Synthesis and Characterization of Nano-doped Zinc Oxide and its Application as Protective Oxidative Changes in the Retina of Diabetic Rats

Soheir N Abd El-Rahman1*, Reda SM2 and Sheikha M AlGhannam2

1College of Science, University of Dammam, Agriculture Research Center, Giza, Saudi Arabia
2Chemistry Department, Benha University, Benha, Egypt

Abstract

Oxidative stress is a basic mechanism behind the development of diabetic retinopathy (DR). Therefore, the present study conducted to evaluate the protective effect of zinc oxide nanoparticles (ZnONPs) doped with fluorine (F:ZnO) and chlorine (Cl:ZnO), on retinal oxidative stress in type II diabetic rats. TEM showed that the F:ZnO and Cl:ZnO have average particle size 17.7 and 59.3 nm, respectively. The results indicated that serum glucose was increased significantly (p ≤ 0.05) and serum insulin was decreased significantly 3 days after treatment with STZ compared to other groups. STZ treatment depleted both retinal and liver TBA and retinal GST contents. While, simultaneous treatment rats with low and high dose of STZ + F:ZnO and STZ + Cl:ZnO were decreased serum glucose induced by STZ and reversed the deplete influence on GSH level of retinal and reduced the highs in TBA levels of livers and retinas in STZ -administered rats. The results investigate the useful effects of high dose of F:ZnO and Cl:ZnO in protection diabetic rats against hyperglycemia and retina against oxidative stress.

Keywords: Nano-doped zinc oxide; Oxidative stress; F:ZnO; Cl:ZnO; Diabetic retinopathy

Introduction

All over the world there are a large number of people suffer from diabetes. Diabetes mellitus, is a result of metabolic diseases and causes high blood sugar in person, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced [1]. Therefore, diabetes mellitus patients would require and several development medications with multiple modes of actions.

Retinopathy is a severely disabling complication of diabetes, however, the biochemical or cellular links between elevated blood glucose levels, and the vascular lesions remain incompletely understood. Understanding of the pathological mechanisms underlying these lesions is paramount to ultimately developing therapeutic interventions. The development of diabetic vascular complications begins with prolonged hyperglycemia, which results in expression of factors which activates the g2 isoform of protein kinase C and stimulate vascular endothelial proliferation and increased capillary permeability [2]. Other mechanisms may also be involved such as increased glucose metabolism via the polyol pathway (aldose reductase), sorbitol is produced via this pathway in possibly toxic concentrations [3]. The high levels of glucose are able to induce non enzymatic glycation of proteins [4-7]. The accumulation of advanced glycation end products contribute to the thickening of basement membranes, as well as several other abnormalities in tissues, especially endothelium [8]. Several studies reported that oxidative stress an integral and possibly causative part of the pathogenesis of diabetic retinopathy [9-14]. A rational extension of this proposed role for oxidative stress is the suggestion that the different susceptibility of diabetic patients to microvascular and macrovascular complications may be a function of the endogenous antioxidant status. Thus, antioxidant therapy may be a suitable approach to determine the roles of intrinsic retinal abnormalities in the development of diabetic retinopathy [11].

Nano-ZnO is a new product whose particle diameter is between 1 to 100 nm. More recently, the study of ZnO nanoparticles is a very active area because their properties can be tuned according to the desired application [15-17]. As a semiconductor, ZnO has a wide direct band gap (Eg=3.37 eV), with a large excitonic binding energy of 60 meV. Additionally, it is a non-central symmetry material, and exhibits bio-compatibility properties. All of these properties make ZnO an important functional oxide. Due to its fast electron transfer capability, ZnO is a key material for fabrication of biomembranes, and enzymatic detective devices [18]. Nano-zinc oxide is a key element for maintenance of the structural and functional integrity of eukaryotic cells and tissues [19]. Many studies have addressed the importance of ZnO as an antioxidant and a therapeutic agent in several free radicals initiating systems [20-24] reported the anti diabetic effects of ZnONPs through induction of insulin, IR and glucose metabolizing enzymes gene expression. In the same line Umrani and Paknikar, [25] proved the ability of ZnONPs for controlling of blood glucose in diabetic rats, these are only two studies that monitored the effect of ZnONPs on diabetic rats, but there is not previous study carried out with F:ZnO and Cl:ZnO nanoparticles on diabetic rats. Therefore, this work was designed to I. increase the carrier concentration and modify the optical properties of ZnO nanoparticles, the fluorescent and chlorine doping. II. investigate the ability of F:ZnO and Cl:ZnO to modulates blood glucose, TBA (MDA) ,GSH and insulin levels in the STZ diabetic rats. III. provide further insights into roles of zinc in diabetes and diabetic retinopathy, which may help set a new direction toward the development of effective treatments.

*Corresponding author: Soheir N Abd El-Rahman, College of Science, University of Dammam, Agriculture Research Center, Giza, Saudi Arabia, Tel: +966553687730; E-mail: soheirkenawy@yahoo.com/skenawy@uod.edu.sa

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Materials and Methods

Experimental

The ZnO nanoparticles doped with fluorine was prepared by a chemical solution method from zinc acetate (ZnAc) and oxalic acid. The procedure is as follows: 20 mL of a 0.5 M ethanolic solution of oxalic acid was added drop-by-drop to 20 mL of a 0.1 M ethanolic solution of ZnAc under stirring and maintained at 60°C for 3 h. Then 0.5 M of aqueous solution of ammonium fluoride was added to the above solution in order to get at 5% F/Zn ratio. A white precipitate was obtained, which was separated by filtration and washed with a mixture of 75:25 water: ethanol. This precipitate was dried in an oven at a temperature of 100°C for 24 h. The obtained precursor was finally calcined at 500°C for 2 h, with a heating rate of 5°C/min.

For the preparation of Cl-doped ZnO nanoparticles, the procedure was the same; however, an aqueous solution of ammonium chloride (NH₄Cl) 0.5 M was added to the ZnAc solution.

All the reagents used in the experiments were of analytical grade and used directly as purchased.

Characterization

The structure was analyzed by FTIR spectra (FTIR Nicolet 6700). The surface properties namely BET surface area was determined using conventional apparatus.

Biological methods

Male albino adult rats (105 animals weighing 200 g ± 50) were obtained from the private market, Helwan, Giza, Egypt, then transported to Animal House of Ophthalmology Research Institute, Giza, Egypt. Rats were housed in individual cages with screen bottoms and fed on basal diet (corn starch 70%, casein 10%, corn seed oil 10%, cellulose 5%, salt mixture 4% and vitamins mixture 1%) for ten days. After equilibration, rats were weighted and divided into six groups (fifteen animals each) everyone was assigned to one of the six diet groups (G1: Negative Control (NC), G2: STZ-treated group that received a single ip dose of STZ (60 mg/kg b.w), G3: treated with STZ (60 mg/kg b.w)+ single daily oral dose of F:ZnO (5 mg/kg b.w), G4: treated with STZ (60 mg/kg b.w)+ single daily oral high dose of F:ZnO (10 mg/kg b.w), G5: treated with STZ (60 mg/kg b.w)+ single daily oral low dose of Cl:ZnO (5 mg/kg b.w), G6: treated with STZ (60 mg/kg b.w)+ single daily oral high dose of Cl:ZnO (10 mg/kg b.w). Rats were sacrificed at 0, 24, 48, and 72 h after STZ treatment. Before the rats were sacrificed, blood was collected from the orbital sinus and serum was prepared and kept frozen at −20°C until the time of assay. The rats were killed by decapitation and the livers were rapidly excised, rinsed with saline, blotted, and weighed. Each eye was immediately enucleated, the lens was removed, and the retina was gently peeled away from the pigmented epithelium and placed in 500 ml ice-chilled 10 mmol/l sodium phosphate buffer, pH 8.0.

Measurements of blood glucose and insulin

Blood glucose (mg/dl) was estimated by glucose oxidase method using the kitsupplied by SPINREACT (SantEstebadeBas, Girona, Spain) according to Tietz, [26], we measured blood glucose in all experimental animals before the beginning of the experimental procedures, after streptozotocin injection. After that, blood glucose was monitored in all experimental animals, and results were obtained at 0, 24, 48 and 72 h of the experimental period. Serum insulin was measured using an insulin radio immunoassay kit.

Measurements of sAST and sALT

Serum transaminases sAST and sALT (Aspartate transferase and Alanine transferase) were measured colorimetrically according to the method described Reitaman and Frankel [27].

Assessment of lipid peroxidation

Retinal and liver homogenates (10% w/v in cold distilled water) were used for the estimation of the degree of lipid peroxidation. The level of lipid peroxidation was estimated by the thiobarbituric acid (TBA) test according to the method described by Uchiyama and Mihrara, [28]. Briefly, an aliquot (0.5 ml) of the retinal or liver homogenate was mixed with 1.0% of aqueous solution of ammonium fluoride was added to the above solution in order to get at 5% F/Zn ratio. A white precipitate was obtained, which was separated by filtration and washed with a mixture of 75:25 water: ethanol. This precipitate was dried in an oven at a temperature of 100°C for 24 h. The obtained precursor was finally calcined at 500°C for 2 h, with a heating rate of 5°C/min.

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Measurements of reduced glutathione (GSH)

Reduced glutathione was measured according to the method of Sedlak and Lindsay, [31]. A 400 mg sample of retina was homogenized in 8.0 ml of 0.02 M EDTA using an all-glass Ten-Broek homogenizer in an ice bath. These ratios of tissue to homogenizing medium were chosen to obtain an absorbance of 0.1 to 0.8 when 5.0 ml was used for the estimation of GSH. Aliquots of 5 ml of homogenates were mixed with 4.0 ml of distilled water and 1.0 ml of 50% trichloroacetic acid (TCA). The tubes were shaken intermittently for 10–15 min and centrifuged for 15 min at approximately 3000g. Two ml of supernatant was mixed with 4.0 ml Tris buffer, pH 8.9, 0.1 ml of DTNB was then added and the sample was shaken. The absorbance was read within 5 min of the addition of DTNB at 412 Am against a reagent blank with no homogenate.

Statistical analysis

The results are represented as mean ± SE and statistically analyzed by using one-way ANOVA. Accepted level of significance (P ≤ 0.05).

Results and Discussion

Characterization

IR spectra: Figure 1 shows the FT-IR absorption spectrum of F: ZnO and Cl/ZnO nanoparticles. The peak at 470 cm⁻¹ is the characteristic distinct stretching vibration of zinc oxide. The broad absorption peak at 3400 cm⁻¹ can be attributed to the characteristic absorption of hydroxyls group.

Scan electron microscope: Figure 2 shows the SEM images of the ZnO nano powders prepared with fluorine and chlorine doping. As can see from Figure 2a, the F:ZnO nanoparticles shows rode shape. But in case of Cl/ZnO the ZnO shows a round shape. The difference in the shape can be attributed to the nature of doping.

Transmission electron microscope: Figure 3 shows that the ZnO nano powders prepared with fluorine and chlorine doping have average particle size 17.7 and 59.3 nm, respectively.
BET measurement: The values of surface area of the F:ZnO and ClZnO nano particles were found to be 3.55 and 41.62 m$^2$/g, respectively. The high value of surface area of chlorine composite facilitates adsorption on its surface.

X-ray: XRD patterns of the ZnO nanocomposites are shown in Figure 4. The diffraction peaks from the ZnO at 2θ = (31.9°), (34.6°), (36.4°), (47.7°), (56.7°), (62.9°), and (68.1°) to the (1 0 0), (0 0 2), (1 0 1), (102), (103), (1 1 2) and (2 0 1) diffraction planes, respectively. These diffraction planes can be indexed to the Zinc its structure of ZnO indicating its high crystallinity [32].

Biological study: Diabetic retinopathy is likely to be multifactorial. Recognition of as many of these factors as possible and study of their interaction may help overcome the vision impairment or blindness that accompany diabetes. Oxidative stress has been found to play an important role in the pathogenesis of diabetes [33-35]. Also, the generation of reactive oxygen species has been shown to play an integral and possibly a causative part in the pathogenesis of diabetic retinopathy [35-37]. Previous studies investigated that ZnONPs have diabetic protection properties, but there is no previous study carried out with F:ZnO, Cl-ZnO and diabetic retinopathy. So, our study conducted to evaluate F:ZnO and Cl-ZnO effects on diabetic retinopathy protection. Also, the demonstrated results might be a base for further studies with F:ZnO and Cl-ZnO.

Table 1 shows the levels of serum glucose concentrations in diabetic rats administration low and high dose of F:ZnO and ClZnO for 3 days. Our results showed a great reduction in blood glucose level in diabetic groups treated with low and high dose of F:ZnOandClZnO, it found to be 119.03, 117.10, 108.97 and 103.97 mg/dl after 72 h, respectively. This showed a great antidiabetic activity of zinc oxide nanoparticles, as zinc has been elucidated to be a potent metal that improves glucose utilization and metabolism through its potent influence on...
enhancement of hepatic glycogenesis through actions on the insulin signaling pathway [38]. These results agree with the results reported by Umran, and Paknikar, [25] they indicated that repeated administration of ZnONPs to diabetic rats showed better effects on glucose intolerance compared with single-dose studies, suggesting improved efficacy after multiple dosing. Single administration of ZnONPs resulted in prominent glucose suppression during oral glucose tolerance test (OGTT), suggesting antidiabetic effects. Improved glucose tolerance in OGTT could be a result of several possible mechanisms. I. ZnONPs treatment might result in inhibition of intestinal α-glucosidase enzyme and thereby reduce glucose absorption. II. glucose uptake increased in the liver and its subsequent storage (glycogenesis) might be lowered blood glucose levels. III. Enhanced glycolysis by ZnONPs could result in improved glucose disposal. Also, the antidiabetic effects of ZnONPs may be due to that zinc is closely involved in general metabolism of protein, carbohydrate, and lipids. In the case of glucose metabolism, zinc is a cofactor of key enzymes. It is an activator of fructose 1-6 diphosphatase, and an inhibitor of fructose 1-6 diphosphatase [39]. ZnONPs treatment indicates inhibitory effects on glycogenolysis and gluconeogenesis, mechanisms that are active during the fasted state. Additionally, Egefjord et al. [40] investigated that zinc regulate glucagon secretion from pancreatic acells. As a result, glucagon-stimulated hepatic pathways (i.e., glycogenesis and gluconeogenesis) would be suppressed in the fasting state [41] contributing to a reduction of fasting glucose levels.

Serum insulin levels in diabetic rats administration low and high dose of F:ZnO and Cl:ZnO for 3 days were presented in Table 2. The results show that the groups administration high dose of F:ZnO and Cl:ZnO gave a best results (326.40 and 367.80 pg/ml), respectively, compared to PC (175.40 pg/ml). There are few studies that have investigated the therapeutic effect of ZnONPs on insulin levels or secretion. zinc could enhance the glucose stimulated insulin secretion from rat isolated pancreatic islets [42]. Umran and Paknikar [25] demonstrated that ZnONPs did not possess the risk of hypoglycemia in living organisms so it can act as an insulin secretor. Additionally, increase serum insulin level in diabetic groups administration of ZnONPs may be due to accumulation of zinc in the secretory vesicle of B cells using transporter 8 [43]. Zinc transporters are also identified in adipose tissues and liver [44]. Quarterman et al. [45] reported that diet induced zinc deficiency in rats resulted in a decrease in the ability of the pancreas to secrete insulin in response to a glucose load. Meyer and Spence [46] indicated that decreased zinc in the pancreas may reduce the ability of the islet b-cells to produce and secrete insulin and zinc deficiency is positively correlated with diabetes and may also affect the progress of Type 2 diabetes [47].

Our results pointed out that there is a significant increase in the levels of concentration of TBA (MDA) in liver and retinal and GSH in retinal of diabetic rats (Tables 3 and 4), in contrast, was significantly reduced after treatment by low and high dose of F:ZnO and Cl:ZnO for 3 days. Zinc is a necessary factor in the variety of antioxidant enzymes e.g. Zn superoxide dismutase, Zn-metallothionein etc. [32]. Also, Zn-metallothionein complex in the islets cells provides protection against free radicals produced in the cell from any cause. The more depleted the intracellular Zn stores, the less able the cell is to defend itself against this oxidative load. Aruoma [48] concluded that Copper and zinc, and manganese are indispensable metals for the activities of Cu,Zn-SOD and Mn-SOD, respectively. Therefore, dietary deficiencies of these minerals markedly decrease tissue Cu,Zn-SOD and Mn-SOD activities and result in peroxidative damage and mitochondrial dysfunction.

### Table 1: Effect of F:ZnO and Cl:ZnO (5 mg/kg b.w and 10 mg/kg b.w) on serum glucose concentration in diabetic rats.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Time</th>
<th>Glucose (mg/dl)</th>
<th>0h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (NC)</td>
<td></td>
<td></td>
<td>95.09 ± 0.079</td>
<td>95.818 ± 0.122</td>
<td>94.582 ± 0.170</td>
<td>95.942 ± 0.100</td>
</tr>
<tr>
<td>G2 (PC)</td>
<td></td>
<td></td>
<td>94.996 ± 0.063</td>
<td>155.402 ± 0.616</td>
<td>204.288 ± 0.525</td>
<td>380.534 ± 0.475</td>
</tr>
<tr>
<td>G3</td>
<td></td>
<td></td>
<td>95.566 ± 0.125</td>
<td>102.612 ± 0.176</td>
<td>112.114 ± 0.273</td>
<td>119.032 ± 0.155</td>
</tr>
<tr>
<td>G4</td>
<td></td>
<td></td>
<td>94.17 ± 0.258</td>
<td>102.612 ± 0.176</td>
<td>110.194 ± 0.288</td>
<td>117.104 ± 0.273</td>
</tr>
<tr>
<td>G5</td>
<td></td>
<td></td>
<td>95.188 ± 0.172</td>
<td>98.05 ± 0.049</td>
<td>102.114 ± 0.273</td>
<td>108.972 ± 0.046</td>
</tr>
<tr>
<td>Cl:ZnO</td>
<td></td>
<td></td>
<td>95.012 ± 0.016</td>
<td>96.39 ± 0.193</td>
<td>98.664 ± 0.209</td>
<td>103.974 ± 0.040</td>
</tr>
<tr>
<td>Negative control</td>
<td></td>
<td></td>
<td>0.417</td>
<td>0.840</td>
<td>0.908</td>
<td>0.693</td>
</tr>
</tbody>
</table>

### Table 2: Effect of F:ZnO and Cl:ZnO (5 mg/kg b.w and 10 mg/kg b.w) on serum Insulin concentration in diabetic rats.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Time</th>
<th>Insulin (pg/ml)</th>
<th>0h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (NC)</td>
<td></td>
<td></td>
<td>469.40 ± 0.93</td>
<td>474.00 ± 1.10</td>
<td>473.40 ± 1.47</td>
<td>476.60 ± 2.73</td>
</tr>
<tr>
<td>G2 (PC)</td>
<td></td>
<td></td>
<td>476.60 ± 1.03</td>
<td>334.80 ± 0.58</td>
<td>203.60 ± 0.60</td>
<td>175.40 ± 0.93</td>
</tr>
<tr>
<td>G3</td>
<td></td>
<td></td>
<td>467.20 ± 0.73</td>
<td>352.00 ± 0.32</td>
<td>301.80 ± 0.37</td>
<td>288.40 ± 0.24</td>
</tr>
<tr>
<td>G4</td>
<td></td>
<td></td>
<td>472.00 ± 1.00</td>
<td>392.00 ± 0.32</td>
<td>365.00 ± 1.30</td>
<td>326.40 ± 0.24</td>
</tr>
<tr>
<td>G5</td>
<td></td>
<td></td>
<td>475.00 ± 0.95</td>
<td>392.40 ± 0.24</td>
<td>341.40 ± 0.40</td>
<td>308.40 ± 0.24</td>
</tr>
<tr>
<td>G6</td>
<td></td>
<td></td>
<td>469.60 ± 1.29</td>
<td>413.20 ± 0.80</td>
<td>387.00 ± 4.53</td>
<td>367.80 ± 1.07</td>
</tr>
<tr>
<td>Negative control</td>
<td></td>
<td></td>
<td>2.924</td>
<td>1.861</td>
<td>5.960</td>
<td>3.700</td>
</tr>
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</table>
The results presented in Table 5 show the levels of sALT and sAST in diabetic rats administration low and high dose of F:ZnO and Cl:ZnO for 3 days. It was observed that there were no significant differences in sALT and sAST levels between the groups treated with high dose of ZnO. The group treated with high dose of Cl:ZnO showed a decrease in sALT and sAST levels compared to the negative control group. The results suggest that Cl:ZnO may have potential in reducing hyperglycemia and the protection of the retina against oxidative stress, but further studies are needed to confirm these findings.

Conclusion

Cl:ZnO and F:ZnO were elucidated as anti-diabetic agents. They lead to induction of insulin synthesis and decreasing of blood glucose levels. Their applications in both controlling hyperglycemia and the protection of the retina against oxidative stress are significant. However, further research is needed to confirm these findings.

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