Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES
January 2023, Volume 17, Number 1

Research Paper

Curcumin Ameliorates Sertraline-mediated Testicular Toxicity in Rats via Inhibition of Oxidative Stress

Ali Louei Monfared[1*], Shahnaz Yousefizadeh[2]

1. Department of Histology and Bacteriology, School of Para-Veterinary Medicine, Ilam University. Ilam, Iran.
2. Department of Laboratory and Clinical Sciences, School of Para-Veterinary Medicine, Ilam University. Ilam, Iran.

Use your device to scan and read the article online

How to cite this paper Louei Monfared A & Yousefizadeh S. Curcumin Ameliorates S ertraline-mediated Testicular Toxicity in Rats via Inhibition of Oxidative Stress. Iranian Journal of Toxicology. 2023; 17(1):25-34. http://dx.doi.org/10.32598/IJT.17.1.977.1

http://dx.doi.org/10.32598/IJT.17.1.977.1

Article info:
Received: 26 May 2022
Accepted: 16 Oct 2022
Online Published: 01 Jan 2023

*** Corresponding author:**
Ali Louei Monfared, PhD.
Address: *Department of Histology and Bacteriology, School of Para-veterinary Medicine, Ilam University. Ilam, Iran.*
E-mail: *a.loueimonfared@ilam.ac.ir*

ABSTRACT

Background: Sertraline is prescribed mainly for the treatment of patients with depression. However, this drug is known to have toxic effects on the male germ cells. Therefore, this study was designed to examine the ameliorative effects of curcumin on the sertraline-induced male reproductive toxicity.

Methods: Thirty-two male Wistar rats were randomly divided into four groups of eight each. The first group served as the control and received only tap water orally. The second group was given sertraline orally at 20 mg/kg. The third group received sertraline at the same dose plus an oral dose of curcumin at 100 mg/kg. The fourth group served as a positive control, which was given curcumin at 100 mg/kg. All treatments were given once daily over 42 consecutive days.

Results: Sertraline exerted testicular toxicity mainly by triggering oxidative stress, resulting in adverse degenerative and atrophic alterations in the seminiferous tubules. Further, the rats' testosterone and luteinizing hormone levels in the serum declined significantly in the sertraline group compared to those of the controls. Curcumin combined with sertraline, mitigated almost all of the histological abnormalities and significantly inhibited the oxidative stress by restoring the antioxidant levels in the testicular tissue. Also, in the combined group, the serum testosterone level significantly increased compared to that of the controls. Lastly, curcumin alone had no adverse effect on any of the examined parameters, similarly to the controls.

Conclusion: We found that curcumin played an ameliorative role in the sertraline-mediated testicular injury in male Wistar rats through its considerable anti-oxidant property.

Keywords: Curcumin, Oxidative stress, Sertraline, Testis, Rat

Introduction

Antidepressant medications are frequently prescribed in the management of patients with depression and anxiety, both in the short- and long-term. Currently, the mostly prescribed drugs for depressive disorders are selective serotonin reuptake inhibitors (SSRI), as the first-line of treatment [1, 2]. Using SSRI, the concentration of serotonin in the synaptic cleft is increased, leading to improvement in the depressive symptoms [3]. Sertraline (SRT) is one of the SSRI drugs prescribed mainly for the treatment of neurological deficits, such as psychotic depression, obsessive-compulsive disorder and anxiety [4]. Moreover, recent investigations support the notion that SRT controls neoplastic conditions because of its chemotherapeutic property [5].

Despite its remarkable efficacy, a recent study has shown that exposure to SRT has toxic effects on the male germ cells, inducing a state of compensatory hypogonadism [6]. Also, another study has suggested that treatment with antidepressant drugs induces oxidative stress. Thus, the resultant oxidative stress may alter the antioxidant enzyme activities, causing testicular toxicity. This can include DNA damage, abnormal sperm morphology, and histopathological outcomes [7]. Further, it is now known that many SSRI drugs, such as SRT, might cause deficits in the testicular tissue structure and function. The structural alterations along with dysfunction in the hypothalamic-pituitary-gonadal axis, as the endocrine controllers of male reproductive system, result in the sperm loss and male infertility during juvenile and puberty periods [8]. In addition, the male infertility has been associated with the oxidative stress with detrimental impacts on the sperm profile and fertility rate [9].

Since male reproductive function is likely to be affected by exposure to SRT, it is crucial to investigate appropriate agents that reduce its side effects. Also, since it has been shown that SRT exerts its deleterious effects in the testis by triggering oxidative stress [2, 7, 10], administration of antioxidant agents could potentially protect the testicular cells against the side effects of this drug. Curcumin (CUR), as a bioactive phytochemical in the rhizome of turmeric plant, is used mainly as a spice for its flavor and to add yellowish color to popular foods in many countries. Also, CUR is considered a free-radical scavenger and a powerful antioxidant. In recent years, there have been numerous investigations on its potential therapeutic and prophylactic effects against various toxicants [11, 12]. Further, CUR has been proposed to have tissue protective effects, which alleviate the oxidative stress caused by the toxicity from many compounds in experimental animals [13, 14]. Testicular cells are the most susceptible to oxidative damage [15], due to their high cell division rate, mitochondrial oxygen consumption, and containing a high level of polyunsaturated fatty acids in their cell membranes. In addition, oxidative stress has been linked to the pathophysiology of impaired spermatogenesis and increased sperm cell apoptosis, secondary to disruption in the cell cycle [16].

Aim of the study: Given the above facts, the aim of the present study was to assess the impacts of rat's exposure to SRT on the testicular structure and function of the putative oxidative stress induction, and to investigate whether these effects may be ameliorated by treatment with curcumin.

Materials and Methods

Study approval & materials: This study was carried out based on the University's guidelines on the care and use of laboratory animals. Also, the study protocol was reviewed and approved by the institutional Ethics Committee at Ilam University of Medical Sciences (ID Number: IR.ILAM.REC.1400.012). In this study, Sertraline hydrochloride with a chemical formula of $C_{17}H_{18}C_{13}N$, was obtained from Sigma-Aldrich Company (USA). Also, curcumin at 99% purity was purchased from the same supplier. Sertraline and curcumin were dissolved in distilled water and olive oil, respectively, prior to the intended application.

Animals and treatments: Thirty-two male Wistar rats, approximately 7-8 weeks old and weighing 200-215g each, were purchased from the laboratory animal center of the Para-veterinary Medicine College of Ilam University. The animals were maintained under a 12 hours of light-dark cycle at 21±4ºC temperature and humidity of 48%±7%. They had free access to tap water and food ad libitum. After 14 days of acclimatization, the rats were randomly divided into four groups of eight animals each described as follows: a) Control, b) Sertraline (SRT), c) Sertraline plus curcumin (SRT+CUR), and d) curcumin (CUR). The first group served as the control and received tap water orally. The second group was given SRT at 20 mg/kg. The third group was concurrently given SRT (20 mg/kg) and CUR (100 mg/kg) orally. The fourth group served as a positive control and administrated only CUR (100 mg/kg). All treatments were once given daily over a period of 42 consecutive days. The doses of SRT and CUR were selected based on the available references for laboratory animals [7, 17, 18].

Tissue preparation & histological examinations: Twenty-four hours after the last treatment in each group, the rats were euthanized under anesthesia, using 50 mg/kg Ketamine and 5 mg/kg Xylazine. Next, the testicles from each animal were dissected, weighed and maintained in Bouin's fixative solution for 48 hours. The tissue specimens were then dehydrated in ethanol, cleared in Xylene, and embedded in paraffin wax, and then five micron sections were made on a microtome. The samples were stained by hematoxylin and eosin (H&E) method and examined under a light microscope (Olympus, Japan) for signs of histological alterations. For the quantification of the structural changes, the epithelial height and diameter of the seminiferous tubules were measured, using a True Chrom Metrics software (China). For each rat, 100 seminiferous tubules were analyzed [19, 20]. In addition, the numbers of Leydig and Sertoli cells were counted based on the method proposed by two earlier studies [21, 22].

Assessment of antioxidant enzymes activity: To evaluate the oxidative stress, first, a homogenate of the testicular tissue sample was prepared in 50 mmol/L phosphate buffer. Then, it was centrifuged at 3000×g at 4˚C for 15 min. Subsequently, the levels of catalase (CAT), glutathione peroxidase (GPx), malondialdehyde (MDA) and superoxide dismutase (SOD) were determined in the supernatant by an established method [23], using appropriate kits purchased from Nanjing Jiancheng Bioengineering Institute (China).

Assessment of reproductive hormones: For sex hormones analysis, the blood specimens were collected from the right ventricle of the rats' heart. Next, the blood samples were centrifuged at 1000×g and 4˚C for 15 min, and the sera were separated. The levels of serum luteinizing hormone (LH) and testosterone were determined using ELISA commercially available kits, based on the supplier's instructions (Monobind, USA).

Statistical analyses: The resultant data from this study were analyzed for the statistical significances, using SPSS software, version 22, and one-way analysis of variance (ANOVA) followed by Tukey's post hoc test to compare the means among the experimental groups. The mean differences were considered significant at a $P<0.05$.

Results

Histological & histo-morphometrical evaluations: Histological sections from the testes of all groups are shown in Figures 1 and 2. The examination of seminiferous tubules and spermatid cells from the control group showed uniform and normal tissue architecture. The testicular tissue from the SRT group showed abnormal changes, including tubular degeneration and atrophy, exfoliation of the germ cells, and interstitial edema (Figures 1 & 2). Also, there were wide gaps among the neighboring spermatogenic cells. Interstitial congestions were also observed in the testicular tissue samples from the SRT group.

The histological abnormalities were reversed in the SRT+CUR group, compared to those observed in the SRT alone group, although there were slight dilations in the interstitial spaces of the testes in this group. Also, the SRT group showed a statistically significant reduction in the epithelial cells' height and tubular diameter, compared to those of the control group ($P<0.05$, Figures 3A & 3B). Otherwise, the treatment with CUR alone increased the epithelial cell height and tubular diameter of testes insignificantly, compared to those observed in the SRT group. Moreover, the SRT treatment signifi-

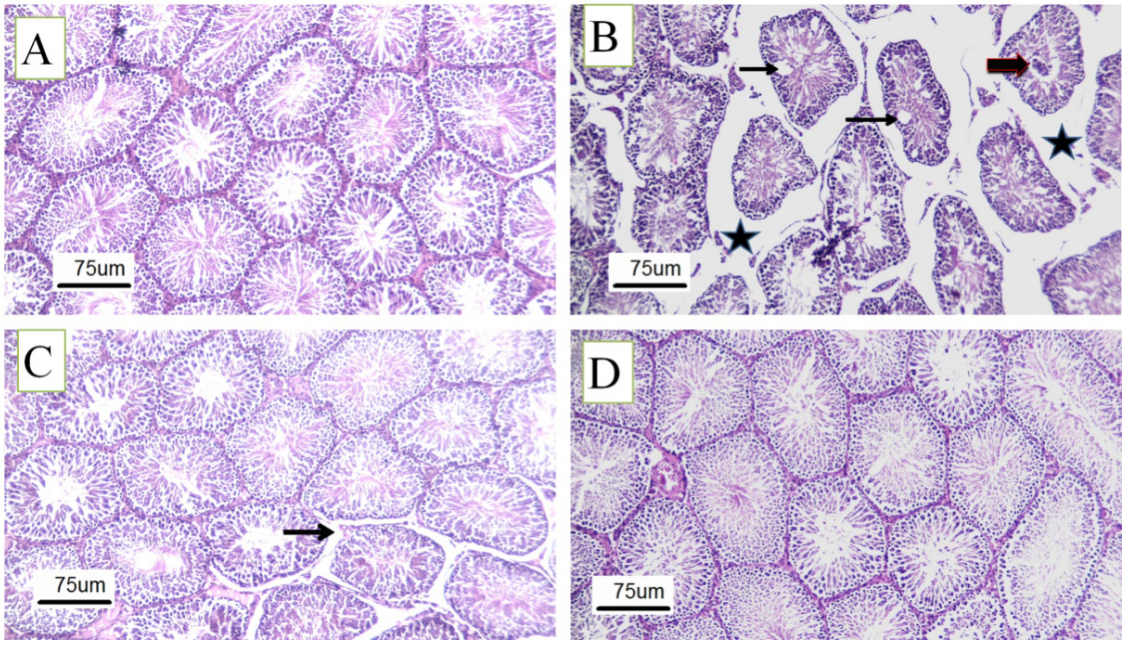

Figure 1. Photomicrographs of sections from seminiferous tubules
A) Control; B) Sertraline treated animals; showingmarked tubular degeneration and atrophy, decreased of the both epithelial height and tubular diameter. Also, wide gaps between neighboring spermatogenic cells (thin arrow), exfoliated germ cells (thick arrow) and interstitial edema (asterisk) are clear; C) Sertraline+curcumin rats: Exhibiting normal epithelial height and tubular diameter, there are yet slight dilation (thin arrow) of interstitial space; D) Curcumin-treated group: Exhibiting typical features of epithelial height and tubular diameter.
Magnification ×100; H&E staining.

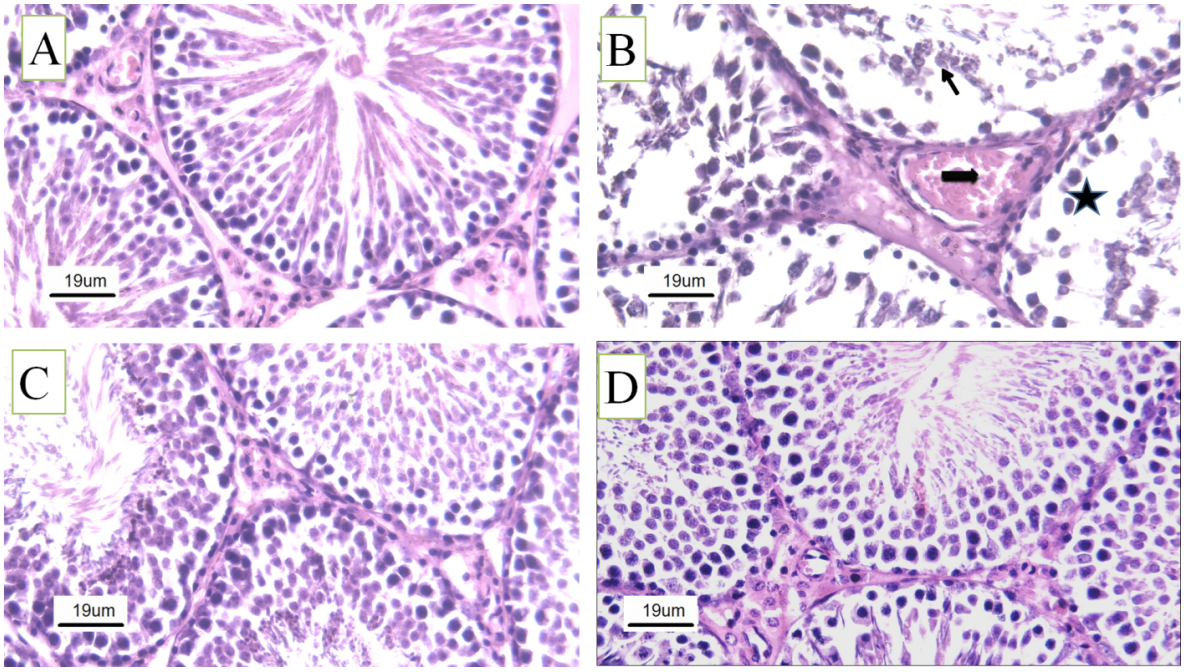

Figure 2. Photomicrograph of sections from seminiferous tubules
A) Control; B) Sertraline-treated rats: Showing testicular tubules contain exfoliated germ cells (thin arrow) with wide gaps (*) among spermatogenic cells as well as congestion of capillaries of interstitial space (thick arrow); C) Sertraline+curcumin group: Showing filled lumen contain compact seminiferous tubules with normal interstitial space; D) Curcumin-treated group: Showing tubules with filled lumen and normal leydig cells apperance in the interstitial space.
Magnification ×400; H&E staining.

cantly decreased the number of Leydig and Sertoli cells, compared to both the controls and SRT+CUR groups (P<0.05; Figures 1-3).

Also, the rats treated with CUR alone showed normal histology of the germinal cells in the testes (Figures 1-3). In the SRT+CUR group, the curcumin treatment remarkably reversed the reduction in the number of Leydig and Sertoli cells compared to those observed in the SRT group (P<0.05). The SRT exposure yielded a significant reduction in the testicular weight, compared to those of the controls (P<0.05; Figure 3A). In the SRT+CUR group, curcumin significantly prevented the decline in the testicular weights compared to those in the SRT group. The animals treated with CUR alone exhibited no significant differences in the testicular weights compared to those of the control group (P<0.05; Figure 3A).

Determination of testicular oxidative stress: The rats treated with SRT showed significant alterations in the antioxidant defense parameters compared to those of the control group. The testicular levels of MDA in the SRT-treated rats were significantly higher than those in the control group (P<0.05). However, in the SRT+CUR group, the CUR presence significantly decreased the testicular MDA levels (P<0.05; Figure 4). However, CUR alone had no statistically significant effect on the testicular MDA level, compared to those of the control group (P<0.05; Figure 4). Compared to rats in the control group, the activities of CAT, GPx and SOD significantly decreased due to exposure to SRT (P<0.05; Figure 4). However, in the SRT+CUR group, the CUR presence significantly increased the testicular levels of CAT and GPx, compared to those treated with SRT alone (P<0.05; Figure 4). Although the SOD levels increased in the SRT+CUR group, it was not significant compared to that observed in the rats treated with SRT alone. The rats treated with CUR alone showed a significant rise in the CAT, GPx and SOD activities compared to those found for the SRT group (P<0.05; Figure 4).

Evaluation of serum reproductive hormones: The hormonal analysis illustrated significant reductions in the serum level of LH in the rats exposed to SRT compared to those of the control group (Figure 5). Although the LH level increased in the SRT+CUR group, it was not significant compared to that in the rats in SRT, control and CUR groups. Also, the level of LH in the rats treated with CUR only was not significantly different from those of the control group (Figure 5). The mean serum level of testosterone was significantly lower in the SRT group than that of the control group. Also, the

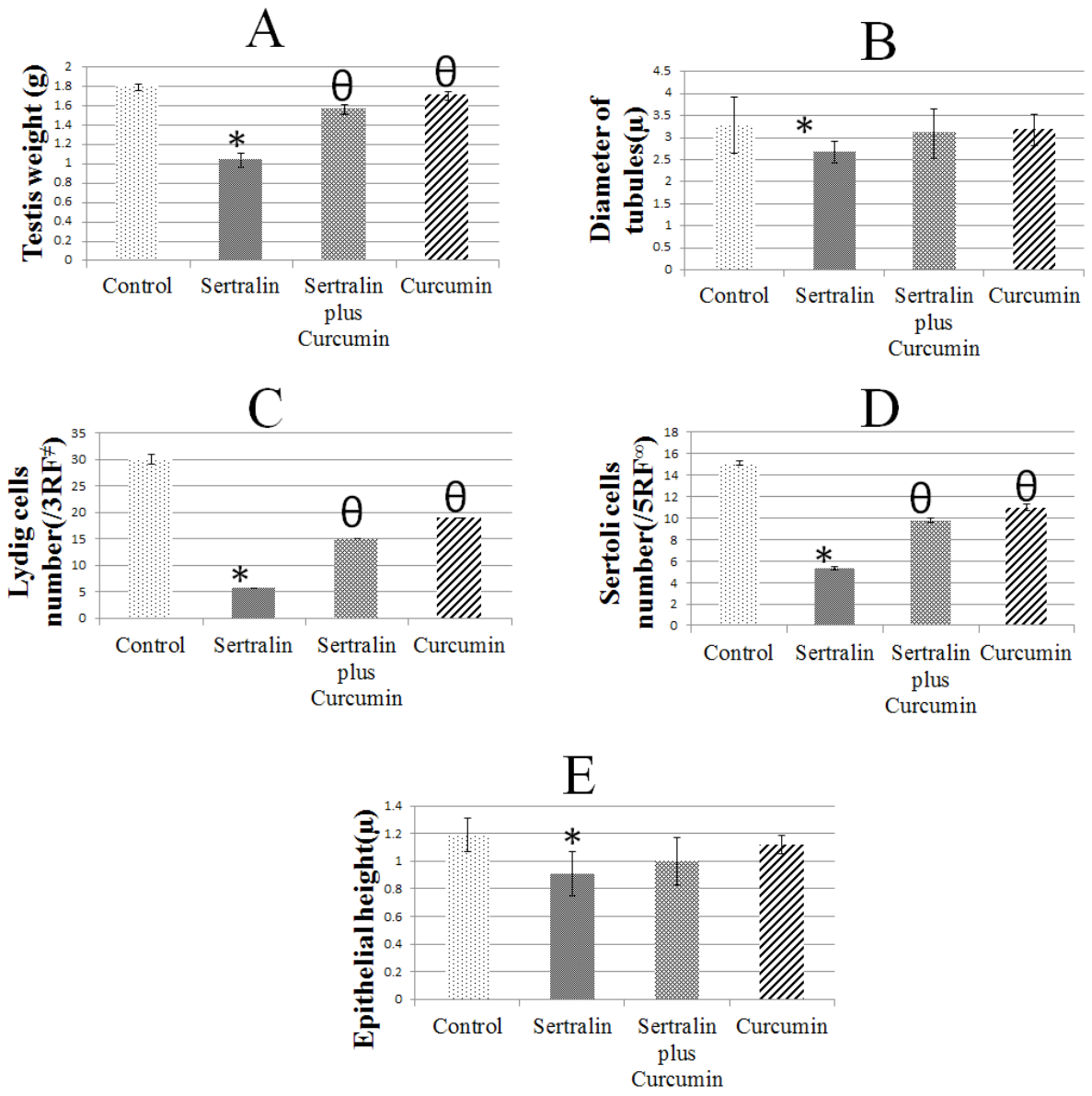

Figure 3. Levels of testicular weight (A) and histomorphometric indices (B-E) in rats exposed to sertralineand curcumin. Data are presented as Means±SD.

*Significant change compared to the control rats; θSignificant change compared to the sertraline-treated rats. Means without symbles do not differ significantly. ≠3RF: Three randomly selected choicesof microscopic fields, ∝5RF: Five randomly selected choicesof microscopic fields.

CUR+SRT treatment resulted in a significant increase in the testosterone level compared to the rats treated with SRT alone ($P<0.05$; Figure 5). The rats treated with CUR alone showed a significant rise in the serum testosterone level compared to that of the SRT group ($P<0.05$; Figure 5).

Discussion

Sertraline, one of the SSRIs, is prescribed mainly for the treatment of depression in humans. However in recent years, several studies have shown that SSRI drugs lead to testicular impairment and sexual dysfunction, although the precise underlying mechanisms are not fully understood [2, 7]. Therefore, we planned the present study to investigate the potential mechanism involved

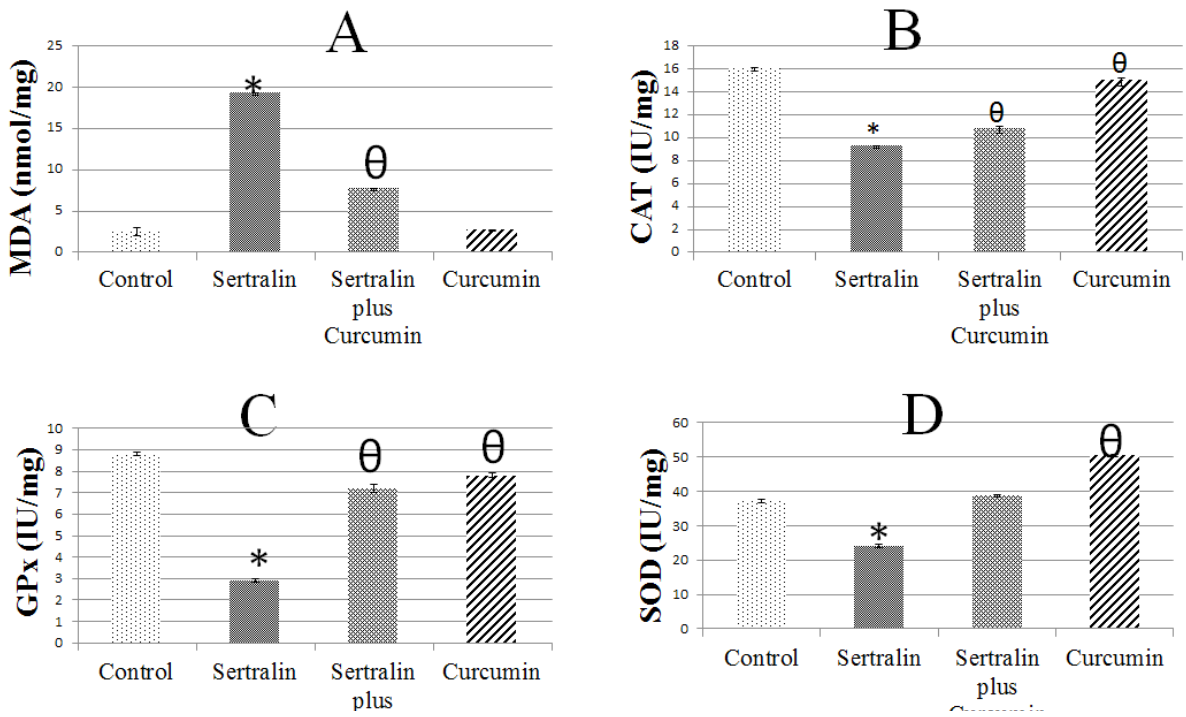

Figure 4. Testicular levels of MDA (A), CAT (B), GPx (C) and SOD (D) in rats exposed to sertralineand curcumin. Data are presented as Mean±SD.

Abbreviations: CAT: Catalase; GPx: Glutathione peroxidase; MDA: Malondialdehyde; SOD: Superoxide dismutase.

*Significant changescompared to the control rats; θSignificant change compared to the sertraline administrated rats. Means without symbles do not differ significantly.

in the SRT toxicity and the ameliorative role of CUR against the testicular toxicity.

Histological findings: Based on our microscopic results, the SRT treatment in the rats caused structural damages to the testes, consistent with the results of a previous study [2]. Based on the majority of the effects found, the lowest observed adverse effect level (LOAEL) for SRT was 20 mg/kg/day over 42 consecutive days. Further, CUR was shown to have ameliorative effect against the SRT-mediated testicular toxicity.

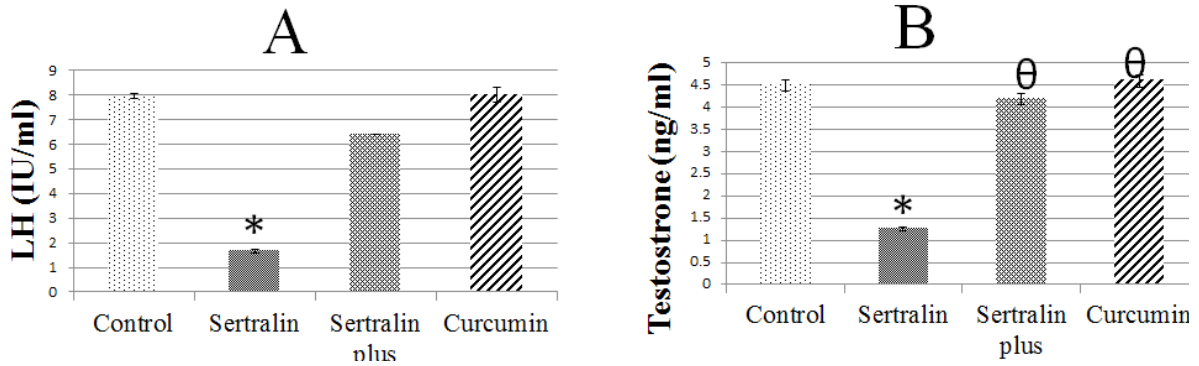

Figure 5. Serum levels of luteinizing hormone (A), and testosterone (B) in the rats exposed to sertraline and curcumin. Data are presented as Mean±SD.

*Significant changescompared to the control rats. θSignificant changescompared to the sertraline-administrated rats. Means without symbles do not differ significantly.

LH: Luteinizing hormone.

Organ weight loss: In the current study, the testicular toxicity of SRT was characterized by a significant decline in the weight of testes, compared to those found for the control rats. Consistent with our results, it has been shown earlier that treating male rats with antidepressant drugs, such as Fluoxetine significantly reduces testicular tissue weight in experimental animals [24]. Since the testes weight is mainly related to changes in the number of germinal cells in the tissue, therefore, the significant weight loss after SRT treatment may be attributed to the resultant testicular hypocellularity and a decline in spermatogenesis [24]. In addition, the significant testicular weight loss is consistent with the degenerative histological observations made in our current study. Conversely, the presence of curcumin considerably reduced the testicular tissue weight loss in the SRT+CUR group compared to those found in the SRT group. Interestingly, a similar observation has been made by an earlier research, using Fluoxetine in rats [21].

Changes in antioxidant enzymes: In this study, it was found that SRT treatment caused a significant increase in the MDA levels despite the reduction in the levels of CAT, GPx and SOD enzymes. These findings indicate that oxidative stress phenomenon may be involved in SRT-mediated testicular toxicity, which is consistent with those reported by a former study [7]. That study found that the SRT-induced testicular toxicity is mediated by a rise in the generation of reactive oxygen species (ROS) with a decline in the glutathione levels [7]. However, another earlier study has reported that SSRI treatment does not lead to a significant alteration in the MDA level [2].

It has been speculated that the reduced levels of antioxidant enzymes in the testicular tissue might lead to a rise in the ROS, which is characterized by a significant increase in the biomarkers of lipids peroxidation. Therefore, as shown in the present study, the remarkable testicular damages found in the SRT group might be associated with the ROS attack against the plasma membranes of spermatid cells, thus leading to disruptions in the testosterone synthesis [2, 7]. Oxidative stress generally occurs due to an imbalance between ROS level and antioxidant contents of the involved cells, running in favor of ROS generation. Therefore, ROS may exert deteriorative effects in the testicular tissue and promote inflammatory processes [25]. Our results clearly demonstrate a significant decline in the MDA levels with a rise in the testicular levels of CAT and GPx enzymes. Thus, the protective effect of CUR against the SRT toxicity in the testes was confirmed by our findings from the oxidative stress assays. In this context, CUR has been suggested as an effective additive in foods to protect against the detrimental effects of such toxins as aflatoxin B_1 [17]. Also, CUR has been known to protect cells against the adverse effects of cadmium on the lipid and protein peroxidation [14].

Effects on sex hormones: In the present study, the protective effects of CUR against SRT toxicity on the testicular tissue were mainly due to its antioxidant features. For instance, the significant reductions in the levels of LH and testosterone in the SRT treated rats were consistent with the observed histological impairments, characterized by a significant decline in the number of germ cells. These results support a previous study on SRT-induced testicular toxicity, in which human subjects were examined at varying ages, from juvenile to puberty [8]. Also, an earlier study has suggested that SRT suppresses the synthesis of LH [26]. Since LH influences the testosterone synthesis in the Leydig cells, it is reasonable to assume that the significant decline in the serum testosterone level is likely due to exposure to SRT.

Putative mechanism of action of curcumin: It has been demonstrated that SRT elevates the serotonin levels in the central nervous system (CNS) [26]. Therefore, the elevation of extracellular serotonin can suppress the biosynthesis of GnRH, and subsequently reduce the gonadotropins biosynthesis [8]. In addition to promoting oxidative stress, another mechanism involved in SRT-induced testicular toxicity might be associated with the disruption of serotonin-mediated hypothalamic-pituitary axis (HPA). In contrast to our findings, a rise in the serum LH level has been reported likely due to the negative feedback from the decreased sex steroids synthesis in the SRT-treated rats [6].

Another mechanism of action for the SSRI-induced testicular toxicity [2] is elevated serotonin level in the synaptic clefts by inhibiting the serotonin reuptake pumps. Excess serotonin can lead to sperm dysfunction, worsen semen parameters and affect the fertility in animals and humans [2]. A former study has reported another putative mechanism, by which SRT inhibits the transcription of special genes that regulate and metabolize steroids, leading to hypogonadism [6]. Conversely, in the rats treated with CUR alone or combined with SRT, the mean serum testosterone and LH levels were higher than those in the SRT group. These results indicate that CUR may have a stimulatory role in activating androgenic enzymes, which promote testosterone biosynthesis. In addition, the compensatory effect of CUR on the morphology and the number of various testicular cells may be due to its proliferative potential as suggested previously [27].

In support of the current study, the protective effect of CUR against testicular toxicity by Fluoxetine has been reported by a former study [27]. The authors of that study proposed that CUR had anti-apoptotic and anti-fibrotic effects [27]. Similarly, supplementation with natural antioxidants, such as wheat germ oil has been shown to prevent the testicular tissue damages caused by Sertraline in rats, likely via inhibiting ROS generation [10]. Considering our experimental results and the facts learned from our literature review, CUR is likely to offer an ameliorative role against SRT-mediated testicular toxicity in rats via its well-known anti-oxidative properties.

Conclusion

Based on our findings, SRT treatment caused significant impairments in both the structural and functional integrities of the rats' testes, which might have affected the reproductive functions. However, these adverse effects could be attenuated by CUR treatment since it boosts the activities of antioxidant defense system. Therefore, natural dietary antioxidants, such as CUR, may protect testicular cells against oxidative stress induced by SRT.

Limitation of the study: The major limitation of this study was the lack of access to an electron microscope and the laboratory to evaluate the fine ultrastructural alterations in the rats' testicular tissue samples.

Recommendation for future studies: Further studies, such as electron microscopic examinations of testicular tissue and identifying potential genes involved in the ameliorative effect of CUR against SRT toxicity, are highly recommended.

Ethical Considerations

Compliance with ethical guidelines

This study was carried out in accordance with the University's guidelines for the care and use of laboratory animals. Also, the protocol was reviewed and approved by the Institutional Ethics Committee and Review Board of Ilam University of Medical Sciences (Code: IR.ILAM.REC.1400.012).

Funding

This study has been supported by a grant from the Research and Technology Management at Ilam University.

Authors' contributions

Conceptualization: Shahnaz Yousefizadeh; Methodology: Ali Louei Monfared and Shahnaz Yousefizadeh; Investigation, writing and editting: Ali Louei Monfared and Shahnaz Yousefizadeh; Data collection: Ali Louei Monfared, Data analysis: Shahnaz Yousefizadeh; Funding acquisition and Resources: Ali Louei Monfared .

Conflict of interest

The authors declareی no conflicts of interests.

Acknowledgements

The authors wish to thank Salman Soltani for his generous assistance with the preparation of histological slides and the light microscopic examinations.

References

[1] Sheehan DV, Mao CG. Paroxetine treatment of generalized anxiety disorder. Psychopharmacology Bulletin. 2003; 37(Suppl):64-75. [PMID]

[2] Erdemir F, Atilgan D, Firat F, Markoc F, Parlaktas BS, Sogut E. The effect of sertraline, paroxetine, fluoxetine and escitalopram on testicular tissue and oxidative stress parameters in rats. International Brazilian Journal of Urology. 2014; 40(1):100-8. [DOI:10.1590/S1677-5538.IBJU.2014.01.15] [PMID]

[3] Lindqvist PG, Nasiell J, Gustafsson LL, Nordstrom L. Selective serotonin reuptake inhibitor use during pregnancy increases the risk of postpartum hemorrhage and anemia: A hospital-based cohort study. Journal of Thrombosis and Haemostasis. 2014; 12(12):1986-92. [DOI:10.1111/jth.12757] [PMID]

[4] Davies SJ, Mulsant BH, Flint AJ, Meyers BS, Rothschild AJ, Whyte EM, et al. SSRI antipsychotic combination in psychotic depression: Sertraline pharmacokinetics in the presence of olanzapine, a brief report from the STOP PD study. Human Psychopharmacology. 2016; 31(3):252-5. [DOI:10.1002/hup.2532] [PMID]

[5] Baú-Carneiro JL, Akemi Guirao Sumida I, Gallon M, Zaleski T, Boia-Ferreira M, Bridi Cavassin F. Sertraline repositioning: An overview of its potential use as a chemotherapeutic agent after four decades of tumor reversal studies. Translational Oncology. 2022; 16:101303. [PMID] [PMCID]

[6] Munkboel CH, Larsen LW, Weisser JJ, Møbjerg Kristensen D, Styrishave B. Sertraline suppresses testis and adrenal steroid production and steroidogenic gene expression while increasing LH in plasma of male rats resulting in compensatory hypogonadism. Toxicological Sciences. 2018; 163(2):609-19. [DOI:10.1093/toxsci/kfy059] [PMID]

[7] Atli O, Bayal M, Aydogan-Kilic G, Kilic V, Ucarcan S, Karaduman B, et al. Sertraline-induced reproductive toxicity in male rats: evaluation of possible underlying mechanisms. Asian Journal of Andrology. 2017; 19(6):672-9. [DOI:10.4103/1008-682X.192637] [PMID] [PMCID]

[8] ElMazoudy R, El-Abd K, Mekkawy D, Kamel K. Developmental effects on hypothalamic, hypophyseal, testicular and steroidogenic patterns of sertraline-exposed male rats by accumulated doses from juvenile to puberty. Ecotoxicology and Environmental Safety. 2020; 30(188):109840. [DOI:10.1016/j.ecoenv.2019.109840] [PMID]

[9] Cai WW, Mo DS, Jiang N, Wang LL. [Association of sperm DNA integrity with seminal plasma oxidative stress and its influence on in vitro fertilization in infertile males (Chinese)]. National Journal of Andrology. 2016; 22(10):892-6. [PMID]

[10] Hamdi H. The preventive role of wheat germ oil against sertraline-induced testicular damage in male albino rats. Andrologia. 2019; 51(10):e13369. [PMID]

[11] Luiza Koop B, Nascimento da Silva M, Diniz da Silva F, Thayres Dos Santos Lima K, Santos Soares L, José de Andrade C, et al. Flavonoids, anthocyanins, betalains, curcumin, and carotenoids: Sources, classification and enhanced stabilization by encapsulation and adsorption. Food Research International. 2022; 153:110929. [DOI:10.1016/j.foodres.2021.110929] [PMID]

[12] Ciftci O, Tanyildizi S, Godekmerdan A. Protective effect of curcumin on immune system and body weight gain on rats intoxicated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). Immunopharmacology and Immunotoxicology. 2010; 32(1):99-104. [DOI:10.3109/08923970903164318] [PMID]

[13] Park JH, Lee BM, Kim HS. Potential protective roles of curcumin against cadmium-induced toxicity and oxidative stress. Journal of Toxicology and Environmental Health, Part B Critical Reviews. 2021; 24(3):95-118. [DOI:10.1080/10937404.2020.1860842] [PMID]

[14] Momeni HR, Eskandari N. Curcumin protects the testis against cadmium-induced histopathological damages and oxidative stress in mice. Human and Experimental Toxicology. 2020; 39(5):653-61. [DOI:10.1177/0960327119895564] [PMID]

[15] Aitken RJ, Roman SD. Antioxidant systems and oxidative stress in the testes. Oxidative Medicine and Cellular Longevity. 2008; 1(1):15-24. [PMID] [PMCID]

[16] Kesari KK, Kumar S, Behari J. Effects of radiofrequency electromagnetic wave exposure from cellular phones on the reproductive pattern in male Wistar rats. Applied Biochemistry and Biotechnology. 2011; 164(4):546-59. [PMID]

[17] Wang Y, Liu F, Liu M, Zhou X, Wang M, Cao K, et al. Curcumin mitigates aflatoxin B_1-induced liver injury via regulating the NLRP3 inflammasome and Nrf2 signaling pathway. Food and Chemical Toxicology. 2022; 161:112823. [DOI:10.1016/j.fct.2022.112823] [PMID]

[18] Rashid K, Sil PC. Curcumin ameliorates testicular damage in diabetic rats by suppressing cellular stress-mediated mitochondria and endoplasmic reticulum-dependent apoptotic death. Biochimica et Biophysica Acta. 2015; 1852(1):70-82. [DOI:10.1016/j.bbadis.2014.11.007] [PMID]

[19] Abou Elhamd AS, Sumayli S, Steger K, Ali AKM, Zayed AE. Effect of Khat (Catha edulis Forsk) extract on testicular maturation in pre-pubertal and pubertal rats: A morphological and biochemical study. Anatomia, Histologia, Embryologia. 2021; 50(2):271-83. [DOI:10.1111/ahe.12626] [PMID]

[20] Karimi S, Khorsandi L, Nejaddehbashi F. Protective effects of Curcumin on testicular toxicity induced by titanium dioxide nanoparticles in mice. JBRA Assisted Reproduction. 2019; 23(4):344-51. [PMID] [PMCID]

[21] Elsedawi BF, Hussein Y, Sabry MA, Aziz JA. Effect of fluoxetine on the testes of adult albino rats and the possible protective role of curcumin. Anatomical Science International. 2021; 96(2):187-96. [DOI:10.1007/s12565-020-00573-9] [PMID]

[22] Sukmawati Y, Arisanty D, Tofrizal A, Amir A. Vitamin E ameliorates testicular histological features and androgen binding protein levels in testicle of rats induced by allethrin. Journal of Advanced Veterinary and Animal Research. 2019; 23; 6(4):486-91. [DOI:10.5455/javar.2019.f372] [PMID] [PMCID]

[23] Drozdz-Afelt JM, Koim-Puchowska BB, Kaminski P. Analysis of oxidative stress indicators in Polish patients with prostate cancer. Environmental Science and Pollution Research. 2022; 29(3):4632-40. [DOI:10.1007/s11356-021-15922-y] [PMID] [PMCID]

[24] Soliman, ME, Mahmoud, BL, Kefafy, MA, Yassien RI, El-Roghy ESA. Effect of antidepressant drug (fluoxetine) on the testes of adult male albino rats and the possible protective role of omega-3. Menoufia Medical Journal. 2017; 30(4):1135-42. [DOI:10.4103/mmj.mmj_521_17]

[25] Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxidants and Redox Signaling. 2014; 20(7):1126-67. [PMID] [PMCID]

[26] Prasad P, Ogawa S, Parhar IS. Serotonin reuptake inhibitor citalopram inhibits GnRH synthesis and spermatogenesis in the male zebrafish. Biology of Reproduction. 2015; 93(4):102. [DOI:10.1095/biolreprod.115.129965] [PMID]

[27] Toydemir T, Kanter M, Erboga M, Oguz S, Erenoglu C. Antioxidative, antiapoptotic, and proliferative effect of curcumin on liver regeneration after partial hepatectomy in rats. Toxicology and Industrial Health. 2015; 31(2):162-72. [PMID]

This Page Intentionally Left Blank