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Ameliorative Effects of Curcumin-Zinc Oxide Nanoparticles Conjugate on Cyclophosphamide-Induced Infertility in Male Rats

Khalifa E. Ahmad[1], Reda M. Abd El-Aziz[2*] and Mahran M. Abd El-Emam[1]
[1]Biochemistry Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt
[2]Physiology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt

Abstract

The present study aimed to investigate the ameliorative effects of Curcumin-ZnO NPs conjugate on testicular tissue damage induced by the anticancer cyclophosphamide. Seventy adult male albino rats weighing 150±15g were used in this study; 10 of them served as a control and 60 rats were intraperitoneal injected with cyclophosphamide at a dose of 30 mg/kg BW every other alternative day for 14 days. They were subdivided into CP group, CP + Curcumin NPs (15 mg/kg B.W), CP + ZnO NPs (10 mg/kg B.W), CP + Curcumin-ZnO NPs conjugate (10 mg/kg B.W), CP + Curcumin-ZnO NPs conjugate (15 mg/kg BW) and CP + Curcumin-ZnO NPs conjugate (20 mg/kg B.W) group. All treatments were given for 30 days. The results reported that curcumin- ZnO NPs conjugate treatment at doses of 15 and 20 mg/kg BW exhibited significant increase in sperm motility percent, sperm count, testicular antioxidant enzymes activities and serum testosterone and FSH levels and significant decrease in sperm abnormalities percent compared to cyclophosphamide treated rats. It was concluded that curcumin- ZnO NPs conjugate at doses of 15 and 20 mg/kg B.W ameliorate the testicular tissue damage induced by the anticancer cyclophosphamide.

Keywords: Cyclophosphamide, Curcumin-ZnO, NPs Conjugate, Oxidative Stress, Rat Testes.

Introduction

The infertility affected 10-15% of population. Researchers showed that 40-50% of human infertility is attributed to male factors [1]. Oxidative stress (OS) becomes the focus of interest as an important cause of male infertility [2]. It is produced as a result of an imbalance between generation and neutralization of reactive oxygen species (ROS) and reactive nitrogen species (RNS) so that the antioxidant capacity of a cell is disrupted [3]. Cyclophosphamide (CP) is one of the most efficient anticancer agents for treating malignant and non-malignant diseases [4]. Gonadal toxicity has become one of the most important long-term side effects of both men and women treated with CP [5].

Nanotechnology permits the use of materials at nanoscale level (1–100 nm), which allows precision engineering to control physicochemical properties of nanoparticles (NPs) and their interactions with biological systems [6]. NPs conjugated with anti-oxidative bio-molecules can be designed to neutralize ROS in order to manage OS of cell [7]. Curcumin is an important natural phytochemical compound found in turmeric. The antioxidant activity of curcumin is well emphasized. It decreases OS in the cells by reducing lipid peroxidation and enhancing cellular antioxidant enzymes [8]. However, low aqueous solubility and poor bioavailability are the major disadvantage of curcumin. To overcome this disadvantage, curcumin NPs makes it more bioavailable and biodegradable materials [9]. Zinc oxide nanoparticles (ZnO NPs) are able to protect cell membrane integrity against OS injury, enhance antioxidant enzymes activity, decrease malondialdehyde (MDA) concentration in tissues and reduce the levels of free radicals [10]. Thus, this study was conducted to investigate the ameliorative effects of Curcumin-ZnO NPs conjugate on testicular tissue damage induced by cyclophosphamide.

Material and methods

Animals, samples collection and biochemical determinations

Seventy adult male albino rats aged 8 weeks were purchased from Laboratory Animal Farm, Faculty of Veterinary Medicine,

***Corresponding author email: (redaabdelazziz81@yahoo.com), Physiology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt**

Zagazig University. They weighed 150±15g at the beginning of the experiment. Rats were fed a standard rat pellet diet and freely accessed water. After two weeks of acclimatization, 10 of them were served as a control, while the others (60 rats) were injected intraperoteneally (IP) with cyclophosphamide (CP; Sigma Aldrich) at a dose of 30 mg/kg BW every alternative day for 14 days. The 60 rats were subdivided into CP group, CP + Curcumin NPs (15 mg/kg BW; NanoTech Egypt for Photo-Electronics), CP + ZnO NPs (10 mg/kg BW; NanoTech Egypt for Photo-Electronics), CP + Curcumin-ZnO NPs conjugate (10 mg/kg BW), CP + Curcumin-ZnO NPs conjugate (15 mg/kg B.W) and CP + Curcumin-ZnO NPs conjugate (20 mg/kg BW) group. All treatments were given for 30 days. Blood samples were collected without anticoagulant to obtain sera. One testis from each rat was immediately removed and kept in deep freezer (-20^{o}C) for further homogenization. The tail of epididymis of one testis was removed and transferred to sterilized Petri dish in 2 mL warm saline at 37 °C, and macerated by sterilized scissor to obtain the epididymal content in suspension that handled exactly as semen [11]. Lipid peroxidation marker (L-Malondialdehyde) concentration [12], catalase enzyme activity, superoxide dismutase activity [13] and reduced glutathione concentration [14] were estimated.

Hormonal analysis

Serum testosterone, luteinizing hormone and follicle stimulating hormone levels were appraised using an enzyme-linked immunosorbent assay (ELISA) with commercial kits, according to manufacturer's instructions.

Statistical analysis.

The obtained data were analyzed by one-way analysis of variance (ANOVA) using SPSS version 20. Data presented as means ±SE (N=10). Duncan's test was applied for comparing between means. Statistical significance was set at $p < 0.05$.

Results

The obtained results revealed significant decrease in sperm motility percent and sperm count in rats administered CP at a dose of 30 mg/kg BW every alternative day for 14 days when compared with the control group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate (10, 15 and 20 mg/kg BW) significantly increased sperm motility percent when compared with CP group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate (15 and 20 mg/kg BW) resulted in a significant increase in sperm cell concentration when compared with CP group, while administration of Curcumin-ZnO NPs conjugate at a dose of 10 mg/kg BW resulted in non significant increase in sperm count when compared with CP group. Sperm abnormalities showed significant increase in rats administered CP at a dose of 30 mg/kg BW every alternative day for 14 days when compared with the control group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate (15 and 20 mg/kg BW) were significantly decrease sperm abnormalities than CP group, while administration of Curcumin-ZnO NPs conjugate at a dose of 10 mg/kg BW resulted in a non significant decrease in sperm abnormalities than CP group (Table 1).

Table 1: Effect of Curcumin and/or Zinc oxide nanoparticles (ZnO NPs) conjugate (10, 15 and 20 mg/kg BW) on sperm characteristics (Means ±SE).

Groups	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Sperm motility (%)	85±2.89^{a}	33±3.33^{e}	67±1.66^{bc}	65±2.89^{c}	55±2.89^{d}	70±2.89^{bc}	75±2.89^{b}
Sperm count (Sp.cc/mL)	85±2.89^{a}	13.67±0.33^{c}	56±0.58^{b}	56±1.73^{b}	21±0.58^{c}	57.33±0.33^{b}	80±5.78^{a}
Abnormalities (%)	4.47±1.90^{c}	29.39±3.64^{a}	11.62±0.63^{b}	13.38±0.10^{b}	23.60±2.08^{a}	11.17±0.64^{b}	8.77±0.02^{bc}

Group 1: control group; group 2: injected (IP) with cyclophosphamide (CP) at a dose of 30 mg/kg BW every other day for 14 days. Group 3: injected IP with CP + Curcumin NPs (15 mg/kg BW); Group 4: injected IP with CP + ZnO NPs (10 mg/kg BW); Group 5: injected IP with CP + Curcumin-ZnO NPs conjugate (10 mg/kg BW); Group 6: injected IP with CP + Curcumin-ZnO NPs conjugate (15 mg/kg BW); Group 7: injected IP with CP + Curcumin-ZnO NPs conjugate (20 mg/kg BW). All treatments were administrated for 30 days. Means within the same raw carrying different superscript letters were significantly different at ($p<0.05$).

The data revealed a significant decrease in catalase activity in rats administered CP I.P at a dose of 30 mg/kg BW every alternative day for 14 days when compared with the control group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate (15 and 20 mg/kg BW) resulted in a significant ($p<0.05$) increase in catalase activity than CP group, while administration of Curcumin-ZnO NPs conjugate at a dose of 10 mg/kg BW resulted in a non significant increase in catalase activity than CP group. Superoxide dismutase activities activity and GSH concentration showed significant decrease in rats administered CP I.P at a dose of 30 mg/kg BW every alternative day for 14 days when compared with the control group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate (10, 15 and 20 mg/kg BW) resulted in significant increase in SOD activity and GSH concentration than CP group. Malondialdhyde concentration showed significant increase in rats administered CP I.P at a dose of 30 mg/kg BW every alternative day for 14 days when compared with the control group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate (10, 15 and 20 mg/kg BW) resulted in significant decrease in MDA concentration than CP group (Table 2).

Table 2: Effect Effect of Curcumin and/or Zinc oxide nanoparticles (ZnO NPs) conjugate (10, 15 and 20 mg/kg BW) on catalase activity, SOD activity, GSH and MDA concentration in testicular tissue (Means±SE).

Groups	Group2	Group2	Group3	Group 4	Group 5	Group 6	Group7
Catalase activity (mmoL/g)	21.67 ± 1.20^{a}	15.00 ± 1.44^{d}	19.33 ± 0.73^{ab}	18.33 ± 0.60^{bc}	16.33 ± 0.44^{cd}	21.00 ± 0.58^{ab}	21.50 ± 0.29^{a}
SOD activity (unit/g)[1]	93.33 ± 0.88^{a}	60.63 ± 0.32^{f}	80.60 ± 0.30^{c}	76.67 ± 0.88^{d}	70.60 ± 0.30^{e}	86.23 ± 0.39^{b}	91.57 ± 0.87^{a}
GSH conc (mg/g)[2]	33.33 ± 0.33^{a}	10.40 ± 0.87^{f}	20.00 ± 1.15^{d}	18.00 ± 1.15^{de}	16.33 ± 0.35^{e}	27.33 ± 0.33^{c}	30.00 ± 1.00^{b}
MDA conc (nmoL/g)[3]	29.00 ± 2.31^{e}	65.00 ± 2.89^{a}	36.00 ± 0.58^{cd}	37.33 ± 1.45^{c}	45.50 ± 0.29^{b}	35.00 ± 0.58^{cd}	31.17 ± 2.31^{de}

Group 1: control group; group 2: injected (IP) with cyclophosphamide (CP) at a dose of 30 mg/kg BW every other day for 14 days. Group 3: injected IP with CP + Curcumin NPs (15 mg/kg BW); Group 4: injected IP with CP + ZnO NPs (10 mg/kg BW); Group 5: injected IP with CP + Curcumin-ZnO NPs conjugate (10 mg/kg BW); Group 6: injected IP with CP + Curcumin-ZnO NPs conjugate (15 mg/kg BW); Group 7: injected IP with CP + Curcumin-ZnO NPs conjugate (20 mg/kg BW). All treatments were administrated for 30 days. [1]SOD activity: superoxide dismutase activities concentration; [2]GSH conc: Glutathione concentration and [3]MDA conc: malondialdhyde concentration.

Means within the same raw carrying different superscript letters were significantly different at ($p<0.05$).

The obtained results revealed a significant decrease in testosterone hormone and FSH levels in rats administered CP at a dose of 30 mg/kg BW every alternative day for 14 days compared with the control group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate (15 and 20 mg/kg BW) significantly increase the testosterone hormone and FSH levels than CP group, while administration of Curcumin-ZnO NPs conjugate at a dose of 10 mg/kg BW resulted in non significant increase in testosterone hormone and FSH levels when compared with CP group. luteinizing hormone level showed significant decrease in rats administered CP at a dose of 30 mg/kg BW every alternative day for 14 days when compared with the control group. Administration of Curcumin NPs, ZnO NPs and Curcumin-ZnO NPs conjugate resulted in non significant increase in LH level when compared with CP group (Table 3).

Table 3: Effect of Curcumin and/or Zinc oxide nanoparticles (ZnO NPs) conjugate (10, 15 and 20 mg/kg BW) on serum reproductive hormones (FSH, LH and testosterone).

Groups	Group1	Group 2	Group3	Group4	Group5	Group 6	Group 7
Testosterone level (pg/mL)	4.55 ± 0.03^{a}	0.75 ± 0.03^{c}	3.00 ± 0.29^{b}	2.50 ± 0.55^{b}	0.88 ± 0.05^{c}	3.09 ± 0.35^{b}	3.29 ± 0.46^{b}
LH level (mlU/mL)[1]	2.10 ± 0.05^{a}	1.50 ± 0.29^{b}	1.67 ± 0.12^{ab}	1.67 ± 0.12^{ab}	1.63 ± 0.14^{ab}	1.80 ± 0.11^{ab}	1.90 ± 0.05^{ab}
FSH level (mlU/mL)[2]	0.80 ± 0.11^{a}	0.06 ± 0.33^{c}	0.30 ± 0.06^{bc}	0.30 ± 0.06^{bc}	0.20 ± 0.06^{bc}	0.40 ± 0.06^{b}	0.70 ± 0.3^{a}

Group 1: control group; group 2: injected (IP) with cyclophosphamide (CP) at a dose of 30 mg/kg BW every other day for 14 days. Group 3: injected IP with CP + Curcumin NPs (15 mg/kg BW); Group 4: injected IP with CP + ZnO NPs (10 mg/kg BW); Group 5: injected IP with CP + Curcumin-ZnO NPs conjugate (10 mg/kg BW); Group 6: injected IP with CP + Curcumin-ZnO NPs conjugate (15 mg/kg BW); Group 7: injected IP with CP + Curcumin-ZnO NPs conjugate (20 mg/kg BW). All treatments were administrated for 30 days. LH level: luteinizing hormone and [2]FSH level: follicle stimulating hormone.
Means within the same raw carrying different superscript letters were significantly different at ($p<0.05$)

Discussion

The reduction in sperm parameter which occurred in our study by CP supported by Ateşşahin *et al.* [18], who recorded that administration of CP decreased epididymal sperm concentration and motility [19]. The current results revealed that administration of Curcumin NPs significantly improved the sperm parameters compared with CP group, which supported by Masuda *et al.* [20] who concluded that Curcumin has an effective antioxidant character with unique conjugated structure, containing two methoxylated phenols and enol form of diketone. This structure of curcumin has typical radical trapping property as a chain-breaking antioxidant. The trapping ability of Curcumin protects sperms from free radicals and increase motility percent and viability. Rats treated with ZnO NPs showed significant increase in sperm count and motility with significant decrease of sperm abnormalities when compared with CP group. ZnO NPs administration resulted in increase sperm motility than CP group that confirmed by Afifi and Abdelazim [21], who recorded that treatment of the diabetic rats with ZnO NPs alone or in combination with insulin prevented the damage in sperm count and motility which may be attributed to the antioxidant characters of ZnO NPs. Administration of Curcumin-ZnO NPs conjugate at a dose of 15 and 20 mg/kg BW significantly increase sperm motility and count with significantly decrease abnormalities when compared with CP group.

The OS induced by CP in testicular tissue of treated rats in this study was agreed with that previously demonstrated by Abraham and Rabi [22] and Nitharwal *et al.* [23] who concluded that exposure of rats to CP can disrupt the reduction–oxidation (redox) balance in the tissues leading to oxidative stress. Our results are comparable with Ilbey *et al*. [24] who reported that treatment with the anticancer CP resulted in elevated levels of MDA due to the excessive generation of free radicals and reduced levels of GSH, CAT and SOD activities in testis. In the present study, the activities of SOD and CAT decreased in CP treated rats as reported earlier by Senthilkumar *et al.* [25] which could be due to inactivation of the cellular antioxidants by the lipid peroxides and ROS that are produced due to CP intoxication.

Administration of Curcumin NPs resulted in a significant increase in CAT and SOD activities, GSH concentration with significant decrease in MDA concentration when compared with CP treated rats. These results were strengthened by Manikandana *et al.* [26] who found that Curcumin decreased the levels of free radicals due to its free radical scavenging activity, increasing the levels detoxification enzymes and its protective action against degenerative diseases. ZnO NPs also significantly increased the antioxidant capacity in testicular tissue when compared with CP-injected group. These results explained by Badkoobeh *et al.* [27] who concluded that ZnO NPs have the ability to protect the integrity of cell membrane against

OS damage, increase the levels of antioxidant enzyme, and decrease MDA level. It can enhance the antioxidant activity, increase the activities of antioxidases and decrease free radicals levels [28]. Administration of Curcumin-ZnO NPs conjugate at a dose of 10, 15 and 20 mg/kg BW produced significant increase in SOD activity and GSH concentration with significant decrease in the concentration of MDA in testicular tissue when compared with CP group. On the other hand, administration of Curcumin-ZnO NPs conjugate at a dose of 15 and 20 mg/kg BW significantly increase the catalase activity than CP group, while Curcumin-ZnO NPs conjugate (10 mg/kg BW) administrated rats showed non significant increase in catalase activity when compared with CP group. The combined effect of Curcumin and ZnO NPs may be the improvement of antioxidant activity and decreasing MDA concentration in testicular tissue in Curcumin-ZnO NPs conjugate.

The current finding revealed that Curcumin NPs-administered rats had significant increase in serum testosterone level, with non-significant increase in serum FSH and LH level when compared with CP group. These results were strengthened by Salama and El-Bahr [29]. Administration of ZnO NPs produced a significant increase in serum testosterone level while non-significant increase in serum FSH and LH level than CP group. ZnO NPs increase serum reproductive hormones level because Zn increased the releasing of LH and FSH from the pituitary gland, which stimulate testosterone production. Zn also inhibits the aromatase enzyme that converts testosterone into excess estrogen [30]. Administration of Curcumin-ZnO NPs conjugate at a dose of 15 and 20 mg/kg BW showed significant increase in testosterone and FSH level when compared with CP group, while Curcumin-ZnO NPs conjugate (10 mg/kg BW) administrated rats showed non significant increase in testosterone hormone and FSH levels when compared with CP group.

Conclusion

The presented results settled that curcumin-ZnO NPs conjugate at doses of 15 and 20 mg/kg BW ameliorated the testicular tissue damage induced by the anticancer cyclophosphamide.

Conflict of interest

The authors declare that they have no conflict of interest.

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الملخص العربي

التأثيرات التحسينية لجزيئات الكركومين النانوية المقترنة بجزيئات أوكسيد الزنك النانوية لنقص الخصوبة الناتج عن السيكلوفوسفاميد فى ذكور الجرذان

خليفة الضوي[١]،رضا عبدالعزيز[٢*]، مهران عبدالامام[٣]

[١]قسم الكيمياء الحيوية- كلية الطب البيطري- جامعة الزقازيق

[٢]قسم الفسيولوجيا- كلية الطب البيطري- جامعة الزقازيق

في محاولة للتحقق من التأثيرات التحسينية لجزيئات الكركومين النانوية المقترنة بجزيئات أوكسيد الزنك النانوية لتلف نسيج الخصية الذى يسببه عقار السيكلوفوسفاميد المضاد للسرطان. ٧٠ من ذكور الجرذان البالغة متوسط أوزانها١٥٠± ١٥ جرام تم استخدامها في هذه الدراسة. ١٠ جرذان منها تم الاحتفاظ بها كمجموعة ضابطة و٦٠ جرذا تم حقنها عن طريق الحقن البروتوني بعقار السيكلوفوسفاميد (٣٠ مجم/كجم من وزن الجسم) كل يوم بديل أخر لمده ١٤يوما. تم تقسيم الجرذان المحقونة بعقار السيكلوفوسفاميد الى ٦ مجموعات كالتالي: مجموعة السيكلوفوسفاميد, مجموعة السيكلوفوسفاميد + جزيئات الكركومين النانوية (١٥ مجم/كجم من وزن الجسم), مجموعة السيكلوفوسفاميد + جزيئات أوكسيد الزنك النانويه (١٠ مجم/كجم من وزن الجسم), مجموعة السيكلوفوسفاميد + جزيئات الكركومين النانوية المقترنة بجزيئات أوكسيد الزنك النانوية (١٠ مجم/كجم من وزن الجسم), مجموعة السيكلوفوسفاميد + جزيئات الكركومين النانوية المقترنة بجزيئات أوكسيد الزنك النانوية (١٥ مجم/كجم من وزن الجسم), مجموعة السيكلوفوسفاميد + جزيئات الكركومين النانوية المقترنة بجزيئات أوكسيد الزنك النانوية (٢٠ مجم/كجم من وزن الجسم). أعطيت جميع العلاجات لمدة شهر. وأظهرت النتائج أن تناول الجرذان لجزيئات الكركومين النانوية المقترنة بجزيئات أوكسيد الزنك النانوية بجرعات ١٥ و٢٠ مجم/كجم من وزن الجسم أدى إلى زيادة ملحوظة فى نسبة الحركة و عدد الحيوانات المنوية ونشاط الانزيمات المضادة للأكسدة في نسيج الخصية ومستويات هرمون التستوستيرون وهرمون FSH فى مصل الدم و إنخفاض ملحوظ فى تشوهات الحيوانات المنوية مقارنة بمجموعة السيكلوفوسفاميد. لقد خلصت الدراسة الى أن استخدام جزيئات الكركومين النانوية المقترنة بجزيئات أوكسيد الزنك النانوية بجرعات ١٥ و٢٠ مجم/كجم من وزن الجسم يخفف بفاعلية من ضرر خصية الجرذان الذى يسببه عقار السيكلوفوسفاميد.