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Review article

The current and future perspectives of zinc oxide nanoparticles in the treatment of diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) is a multifaceted and costly disease, which requires serious attention. Finding a cheaper anti-diabetic alternative that can act on multiple disease-related targets and pathways is the ultimate treatment goal for DM. Nanotechnology has offered some exciting possibilities in biomedical and drug delivery applications. Zinc oxide nanoparticles (ZnO-NPs), a novel agent to deliver zinc, have great implications in many disease therapies including DM. This review summarizes the pharmacological mechanisms by which ZnO-NPs alleviate DM and diabetic complications. Research implications and future perspectives were also discussed.

1. Introduction

Diabetes mellitus (DM) is a worldwide health issue that requires urgent attention. This disease is a metabolic disorder caused by insulin deficiency or insulin resistance or both. DM is related to a wide range of pathological conditions such as cardiomyopathy, retinopathy, nephropathy, and neuropathy [1]. DM is a complex disease and therefore requires a multifaceted treatment approach [2]. Anti-diabetics are expensive due to the multifaceted nature of the disease [3]. This is because the current anti-diabetic drugs are commonly used in combination with other agents or with insulin thus increasing the overall cost of treatment. A cost-effective anti-diabetic treatment with a multi-target mode of action is the ultimate therapeutic goal.

DM has been linked to disruptions of zinc homeostasis. Zinc is an essential trace metal that regulates many enzymatic functions and cellular processes in the human body, including apoptosis, oxidative homeostasis, immune function, biological control of metabolism as well as signal transduction [4,5]. Zinc supplementation has been reported to exhibit beneficial effects in enhanced glycemic control in diabetic animals and humans [6,7]. Furthermore, this metal can also improve the conditions associated with diabetic complications such as nephropathy and cardiomyopathy [8]. The underlying mechanisms of the beneficial effects of zinc on DM have been extensively described [9].

Nanoparticles, in general, are suitable for a wide range of biological applications. Their ultra-small size permits cellular internalization of the particles, and thus potentially allows them to interact with biomolecules and subsequently, to induce selective cellular responses [10]. Zinc oxide nanoparticles (ZnO-NPs) have received much attention for biomedical applications and the treatment of several diseases including cancer [11]. ZnO-NPs are currently under investigation for the treatment of DM and diabetic complications due to their ability to deliver zinc ions. This review summarizes the anti-diabetic properties exerted by ZnO-NPs (Fig. 1). The changes in diabetic parameters upon exposure to ZnO-NPs were summarized in Table 1. Towards the end of the article, the future challenges associated with ZnO-NPs and DM research were discussed.

2. Anti-diabetic effects of ZnO-NPs

2.1. Anti-hyperglycemic

DM is characterized by the presence of chronic hyperglycemia, a condition in which fasting and postprandial blood glucose levels are more than 140 and 200 mg/dL, respectively [12]. Numerous studies have shown that ZnO-NPs reduce blood glucose levels in diabetic animals [13–19]. Orally-administered ZnO-NPs (1–10 mg/kg/day) for 56 consecutive days decreased blood glucose levels in diabetic rats in a concentration- and time-dependent manner [15].

The oral glucose tolerance test indicated that ZnO-NPs could improve glucose tolerance in experimental DM. The area under the curve (AUC) that is derived from the oral glucose tolerance test is commonly used to clinically diagnose impaired glucose tolerance. The AUC value of diabetic rats was increase by ~3.8-fold in comparison to the untreated control group [20]. The effect was alleviated by ZnO-NPs in a dose-dependent fashion to ~40–70% of the diabetic group at the

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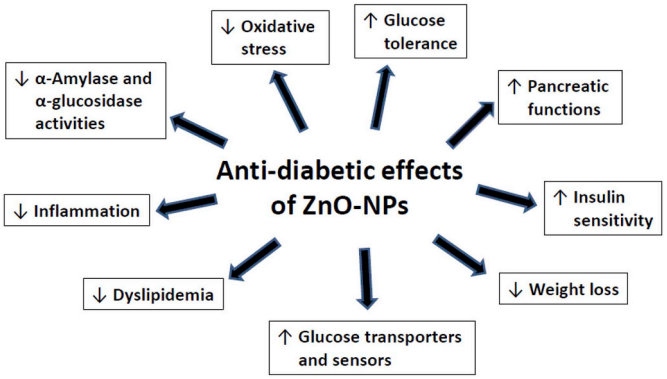

Fig. 1. Anti-diabetic effects of zinc oxide nanoparticles (ZnO-NPs).

concentration of 10 mg/kg/day [14,20]. The anti-hyperglycemic effect of ZnO-NPs is likely mediated by the factors as discussed in the following sections.

2.2. Enhancement of pancreatic functions

Blood glucose homeostasis is tightly regulated by two main pancreatic hormones, namely insulin and glucagon [21]. Pancreatic dysfunction and damage are fundamental in the manifestation of DM, although the underlying mechanisms are unclear [22]. Diabetic rats showed signs of injury such as a reduction in pancreatic islet cell number and organ density, as evidenced by histological studies [16,17,20]. However, oral treatment of 10 mg/kg/day ZnO-NPs, either alone for 4 weeks or with a dipeptidyl peptidase-IV inhibitor vildagliptin (10 mg/kg/day, p.o.) for 7 weeks, mitigated these histopathological changes in diabetic rat pancreas [16,20]. In alloxan-induced diabetic mice, treatment with ZnO-NPs at the concentrations of 0.1 and 0.5 mg/kg diminished the drop in the mean islet volume, islets per square micrometer, and volume density of the pancreas [17]. Incubation with ZnO-NPs (1–10 μg/ml) for 24 h also enhanced the proliferation of insulin-secreting RIN-5F cells in a concentration-dependent trend [23].

Insulin, a hormone produced by the pancreatic β cells, plays a crucial role in blood glucose homeostasis and utilization [21]. The release of insulin from the pancreas is stimulated by elevated blood glucose levels, particularly after taking carbohydrate-rich meals. Insulin receptors are found in all tissues that respond to insulin [13]. Thus, a reduction in the number of insulin receptors may lead to insulin resistance. The decrease in insulin production or sensitivity causes hyperglycemia in DM. In comparison to the healthy counterpart, a lower level of serum insulin was found in diabetic rats [13–16,20]. ZnO-NPs attenuated the decline of serum insulin levels in these rats [13–16,20]. A cell culture experiment indicated that ZnO-NPs could also increase insulin release in rat insulinoma RIN-5F cells in a concentration-dependent fashion [14]. Insulin gene expression was downregulated to ~40% of the control value in streptozotocin (STZ)-induced diabetic rats [13]. A month of treatment with ZnO-NPs at 10 mg/kg/day mitigated the downregulation of the insulin gene in these animals. Furthermore, the same concentration of ZnO-NPs also elevated the gene expression of insulin receptor A by ~1.3-fold compared to the untreated control [13].

Glycogenolysis and gluconeogenesis are important pathways in glucose production. Glucagon, secreted by the pancreatic α cells, stimulates glycogenolysis in the liver and skeletal muscles. The final step of glycogenolysis and gluconeogenesis is mediated by the enzyme glucose-6-phosphatase, which converts glucose-6-phosphate into free glucose that is released into plasma, thereby restoring blood glucose levels to normal [24]. Glucose-6-phosphate levels were increased by 4-fold in disrupted liver microsomes of diabetic rats in comparison to the control [25]. Treatment with ZnO-NPs (1–10 μg/ml, 24 h) could dose-dependently decrease the expression of glucose-6-phosphatase gene in human hepatocarcinoma HepG2 cells [23]. Additionally, ZnO-NPs also downregulated the gene expression of phosphoenolpyruvate carboxykinase, another enzyme in the gluconeogenic pathway, to less than half of the control value [23].

2.3. Upregulation of glucose transporters and biosensors

There are a number of glucose biosensors in the body. For instance, glucose transporter type 2 (GLUT2), a glucose transporter, is expressed in many tissues. GLUT2 is important in regulating glucose passage across hepatocytes [26]. In pancreatic β cells, GLUT2 may function as a glucose sensor to regulate insulin secretion [27]. Glucokinase, another glucose sensor found mainly in the liver and pancreas, is an enzyme that facilitates the phosphorylation of glucose to glucose-6-phosphate [28]. The gene expression of GLUT2 and glucokinase was reduced to < 80% in diabetic animals and the effect could be reversed by the oral treatment with ZnO-NPs (10 mg/kg/day) for 30 days [13]. Unlike GLUT 2, glucose transporter type 4 (GLUT4) is an insulin-sensitive glucose transporter that is found mainly in skeletal muscle and adipose tissue [26]. A study employing immunohistochemistry has demonstrated that a day of treatment with ZnO-NPs (1–10 μg/ml), similar to the action of 0.1 IU/ml insulin, enhanced GLUT4 translocation and glucose uptake in mouse 3T3-L1 adipocytes and rat L6 myoblasts [23].

2.4. Weight maintenance

When the blood glucose level is high, insulin has a profound effect in promoting glycogenesis, a process of glycogen synthesis from glucose, in the liver and muscle cells [29]. Glycogen serves as energy storage in many organisms [30]. In diabetic patients, insufficient insulin hinders this process from occurring. When this happens, the body starts utilizing other forms of energy, mainly from fat and muscle, causing an overall weight loss. The experimental diabetic rat model also exhibited this symptom [16,20]. Administration of ZnO-NPs (10 mg/kg/day, p.o.) for 4 or 7 weeks alleviated the weight loss symptom in these animals to some extent [16,20].

2.5. Anti-dyslipidemic

Dyslipidemia is one of the major risk factors for the development of type 2 DM [31]. Serum lipid abnormalities, which include elevated triglyceride and low-density lipoprotein (LDL), and reduced high-density lipoprotein (HDL) levels, are linked to an increased risk of cardiovascular complications in patients with type 2 DM [32]. Although lifestyle changes such as diet and exercise can improve dyslipidemia, pharmacological treatment is often necessary for most diabetic patients [32]. ZnO-NPs mitigate the rise in LDL, lipoprotein(a), triglyceride, free fatty acids and total cholesterol levels in diabetic animals [12,14,17,20,33]. Treatment with 3 mg/kg/day ZnO-NPs orally for 8 weeks also alleviated the reduction of HDL levels in diabetic rats [20,33].

Hormone-sensitive lipase (HSL) is an intracellular lipase that has prominent effects on cell signaling, glucose homeostasis, and lipid metabolism [34]. HSL can hydrolyze a broad range of lipids which include monoglycerides, diglycerides, triglycerides, cholesterol esters and retinyl esters [34]. Type 2 DM is associated with increased lipolysis [35]. Moreover, HSL knockout mice exhibited greater insulin sensitivity in skeletal muscles [36]. Incubation with ZnO-NPs (1–10 μg/ml) for a day caused HSL inactivation in 3T3-L1 adipocytes in a dose-dependent trend [23]. Interestingly, the effect could not be mimicked by insulin treatment.

2.6. Anti-inflammatory

Although the precise role of inflammation in DM is largely unclear, it can cause peripheral insulin resistance and hyperglycemia [37]. Tumor necrosis factor (TNF)-α, interleukin (IL)-1α, IL-1β, IL-6, and IL-8 are the pro-inflammatory cytokines that were identified in diabetic

Table 1
A summary of the parameter changes induced by ZnO-NPs on experimental diabetic models.

References	Induction of experimental diabetes	Testing subject	Nanoparticle type	Nanoparticle doses	Route of administration	Duration of treatment	Diabetic parameter changes
Alkaladi et al., 2014 [13]	STZ (100 mg/kg, i.p.), HFD	Sprague-Dawley rats	ZnO-NPs	10 mg/kg/day	p.o.	30 days	↓ blood glucose, ↑ serum insulin, ↑ glucokinase activity, ↑ expression of insulin receptor, GLUT-2 and glucokinase genes
Umrani and Paknikar, 2014 [14]	Type 1 DM: STZ (45 mg/kg, i.v.); Type 2 DM: STZ (90 mg/kg, i.p.) to 5-day-old rat pups and the pups were allowed to grow until 12 weeks	Wistar rats	ZnO-NPs	1, 3 and 10 mg/kg	p.o.	4 weeks	↑ glucose tolerance, ↑ serum insulin, ↓ blood glucose, ↓ nonesterified fatty acids, ↓ triglycerides
Afifi et al., 2015 [65]	STZ (100 mg/kg, i.p.), HFD	Sprague-Dawley rats	ZnO-NPs	10 mg/kg/day	p.o.	30 days	↑ Sperm count and motility; ↑ testicular SOD, CAT, GPx, GRD, GST, GSH, ↓ testicular MDA
Kitture et al., 2015 [50]	α-Amylase and α-glucosidase inhibition assays	Porcine pancreatic α-amylase; murine pancreatic and small intestinal extracts	ZnO-NPs-red sandalwood conjugate		*in vitro* assays		↓ α-amylase activity, ↓ α-glucosidase activity
Asani et al., 2016 [23]		Human HepG2 cells; rat L6 myoblasts; mouse 3T3-L1 cells; rat RIN-5F cells	ZnO-NPs	1, 3 and 10 μg/ml	cell culture	24 h	↑ Akt, ↓ PTP1B, ↑ GLUT4, ↑ glucose uptake, ↓ G6Pase, ↓ PEPCK, ↓ HSL, ↑ β cell proliferation
El-Gharbawy et al., 2016 [20]	STZ (35 mg/kg, i.p.), HFD	Wistar rats	ZnO-NPs	1, 3 and 10 mg/kg/day	p.o.	7 weeks	↑ glucose tolerance, ↑ insulin levels, fructosamine levels, ↑ pancreatic SOD activity, ↓ pancreatic damage, ↓ weight loss, ↓ miR-103 and miR-143 expression
Nazarizadeh and Asri-Rezaie, 2016 [15]	STZ (50 mg/kg, i.p.)	Wistar rats	ZnO-NPs	1, 3 and 10 mg/kg/day	p.o.	8 weeks	↓ blood glucose, ↑ serum insulin, ↑ zinc status. At doses ≥3 mg/kg/day: ↑lipid peroxidation, ↓ total antioxidant capacity
Wahba et al., 2016 [16]	STZ (50 mg/kg, i.p.)	Albino rats	ZnO-NPs	10 mg/kg/day	p.o.	4 weeks	↓ weight loss, ↓ pancreatic damage, ↓ blood glucose, ↑ serum insulin.
Asri-Rezaei et al., 2017 [33]	STZ (45 mg/kg, i.p.)	Wistar rats	ZnO-NPs	1, 3 and 10 mg/kg/day	p.o.	8 weeks	↓ cardiac damage, ↓ serum cholesterol, ↓ lipoprotein (a), ↓ atherogenic index, ↓ TNF-α, ↓ cardiac MDA and BNP levels, and caspase-3 activity
Rehana et al., 2017 [75]	α-Amylase and α-glucosidase inhibition assay; antioxidant activity assays		ZnO-NPs from plant extracts of Azadirachta indica, Hibiscus rosa-sinensis, Murraya koenigii, Moringa oleifera, and *Tamarindus indica*	1.56–100 μg/ml	*in vitro* assays		↓ α-amylase activity, ↓ α-glucosidase activity, ↑ antioxidant activity
Shaik and Kumar, 2017 [51]	α-Amylase inhibition assay	Human saliva	thioglycerol- and acarbose-capped ZnO-NPs	10-60 μg/ml	*in vitro* assays		↑ α-amylase activity
Amiri et al., 2018 [17]	Alloxan (180 mg/kg, i.p.)	Syrian albino mice (female)	ZnO-NPs	0.1 and 0.5 mg/kg/day	i.p.	20 days	↓ pancreatic damage, ↓ blood glucose, ↓ serum triglyceride, LDL and total cholesterol levels
Bayrami et al., 2018 [18]	Alloxan (170 mg/kg, i.p.)	Wistar rats	ZnO-NPs from the dried fruit extract of Vaccinium arctostaphylus L.				↓ blood glucose, ↓ cholesterol, ↑ HDL
Hussein et al., 2018a [19]	STZ (60 mg/kg), s.c.)	Sprague-Dawley rats	ZnO-NPs	10 mg/kg/day	p.o.	30 days	↓ CRP, ↓ IL-1α, ↓ADMA
Hussein et al., 2018b [40]	STZ (60 mg/kg), s.c.)	Sprague-Dawley rats	ZnO-NPs	10 mg/kg/day	p.o.	30 days	↓ blood glucose, ↓ erythrocyte MDA and DNA damage, ↓ AOPPs, ↑ PI3K
Rajakumar et al., 2018 [76]	α-Amylase inhibition, antioxidant, and anti-inflammatory assays		ZnO-NPs from *Andrographis paniculata* leaf extract		*in vitro* assays		↓ α-amylase activity, ↑ antioxidant activity, ↑ anti-inflammatory activity
El-Behery et al., 2019 [71]	STZ (60 mg/kg), i.p.)	Wistar rats	ZnO-NPs	10 mg/kg/day	p.o.	30 days	↓ testicular damage

Abbreviations: ADMA, asymmetrical dimethylarginine; AOPPs, advanced oxidation protein products; BNP, B-type natriuretic peptide; CAT, catalase; CRP, C-reactive protein; DM, diabetes mellitus; G6Pase, glucose 6-phosphatase; GLUT2, glucose transporter type 2; GLUT4, glucose transporter type 4; GPx, glutathione peroxidase; GRD, glutathione reductase; GSH, reduced glutathione; GST, glutathione S-transferase; HDL, high density lipoprotein; HFD, high-fat diet; HSL, hormone-sensitive lipase; IL, interleukin; LDL, low density lipoprotein; MDA, malondialdehyde; miR, microRNA; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphoinositide 3-kinase; PTP1B, protein tyrosine phosphatase 1B; SOD, superoxide dismutase; STZ, streptozotocin; TNF, tumor necrosis factor; ZnO-NPs, zinc oxide nanoparticles.

patients [38]. TNF-α, for instance, plays a crucial role in causing insulin resistance [39]. Serum TNF-α levels were ~3.6-fold higher in diabetic rats than those in control animals [33]. Oral treatment with ZnO-NPs at 3 mg/kg/day for 8 weeks reduced the level of TNF-α in the serum of diabetic rats to < 30% [33]. It has also been shown that the level of IL-1α was ~1.8-fold higher in STZ (60 mg/kg, s.c.)-induced diabetic rats compared to the control group [40]. The increase, however, was mitigated when the rats were treated with 10 mg/kg/day ZnO-NPs for a month [40]. IL-1β can disrupt glucose homeostasis and β-cell function [39,41]. However, it has been demonstrated that ZnO-NPs could increase IL-1β and IL-8 in human eosinophils [42]. Thus, additional *in vivo* investigations on this aspect using diabetic models are warranted.

C-reactive protein (CRP), a polypeptide molecule belonging to the family of pentraxins, plays an essential role in inflammation reaction. It has also been recognized as a key biomarker of inflammation [43,44]. This molecule is produced mainly by the liver in response to certain pro-inflammatory cytokines [44]. On a different note, asymmetrical dimethylarginine (ADMA), an inhibitor of NO synthase, is involved in oxidative stress and inflammation. Elevated ADMA levels have been reported in patients and animal models with diabetic microvascular complications [45]. CRP and ADMA levels were increased by ~6.3- and ~3.1-fold, respectively, and the level of NO was decreased by two thirds in diabetic rats [40]. Oral administration of ZnO-NPs at the concentration of 10 mg/kg/day for 30 consecutive days alleviated these changes [40].

2.7. Inhibition of α-amylase and α-glucosidase

α-Amylase and α-glucosidase are digestive enzymes that involved in breaking down carbohydrates to simple sugars before being absorbed by the intestines [46,47]. The inhibition of these enzymes is ideal for lowering the postprandial increase of blood glucose and therefore can be an effective strategy in managing type 2 DM [48]. α-Glucosidase inhibitors such as acarbose, miglitol, voglibose, and emiglitate are clinically available to treat type 2 DM [49]. Enzyme inhibition studies have shown that ZnO-NPs inhibited α-amylase from porcine pancreas and human saliva [50,51]. ZnO-NPs also reduced the activity of α-glucosidase from the murine pancreas (21% inhibition) and intestine (98% inhibition) [50]. The inhibitory activity of ZnO-NPs against murine intestinal glucosidase was marginally greater than acarbose [50].

2.8. Improve insulin sensitivity

MicroRNA (miR)-103 and miR-143 have been implicated as a novel regulator of type 2 DM. Studies have shown that miR-103 expression is upregulated in obese mice [52] and diabetic rats [20]. The expression of miR-103 and miR-143 was also upregulated by ~6- and ~2-fold, respectively, in the diabetic rat peripheral blood mononuclear cells [20,53]. Inhibition of plasma circulating miR-143–3p could protect against insulin resistance in obese mice [54]. Treatment with 3 and 10 mg/kg/day of ZnO-NPs for 7 weeks, either alone or with vildagliptin, alleviated the increase in miR-103 and miR-143 expression in diabetic animals [20]. Many other miRNAs are involved in regulating the insulin pathway and insulin resistance [55]. Whether ZnO-NPs could regulate other miRNAs remains to be discovered.

MiR-143 negatively regulates oxysterol-binding protein related-protein 5 and thus inhibiting phosphoinositide 3-kinase (PI3K)/AKT insulin signaling pathway [56]. In diabetic rats, plasma PI3K levels were lowered by half [19]. ZnO-NPs (10 mg/kg/day for 30 days) mitigated the drop in PI3K levels in the plasma of diabetic rats [19]. In accordance, a day of treatment with 10 μg/ml ZnO-NPs also increased Akt activation in HepG2 and L6 cells, as indicated by an increase in the protein phosphorylation by ~1.4- and ~1.7-fold, respectively to these cell types [23]. The increase in Akt activation could be mimicked by insulin treatment at the concentration of 0.1 IU/ml [23].

Protein tyrosine phosphatase 1B (PTP1B) is a negative regulator insulin signaling pathway [57]. Thus, inhibiting this enzyme could be a promising treatment for type 2 DM. In HepG2 cells, ZnO-NPs at 10 μg/ml inactivated PTP1B remarkably, as indicated by an increase in PTP1B phosphorylation by ~1.5-fold [23].

2.9. Anti-oxidative

Oxidative stress, an imbalance cellular process between oxidative and anti-oxidative systems, is also known to be associated with the development of DM [58]. It occurs as a result of the over-production of reactive oxygen species (ROS). It has been shown that ZnO-NPs (1–10 μg/ml) could rescue rat insulinoma RIN-5F cells from hydrogen peroxide-induced oxidative injury by reducing the level of ROS [59]. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) are useful as these enzymes can eradicate ROS [15]. A study has reported that STZ-induced diabetic rats exhibited lower CAT and GSH-Px activities, with 24% and 54% of the control value, respectively [15]. The pancreatic SOD activity was also remarkably reduced by two thirds in the diabetic group compared to control animals [20]. On the other hand, erythrocyte SOD activity in diabetic animals is still controversial. Nazarizadeh and Asri-Rezaie have shown that diabetic induction with STZ increased erythrocyte SOD activity in a time-dependent manner up to 8 weeks [15]. Notwithstanding, another research group has demonstrated that SOD activity was reduced by > 50% in STZ-induced diabetic rats [19]. These discrepancies might be due to differences in animal strains as well as to differences in the experimental protocols relating to the time course of administration of ZnO-NPs.

Nevertheless, ZnO-NPs could dose-dependently increase the activity of SOD in healthy rat erythrocytes [15]. ZnO-NPs, at concentrations up to 10 μg/ml, also elevated the activity of SOD and the level of reduced glutathione in RIN-5F cells [14,59]. Furthermore, ZnO-NPs could also alleviate the STZ-induced reduction of SOD activity in rat erythrocyte and pancreas [19,20]. ZnO-NPs also restored the activity of CAT in serum and erythrocytes of diabetic rats [15].

MDA, a biomarker of oxidative stress, is a molecule generated from lipid peroxidation [60]. ZnO-NPs reduced lipid peroxidation, as indicated by the reduction in MDA levels, in cardiac tissue and erythrocytes of diabetic animals [19,33]. ZnO-NPs at the concentrations of ≥3 mg/kg, however, could elevate lipid peroxidation, and reduce serum total antioxidant capacity and erythrocyte GSH-Px activity in both healthy control and diabetic rats [15]. In accordance, it has also been demonstrated in RIN-5F cells that treatment with ZnO-NPs at concentrations of 30 μg/ml and above is detrimental and could cause oxidative damage and apoptosis [59].

3. ZnO-NPs ameliorate diabetic complications

3.1. Cardiovascular complications

B-type natriuretic peptide (BNP) is a hormone produced by the heart. BNP is extensively used as clinical biomarkers for cardiac dysfunction and heart failure [61]. Treatment with ZnO-NPs at 3 mg/kg/day for 8 weeks reduced the level of BNP by half, and the atherogenic index by 80%, in diabetic rats [33]. Histopathological characteristics of cardiac muscle were also improved in ZnO-NP-treated diabetic animals [33]. ZnO-NPs (3 mg/kg/day, 8 weeks) suppressed apoptosis in diabetic cardiac tissue by inhibiting the activity of caspase-3 by two thirds [33]. However, a high dose of ZnO-NPs at 30 mg/kg was toxic to cardiac tissue [33].

Advanced oxidation protein products (AOPPs) are carried mainly by plasma albumins and can be accumulated in subjects with kidney disease and heart disease [62]. ZnO-NPs attenuated the rise in plasma AOPPs in STZ (60 mg/kg, s.c.)-induced diabetic rats [19]. Lipid peroxidation is also considered an effective atherogenic process. Plasma paraoxonase plays an important role in protecting LDL against peroxidation [63]. In diabetic rats, the activity of plasma paraoxonase was reduced to < 40% compared to the control. A month of treatment with 10 mg/kg/day ZnO-NPs could mitigate the reduction of plasma paraoxonase activity in these animals [19].

3.2. Reproductive impairments

Oxidative stress can lead to reduced fertility in diabetic men [64]. In testicular tissue of diabetic rats, the activity and mRNA expression of antioxidant enzymes such as SOD, CAT, GSH-Px, glutathione S-transferase, and glutathione reductase were reduced by > 50%. Concurrently, GSH levels were dropped to ~30%, and MDA levels were increased by ~5-fold [65]. Orally-administered ZnO-NPs at 10 mg/kg/day for 30 consecutive days attenuated these parameter changes [65].

Glucose metabolism is crucial for sperm production and maintenance [66]. The subfertility prevalence rate among diabetic males is high as DM can adversely affect sperm function, motility, and quality [66–68]. DM can also impair the synthesis of testosterone [69], the androgen in the testis that promotes spermatogenesis [70]. A significant reduction of serum testosterone level to ~60%, in comparison to the control rats, was reported in experimental DM induced by a single dose of STZ at 60 mg/kg [71]. ZnO-NPs increased sperm count and motility, as well as serum testosterone levels in diabetic rats [65].

The histopathological findings from the rat testis, such as disorganized seminiferous epithelium and hyalinized interstitial tissue, indicate spermatogenesis impairment in the diabetic group [71]. ZnO-NPs also reinstated the architecture of seminiferous epithelium and interstitium [71]. The immunohistochemical analyses also indicated that ZnO-NPs could restore the number of primary spermatocytes, spermatogonia cells, and Sertoli cells that have a supportive and nutrient function [71].

DNA methylation of germ cell-specific genes is required to regulate spermatogenesis and male fertility [72]. Testicular cells with DNA methylation were less commonly found in diabetic groups [71]. ZnO-NPs increased the number of DNA-methylated cells [71]. It has been shown that DNA methylation can be regulated by nuclear respiratory factor 1 (NRF1) [72] and sirtuin 1 (SIRT1) [73]. Thus it may be possible that ZnO-NPs regulate DNA methylation via activating NRF1 and SIRT1.

DM can impair reproductive functions in women [74]. It has been demonstrated that the female reproduction performance was impaired in pregnant diabetic Wistar rats. The features of the offspring such as fetal, craniofacial and placental dimensions were also negatively affected. Therefore, it is equally crucial to evaluate the possible role of ZnO-NPs in restoring female reproductive impairments.

4. Future perspectives

The synthesis of nanoparticles from the plant source, namely the green method, has been proposed as environmentally friendly and cost-effective comparing to chemical and physical methods. ZnO-NPs synthesized by the green method using plant extracts also revealed substantial *in vitro* antioxidant and free radical scavenging activities [75,76]. Surprisingly, ZnO-NPs synthesized by the chemical method did not exhibit any free radical scavenging activity [75]. ZnO-NPs obtained by the green method also exhibited significant cholesterol reduction in alloxan (170 mg/kg, i.p.)-induced diabetic rats [18]. But, this reduction was not seen in rats treated with chemically-synthesized ZnO-NPs or insulin. Nevertheless. both chemically- and biologically-prepared ZnO-NPs are better than insulin in reducing fasting blood glucose levels [18]. Further comparative studies should be also extended to ZnO-NPs obtained from different medicinal plants.

Toxicity and uptake of ZnO-NPs versus their bulk-size counterparts have recently been studied [77,78]. Furthermore, oral administration of ZnO-NPs and ZnO bulk could trigger a broad range of zinc-transport-related gene transcription in the mouse small intestine [79]. Zinc transporters are also present in β cells of the pancreas, for instance, zinc transporter 8 which has a crucial role in insulin release. The beneficial role of zinc in DM has been implicated by supplying zinc to diabetic rats [80]. ZnO-NPs showed greater anti-diabetic activity compared to zinc sulfate evidenced by enhanced glucose clearance, and elevated serum zinc and insulin levels in STZ (50 mg/kg, i.p.)-induced diabetic rats [15]. ZnO-NPs produced from *Andrographis paniculata* leaf extract also exhibited α-amylase inhibition and anti-inflammatory potential but the effects were slightly weaker than zinc nitrate [76]. Nevertheless, very few studies compare the effectiveness of ZnO-NPs with their bulk and salt counterparts in alleviating other diabetic hallmarks and complications.

Synergistic effects between chemical compounds have long been a point of focus in diabetic treatment as anti-diabetic drugs are available with different mechanisms of action. For instance, patients who undergo sodium-glucose cotransporter 2-metformin combination therapy exhibited better glycemic control compared with either compound alone [81]. It has also been shown in the experimental DM that synergistic interactions do occur between ZnO-NPs and other compounds such as vildagliptin and thiamine [17,20]. Thus, synergistic properties between ZnO-NPs and other diabetic drugs or dietary supplementations should be further explored.

5. Conclusions

Finding an effective treatment for DM is essential as the global prevalence of the disease is rising continuously. The advancement of nanotechnology has allowed many materials including ZnO-NPs to be considered for biomedical applications and disease-modifying therapies. This review indicates that ZnO-NPs can target a number of different hallmarks of DM. Thus, it can be concluded that ZnO-NPs are a promising anti-diabetic agent that warrants further investigations and clinical trials.

Declaration of Competing Interest

The author has no conflict of interest to report.

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