Histological changes in pituitary-testes axis in rats exposed to cadmium chloride: Protective role of *Eruca sativa* seeds

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Summary

The present study was carried out to investigate the protective effect of *Eruca sativa* seeds against changes of pituitary and testes in cadmium treated rats. Forty adult male albino rats were used and divided into 4 equal groups and treated for 8 weeks as follows: The first group was given distilled water and used as a control group. The second group (G1) was administered with tap water containing 30 ppm/ L of cadmium chloride. Animals in third group (G2) received tap water containing Cadmium chloride as in G1 plus 250 mg/Kg B.W ethanolic extract of *Eruca sativa* seeds, while rats in fourth group (G3) were administered 250 mg/Kg B.W of ethanolic extract of *Eruca sativa* seeds only. After 8 weeks of experiment the animals were anesthetized, the pituitary and testes were excised for histological studies. Results showed that cadmium chloride intake caused severe alterations in the pituitary gland manifested by a marked apoptotic cells of pars distalis, accompanied with marked necrosis leading to left large multiple spaces in their parenchyma. Whereas testes revealed shrinkage, irregular arrangement of seminiferous tubules and increased intertubular spaces. A considerable change was also found in the seminiferous tubules with the loss of most of their epithelial layer and filled with cellular debris, incomplete spermatogenesis, congested blood vessels and few Leydig's cells. Administration of *Eruca sativa* extract reduced the deleterious effects of cadmium chloride on pituitary gland as well as more or less complete spermatogenesis process with thickness of interstitial tissue in most of seminiferous tubules. It could be suggested that the antioxidant properties of *Eruca sativa* extract protects the deleterious histological damage induced by cadmium chloride in adult rats.

Keywords: Cadmium chloride, Pituitary gland, Testes, *Eruca sativa*, Rats.

Introduction

Cadmium (Cd) is known as an inorganic highly toxicant and widely distributed in the environment and causes various disease conditions (1). It is well known that smoking remain a major health problem causing lung disease and cancer may be more serious than cadmium in food (2). (3) Stated that drinking water contaminated with Cd, regarded as the most important source of human exposure to Cd. Some studies reported that the level of cadmium exceeded the acceptable limit**,** as in Shatt Al-Hilla River (4) and in Al-Wihda and Al-Qadisiya units for water treatment (5) in Iraq. Thus, cadmium toxicity could be due to ingestion of the contaminated fishes (6). High levels of cadmium were found in algal formulations, fungi, seaweeds and some oil seeds (7), leafy vegetables, potatoes, tomatoes (8) and sunflower oil (9). Another researcher (10) showed that metals may have an effect on the male reproductive system directly or indirectly when they act on the neuroendocrine system causing an endocrine disruptor and disorder in oxidant/ antioxidant status leading to oxidative stress (11). Long-term exposure to low doses of Cd caused spermatogenic damage and histological alteration in testes of rats (12). It is noteworthy that cadmium can cause testicular injury via their initial action at the blood-testis-barrier (BTB) (13) and induced destruction of seminiferous tubules with sever necrotic area in birds and mammals (14) and thereby leading to infertility

In fact, small amounts of reactive oxygen species (ROS) are necessary for normal functions of spermatozoa like capacitation and fertilization (15). Whereas, an increase production of ROS has an effect on the sperm axoneme as a result of ATP depletion (16), inhibit both of mitochondrial functions (17) and synthesis of DNA (18). Consequently excessive production of ROS might be one major factors of infertility (15), as well as (19) showed that Cd may induce apoptosis through altered activity of protein kinases, transcription factors and activation caspase (20).

Antioxidants are substances that either directly or indirectly protects cells against the adverse effects of xenobiotic, drugs and toxic radical reactions through simple or complex mechanisms, including radical scavenging or binding of metal ions (21). *Eruca sativa* that is often known as rocket is utilized in this study. Analysis of *Eruca sativa* seed oil proved the presence of fatty acids, saturated acids, erucic acid, oleic acid, linoleic acid and linolenic acid (22), Furthermore, phytochemical analysis of *Eruca* seeds indicates that alkaloids, cardiac glycosides, flavonoids, phenolics, ascorbic acid and saponins are present in the seed (23). The beneficial effects of *Eruca sativa* have been attributed to the range of phytochemicals constituents such as vitamins A and C, erucin and glucosinolates (24). Therefore, the objective of this study was to explore the protective effect of *Eruca sativa* seeds extract on pituitary-testes axis against cadmium chloride in adult rats.

Materials and Methods

The seeds of *Eruca sativa* were purchased from the local market (Shorje in Baghdad) and certified in the Iraqi National Herbarium, in Abu Ghreb, at the Ministry of Agriculture. The seed of *Eruca sativa* were ground into a fine powder using coffee grinder and weighting crushed seeds powder 100 g then put it in a volumetric conical flask, then 1000 ml of 70 % ethyl alcohol was added to the powder which makes the ratio (1/10) (W/V). After that the solution was mixed by using magnetic stirrer apparatus for 24 hrs. , the mixture was filtered by using 4 layers of medical gauze, then was filtered again using Whatman (No.1) filter paper. The filtered mixture was concentrated by using incubator at 40°C for 72 hrs. to obtain crude extract. The yield equal to 3 g. The extract was stored in a dark bottle at 4°C until used (25).

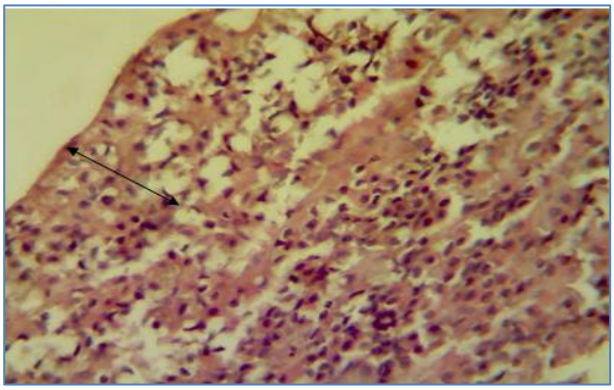
Forty adult male rats were randomly divided to four equal group and handled as follows for 8 weeks: Control group administered tap water; group G1 administered tap water containing 30 ppm/ L of cadmium chloride; group G2 received tap water containing 30 ppm/ L of cadmium chloride and administered 250 mg/Kg B.W of ethanolic extract of *Eruca sativa* seeds; group G3 administered 250 mg/Kg B.W of ethanolic extract of *Eruca sativa* seeds only. At the end of experiment, after sacrificed the rats, testis and pituitary gland were excised and fixed in 10% formalin buffer solution. Several tissue sections with thickness 5-6 µ of the testis and pituitary gland were prepared and stained with hematoxylin-Eosin stain (H and E) according to (26) for study the histological changes.

Results and Discussion

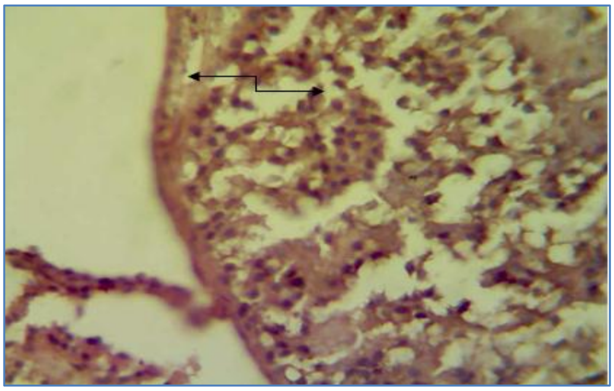
Histological examination of pitutary gland sections in cadmium treated group (G1) showed marked apoptotic cells of pars distalis characterized by multiple spaces in their parenchyma (Fig.1) accompanied with marked depletion of the cells in pars distalis due to necrosis and apoptosis leading to left large multiple spaces in their parenchyma (Fig. 2) comparing to control (Fig. 3 and 4). While section of pituitary gland of rats treated with cadmium and ED50 of *Eruca Sativa* (group G2) showed few vacuolation in the pars distalis (Fig.5), together with clear chromophobes cells and chromophils cells (Fig. 6). In (G3), microscopic examination of pituitary gland shows active cellular composition of the pars distalis (chromophobes cells and chromophils cells) and no clear lesions. Also there was no abnormality was detected in other sections (Fig. 7 and 8) as compared to control (Fig. 3 and 4).

Group 1 showed marked histological alterations in architecture of pars distalis of pitutary gland. The results of the current study agreement with other research suggest that cadmium toxicity induce changes in the morphology of the pituitary gland characterized by perivascular inflammatory cells and vacuolation with accumulation of this metal in the brain and alteration of the normal function of the pituitary gland (27). Many studies described that pituitary secretions activity has been shown to be affected by metals and this endocrine gland is a particularly sensitive target to cadmium toxicity (28). Another study (29) explained that Cd may be cause modification in lipid contents of pituitary gland and directly or indirectly alteration the levels of prolactin (PRL) and growth (GH) hormones in serum or a decrease in the content of glutamate and aspartate in anterior hypothalamus may be partially explained the inhibitory effect of cadmium on PRL and luteinizing hormone (30 and 31) reported that Cd modifies the lactotrophs activity of pituitary gland through genomic and morphological changes, consequently leading to pituitary dysfunction. Whereas, some research indicate that cadmium could compete with calcium at the pituitary gland cell membrane and subsequently alters the cytoarchitectural integrity of the gland (32).

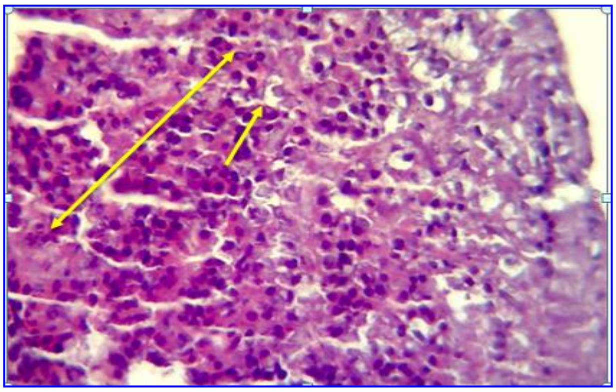
The well fact that an accumulation of ROS exerts a potent damag effects on the cells especially phospholipids, proteins and DNA. The most affected organelles in the pars distalis cells were the mitochondria, which might explain the subsequent increase in ROS generation mechanism (33). Therefore, in the present study lesions may be result from free radical generated from CdCL2 through binds with polyunsaturated fatty acid to produce alkoxy (R*) and proxy radicals (ROO*), that in turn, generate lipid peroxidation and finally induce injury or necrosis (34). Further researches are however certainly required to illustrate the mechanism of cytotoxic action of cadmium on the pituitary cells. From the results of the present study *Eruca sativa* extract caused ameliorating the unfavorable effects produced in the pituitary gland by $CdCl_2$. *Eruca sativa* (ES) act as antioxidant and play important role in reduction of oxidative stress (35). Researchers (36) reported that polyphenols found in ES have more powerful antioxidant activity. It enhances the expression of intracellular endogenous antioxidants such as glutathione, glutathione peroxidase, glutathione peroxidase catalase by reducing the generation of reactive radicals (37), therefore, the histological examination of pituitary gland of rats in G2 pointed a modifications in the pars distalis together with few vacuolation, as well as, an improvement of the cell membranes destructed by $CdCl_2$ (15) and inhibits irregular cell growth and apoptosis via modulation of proteins regulating apoptosis (38). So, ES probably arrest the harmful mechanism of pituitary injury through protection of cells and tissues from oxidative damage by scavenging free radicals and stimulate the regeneration of damaged tissues and cells.



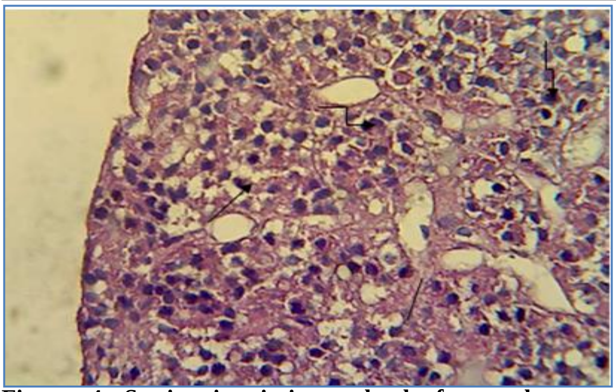
Figure, 1: Section in pituitary gland of animal treated with cadmium chloride (G1) shows marked apoptotic cells of pars distalis characterized by multiple spaces in their parenchyma (↔), (H and E stain 40X).



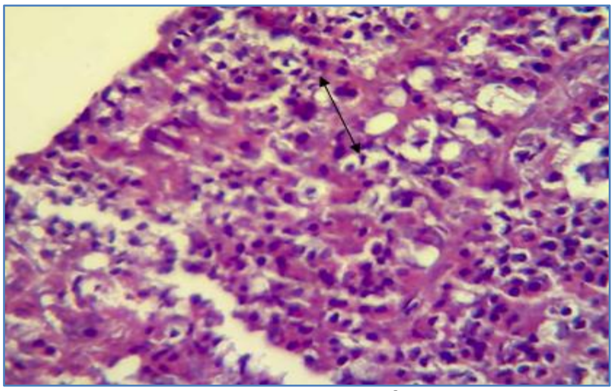
Figure, 2: Section in pituitary gland of animal treated with cadmium chloride (G1) shows marked depletion of the cells of pars distalis due to necrosis and apoptosis left large multiple spaces in their parenchyma (↔), (H and E stain 40X).



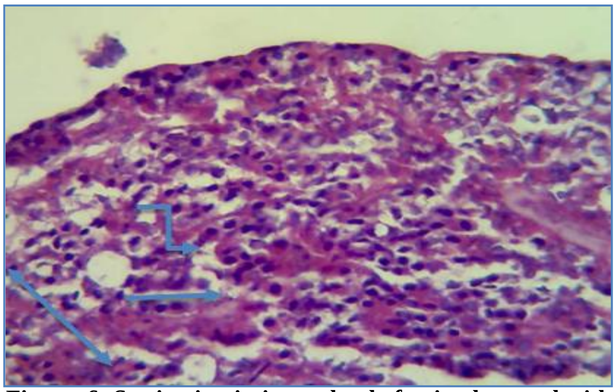
Figure, 3: Section in pituitary gland of control group shows normal structure of cellular composition of the pars distalis, chromophobes cells (↗) and chromophils cells (↔) (H and E stain 10X).



Figure, 4: Section in pituitary gland of control group shows normal structure of cellular composition of the pars distalis, chromophobes cells (↗) and chromophils cells (↔) (H and E stain 40 X).

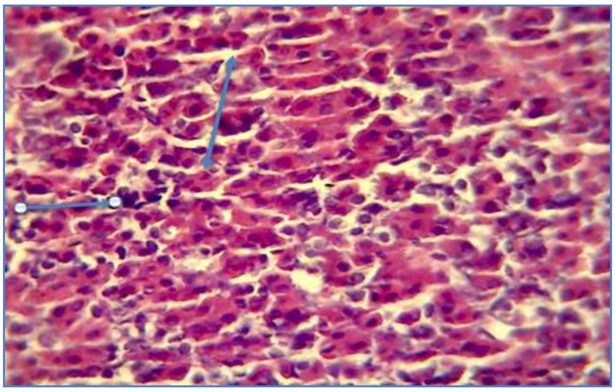


Figure, 5: Section in pituitary gland of animal treated with cadmium chloride and *Eruca Sativa* (G2) shows few vacuolation in the pars distalis (↗), (H and E stain 10X).

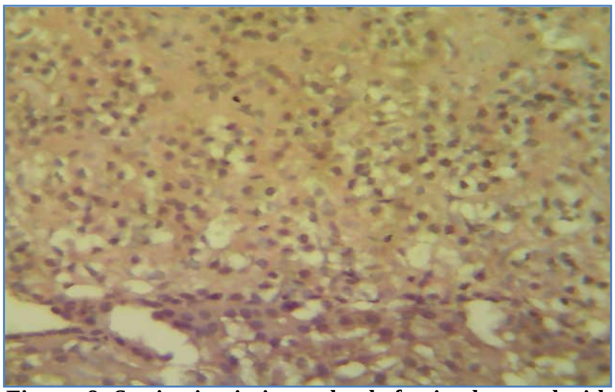


Figure, 6: Section in pituitary gland of animal treated with cadmium chloride and *Eruca Sativa* (G2) shows few vacuolation in the pars distalis (↳) with clear chromophobes cells (↗) and chromophils cells (↔) (H and E stain 40X).

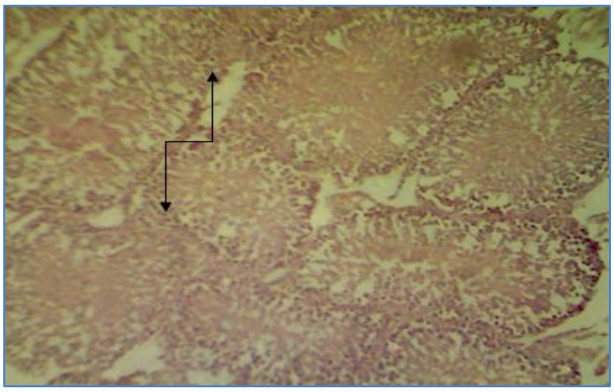
Comparing to the control (Fig. 9 and 10) which showed no pathological lesions, testicular sections of rats treated with $CdCl_2$ (G1) revealded shrinkage, irregular arrangement of seminiferous tubules and increase intertubular spaces (Fig. 11).



Figure, 7: Section in pituitary gland of animal treated with *Eruca Sativa* (G3) shows normal cellular composition of the pars distalis, chromophobes cells (→) and chromophils cells (↔) (H and E stain 40X)

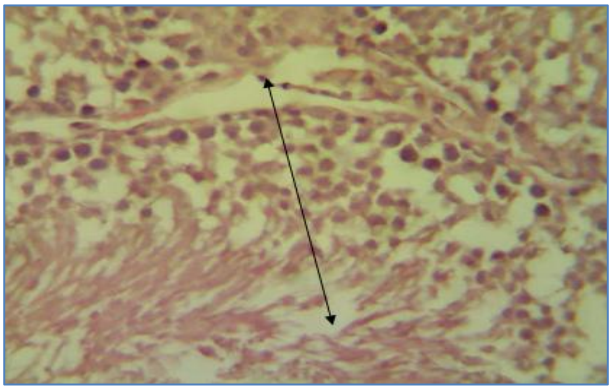


Figure, 8: Section in pituitary gland of animal treated with *Eruca Sativa* (G3) shows no clear lesions (H and E stain 40X).

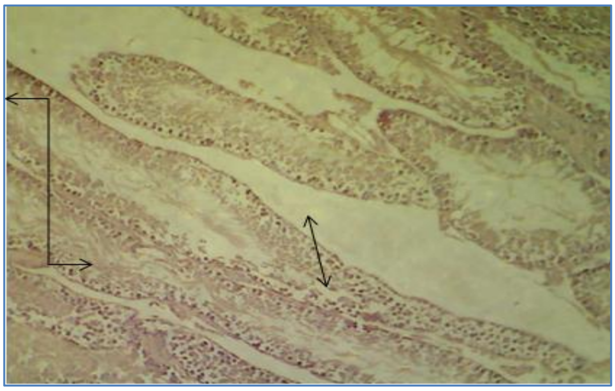


Figure, 9: Section in testis of control group shows normal architecture of seminiferous tubules (↳) (H and E stain 10X).

A considerable changes was also found in the seminiferous tubules with loss most of their epithelial layer and filled with fluid and cellular debris (Fig. 12), the seminiferous tubules expressed thickness of basement membrane lined only by Sertoli cells with congested blood vessels and few Leydigs cells and filled with cellular debris (Fig. 13). In other section, deformity seminiferous expressed one part with incomplete spermato -genesis process was seen (Fig. 14). More so, histological section in testis of animal treated with cadmium chloride and *Eruca sativa* G2 shows normal arrangement of seminiferous tubules (Fig. 15), complete spermatogenesis process (Fig. 16), thickness of interstitial tissue with complete spermatogenesis process in most seminiferous tubules but few of them expressed incomplete spermatogenesis process (Fig. 17). However, *Eruca Sativa* extract treatment (G3) showed normal arrangement of seminiferous tubules with complete spermato -genesis and filled their lumen with sperms (Fig. 18 and 19) and proliferation of Leydig's cells as compared to control.

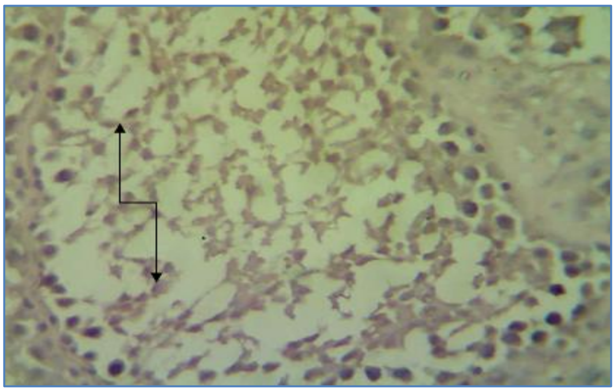


Figure, 10: Section in testis of control group shows normal structure of seminiferous tubules (↔), (H znd E stain 40X)

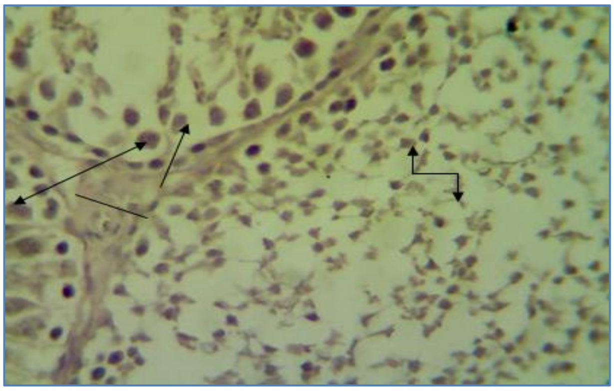


Figure, 11: Section in testis of animal treated with cadmium chloride (G1) shows most of them were shrinkage, irregular arrangement of seminiferous tubules (↰↳) and increase intertubular spaces (↔) (H and E stain 10X).

Herein study indicated that histological examination of the testes treated with cadmium chloride 30 ppm/l in the drinking water showed a sharp occurrence of histopathological changes. Cadmium can negatively affect the male reproductive system via degenerative changes in testes, epididymis and seminal vesicles. The results regarding the effect of cadmium in the current study is in accordance with other studies (12 and 39). Acute Cd exposure has a susceptibility to cross the endothelial cell layers of the blood-testis barrier and to drastically increase the vascular permeability of testis, which overwhelms the draining function of the lymphatic system causing interstitial edema, hemorrhage, ischemia, necrosis (40) and finally testicular atrophy (41) due to circulatory vascular failure.

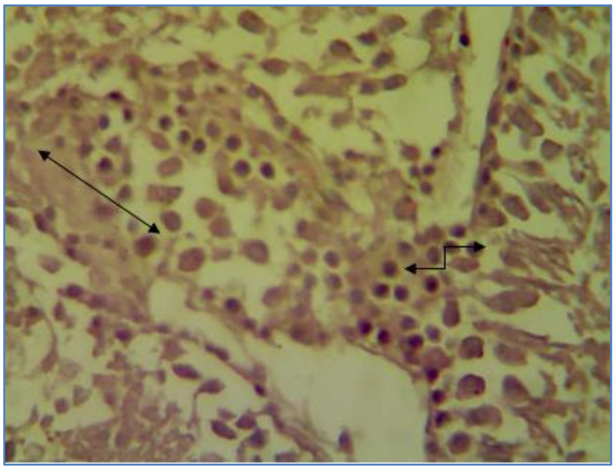


Figure, 12: Section in testis of animal treated with cadmium chloride (G1) shows that seminiferous tubules were loss most of their epithelial layer and filled with fluid and cellular debris (↰↳) (H and E stain40X).

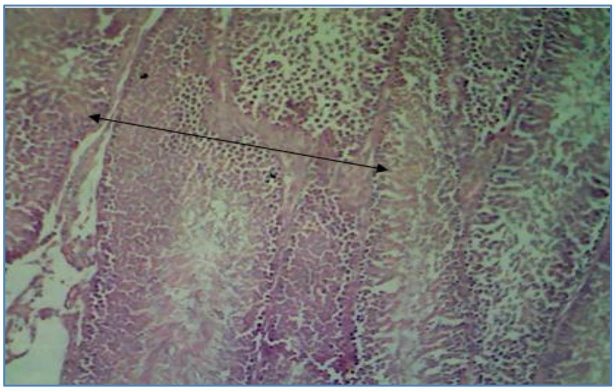


Figure, 13: Section in testis of animal treated with cadmium chloride (G1) shows that seminiferous expressed thickness of basement membrane (↔) line only by Sertoli cells (→) with congested blood vessels and few Leydig cells (↰↳) and filled with cellular debris (—), (H and E stain40X).

It was supposed that there is a correlation between the histological changes and oxidative status induced by $CdCl_2$ in the present study .So a case of oxidative stress associated to induced lipid peroxidation (LPO) after Cd exposure could be attributed to findings of this research with a serious damage in testicular tissue (12) and incomplete spermatogenesis may be due to an increase production of ROS (42) by inducing LPO and DNA damage (43) and such degenerative changes leads to cell necrosis and atrophy of testicular tissue (44). Accordingly, could be postulated that a decrease in LPO in $CdCl_2$ plus *Eruca sativa* treated group compared with cadmium treated group (G1) due to its antioxidant activities (45) could lead to improvement in processes of spermatogenesis.

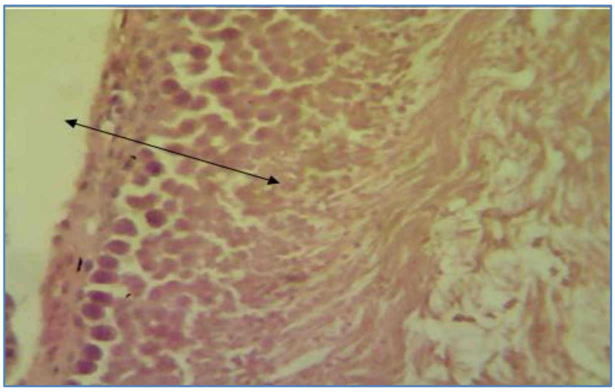


Figure, 14: Section in testis of animal treated with $CdCl_2$ (G1) shows deformity Seminiferous expressed one part with incomplete spermatogenesis (↰↳) process (⟷), (H and E stain40X).

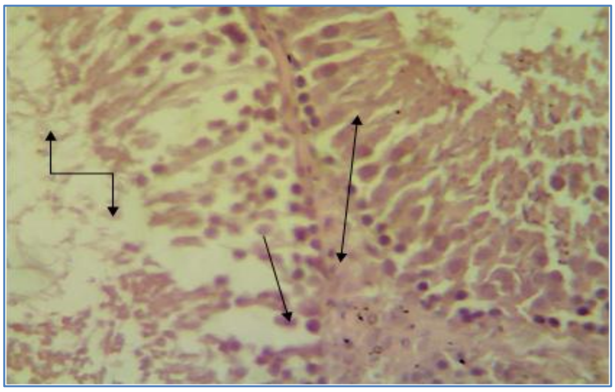


Figure, 15: Section in testis of animal treated with $CdCl_2$ and *Eruca Sativa* (G2). Shows normal arrangement of seminiferous tubules (⟷) (H and E stain 10X).

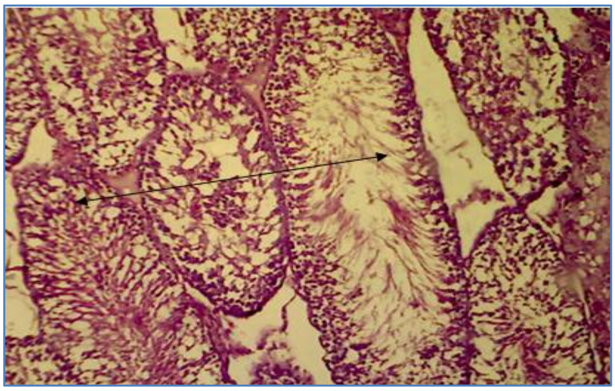
It has been proved that *Eruca sativa* contains antioxidant agents including glucosinolate, polyphenolic compounds, saponins and a crude gonadotrophic substance (46) which increase FSH and LH concentrations lead to improved Leydigs cells maturation (47). Therefore, the modification of hormonal profile can stimulate the spermato -genesis, may increase sperm concentration in the center of seminiferous tubules (48). Also, the presence of bio-active isthiocyanates in *Eruca sativa* extract which results from glucosinolate (49) have antioxidant properties and induce metabolizing enzymes such as glutathione-s-transferase and NADPH, which play an important role in detoxification and protection against oxidative stress (35). So it can be suggested that the component of *Eruca sativa* extract have a potential role to improvement male reproductive functions attributed to its antioxidant and androgenic properties.



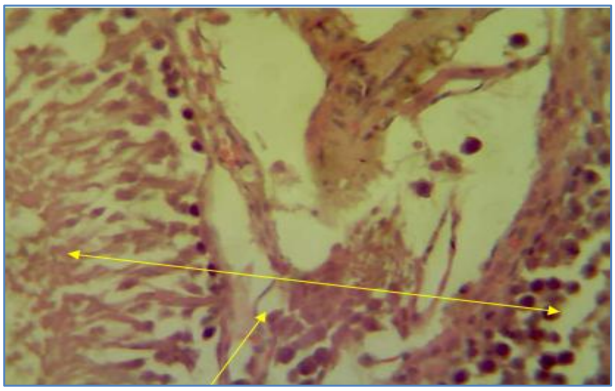
Figure, 16: Section in testis of animal treated with $CdCl_2$ and *Eruca Sativa* (G2) shows complete spermatogenesis process (⟷), (H and E stain 40X)



Figure, 17: Section in testis of animal treated with $CdCl_2$ and *Eruca Sativa* (G2) shows thickness of interstitial tissue (⟶) with complete Spermatogenesis process in most seminiferous tubules (⟷) but few of the expressed incomplete spermatogenesis process (↰↳), (H and E stain 40X).



Figure, 18: Section in testis of animal treated with *Eruca Sativa* (G3). Shows normal arrangement of seminiferous tubules (⟷) with complete spermatogenesis (H and E stain 10X).



Figure, 19: Section in testis of animal treated with *Eruca Sativa* (G3) shows normal arrangement of seminiferous tubules with complete spermatogenesis (⟷) and proliferation of Leydig cells (⟶) (H and E stain 40X).

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التغيرات النسجية في محور النخامية – الخصى للجرذان المعرضة لكلوريد الكادميوم: الدور الوقائي لبذور الجرجير

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الخـــلاصة

أجريت هذه الدراسة لمعرفة مدى التأثير الوقائي لبذور الجرجير كمادة مضادة للاكسدة وللحد من التأثيرات الضارة على محور الغدة النخامية - الخصى الناتجة عن كلوريد الكادميوم. استعمل 40 جرذ بالغ، قسمت إلى أربع مجاميع متساويةً وعوملت لمدة 8 أسابيع كالأتي: جرّعت المجموعة الأولى الماء المقطر واعتبرت مجموعة سيطرة، أما المجموعه الثانية فقد أعطيت كلوريد الكادميوم بتركيز 30 جزء بالمليون/ لترمن ماء الشرب. في حين أعطيت حيوانات المجموعة الثالثة كلوريد الكادميوم في ماء الشرب كما في الجموعة الأولى فضلاً عن تجريعها المستخلص الكحولي لبذور الجرجير بجرعه 250 ملغم/ كغم من وزن الجسم في حين جرعت المجموعة الرابعة بالمستخلص الكحولي لبذور الجرجير بجرعة 250 ملغم/ كغم من وزن الجسم. بعد ثمانية أسابيع من التجربة خُدرت الحيوانات وأخذت الغدة النخامية والخصى وعمل لها مقاطع لدراسة التغيرات النسجية. أظهرت نتائج الفحص النسيجي للجرذان المعاملة بكلوريد الكادميوم إنها تسبب في حدوث تغيرات حادة في الغدة النخامية الذي تجلت بزيادة

ملحوظة في الموت المبرمج لخلايا الجزء القاصي، ترافق مع نخر ملحوظ مؤديا إلى ترك مساحات كبيرة متعددة في متن الغدة. في حين بين الفحص النسجي للخصى وجودانكماش، وعدم الانتظام في ترتيب النبيبات المنوية وزيادة المساحات بين النبيبات، تغيرات كبيرة أيضا في النبيبات المنوية مع فقدان معظم طبقات الخلايا الظهارية ومليئة بالبقايا الخلوية، عملية تكويت الحيامن غير مكتملة، احتقان في الأوعية الدموية وعدد ضئيل جداً من خلايا ليدك. وعلاوة على ذلك، فقد بينت النتائج الدور الأيجابي المستخلص الكحولي لبذور الجرجير في تقليل حدة الآثار الضارة لكلوريد الكادميوم على الغدة النخامية، فضلاً عن أن عملية تكوين الحيامن قد كانت أكثر أو أقل اكتمالاً مع سمك النسيج الخلالي في معظم انبيبات المنوية. لذا يمكن أن نستنتج أن المستخلص الكحولي لبذور الجرجير يمتلك خصائص مضادة للأكسدة ضد الضرر الناجم عن كلوريد الكادميوم.

الكلمات المفتاحية: كلوريد الكادميوم، الغدة النخامية، الخصى، الجرجير، الجرذان.