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Original Article

Evaluation of Ferulic Acid (FA) Effects on Testicular Tissue and Sperm Parameters in Rats with Lead Toxicity

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Abstract

Introduction: Lead is one of the environmental pollutants and it is among the most important causes of oxidative stress in biological tissues. In this study, the effects of lead acetate on testicular tissue destruction were investigated. Ferulic acid (FA), which is an antioxidant and reduces free radicals, is expected to be effective in improving testicular function in lead-infected rats.

Materials and methods: For this study, 24 white male Wistar rats, categorized in four groups: control, lead acetate toxicity, FA control, and lead-Ferulic Acetate, were treated in the laboratory for 56 days. At the end of the treatment period, the rats were anesthetized and after blood sampling, they were analysed. Then, histological analysis was performed after testicular resection. To evaluate sperm characteristics, the distal part of the testicular epididymis was finally cut and fragmented.

Research Findings: In examination of testicular tissue sections in the samples, it was observed that the mean diameter of seminiferous tubules in samples with lead acetate poisoning was decreased more than the control, whereas in the group with FA treatment, the diameter was increased. Increased bleeding in the space between seminiferous tubules and tissue vacuolation were also recorded in the lead acetate group, but it was improved in the treatment group. The number, motility, percentage of normal sperm, and survival percentage of sperm which had a significant decrease in the lead acetate group, and were increased in the FA-treated group. Likewise, testosterone levels, which had a significant drop in the lead acetate poisoning group, were increased in FA-treated group.

Discussion: The result showed that lead acetate, with its destructive effects on testicular tissue, reduces the number of healthy and mature sperms, and ultimately leads to mice fertility of these mice, but ferulic acid which acts as an antioxidant has recovery effects against lead acetate.

Keywords: Ferulic Acid, Lead, Oxidative stress, Free radicals, Sperm.

1. Introduction

Heavy metals are available in different concentrations around us. Lead, mercury, and cadmium are known as the most frequent pollutants. High frequency of these three elements in nature and high rates of human contact with these materials is a reason for their pollution prevalence so that numerous attempts are done to limit them in the air and foods [1]. According to the statistical data, millions of tons of lead are produced each year, and this element is the fourth frequently-used element in the world [2], lead is one of the most commonly-found poisons in modern life which deals with all biological systems. In fact, exposure to lead has caused great problems in most countries [3]. Some major sources of lead in our modern industrialized life are foods, drinkable water, trashes, batteries, paints, and many other materials. Lead-exposure is introduced as the most important reason for most physiological, biological, and behavioral disorders both in humans and in laboratory animals [4].

Lead can be found in two forms, organic and non-organic, in nature. Its non-organic form can impact the nervous system, blood circulation, as well as urinary, gastrointestinal and genital systems; whereas its organic form can leave adverse effects on the nervous system. The uptake of its non-organic form occurs mostly through respiratory or gastro intestinal systems. Moreover, lead has poisonous effects on the immunity system and genital system, both in males and females [5].

If the LH and FSH hormone levels of lead exposure are normal, direct exposure to lead can further reduce testosterone and progesterone hormones in male and female rats. The negative effects of lead on these hormones are caused by low expression of cytochrome enzymes, P450Scc, and 3-beta-HSD enzyme [6]. Although the accurate mechanism of poisoning and the lead effects on sperms has not been thoroughly clarified so far, there are numerous findings representing the synthesis of free radicals and prevention of anti- oxidant activities in testicular tissues which are among the results of lead poisoning in this tissue [7].

Ferulic acid or 4-Hydroxy-3-methoxy cinnamic acid which is a Phenolic compound found in most plant tissues has anti-oxidant properties and high UV absorption. Ferulic acid is mostly found in rice bran, citrus fruits, bananas, beetroot, cabbage, spinach, and broccoli more than other plants [8,9].

A recent study found that ferulic acid plays an effective role in improving sperm parameters (sperm viability, motility, and number) in diabetic mice [10]. Ferulic acid lowers blood glucose, biochemical parameters, ROS, pro-inflammatory cytokines, apoptosis, and elevates serum testosterone, plasma insulin, and AKT proteins in diabetic rats, which may have a protective effect on postoperative traumatic events such as Testicular injuries [11].

The results of the studies have revealed that ferulic acid is the limiting factor of testosterone hormone to its normal level in diabetic rats. Moreover, it is found that severe reduction in the sperm parameters among diabetic rats can be treated with ferulic acid [12].

In recent years, the adverse effects of the environmental chemical factors on genital system of males have made great concerns. Despite numerous experiments carried out on possible complications of lead poisoning as well as side effects of FA uptake, no research has focused on the FA anti-oxidant effects on infertility caused by lead- induced poisoning. Along with the modern industrial advances, especially air pollution in megacities, a great number of problems in terms of human health are reported among which lead is one of the mostly found materials in such pollution. of course, lead has also resulted in many diseases among which infertility is increasing leaving numerous problems on families; thus, it is necessary to find medicines and compounds with plant origin to solve this problem. This is one of the most important reasons for carrying out the present research.

2. Materials and Methods

In this study, 24 male rats were purchased from Pasteur Institute of Tehran, Iran and were divided into four sub-groups (each with six rats): Control group (with water and normal diet), lead acetate poisoning in oral water (at a concentration of 500 mg/L), control ferulic acid (at a concentration of 20 mg/kg) by daily gavage, and lead acetate (at a concentration of 500 mg/L-ferulic (at a concentration of 20 mg/kg), and then they were treated for 56 days. At the end of the treatment period, the rats were anesthetized and blood samples were taken from the heart of the animal to measure testosterone levels. After serum centrifugation and separation, testosterone hormone level was measured by a kit using ELISA method. Then, male testes were extracted from the bodies of the rats for further histological analysis.

For histological examinations, the testes of rats were strained according to the following steps: First, the testis was placed in Bowen fixative solution and the dehydration and clarification steps were performed by passing through alcohol with ascending and xylene degrees, respectively. The tissues were then molded with paraffin and cut into sections 5 microns thick using a microtome. Finally, the cut tissues were stained by hematoxylin-eosin method and the stained slides were examined with a light microscope.

For further evaluation of the sperm parameters, cut the tail of the epididymis section [13]. Then, dissect the epididymis with a razor blade containing 10 mL of Ringer's solution [14] incubated in advance for an hour at 37 °C. After 30 minutes, the sperms left the epididymal ducts to make a homogeneous solution. The solution was further evaluated using a sampler to study the sperm factors including sperm motility, sperm morphology, and sperm viability.

In order to count the sperms, 15 μL of sperm-containing suspension was poured on the central square of the Neobar lam, and was covered with a small lam. After 5 minutes, the sperms were settled, and the remaining sperms with head, the middle region, and tail were counted by using *400 Optic Inspection Microscope [13]. It is worth to note that the available sperms on the center of the squares were counted, and in case of sperms which cut the edges, only those were counted that were in contact with the upper edge and the right side of the squares [14].

3. Results and Discussion

3.1. Histology

In microscopic observations of the stained tissue sections, the testes of rats in the control group had a normal appearance with normal seminiferous ducts and interstitial tissue. The seminiferous tubules included sperms and its epithelium was uniform with no gaps. Analysis of the FA control group showed similar results as the control group. The observation of testicular tissue sections in the lead acetate poisoning group showed a significant decrease in spermatid count and mature sperm count in the seminiferous tubules. Moreover, the vacuoles in various sizes and blood content were reported in epithelium. In the experimental group (led acetate-ferulic acid), the count of adult spermatids and sperms was also increased, but a reduction in the size and number of vacuoles was further reported (Figure 1).

The mean diameter of seminiferous tubules in lead acetate group compared with the control group showed a significant decrease, which indicates the destructive effect of lead acetate on reproductive tissues. The mean diameter of seminiferous tubules in the ferulic acid group showed a relative increase compared with the control group. The mean diameter of seminiferous tubules in the lead-ferulic acid acetate group indicated a significant increase compared with the lead acetate group. It appears to increase the diameter of semen and spermatide cells and sperm cells due to the improvement and antioxidant properties of the Ferulic acid (Table 1).

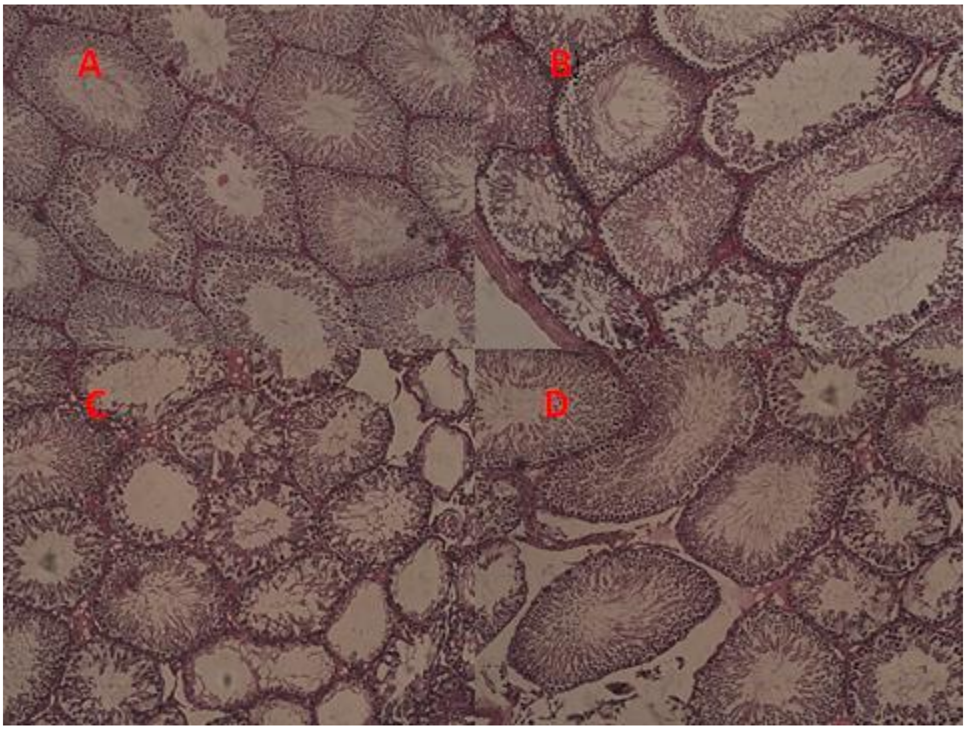

Figure 1. Image of sections stained (H&E) for histopathological examination of testis tissue in different groups of samples: A: Control group, B: FA-treated control group, C: lead acetate group, and D: FA treatment group. Scale bar =100 μm

3.2. Sperm parameters (count, viability, and morphology)

A significant decrease in sperm count was observed in the lead acetate group compared with the ferulic and control groups ($p<0.001$). An increase in the mean sperm count in the two groups, ferulic acid and lead-ferulic acetate, was also recorded. The significance of this difference was further observed with the lead acetate and control groups (Table 1). According to the results, the highest content of sperm survival, recorded in the FA group, was significantly different from the ferulic and lead-ferulic acid acetate groups ($p<0.001$). On the other hand, the lowest content of sperm survival was observed in the lead acetate group, which had a significant difference with the control group ($p<0.001$) (Table 1).

The mean content of sperm with normal morphology in the lead acetate-treated group had also a significant decrease. In the lead-ferulic acetate group, ferulic acid could significantly reduce the destructive effects of lead acetate on sperm with normal morphology compared with the lead acetate group (p<0.001). In addition, treatment of animals with FA itself caused a significant increase (p<0.001) in sperm content with normal morphology compared with lead acetate group (Table 1).

Based on the results of making a comparison between the mean values of testosterone, a more remarkable decrease in testosterone content was observed in the lead acetate group compared with the control (p<0.001). Likewise, the mean increase of the hormone in the ferulic acid group was significant with the control (p<0.01). Moreover, the difference in the amount of this hormone between the lead acetate and ferulic acid groups (p<0.001) and the lead-ferulic acetate group (p<0.05) was significant (Table 1).

Table 1. Comparison of mean sperm parameters of blood testosterone (ng/mL) and seminiferous tube diameter (mm) in different groups of samples (One-way ANOVA)

Groups	Sperm count (million/mL)	Normal sperm morphology (%age)	Sperm viability (%age)	Seminiferous tubule diameter (mm)	Testosterone (ng/mL)
Control	65.46±2.68	74.57±1.28	73±4.23	0.26±0.03	2.45±0.2
Ferulic acid	82.49±5.9*###	86.43±1.2**###	91.28±3.71**###	0.23±0.02##	3.8±0.21**###
Lead acetate	31.57±2.21***	54.21±3***	36.42±2.85***	0.16±0.01**	0.83±0.17***
Lead acetate-ferulic acid	52.42±4##	68.89±2###	76.53±4.14###	0.21±0.009#	0.78±0.27#

*Significant difference with the control group in the same column (*** P <0.001, ** P <0.01, and * P <0.05)
#Significant difference with lead acetate group in the same column (### P <0.001, ## P <0.01, and #P <0.05)

3.3. Sperm motility

A significant decrease was recorded in the mean percentage of sperm with progressive motility in the group treated with lead acetate compared with the control (p<0.001). In turn, the mean percentage of sperm with progressive motility in the lead-ferulic acetate group compared with the lead acetate group had a significant increase (p<0.001). Furthermore, treatment of animals with ferulic acid alone caused a significant increase (p<0.001) in the progressive sperm content in this group compared with the lead acetate group, yet, this percentage had a significant difference in terms of progressive sperm content in the lead-ferulic acetate group. (P<0.05) (Table 2).

Findings in the present study conducted on rats exposed to lead acetate and FA-treated group for 56 days showed that lead acetate had destructive effects (tubular atrophy, increased bleeding, and vacuolation of testis tissue) and reduced the diameter of the seminiferous tubules in the testis. These findings were in line with those found in Klein *et al*. (2019) reporting progressive degradation in the testicular tissue of lead-exposed organisms and interstitial tissue of the testes [17]. The researchers stated that lead acetate causes this cell damage through inducing oxidative stress and increasing oxygen radicals. In Hassan *et al*. (2019), a dose of 20 mg/kg which was used on the testicular tissue of adult rats for 56 days indicated a reduction in the number of spermatogonia cells and resulted in wrinkled seminal vesicles, decreased the tube diameter, and destroyed the germinal epithelium, as well [18]. Toxic effects of lead may form dysfunction of various body organs, including hormones and the reproductive system, through building free radicals and increasing lipid peroxidation [19].

Table 2. Comparison of mean sperm motility in different groups of values is mean ± SD. (One-way ANOVA)

Groups	Mean sperm motility (%age) of standard deviation				
	Progressive	Non-progressive	In place	Static	%age of sperm mobility
Control	76.44±3.77	12.33±2.44	4.95±2.25	6.28±3.11	2.49±77
Ferulic acid	77.13±5.44###	7.30±2.20	6.02±2.75	9.55±3.29	90.2±4.17**###
Lead acetate	24.59±8.31***	15.59±8.38***	16.31±5.00***	43.57±11.37***	50±3***
Lead acetate-ferulic acid	65.21±9.34###	14.91±6.34	10.58±3.70##	9.30±4.24###	65.57±2.1##

*Significant difference with the control group in the same column (*** P <0.001, ** P <0.01, and * P <0.05)
#Significant difference with lead acetate group in the same column (### P <0.001, ## P <0.01, and #P <0.05)

The results in Park & Han (2013) revealed that Yacon extract, containing chlorogenic and FA compounds, could increase sperm number, testosterone content, seminiferous tubule number and diameter, and spermatogenesis in rat testis [20].

In analysis of sperm parameters in the lead acetate group, a decrease in number of spermatid cells, healthy sperm content, and sperm motility was observed in testicular tissue, yet in FA control group, these complications were not recorded. Moreover, in the group treated with FA, the tissue analysis indicated an improvement in destructive effects of lead acetate along with an increase in diameter of seminiferous tubules and number of spermatid and sperm cells.

Studies carried out on laboratory animals also showed that lead exposure during pregnancy and infancy leads to delayed puberty, lower sperm count, loss of male sexual behavior, irregular menstrual cycle, decreased corpus luteum and amniotic fluid, and disorder in time pattern of gonadotropin release in adult offspring [21]. In addition, the percentage of normal sperm in lead acetate group was significantly lower than the control. In a study by Shan *et al*. (2009), it was found that the number of abnormal sperms in the epididymal region increased following lead administration [22].

Large amounts of lead can lead to male infertility. It is generally accepted that lead can both directly affects the male reproductive system and reduce the number and motility of sperms and indirectly reduces libido through endocrine [23].

Lead-induced oxidative stress can further reduce fertility by damaging sperm membrane, increasing abnormal sperm rate, reducing sperm motility, and decreasing its ability to penetrate the egg cell [24, 25]. Lead also affects the hypothalamic-pituitary-gonadal axis, upsetting the balance of reproductive hormones, which in turn, reduces fertility rate [24].

Generally, studies indicate that by administering lead orally or intraperitoneally, the number of sperms inside the testicular tissue or inside the epididymis may decrease [22,26]. In a study by Rahman (1984), sperm production in rats exposed to lead was significantly lower than the control group. This result revealed higher production of free radicals which was due to membrane lipid peroxidation [27]. Antioxidants protect lipids (as the basic compounds of cells, especially cell membranes) against peroxidation to prevent testicular oxidative stress [28].

Ferulic acid has antioxidant, anti-hypertensive, lipid-lowering, anti-microbial, anti-cancer, anti-diabetic, anti-inflammatory, liver and neuroprotective properties as well as medicinal properties for age-related diseases [29]. Seemingly, this greater increase in sperm number and motility in FA group than in the lead acetate group as observed in the results of this study was caused by the same antioxidant properties of FA. Hydroxy Cinnamic acid derivatives of some acids (such as caffeic acid and ferulic acid) have effective radical inhibitory activity [30].

There are enzymes in epididymis which own free radical scavenging properties to protect sperms against oxidative damage, so it is possible that any increase in sperm quality and its number can be related to antioxidant activity in FA. The enhancing effect of the ferulic acid on spermatogenesis is also reported by increasing serum testosterone and sperm parameters (viability, motility, and number) in FA-treated diabetic rats [10].

In the present study, it was found that lead acetate caused a significant decrease in sperm viability compared with the control group, but a significant increase was recorded in FA group with the control group. The increase in the mean percentage of live sperm in the two groups (FA and lead-ferulic acetate) was further more significant than the lead acetate group. In Sharp (2010), it was indicated that lead and cadmium, with their cytotoxic effects, can reduce sperm viability and have a detrimental effect on fertility and spermatogenesis [31]. Lead delays the activity of live sperm; thus, it can reduce the survival rate of sperms. Decrease in motility and viability of sperm is caused by the increase in synthesis of free radicals by lead, which in turn, leads to lipid oxidation, especially in membrane lipids, and affects the fluidity of plasma membranes [32].

The results of the present study showed a more significant decrease in testosterone level in lead acetate group than the control. Likewise, the results of the study carried out by Sheikh *et al*. (2020) on 8-week-old rats which were treated for three weeks by a dose of 100 mg/kg lead acetate revealed an increased blood lead concentration, decreased level of spermatozoa, less fluid Semen, and decreased serum testosterone along with multiple tissue damage [33].

In a study by Pillay *et al*. (2009), it was found that in rats injected daily with 0.05 mg/kg body weight of lead acetate; there was a significant decrease in activity level of key testicular steroid-building enzymes and testosterone, which was accompanied with decrease in levels of Cholesterol, ascorbic acid, and glutathione [34]. Such reductions in blood plasma prolactin can a reason for decreased testosterone, since prolactin plays a key role in regulating the binding sites of LH hormone in rodent testes [35]. In another study, Park and Han (2013) recognized the effects of FA enzymatic inhibition on the rate of testosterone breakdown in rat liver tissue [20]. The FA remedial effects on testosterone levels, as also identified in the present study, may depend on inhibition of testosterone-degrading enzyme in liver caused by ferulic acid. Apparently, this may be a part of the mechanism including the direct effect of ferulic acid on increasing testosterone and spermatogenesis.

4. Conclusions

It seems that lead-induced oxidative stress along with increased production of free radicals has destructive effects on cell membranes, especially sperm membranes so that by increase in the number of abnormal sperms, the motility of sperms reduces, and finally, it leaves destructive effects on entire reproductive system. Therefore, ferulic acid, as a key factor in absorption of free radicals, will have a positive effect on reproductive factors in male rats, and in turn, reduces and hinders such negative effects. Due to the presence of lead in various forms in the environment and its toxic effects on soft tissues and by considering the results of studies on the relationship between infertility problems and reduced reproductive capacity with lead compounds and the FA antioxidant nature, it seems essential to do further comprehensive studies on the positive effects of this substance on reproductive capacity in lead-infected rats.

Abbreviation

FA: Ferulic acid
ROS: Reactive Oxygen Species
H&E: hematoxylin and eosin

Conflict of interest

The author declare no conflict of interest.

Consent for publications

The authors of this article have full consent to publish this manuscript.

Ethics approval

Our paper has received ethical approval of Bu-Ali Sina University and all procedures were performed in accordance with the recommendations for the proper care and use of laboratory animals.

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