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The impact of Gabapentin on Testes and Epididymis and Antioxidant Status of Adult Male Mice

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Abstract

The study aimed to evaluate the effects of different doses of gabapentin on the testes and epididymis of adult male mice and on oxidative stress markers. It also investigated its impact on sperm quality and overall reproductive function. Twenty-four adult male mice were randomly divided into 4 groups. Mice of group 1 served as control and were administered with 0.1 ml sterile saline, and other groups were treated with Gabapentin orally administered with 0.1 ml of a daily dose of concentrations (5, 10, 20) mg/kg for 60 consecutive days. Gabapentin significantly decreased ($p<0.05$) the absolute weight of body, testis, and tail of epididymis of treated mice, significantly increased ($P\leq 0.05$) malondialdehyde serum level , catalase, and superoxide dismutase, and also showed significantly decreased ($P\leq 0.05$) glutathione levels and vitamin E levels . The results observe several histological changes in the testes and cauda epididymis, including azoospermia, detaching spermatogonia, Necrosis, Edema, Congestion, Amyloid deposition, irregular tubules, Rupture of seminiferous tubule epithelium, Slephinggerm cells, Atrophy Tubules, Shrinkage tubule, hemorrhage, Hyperplasia, and Pyknosis. The sperm of mice treated with the drug at its three concentrations showed several abnormalities. including coiled, folded, and broken tails, bent neck, tailless, as well as sperms with cytoplasmic droplets. Gabapentin administration negatively affects the testes and epididymis, impairing sperm quality and overall reproductive function in mice. These findings suggest that long-term gabapentin use may pose risks to male fertility.

Keywords: Antioxidant enzymes, Epididymis, Gabapentin, Mice, Testes

Introduction

Gabapentin is an anticonvulsant drug and is mostly used to treat neuropathic pain and partial seizures. It is marketed under the brand name Neurontin, among others [1]. It is a widely used medication to treat central pain, neuropathic pain resulting from diabetic neuropathy, and postherpetic neuralgia [2]. The effectiveness of gabapentin is moderate; approximately 30–40% of patients prescribed it for postherpetic neuralgia or diabetic neuropathy report a notable improvement [3]. It causes a toxic effect on the reproductive system and changes in the levels of oxidative enzymes, gabapentin (GBP), which has the chemical name 1-(aminomethyl) cyclohexaneacetic acid. The molecular formula of the drug is (C9H17NO2) , molecular weight is 171.24 [4]. Since its initial approval for use in 1993, gabapentin has been accessible as a generic drug in the US since 2004 [5] . With almost 47 million prescriptions, it ranked as the tenth most frequently prescribed drug in the US in 2021 [6]. Parke-Davis, a Pfizer company, employed several illicit tactics in the 1990s to persuade US doctors to prescribe gabapentin for unapproved purposes [7]. Millions of dollars have been spent by them to resolve legal disputes pertaining to these activities [8]. Gabapentin significantly decreased inflammation and oxidative stress caused by septic shock, as evidenced by the reduction of MDA, TNF-α, IL-1β, and IL-6 levels and an increase in GSH and SOD levels [9]. Damage from oxidative stress may have resulted in cell death, cardiovascular illness, cancer, and other neurological disorders [10-11] . Disturbances in reproduction have been connected to oxidative stress and reproductive harm caused by gabapentin[12] . Men's serum levels of sex hormone-binding globulin were elevated as a result of the oxidative stress brought on by long-term gabapentin therapy; the resulting decreased bioactivity of serum androgens led to decreased sexual activity [13].

These centrally acting medications have been demonstrated to have a downside on male reproductive function in both clinical and experimental investigations [14]. Gabapentin, when used orally, decreases plasma testosterone, FSH, LH , testicular weight, and sperm cell concentration . Long-term gabapentin use also raised plasma prolactin levels, which ultimately results in testicular histological deterioration [15]. In addition, gabapentin administration dramatically lowered the epididymal sperm count and morphology, and chronic gabapentin administration affected testicular physiology in male rats; also, gabapentin considerably reduced the weight of the testis and epididymis [16].

The aim of this study is to demonstrate the side effects of gabapentin on the oxidative stress and histopathological changes of the testes and tail of the epididymis in white male mice.

Materials and Methods

Preparation of gabapentin

The dosage of gabapentin is calculated based on the drug's half-lethal dose (LD50), which is 620 mg/kg b.w. [17]. One dose of gabapentin is selected at 800 mg/kg to test its toxic effect . Mice in the present study had an age range of 8-10 weeks and a weight range of 25-35 gm . All mice received a dosage of the medication orally, once daily for 60 days, at three different concentrations. The following equation was used to determine the dosage of medication given to the mice in this study.

X/D = W/1000: W-Weight required D-Dose or concentration W-Final volume

Samples collection

Adult mice weighing between 25 and 30 g . mice (*Mus musculus*) were used in the

present study with an age range of 8-10 weeks . The study was conducted on 24 male mice obtained from the Animal House of the Biotechnology Research Center / Nahrain University. They were divided randomly into four groups . Mice were grouped into sets of 6 animals and treated for 60 consecutive days with gabapentin 5mg/kg , 10 mg/kg , 20 mg/kg body weight and the control group givennormal sterile saline . In each cage, six mice were kept in suitable environmental conditions of 20-25°C. with free access to diet and water.

Body and organ weight of mice

Absolute mice body weight was taken before and after treatment using a regular scale, difference between the two weights was recorded. The testicles and tail ofepididymis were weighed separatelyusing a sensitive balance (Sartorius).

Analysis of enzymes

This experiment use ELISA technique . Serum enzymes was determined using enzyme linked immunsorbent assay (ELISA) . Kit was obtained from Cusabio (USA) .

Histological preparation

After the end of the treatment, the treated animals were dissected by cervical dislocation, after which the abdomen was opened with a longitudinal incision, the surrounding tissues were carefully removed, and the incision site was washed with a physiologic solution .

Samples of the testes and tail of the epididymis were fixed in 10% formalin. These samples were fixed with formalin 10% and transferred to ethanol 70%. After fixation, itsections were processed, wax blocks were produced and slides were prepared and stained with hematoxyline and eosin (H&E) . The slides were examined and photographed using a compound light microscope (Meiji) with a camera[18].

The tail of the epididymis was eliminated , and mixed with 2 ml of saline solution (NaCl 0.9) on a dish in order to examine the sperm specifications. Then, a drop of the solution was combined with a drop of the eosin on a glass slide with necrosin stains on a clean glass slide. The mixture was then smeared along the slide, dried, and incubated at 37 °C. Following the equation below, the random fields of the sperm preparation were microscopically examined in order to determine the percentage of sperm with abnormalities, including abnormalities in the sperm head and tail .

Statistical Analysis

The statistical analysis system SAS (2012) was used for the least significant difference (LSD) test (ANOVA) to compare the means in a meaningful way[19] .

Results

The results in (Table 1) show a significant decrease ($P<0.05$)in the net body weights of mice dosed with concentrations of 5 mg/kg (23.1 ± 0.45), 10 mg/kg (22.8 ± 0.71), and 20 mg /kg (21.2 ± 0.86) gabapentin , compared to the control group (28.0 ± 1.52) . Results recorded a significant decrease ($P<0.05$) in the average testicle weights of animals dosed with concentrations of 5 mg/kg (288.91 ± 8.09) , 10 mg/kg (189.96 ± 4.95), and 20 mg/kg (171.21 ± 8.84) of gabapentin , compared to the control group (316.87 ± 20.6). As for the weights of the tail of the epididymis, the results recorded a significant decrease ($P<0.05$) for animals treated with gabapentin and for all concentrations (5,10,20 mg/kg) (120.54 ± 9.18), (111.23 ± 5.3), (101.63 ± 8.21) successively , compared with the control group (132.36 ± 9.52) .

Table 1: Effect of the oral administration of Gabapentin on body weight and weight of testis, epididymis (values are mean ± SE of five animals)

	Body weight (g)		Weight of the reproductive organs (mg/100 g/bw)	
Group	Initial B.W	inal B.W	Testis	Epididymis
Control	a23.2 ± 1.35	a28.0 ± 1.52	a316.87 ± 20.6	a132.36 ± 9.52
Gabapentin (5mg/kg/bw)	a25.8 ± 0.48	b23.1 ± 0.45	b288.91 ± 8.09	b120.54 ± 9.18
Gabapentin (10mg/kg/bw)	a24.4 ± 1.32	b22.8 ± 0.71	c189.96 ± 4.95	b111.23 ± 5.3
Gabapentin (20mg/kg/bw)	a27.6 ± 0.51	b21.2 ± 0.86	c171.21 ± 8.84	b101.63 ± 8.21
*** Similar letters in the same column indicate insignificant differences (P <0.05) .**				

In this experiment a significant increase (P≤0.05) was found in MDA concentration of animals treated with gabapentin and for concentration (5.10,20) mg/kg of body weight (0.30± 3.60) (0.27 ± 4.45) (0.30±5.50) mmol/l , while in control group (0.30±3.40) mmol/l the results also showed a significant increasing (P≤0.05) found in the Catalase enzyme concentration of animals that treated with gabapentin and for concentrations (5.10,20) mg/kg of body weight (300.51 ± 14.35) (399.78±20.50)(801.75± 11.51) pg/ml ,while in control group (196.26± 9.24).As for the enzyme SOD level, the results showed a significant increase (P≤0.05) found in the SOD concentrations of animals that treated with gabapentin and for concentrations(5.10,20) mg/kg of body weight (1500.23±182.05) (2381.63± 190.40) (3440.50 ± 268.64) pg/ml compared with the control group (917.76±56.67) Table 2 . Resultsshowed a significant decreasing in vitamin E concentration in groups treated with gabapentin for concentrations (5.10,20) mg/kg of body weight (36.89± 4.55) (30.98± 1.98) (20.31±1.01) Mml/ml compared with

control group (50.13± 3.56).The results also showed a significant decrease in concentrations GSH in group treated with a drug for concentrations (5.10,20) mg/kg of body weight (10.26±2.74) (7.36±0.10) (6.10 ± 0.94) ng/ml compared with the control group (19.70± 4.01) ng/ml in (Table 2) .

Table 2 : Effect of different concentrations of gabapentin on the levels of Malondialdehyde, Catalase enzyme, SOD ,VIT.E , and Glutathione(Mean ± SE)

Group	MDA(PI/I)	CAT (Pg/ml)	SOD(Pg/ml)	VIT.E(uml/ml)	GSH(ng/ml)
Control	c 0.30±3.40	c196.26± 9.24	c917.76±56.6	a50.13±3.56	a 19.70± 4.01
Gabapentin (5mg/kg/bw)	c 0.30± 3.60	bc300.51 ±14.3	c1500.23±18 2	b36.89± 4.55	b10.26± 2.74
Gabapentin (10 mg/kg/bw)	b 0.27 ± 4.45	b399.78±20.5 0	b2381.63± 190	b30.98± 1.98	c 7.36± 0.10
Gabapentin (20mg/kg/bw)	a 0.30±5.50	a801.75± 11.51	a3440.5 ± 268	c20.31±1.01	b 6.10 ± 0.94
LSD value	0.842*	165.40*	569.49 *	8.68 *	2.03 *
Means with different letters in same column means that differed significantly . (P≤0.05)					

Histological sections of testicles in control group mice showed that the testicles appear in their normal shape with the presence of seminal tubules containing germ cells (G. C .) that make up sperm, and Leydig cells (L.C.) between the seminal tubules and each one contain cavity called Lumen (L.).

By examining histological sections of rat testes from groups treated with gabapentin at a concentration of (5) mg/kg , drug effects

were observed, which were represented by the occurrence of isolation of germ cells (D.Sp.) from the basal membrane of the seminiferous tubule, the occurrence of cellular Necrosis (N) with Edema (E) occurring between the seminiferous tubules.

By examining histological sections of rat testes of groups treated with gabapentin at a concentration of (10) mg/kg, the effects caused by drug were clearly observed, which were the occurrence of Congestion (Co.), Edema, as inFigure 1.

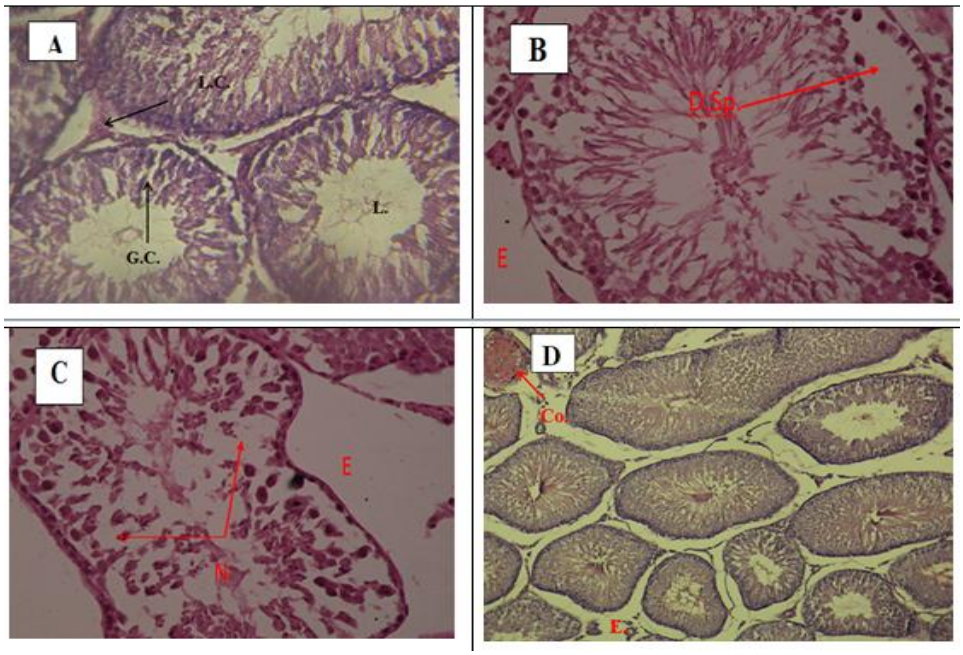

Figure 1: Microscopic images of Testes control section(A 400X) Gabapentin 5mg/kg (B , C 400X) Gabapentin 10 mg/kg (D 100X) .H&E stains

Deposition of Amyloid (Am.) in the seminiferous tubules , the cases of visible damage (Rupture) (R.) in the seminal tubule sections increased through the appearance of congestion and isolation of germ cells (S.C.), which led to atrophy of the seminal tubules (At.T) .

The histological study showed, by examining sections of mice testes for groups administered gabapentin at a concentration of (20) mg/kg, that the effects caused by the drug were observed, which were represented by the occurrence ofShrinkage in seminiferous tubule (Sh.T) and increase of Edema (E) , in addition to the effects caused by the drug, it was represented by amyloid deposition and bleeding (Hemorrhagic)) (Hm.) , as in Figure2 .

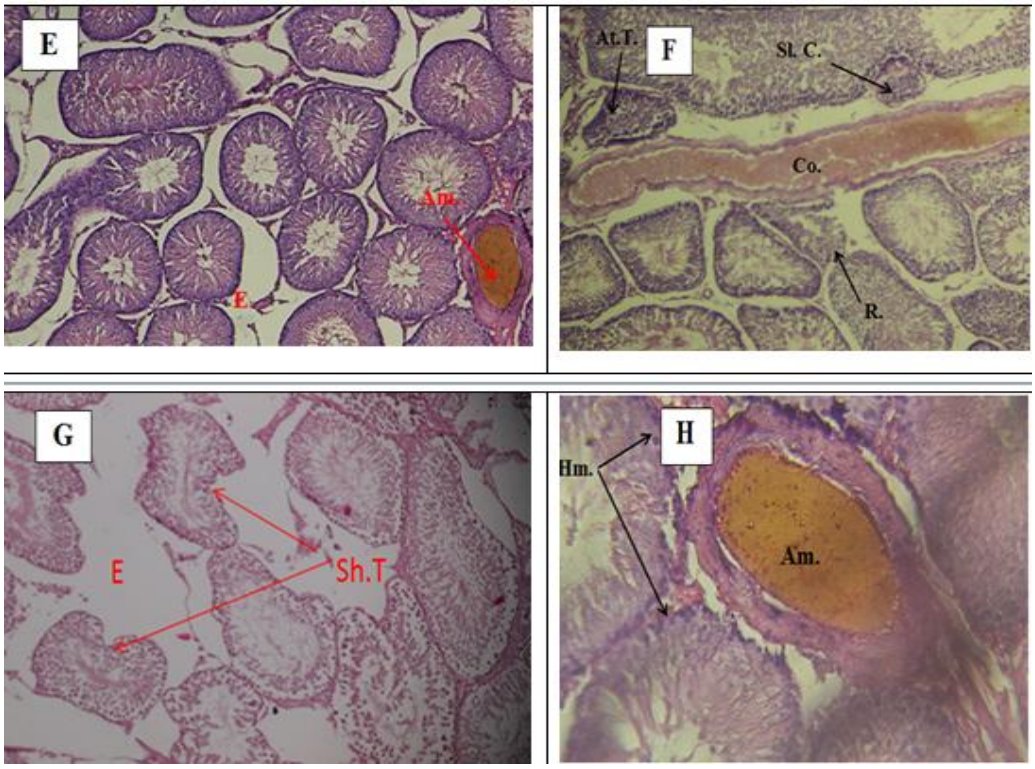

Figure 2 : Microscopic images of Testes with Gabapentin 10 mg/kg (E , F 100X), Gabapentin 20 mg/kg (G 100X) , (H400X). H&E stains

The examination of the cauda epididymis section in control group showspresence of sperms (SP.) in the lumen of tubules (T) . In the sections of treated groups with gabapentin for concentrations (5mg/kg) shows Amyloid deposition (Am.) between the tubules of tail of epididymis andAbsence sperms (A.S.), Necrosis (N) in cells and Rupture (R) of epithelium of tubules .

The study showed , by examining sections of mice testes for groups treated with gabapentin at a (10) mg/kg concentration , that occurrence hyperplasia (H) in the epithelial cells in tail of epididymis with the beginning of cilia falling in some cavities (CD) of the tubes of the tail of the epididymis, as well as the presence of degeneration (D) in the epithelial cells and the widening of the interspaces between the tubules and the occurrence of edema (E) as in Figure 3.

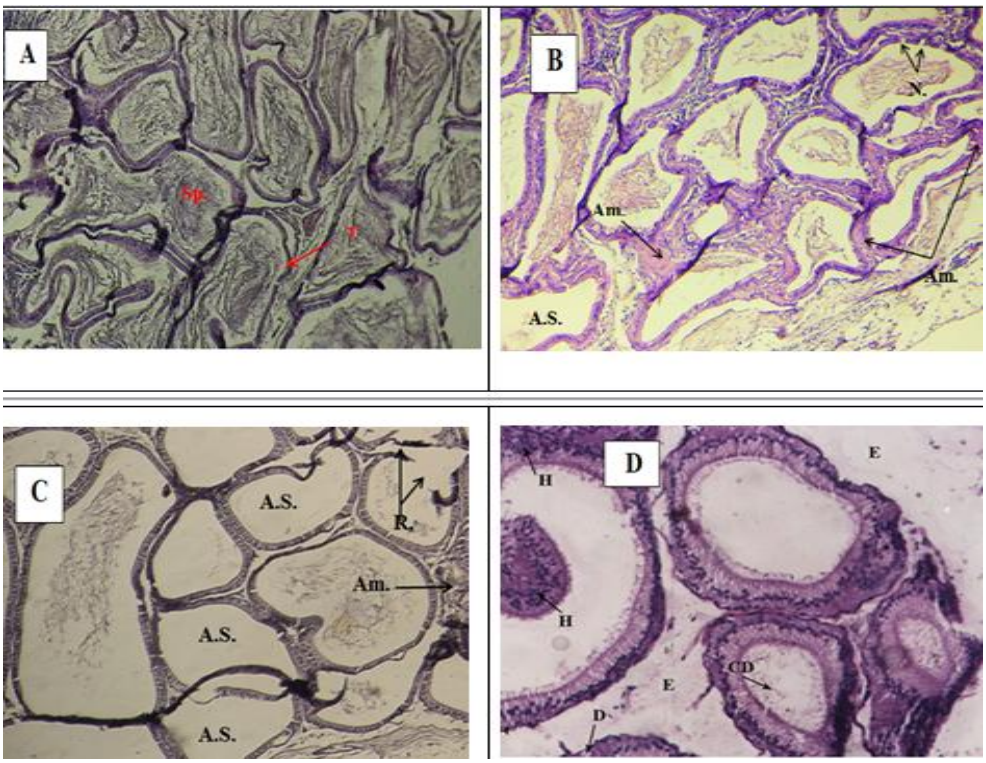

Figure 3 : Microscopic images of Cauda epididymis control section(A 100X), Gabapentin (5) mg/kg (B,C 100X), Gabapentin (10) mg/kg (D 100X) . H &E stains .

Pathological conditions continued to appear in the epididymis tissue of the third group treated with gabapentin at a concentration of 20 mg/kg, showing the occurrence of edema (E), amyloid deposition (Am.), and irregularity in the shapes of the tubules (Ir.T.), which were also observed in Figure 4.

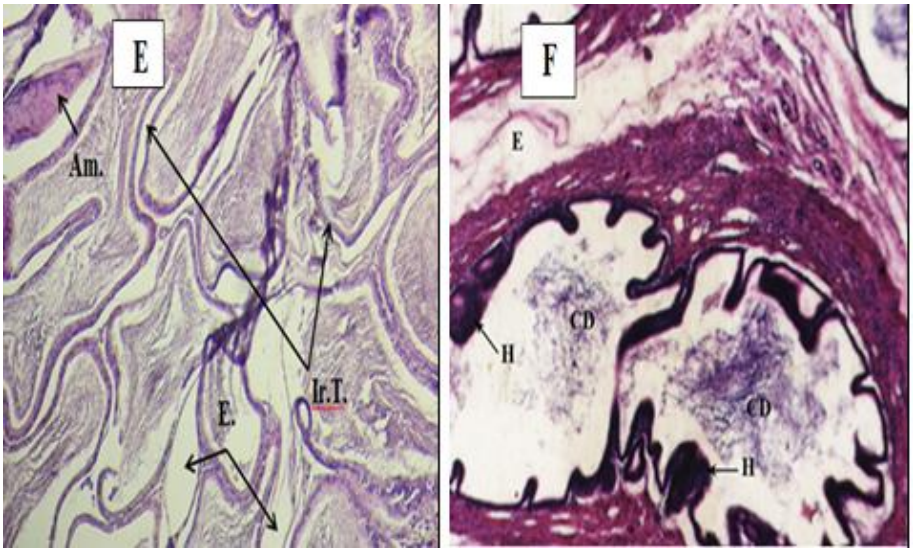

Figure 4 : Microscopic images of the cauda epididymis with Gabapentin (20) mg/kg (E,F 100X) . H&E stains .

The resultsshowedthe appearance of abnormal sperms in all concentration of gabapentin (5,10,20) mg/kg , including coiled , folded and broken tails,bent neck, , tailless , headless sperms , and sperms with cytoplasmic droplets, compared with the normal shape of the sperm, which consists of a head and a tail, as shown in Figure 5 .

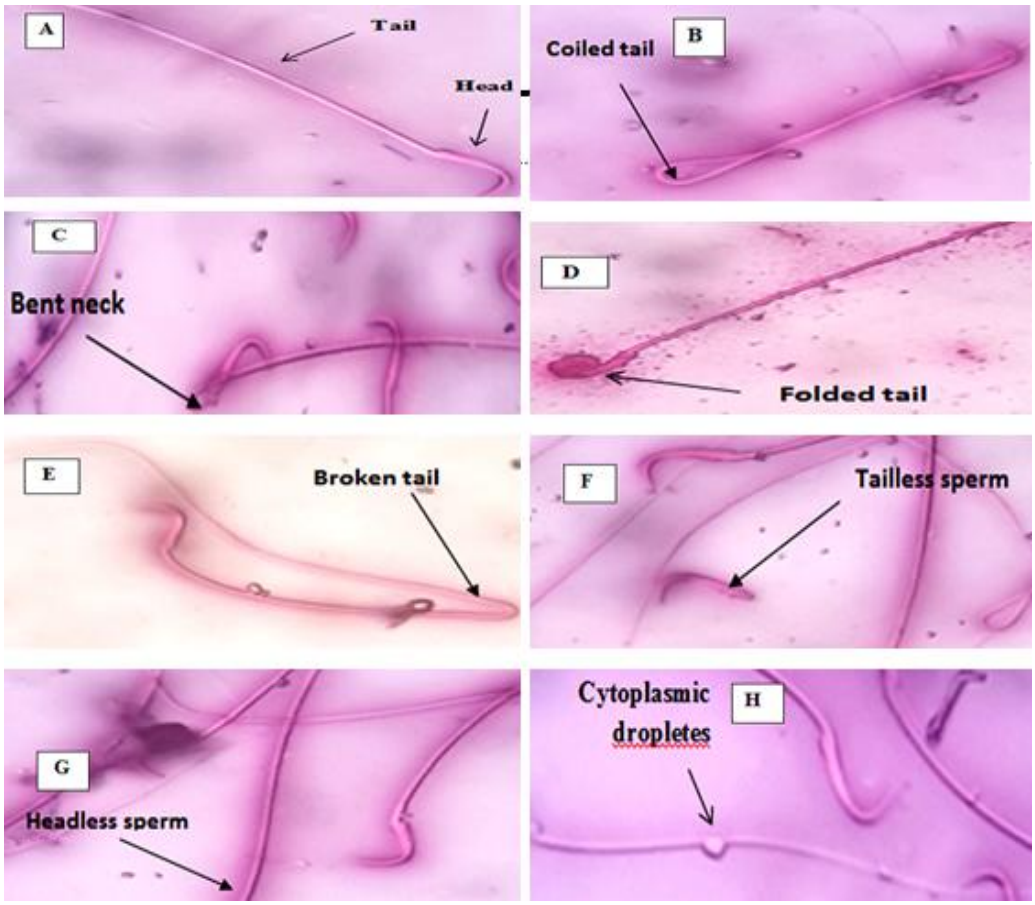

Figure5:Microscopic images of sperms : Normal (A) Sperm with Coiled tail (B) Bent neck (C) Folded tail (D) Broken tail (E Tailness sperm (F) Headless sperm(G) and Cytoplasmic droplets . (100X) .H&E stains .

Discussion

Drugs of Antiepileptic are associated withweightloss are felbamate , gabapentin, and zonisamide [20] .Numerous researchers have demonstrated that oral gabapentin intake causes rodents, rabbits, and canines to lose weight [21] . Epileptic drugs cause endocrine disruptors that increase the risk of body weight, reproductive function, growth disorders, and cancer through plastic products and industrial chemicals [22].However, research on endocrine disruptors that causes adecline in body weight, testicles, and epididymis in order to create reproductive failure, as well as tests on male fertility using high doses of epileptic medicines, have led to an increase in infertility rates [23].

Results indicated in the present study that a changes occurred in levels of (MDA,CAT, SOD, vitamin E, GSH) during gabapentin medication . MAD increase levels after gabapentin treatment in animals. Increasing level of plasma lipid peroxidation (LPO) due

to secondary metabolites formed during gabapentin administration [24]. Free radicals can start the peroxidation of membrane polyunsaturated fatty acids, which can then break them down into alkanes and aldehydes in the absence of an effective defensive mechanism [25]. Peroxidation of Lipidis thought to occur when chains of polyunsaturated fatty acid side are common [26].The peroxyl radical is produced when these chains combine with oxygen , which can get H+ from a different fatty acid, producing an ongoing process [27] .Our study indicate that significant increases in CAT and SOD activity, which may contribute to hinder organism from higher LPO levels at treatment by gabapentin [28]. Our study indicated that significant reduce in vitamin E levels. An increase of LPO formation is one of the possible mechanisms responsible for lower vitamin E levels [29]. When AEDs are metabolized in liver microsomes, lipid peroxidation increased due to the formation of superoxide therefore the mobilization of vitamin E may be increase of lipid peroxidation [30]. After dosage gabapentin treatment a substantial decrease in hepatic GSH levels was observed in this investigation. Decrease in GSH levels causes GSH conjugating with gabapentin's electrophilic metabolites in the labile pool [31], the levels of LPO also increased significantly after exposure to gabapentin, the decline in the GSH ratio in D. neapolitana was another indication of gabapentin harms [32] .

The results of a histological study of the male tract of rats showed the presence of pathological changes in both the testicles and the tail of the epididymis. The reason is that gabapentin causes disturbances in the hormonal balance, including androgen levels, which can cause a reproductive disorder [33].

Antiepileptic drugs (AEDs) have a direct effect on germ cells and sperm, and are well soluble in fats, so they are able to cross the vascular barrier of the testicle into the seminiferous tubules and cause the effect [34]. Under normal conditions of the spermatogenesis process, there are intercellular bridges that connect the germinal cells during the sperm formation stage. Spermatid bridges remain connected after released into seminiferous tubules lumen [35],but in the case of treatment with gabapentin, these bridges are destroyed due to the effect of the drug [36].In addition to the ability of gabapentin to directly interfere with germ cells, causing necrosis [37].

Gabapentin works to inhibit nerve receptors such as (GABA A), so it affects the nervous regulation of hormones, especially androgens such as testosterone, which has a negative impact on testicular function [38]. During epilepsy seizures hypothalamus gland receives variable signals from cerebral cortex, amygdala, hippocampus. Neural signals Gamma-Aminobutyric acid (GABA) and (Glutamate) have a role in disturbances of these signals, where a study showed the presence of Gamma-Aminobutyric acidA receptors also in testes and central nervous system (CNS) [39] .Antiepileptics toxicity has an effect on the testicles, in addition to atrophy of the seminal tubules, loss of germinal epithelium, and its effect on the quality of semen [40]. Low testosterone hormone levels stimulate the process of phagocytosis of the interstitium and sperm, which may stimulate the construction of lysosomal enzymes that contribute to the autolytic process, which causes increased levels of protein in the testicles and epididymis [41].

The oxidative damage caused by gabapentin results from the production of excessive amounts of proteins that accumulate in the epididymis and testicles, causing amyloid deposition [42]. Amyloid is a homogeneous protein cellular material deposited on the walls of blood vessels and basement

membranes , and its accumulation leads to the loss of cellular functions by preventing diffusion processes between cells. This occurrence is attributed to a defect in Protein synthesis [43].

As explained by [44] ,a decrease in the level of testosterone causes damage to the epididymis epithelium, and the reason is that the activity and growth of the epididymis are under the control of the testosterone hormone , as treatment with testosterone after castration Animals: It leads to the growth of the epididymis epithelium again as a result of its effect on the durability and continuity of the cells [45]. The histological sections also showed the presence of hyperplasia, which is a physiological disorder represented by a disturbance in the hormonal regulation of the cell division processes, as steroid hormones have a role in the gene expression of the cell division processes [46].

Antiepileptic drugs (AEDs) have a direct effect on germ cells and sperm, and are well soluble in fats, so they are able to cross the vascular barrier of the testicle into the seminiferous tubules and cause the effect[47-48].

Gabapentin affects the maturation and differentiation of Sertoli cells and causes damage to testicular cells [49]. On the other hand, the study showed its effect on the stages of sperm formation, its inhibitory action on the axis of Pituitary – Testicular, which leads to decreased concentration of sex hormones [50] .

Gabapentin can reduce sperm quality by decreasing testosterone and increasing estradiol levels through the anti-androgen effect [51]. BPA interferes with sperm formation by activating apoptotic pathways in reproductive cells and decreasing sex hormone levels, FSH , LH, and gonadotropin-releasing hormone (GnRH) in rats [52]. Consistent with earlier studies, the sperm count in the epididymis of rats exposed to gabapentin 50 mg/kg per day was reduced compared with the control [53].

Gabapentin stimulates the synthesis of large amounts of free radicals [54],so it causes oxidative damage to the testicles by changing the state of antioxidants in the body, in addition to stimulating the process of fat oxidation (lipoperoxidation), which affects the process of testosterone production. (Testosterone Hormone) by Leydig Cells , which gives testosterone a role in sperm maturation and their ability to fertilize [55].

A study [56]showed the occurrence of abnormal cases (deformed), represented by headless sperm, containing a cytoplasmic droplet, sperm with a wavy tail (wavey), sperm witha hooked tail and an unclear head (amorphous head with hook tail), a sperm with a coiled tail and a folded head (atrophy head with folded tail), and another with a folded tail, results explained that administration of chronic carbamazepine causes adverse reproductive outcome relatively hormonal disorders and oxidative risks as showed by biochemical andhormonal [57] .

Conclusion

The findings indicate that long-term gabapentin administration induces oxidative stress and significant histological alterations in the testes and epididymis of adult male mice . These changes impair sperm quality and suggest potential adverse effects on male fertility .

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Ethics Statements: All locations where samples were obtained were given administrative approval .

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تأثير عقار الغابابنتين على الخصيتين والبربخ وحالة مضادات الأكسدة لدى ذكور الفئران البالغة

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الملخص:

هدفت الدراسة إلى تقييم تأثيرات جرعات مختلفة من غابابنتين على الخصيتين والبربخ لدى ذكور الفئران البالغة، وعلى مؤشرات الإجهاد التأكسدي، كما بحثت تأثيره على جودة الحيوانات المنوية والوظيفة التناسلية العامة. قُسِّمت أربعة وعشرون فأراً بالغاً من الذكور عشوائياً إلى أربع مجموعات. كانت المجموعة الأولى ضابطة، حيث أُعطيت 0.1 مل من محلول ملحي معقم، بينما عُولجت المجموعات الأخرى بالغابابنتين عن طريق الفم بجرعة يومية مقدارها 0.1 مل بتراكيز (5، 10، 20) ملغم/كغم لمدة 60 يوماً متتالية. أدى الغابابنتين إلى انخفاض معنوي ($p < 0.05$) في الوزن المطلق للجسم والخصيتين وذيل البربخ لدى الفئران المعالجة، وزيادة معنوية ($P \leq 0.05$) في مستوى مالونديالدهيد في مصل الدم، وإنزيم الكاتالاز، وإنزيم ديسموتاز الفائق، بالإضافة إلى انخفاض معنوي ($P \leq 0.05$) في مستويات الجلوتاثيون وفيتامين هـ . أظهرت النتائج عدة تغيرات نسجية في الخصيتين وذيل البربخ، شملت : انعدام النطاف، وانفصال الخلايا المنوية الأولية، والنخر، والوذمة، والاحتقان، وترسب الأميلويد، وعدم انتظام الأنابيب المنوية، وتمزق ظهارة الأنابيب المنوية، وتحلل الخلايا الجرثومية، وضمور الأنابيب، وانكماشها، والنزف، وتضخم الخلايا، وتكثف النواة. كما أظهرت الحيوانات المنوية للفئران المعالجة بالدواء بثلاثة تراكيز مختلفة عدة تشوهات، منها: ذيول ملتفة، ومطوية، ومكسورة، وعنق ملتوي، وحيوانات منوية بلا ذيل، بالإضافة إلى حيوانات منوية تحتوي على قطرات سيتوبلازمية. يؤثر تناول الجابابنتين سلبًا على الخصيتين والبربخ، مما يُضعف جودة الحيوانات المنوية والوظيفة التناسلية العامة لدى الفئران. تشير هذه النتائج إلى أن الاستخدام طويل الأمد للجابابنتين قد يُشكل خطرًا على خصوبة الذكور.

الكلمات المفتاحية : إنزيمات مضادة للأكسدة، البربخ، غابابنتين، الفئران، الخصيتان