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ALLEVIATING REPRODUCTIVE DYSFUNCTION OF LEAD ACETATE IN MALE RAT: THE ROLE OF CURCUMIN AND METFORMIN

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To evaluate the ameliorative consequences of curcumin and metformin or their combination on lead reproductive toxic effect, 30 male Wister rats divided in to five groups as follow: Group 1 negative control. Group 2 lead acetate (50mg\kg B.W) orally for 6 weeks. Group 3 treated with same lead dose and curcumin (400mg\kg B.W) orally. Group 4 treated with same lead dose and metformin (30mg\kg B.W) orally and Group 5 treated with same lead dose and combination of curcumin with metformin (400mg\kg and 30mg\kg B.W) orally respectively. With completion of study duration, all animal sacrificed, blood, serum sample obtained for hormonal evaluation along testes tissue for histopathological study. Result shows an improvement of hormonal levels and alleviation of structural changes induced by lead with curcumin and\ or metformin thus protective reproductive function achieved

***Keywords**: Curcumin, Metformin, Lead acetate*

INTRODUCTION

Numerous heavy metal elements exert an inhibitory impact on human fertility, lead is one of these metal that has an adverse effect on male fertility via affecting sperm count, morphology, function together with hormonal changes[1,2]. Lead is recognized as a pervasive pollutant that poses health risks even at minimal concentrations[3]. Moreover, serum lead levels ranging from 10 to more than 40µg/dl were associated with higher the risk of infertility[4]. Due to the existence of lead in various environmental media and in numerous manufactured products, pigments, water pipes, gasoline additives and cable sheathing[5], the contamination of food, water, and air by lead constitutes a significant source of exposure for both humans and animals. Because of lead extended biological half-life, it ranks among the most toxic heavy metals, with a propensity to accumulate in different tissues over time[6]. This accumulation can lead to numerous histopathological changes and a wide range of biochemical and neurological dysfunctions. Presently, numerous studies indicating it is ability to impair male reproductive system, particularly in workers employed in lead-based industries[7]. This toxicant reduces reproductive capacity by interfering with the development of spermatogonial cells, Leydig cells, and Sertoli cells[8]. Mahdi and Ghadhban,[9] reported that lead causes an elevation in oxidative stress markers MDA and a decrease in antioxidant enzymes consequently, resulting damage to whole body system including liver and kidney associated with elevation in liver enzymes AST, ALT, ALP, urea and creatinine. Increasing incidence of male infertility during the last few decades with no clear etiologies necessitate more comprehensive studies of the suspected causes including a wide range of environmental and occupational hazards.

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Curcumin derived from the root of curcuma plant, known for it is yellow color in curry and exhibits strong antioxidant effect[10]. Polyphenolic natural product is the main components of curcumin with a variety of therapeutic potential[11] that produce multiple biological and functional properties including anticancer and anti-inflammatory characteristic, because these wide range effect of curcumin make it a subject of increasing interest for their administration in different fields[12].

The ROS scavenging properties of curcumin promote that synthetic curcumin analogue can be used to prevent and treat of diabetic nephropathy as anti-inflammatory potent agent[13]. Several research stated that curcumin attenuate testicular damage and protective functional and histological architecture in diabetics and heavy metal toxicity[14,15].

Metformin is a well-known oral hypoglycemic drug especially for type II diabetes[16] with a lot of proved beneficial effect on male fertility where it dampens the blood testicular barrier damage by ROS and enhance better spermatogenesis by its antioxidant property and reducing testicular hypoxia induced oxygen free radical excess[17]. Glucose tolerance has been treated through controlling serum glucose postprandial[18] and alleviating insulin resistance[19] with metformin, furthermore it is antioxidant and anti-inflammatory effect[20]. Activation of protein kinase complex with metformin mediate alteration of ovarian and testicular function through enhancing of sperm characteristic, oocyte properties thus, increasing fertilization rate[21]. All these parameters is maintained by metformin along with eradication of oxidative stress and enhancing hormonal balance of testicular tissue[22].

Therefore, this study is designed to evaluate the protective effect of curcumin and metformin in male rat reproductive exposed to lead acetate.

MATERIALS AND METHODS

Laboratory animals

Thirty male wistar rats weighing approximately 130-200 gm (aged 6-9 weeks) divided for five groups placed in plastic cages in a room temperature kept at 25±3 ^{o}C with cycles of 12 hr light on/off.

These Thirty male rats randomly separated into five group as follow:

a. Negative control group: they did not receive any chemical.
b. Positive control group: received 50 mg/kg[23] of Lead acetate daily via oral gavage for 6 weeks.
c. Curcumin group: the received curcumin 400 mg/kg23.
d. Metformin group: they received 30 mg/kg24.
e. Curcumin-metformin group: 400/30 mg /kg of curcumin and metformin respectively.

Each rat in Curcumin group, Metformin group and Curcumin-Metformin group received the planned antioxidant once daily via oral gavage for 6 weeks two hours before oral gavage administration of lead acetate. A blood sample of 10 cc collected from rats after being anesthetize and sacrificed with chloroform inhalation, serum obtained for biochemical and hormonal analysis. Testis excised and preserved in 10% formalin for histopathological assessment. The sperm characteristic assessed from cauda epididymis.

Ethical approval

Animal care was permit according to the local ethical committee at the College of Pharmacy, University of Basrah, (with approval number EC58).

Materials

a. Lead acetate purchased from Sigma-Aldrich (USA).
b. Curcumin was purchased from protocol of life balance (USA)
c. Metformin 500 mg tablet (Pfizer/USA)

Biochemical tests

a. Serum LH level was calculated according to method Okamura and Mori method [25].
b. Serum testosterone level was detected by Radioimmunoassay kit Siemens ADVIA Centaur XP (Siemens; Germany) [25].
c. Serum Cholesterol and ALT level detected with ACENT200.

Histopathological test

testes preserved in 10% formalin for pathological analysis.

Semen analysis[26]

a. Sperm count: Total number of spermatozoa calculated via improved Neuber's counting chamber (hemocytometer). Diluted sperm suspension of about 10 ml spread and allowed to stand over counting chamber of the hemocytometer then observed after 5min with a light binocular microscope.
b. Sperm motility: sperm suspension about 10 ml checked by visual estimation (400x magnification) to count all motile (move forward), non-motile (twitching) and immotile sperm. The percentage of motile spermatozoa calculated subsequently.
c. Sperm morphology: one drop collected of freshly semen spread over counting chamber of hemocytometer and examined for normal and abnormal spermatozoa morphology.

Statistical analysis

SPSS version 23.0, Chicago, USA, used for statistical analysis of collected data. The mean±SD, of each parameter recorded. A one-way T test used to assess the data among the five groups. Difference considered significant with ($p<0.05$).

RESULT AND DISCUSSION

Results

Serum testosterone concentration decreased significantly (*p<0.05*) at lead acetate exposed positive control group (0.4±0.1) as compared to negative control and all study group. However, testosterone level increased significantly (*p<0.05*) at Curcumin, Metformin and Curcumin-metformin groups as compared to positive control group (1.8±0.8), (5.9±1.4) and (3±1.5) respectively as shown in **table 1**.

Furthermore, LH level increased in positive control group (6.5±0.7) and the difference was statistically significant (*p<0.05*) as compared to negative control group. LH level was normalized in curcumin and Curcumin-Metformin group with a significant (*p<0.05*) difference as compared to positive control group (1.9±0.9) and (3.6±1.9) respectively. Metformin group showed a lesser reduction in LH level but it still significantly (*p<0.05*) lower than that of lead acetate group was illustrated in **table 1**.

The seminal analysis results demonstrated in **table 2** revealed that total sperm count, sperm motility and sperm morphology significantly (*p<0.05*) decreased in positive control group (105±2.9), (12±2) and (46±2)as compared to the negative control (187±2.9), (83±3) and (89±1.3) respectively; a group which does not receive neither Lead acetate nor any antioxidant. On the other hand, Curcumin, Metformin and Curcumin-Metformin groups improved total sperm count, sperm motility and sperm morphology significantly (*p<0.05*) when compared to positive control group and as showed in **table 2**.

Serum cholesterol level is significantly (*p<0.05*) increased in positive control group (6.5± 0.7) as compared to negative control. Curcumin, Metformin and Curcumin-Metformin groups failed to normalize serum cholesterol and the difference were also significant (*p<0.05*) as compared to positive control group, where means (5.8±0.3), (7.7±4.3) and (5.4±1.6) respectively showed in **table 3**.

Moreover, **table 3** represent a significant (*p<0.05*) increase in alanine aminotransferase (ALT) concentration at lead acetate exposed group (96±14) when compared to negative control (14±4). Serum ALT level also increased significantly (*p<0.05*) in Curcumin, Metformin and Curcumin-metformin groups as compared to negative control group, where means were (69±14), (75±5) and (73±16) respectively as mentioned in **table 3**.

Table 1: Represent changes in hormonal levels.

Parameters/ Groups	Testosterone (ng/ml)	LH (mIU/ml)
	Mean ± SD	
Cont Negative	**3.3 ± 1.2** b	**3.6 ± 1.3** c
Cont Positive	**0.4 ± 0.1** d	**6.5 ± 0.7** a
Curcumin	**1.8 ± 0.8** c	**1.9 ± 0.9** d
Metformin	**5.9 ± 1.4** a	**4.6 ± 2.5** b
Cur. and Met.	**3.0 ± 1.5** b	**3.6 ± 1.9** c

Table 2: Showed changes in sperm characteristic.

Sperm analysis / Groups	**Sperm count *10^6**	**Normal sperm motility**	**Normal sperm morphology**
	Mean ± SD		
Cont Negative	**187 ± 2.9** a	**83 ± 3** a	**89 ± 1.3** a
Cont Positive	**105 ± 17** c	**12 ± 2** d	**46 ± 2** c
Curcumin	**177 ± 13** a	**65 ± 13** b	**60 ± 8** b
Metformin	**160 ± 40** b	**63 ± 13** b	**63 ± 13** b
Cur. and Met.	**171 ± 8.5** a	**52 ± 12** c	**72 ± 17** b

Table 3: Illustrate changes in biochemical parameters.

Parameters/ Groups	Cholesterol (mg/dl)	ALT (U/L)
	Mean ± SD	
Cont Negative	**3.5 ± 1.4** d	**14 ± 4** d
Cont Positive	**6.3 ± 2.2** b	**96 ± 14** a
Curcumin	**5.8 ± 0.3** b	**69 ± 14** c
Metformin	**7.7 ± 4.3** a	**75 ± 5** b
Cur. and Met.	**5.4 ± 1.6** c	**73 ± 16** b

Histopathological study

Normal testicular architecture is noted in control group **(fig. 1A)**. Lead positive control showed hyaline like materials between morphologically altered seminiferous tubules, area of vacuolation of germinal epithelial and absence of spermatid **(fig. 1B)**. Curcumin group, noticed a restoration of seminiferous tubules structure and germinal epithelium layers along with presence of spermatid **(fig. 1C)**. Metformin group, presented with germinal epithelium disorganization with their vacuolation and morphological alteration of seminiferous tubules and interstitial edema **(fig. 1D)**. Combination (Met.+Cur.) group notice a near normal testes architecture with presence of spermatid in seminiferous tubules, presence of hyaline like substance between seminiferous tubules and presence of spermatid **(fig. 1E)**.

Discussion

Lead acetate has multiple organs target especially reproductive organs through interfering with their structural functional unit and hormonal production. These changes achieved by interaction with cell membrane integrity, mitochondrial function, calcium homeostasis and oxidative stress[6,27].

Disturbance of hormonal balance resulted from lead toxicity occur via alteration of hypothalamus- testicular pathway or damaging of Sertoli and Leydig cells, ultimately decrease serum testosterone and derangement of LH and FSH hormones[28,29] this result is in line with present study. However, our result is disagreed with[30] who found an elevation of serum testosterone with lead administration. Testicular damage through lipid peroxidation because of polyunsaturated fatty acid abundance due to oxidative stress, consequently germ cell disorder, distortion of steroidogensis and abnormal spermatogenesis[31,32].

Curcumin and metformin treatment showed an increase in testosterone and a decrease in serum LH level this result in similarity with[10,33,34], this result may be related to the mitigation of oxidative stress produced from lead toxicity and enhancement of inflammatory condition with curcumin, metformin or combination[35,36]. On the other hand, metformin result is not in line with[37] who reported that administration of metformin cause a decrement in serum level of testosterone. Several research inferred an elevation of antioxidant enzymes including superoxide dismutase (SOD) and glutathione peroxidase (GPx) along with a decrease in malon dialdehyde (MDA) level with curcumin and metformin administration, thereby exhibiting free radical scavenger[10,38,39].

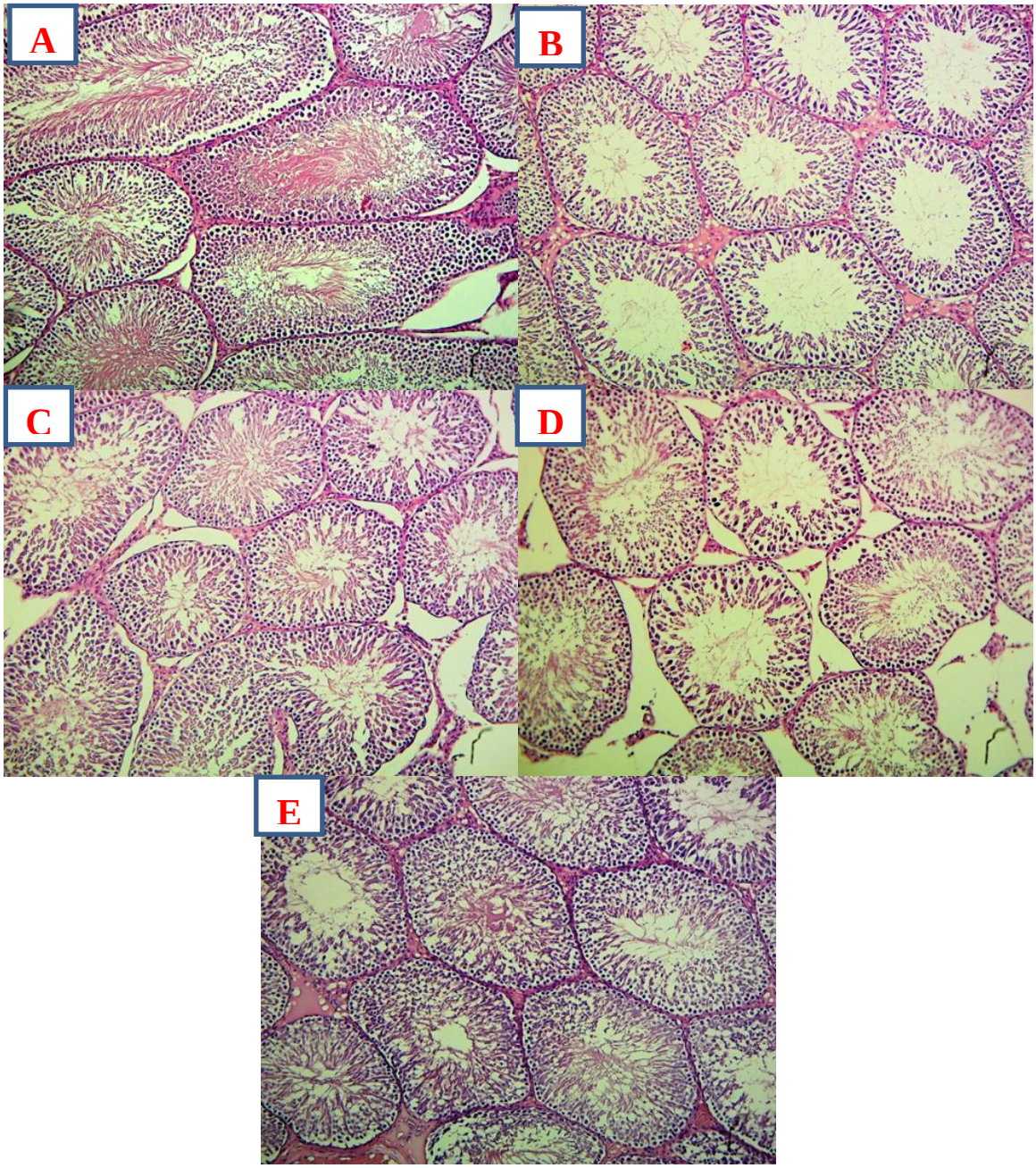

Fig. 1: (A) H&E stain, x100 of control group with normal testicular architecture. **(B)** H&E stain, x100 of Lead acetate positive control group, presented with hyaline like materials between seminiferous tubules, area of vacuolation of germinal epithelial and absence of spermatid. **(C)** H&E stain, x100 of Curcumin treated group, noticed a restoration of seminiferous tubules structure and germinal epithelium layers along with presence of spermatid. **(D)** H&E stain, x100 of Metformin treated group, showed germinal epithelium disorganization with vacuolation, seminiferous tubules morphological alteration along with interstitial edema. **(E)** H&E stain, x100 of combination group (Met. + Cur.) notice with almost normal testes architecture with presence of spermatid in seminiferous tubules and presence of hyaline like substance between seminiferous tubules.

Sperm parameters including count, morphology and motility appear to be altered through ischemic changes, reactive oxygen species (ROS) and hyperglycemia[40-42]. The result in table 2 reveals a decrease in sperm count, normal motility and normal morphology treated with lead acetate, this result is matching with[23]. Likewise, Kumar[43] also mentioned

reproductive toxic effect and infertility occur via lead exposure. Nevertheless, there is an improvement in all sperm findings in groups treated with curcumin, metformin along with combination groups this result may be related to the prevalence of both curcumin and metformin on glucose level[22] and eliminating of peroxidative changes[44] resulting from lead toxicity, thus enhancing sperm characteristic. This result is in similarity with[45,46]. Pourheydar and his colleagues[39] recorded that administration of metformin with silymarin in streptozotocin induced diabetic rat presented with amelioration of glucose, testosterone level in addition, to enhancement of germ cell function, sperm numbers and morphology.

Serum cholesterol and alanine transaminase (ALT) level increased in lead group this result is matching with[47,48]. This result may be associated altered hepatocyte adaptation and liver dysfunction via toxic lead level. Additionally curcumin, metformin and combination groups decrease neither serum cholesterol nor ALT level when compared to negative control, this result could be related to the deleterious consequence of lead thereby injured liver tissue result with high level of transaminase. This result is not matching with[48,49] they found that curcumin enhance lipid profile, decrease serum cholesterol in diabetic rat and ALT level reduced with curcumin due to lead toxicity respectively and in line with[36,50].

Several research notice the deleterious histopathological changes of testicular tissue exposed to lead acetate representing with atrophy of seminiferous tubules, in complete series of spermatogesis along with Leydig cell degeneration and vacuolation of some spermatogenic cells[3,29] these result are in line with present study. On the other hand, curcumin and metformin showed an improvement germinal epithelium and seminiferous tubules likewise to control group filled with spermatid in their lumen. These findings are matching with[39,23,47] and related to curcumin role in increasing testosterone hormone and apoptosis inhibition through suppression of mitogen-activated protein kinase (MAPK)[10]. Similarly, metformin also exert a protective effect through apoptosis suppression of caspase-3 level[46].

Conclusion

The present study reveals a mitigation of hormonal picture and hitopathological changes produced by lead acetate toxicity with curcumin, metformin and combination through their antioxidant, anti-inflammatory and glucose level control, thereby enhancement of reproductive function. Moreover, curcumin appears to be more effective than metformin related to their better effect on reproductive organs.

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تخفيف الخلل التناسلي الناتج عن أسيتات الرصاص في ذكور الجرذان: دور الكركمين والميتفورمين

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لتقييم العواقب التحسينية للكركمين والميتفورمين أو مزيج منهما على التأثير التكاثري السام للرصاص، تم تقسيم ٣٠ ذكر من الجرذان نوع ويستر إلى خمس مجموعات على النحو التالي: المجموعة الاولى ضابطة سلبية. المجموعة الثانية أسيتات الرصاص (٥٠ مجم/كجم من وزن الجسم) عن طريق الفم لمدة ٦ أسابيع. المجموعة الثالثة عولجت بنفس جرعة الرصاص والكركمين (٤٠٠ مجم/كجم من وزن الجسم) عن طريق الفم. المجموعة الرابعة عولجت بنفس جرعة الرصاص والميتفورمين (٣٠ مجم/كجم من وزن الجسم) عن طريق الفم والمجموعة الخامسة عولجت بنفس جرعة الرصاص ومزيج الكركمين والميتفورمين (٤٠٠ مجم/كجم و٣٠ مجم/كجم من وزن الجسم) عن طريق الفم على التوالي. مع اكتمال مدة الدراسة، تم الحصول على عينات الدم والمصل من جميع الحيوانات المذبوحة للتقييم الهرموني بالإضافة الى نسيج الخصية للدراسة النسيجية المرضية. اظهرت النتائج تحسنًا في مستويات الهرمونات وتخفيف التغيرات البنيوية الناجمة عن الرصاص مع الكركمين و/أو الميتفورمين وبالتالي تحقيق وظيفة التكاثر الوقائية.