clinical testing and reducing its problems, which can be assessed further. The synergistic characteristics of ZnO NPs with other diabetes medications or dietary supplements should be investigated further. It is predicted that the use of ZnO NPs for diverse purposes will expand soon. Unfortunately, scanty reports studied the toxicity of these particles in various body organs and systems so before using these particles, their toxicity should be properly evaluated in different organs. Comparative studies should be expanded to include ZnO NPs derived from various medicinal plants.

Conflict of Interest

The authors have no conflict of interest to declare.

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الملخص العربي

الدور المحتمل من جزيئات أكسيد الزنك النانوية في علاج داء السكري: مقال محدث

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لقد حققت تقنية النانو تطورًا جادًا في العديد من المجالات العلمية. الجسيمات النانوية هي مركبات صغيرة الحجم لها سمات خاصة (على الأقل 100 نانومتر في بعد واحد). عندما تنخفض المواد إلى المقياس النانوي ، عادة ما يتم تعديل خصائصها ، مما يسمح لها بالإتحاد على وجه التحديد مع الجزيئات الحيوية للخلية. يتم تحميل المواد الكيميائية العلاجية في جسيمات نانوية ونقلها إلى الخلايا المستهدفة. وجدت الجسيمات النانوية المعدنية ، مثل الجسيمات النانوية للذهب والفضة والحديد والزنك وأكسيد المعادن ، عقبات خطيرة في مجال الطب واستخدامه في السنوات الأخيرة. تم الكشف عن جسيمات أوكسيد الزنك النانوية لإظهار خصائص محفزة ، وكهربائية ، وكيميائية ضوئية ، ومضادة للتآكل ، وفولتية ضوئية ، ومضادة للفطريات ، ومضادة للبكتيريا ، ومضادة للفيروسات. تم استخدام جسيمات أوكسيد الزنك النانوية في المجال الطبي الحيوي لإنتاج أجهزة استشعار حيوية لنطاقات متعددة من الجزيئات ذات الأهمية ، ولتعزيز التشخيص عن طريق التصوير ، وتنظيم إطلاق الدواء ، وتقديم العلاج الجيني ، وكعوامل علاجية. العديد من الدراسات التي تدرس الأنشطة المضادة للسرطان ومضادات السكر والبكتيريا من جسيمات أوكسيد الزنك النانوية تعطي بيانات علمية واعدة لعلاج الأمراض ذات الانتشار العالمي المرتفع. على وجه العموم, مرض السكري هو مشكلة صحية خطيرة تؤثر على الناس في جميع أنحاء العالم. تنجم غالبية مشاكل مرض السكري عن الإجهاد التأكسدي الذي يتبعه إنخفاض في مستويات الزنك الخلوية وإنزيمات مضادات الأكسدة المعتمدة على الزنك. تم تلخيص التجارب الدوائية التي من خلالها يقلل جسيمات أوكسيد الزنك النانوية مرض السكري والعقابيل السكرية في هذه المراجعة