Oxidative stress (OS) has been suggested as one of basic mechanism behind the development of type 2 diabetes especially diabetic retinopathy (DR). Isoprostanes (IsoPs) are involved in type 2 diabetes and increased in pathological conditions associated with OS. Our present study was designed to prepare Cl: ZnO nano particles (Cl: ZnONPs) and evaluate the effect of ZnCl₂ and Cl: ZnONPs at (5 and 10mg/kg bw) on retinal oxidative stress in STZ-induced diabetic rats. The male albino rats treated with one dose of streptozotocin (60mg/kg bw). The diabetic rats were administrated Zn Cl₂ and Cl: ZnONPs (5 and 10mg/kg bw) orally for 3 days. The results investigated that TEM of Cl: ZnONPs has average particle size 14.5-70nm. Serum insulin and SOD were decreased and serum glucose and IsoPs were increased significantly (P≤0.05) 72h after treatment with STZ (60mg/kg bw) than other groups. A significant decreased (P≤ 0.05) in glucose and F₂-IsoPs levels and significant increase in insulin and SOD levels were detected also in retina in STZ diabetic rats which treated with ZnCl₂ and Cl: ZnONPs (5 and 10mg/kg bw). Cl: ZnONPs (10mg/kg bw) + (60mg/kg bw) gave the best results compared to ZnCl₂ (5 and 10mg/kg bw) + STZ and Cl: ZnONPs (5mg/kg bw) + STZ. In conclusion, Cl: ZnONPs have a highly protective effect against hyperglycemia and diabetic retinopathy oxidative stress, especially at (10mg/kg bw) dosage.
F2-like products termed F2-isoprostanes (F2-IsoPs). [17,18] Increased levels of F2-IsoPs can be found in the plasma of patients affected with type I and type II diabetes [11,19] and in animal models of diabetes [20] and currently are used as in vivo indicators of lipid peroxidation [1,13,21,22]. Zinc (Zn) is the most abundant trace intracellular element required for several cellular processes, including cell proliferation, reproduction, immune function and defense against free radicals [23]. It plays an important role as an antioxidant, protects cellular components from oxidation, [24] an activator for more than three hundred enzymes in the body [25] and in different metabolic pathways including glucose metabolism. [26] Also, Zinc promotes hepatic glycogenesis through its actions on the insulin pathways, storage, secretion [27] and thus improves glucose utilization [28]. Due to its fast electron transfer capability, ZnO is a key material for fabrication of bio membranes, and enzymatic detective devices [29]. Many studies have addressed the importance of ZnO as an antioxidant and a therapeutic agent in several free radicals initiating systems [26,30]. Nano-ZnO is a product whose particle diameter is between 1 to 100nm. More recently, the study of ZnO nanoparticles is a very active area [31,32]. Umran, and Palkinjak, [33] reported that the anti diabetic effects of ZnONPs through induction of insulin, also, they proved the ability of ZnONPs for controlling of blood glucose in diabetic rats. Soheir et al. [34] investigate the useful effects of high dose of F: ZnO and Cl: ZnO nanoparticles in protection diabetic rats against hyperglycemia and retina against oxidative stress. There is only one study that monitored the effect of Cl: ZnO nanoparticles on diabetic rats, but there is not previous study carried out with Cl: ZnO nanoparticles on the role of iso prostane during diabetic rats. Therefore, this work designed to prepare ZnO nanoparticles doped with chlorine (Cl: ZnOPNs) and reviews the role of ZnCl2 and Cl: ZnOPNs on F2-Iso prostanate as biomarkers of oxidative stress in retina in relation to type II diabetes in rats.

Materials and Methods

Experimental

The ZnO nanoparticles doped with chlorine was prepared by a chemical method from zinc acetate (ZnAc) and oxalic acid. The preparation is as follows: 20mL of a 0.5 M ethanolic solution of oxalic acid was added drop-by-drop to 20mL of a 0.1 M ethanolic solution of ZnAc under stirring and maintained at 60°C for 3h. Then 0.5 M of aqueous solution of ammonium chloride (NH₄Cl) was added to the above solution to get at 5% Cl/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. 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). Surface Morphology was analyzed by SEM (Quanta 3D FEG/FEI) and TEM (JEOL, Tokyo, Japan) operating at 60 kV.

Biological Methods

Male albino adult rats (60 animals weighing 130g±5) 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 (ten animals per each) everyone was assigned to one of the six diet groups (G1: Negative Control (NC), G2: STZ-treated group that injected with a single ip dose of STZ (60mg/kg bw), G3: treated group that received a single dose of STZ (60mg/kg bw)+ single daily oral low dose of ZnCl2 (5 mg/kg b.w), G4: treated group that received a single dose of STZ (60mg/kg bw) + single daily low dose of Cl: ZnONPs (5mg/kg b.w), G5: treated group that received a single dose of STZ (60 mg/kg b.w.) + single daily oral high dose of ZnCl2 (10 mg/kg b.w), G6: treated group that received a single dose of STZ (60mg/kg bw) + single daily high dose of Cl: ZnONPs (10mg/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. Each eye was immediately enucleated, the lens was removed, and the retina was gently peeled away from the pigment epithelium and placed in 500 ml ice-chilled 10mmol/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 kit supplied by SPINREACT (Sant Esteve de Bas, Girona, Spain) according to, [35] 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 72h of the experimental period. Serum insulin was measured using an insulin radio immunoassay kit.

Superoxide Dismutase (SOD) and F2-Isoprostanes (F2-IsoPs) Assay

The enzymatic activity of retinal SOD was measured as described by ohkuma et al. [36]. Retinal F2-IsoPs were measured using a competitive enzyme-linked immunoassay (ELISA) kit according to instructions (Cayman Chemical, Ann Arbor, MI) [37].

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**

**IR Spectra**

Figure 1 shows the FT-IR at sorption spectrum prepared sample (Cl: ZnONPs). 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. These results agree with Soheir et al. [34]. They reported that the undoped ZnO, an absorption peak is observed centered at 372nm (3.33 eV), which is in good agreement with previously reported works of ZnO single crystals and Cl: ZnONPs.

![FTIR spectra of Cl: ZnONPs powder.](image)

**Scanning Electron Microscopy (SEM)**

Figure 2 (a and b) shows the SEM images of the Cl: ZnONPs powder prepared with chlorine doping. Cl: ZnONPs shows a rode shape. The results of this study agree with Soheir et al. [34] and they reported that the ZnO nano powders prepared with fluorine and chlorine and doping have average particle size 17.7 and 59.3nm, respectively.

![SEM spectra of Cl: ZnONPs powder.](image)

**Transmission Electron Microscopy (TEM)**

Figure 3 shows the Cl: ZnO NPs powder prepared with chlorine doping have average particle size 14.5-70.0nm.

![TEM spectra of Cl: ZnONPs powder.](image)
Biochemical Markers

Table 1 Shows the changes of serum glucose levels induced by ZnCl₂ and Cl: ZnONPs in diabetic rats. Experimental groups treated with ZnCl₂ and Cl: ZnONPs (5 and 10mg/kg bw) for 3 days, showed a significant (P≤0.05) decrease in serum glucose levels, it found to be (138.02±116.09 mg/dl), (117.96±102.96 mg/dl) at 5 and 10 mg/kg bw, respectively after 72h. Additionally, Cl: ZnONPs (10mg/kg bw)+STZ (60 mg/kg bw) treated group results were close to normal values that showed in NC group. 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 [34]. Alkaladi et al. [31] showed a great reduction in blood glucose level in diabetic groups treated with ZnONPs, SNPs and insulin. However, ZnONPs induce more reduction than SNP. Rehal et al. [38] reported that at 30, 60, 90 and 120 min, the plasma glucose levels in the STZ-induced rats were treated with Vildagliptin, ZnONPs, and various combinations of the two, groups, for 7 weeks showed significant improvements compared to the diabetic group (group II). The maximum improvement in the reduced plasma glucose levels was observed in the rats treated with the combination therapy (Vildagliptin plus 10mg/kg/d ZnONPs, group IIIh) compared to diabetic group and the other treated groups [38]. Also, a great reduction in blood glucose level in diabetic groups treated with low and high dose of F: ZnONPs and Cl: ZnONPs, it found to be 119.03, 117.10, 108.97 and 103.97 mg/dl after 72 h, respectively [34].

Table 1: Effect of ZnCl₂ and Cl:ZnONPs (5 and 10mg/Kg bw) on Serum glucose concentration in diabetic rats.

| Treatments | Glucose (mg/dl) |
|------------|-----------------|
|            | 0h              | 24h             | 48h             | 72h             |
| G1 (NC)    | 94.080±0.078    | 94.080±0.121    | 93.572±0.169    | 94.932±0.099    |
| G2 (PC)    | 93.966±0.062    | 154.392±0.615   | 203.278±0.524   | 379.524±0.474   |
| G3         | 94.556±0.124    | 101.602±0.175   | 141.104±0.272   | 138.02±0.154    |
| G4         | 93.160±0.257    | 101.602±0.175   | 109.184±0.287   | 116.09±0.272    |
| G5         | 94.178±0.171    | 97.380±0.048    | 121.104±0.272   | 117.96±0.045    |
| G6         | 94.002±0.015    | 95.380±0.192    | 97.654±0.208    | 102.96±0.039    |

G1(NC) = Negative control, G2 (PC) = positive control, G3 = STZ + ZnCl₂ (5mg/kg bw), G4 = STZ + Cl: ZnONPs (5mg/kg bw), G5 = STZ + ZnCl₂ (10mg/kg bw), G6 = STZ + Cl: ZnONPs (10mg/kg bw)

Our results revealed that ZnCl₂ and Cl: ZnONPs (5 and 10mg/Kg bw) + STZ (60mg/Kg bw) were significantly (P≤0.05) increased serum insulin level (290.40, 328.40 uIU/ml),(310.40,369.80 uIU/ml) at (5 and 10mg/kg bw), respectively, compared to (PC) (177.40 uIU/ml) (Table 2). The serum insulin levels were significantly decreased in the diabetic group compared to the control group [38]. This results may be due to zinc could enhance the glucose stimulated insulin secretion from rat isolated pancreatic islets [40] Umrani and Paknikar [33] demonstrated that ZnONPs did not possess the risk of hypoglycemia in living organisms so it can act as an insulin secretor/due to accumulation of zinc in the secretory vesicle of B cells using transporter 8 [40]. Zinc transporters are also identified in adipose tissues and liver [34,41]. Treatment with ZnONPs induced a significant increase in the serum insulin levels compared to the diabetic group (NC) [38]. The groups administration high dose of F: ZnONPs and Cl: ZnONPs gave a best result (326.40 and 367.80 pg/ml), respectively, compared to PC (175.40 pg/ml) [34]. ZnONPs and SNP could increase serum insulin level in diabetic groups, it found (79.4% and 3%), respectively if compared with diabetic groups treated with insulin (97.3%). It appeared that ZnONPs also induced more insulin secretion if compared to the effect of SNPs [31]. ZON treatment showed a trend towards a dose-dependent increase in nonfasted serum insulin levels (35% increase at 10 mg/kg dose). However, no significant effects were seen on fasted serum insulin levels after ZON treatment, indicating no risk of hypoglycemia [33]. The best results were observed in diabetic rats treated with ZnONPs in a dose of (10mg/kg b.w)[42].

Table 2: Effect of ZnCl₂ and Cl:ZnONPs (5 and 10mg/Kg bw) on Serum insulin concentration in diabetic rats.

| Treatments | Insulin (uIU/ml) |
|------------|-----------------|
|            | 0h              | 24h             | 48h             | 72h             |
| G1 (NC)    | 471.40±0.91     | 476.00±1.08     | 475.40±1.45     | 480.60±2.71     |
| G2 (PC)    | 478.60±1.01     | 336.80±0.56     | 205.60±0.58     | 177.40±0.91     |
| G3         | 469.20±0.71     | 354.00±0.30     | 303.80±0.35     | 290.40±0.22     |
Isoprostanes in contrast to lipid hydroperoxides, are chemically stable end products of lipid peroxidation, and the measurement of their levels in plasma or urine may permit a sensitive and specific method for detection of lipid oxidative damage in vivo [22]. In the present study the retinal F2-IsoPs levels were significantly (P≤0.05) increased in the diabetic group (0.7162 pg/ml bw) compared to the NC (0.2762 pg/ml bw) after 72h (Table 3). Treatment with ZnCl2 and Cl: ZnONPs (5 and 10 mg/kg bw) + STZ (60 mg/Kg bw) induced a significantly decreased of F2-IsoPs the retina levels compared to (PC). The results of Cl: ZnONPs (10 mg/kg bw) + STZ (60 mg/kg bw) was close to normal value that showed in NC group (Table 3). Increase in plasma level of total F2-IsoPs in type 2 diabetic nephropatic patients (P≤0.01) with respect to controls [43]. Increased F2-IsoPs synthesis during diabetes appears to be responsible in part for the increase in renal TGF-β,α well-known mediator of diabetic nephropathy [6].

 Plasma F2-IsoPs levels in STZ-induced diabetic rats were significantly higher than in nondiabetic animals[44]. ZnCl2 and Cl: ZnONPs (5 and 10 mg/kg bw) + STZ (60 mg/kg bw) treatment to STZ-induced diabetic rats are shown in Table 4. The results show significantly (P≤0.05) increased in retina SOD activity (16.29,21.95 U/ml), (17.15,24.12 U/ml) after treatment with (5 and 10 mg/kg bw), respectively for 72h than PC group (11.31 U/ml). ZON treatment increased serum SOD and catalase activity, suggesting antioxidant effects [34].

Table 3: Effect of ZnCl2 and Cl:ZnONPs (5 and 10 mg/Kg bw) on retinal F2-isoprostans concentration in diabetic rats.

| Time   | F2-isoprostans (pg/ml) | 0h     | 24h     | 48h     | 72h     |
|--------|------------------------|--------|---------|---------|---------|
|        |                        |        |         |         |         |
| G1 (NC)| 0.2776±0.001           | 0.2750±0.000 | 0.2762±0.001 | 0.2762±0.001 |
| G2 (PC)| 0.2766±0.002           | 0.5622±0.003 | 0.6622±0.003 | 0.7162±0.003 |
| G3     | 0.3250±0.002           | 0.3620±0.003 | 0.3652±0.001 | 0.3282±0.003 |
| G4     | 0.2762±0.002           | 0.3044±0.002 | 0.3038±0.001 | 0.3048±0.002 |
| G5     | 0.2774±0.001           | 0.2942±0.002 | 0.2956±0.001 | 0.2952±0.001 |
| G6     | 0.2748±0.001           | 0.2724±0.002 | 0.2760±0.001 | 0.2764±0.001 |
| LSD    | 0.004                  | 0.006   | 0.005   | 0.006   |

G1 (NC) = Negative control, G2 (PC) = positive control, G3 = STZ + ZnCl2 (5mg/kg bw), G4 = STZ + Cl: ZnONPs (5mg/kg bw), G5 = STZ + ZnCl2 (10mg/kg bw), G6 = STZ + Cl: ZnONPs (10mg/kg bw)

Table 4: Effect of ZnCl2, Effect of ZnCl2 and and Cl: ZnONPs (5 and 10mg/Kg bw) on retinal SOD concentration in diabetic rats.

| Time   | SOD (U/ml) | 0h    | 24h    | 48h    | 72h    |
|--------|------------|-------|--------|--------|--------|
|        |            |       |        |        |        |
| G1 (NC)| 25.56±0.2  | 25.36±0.2 | 25.24±0.17 | 25.09±0.03 |
| G2 (PC)| 25.36±0.17 | 20.19±0.03 | 14.22±0.02 | 11.31±0.17 |
| G3     | 25.08±0.07 | 21.04±0.02 | 17.63±0.08 | 16.29±0.11 |
| G4     | 25.17±0.05 | 22.47±0.04 | 19.32±0.04 | 21.95±0.15 |
| G5     | 24.93±0.13 | 21.81±0.12 | 18.94±0.05 | 17.15±0.09 |
| G6     | 24.82±0.14 | 24.38±0.23 | 23.57±0.23 | 24.12±0.02 |
| LSD    | 0.399      | 0.392 | 0.360  | 0.320  |

G1 (NC) = Negative control, G2 (PC) = positive control, G3 = STZ + ZnCl2 (5mg/kg bw), G4 = STZ + Cl: ZnONPs (5mg/kg bw), G5 = STZ + ZnCl2 (10mg/kg bw), G6 = STZ + Cl: ZnONPs (10mg/kg bw)
Conclusion

Based on our results, we can conclude that ZnCl₂ and Cl: ZnONPs lead to activation of insulin mechanism of action and induction of its synthesis. Cl: ZnONPs + STZ increased SOD and decreased F₂-Isop activites significantly (P ≤ 0.05). Furthermore, the results elucidated the beneficial effects of high dose of Cl: ZNOnPs gave the best results protection retinal against oxidative stress and controlling hyperglycemia.

Acknowledgement

The author is grateful for the assistance of the Field Crop Technology Research Department, Food Technology Research Institute, Agricultural Research Center, Giza, Egypt. We gratefully acknowledge the assistance of the animal house of Ophthalmology Research Institute, Giza, Egypt.

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ISSN: 2574-1241
DOI: 10.26717/BJSTR.2020.30.004995
Soheir N Abd El-Rahman, Biomed J Sci & Tech Res

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