Journal of Recent Advances in Medicine

JRAM
Journal of Recent Advances in Medicine
مجلة التطورات الحديثة في الطب
Print ISSN 2636-252X - Online ISSN 2636-2538

Original Article

Effect of duloxetine hydrochloride on the testes of albino rat offspring and possible protective effect of L-carnitine (histological study)

Embryology

Samia A. Ismael[1], Samir A. Maleek[1], Amany M. Abo-Ouf[1,2]

[1]Anatomy and Embryology Department, Faculty of Medicine for Girls, Cairo, Al-Azhar University, Egypt.

[2]Anatomy and Embryology, Basic Medical Science Department, College of Medicine, Prince Sattam Bin AbdulAziz University, Al- kharj, Kingdom of Saudi Arabia.

ABSTRACT

Background: Duloxetine was a widely used antidepressant approved in 2004 with indications for use in the treatment of major depressive disorder, diabetic neuropathy, fibromyalgia, and generalized anxiety disorder. It induced toxic effects on male reproductive system. L-carnitine improved different parameters of oxidative stress.

Objective: to explore the impact of duloxetine hydrochloride treatment and the protective effects of L-carnitine on the histological structure of the testes of male albino rats born to treated mothers.

Methodology: In this study, 100 offspring out of 25 adult female albino rats were utilized. Rat females were divided equally into 5 groups as the following: first control group (CA), second control group (CB), L-carnitine group (group L) duloxetine hydrochloride treated group (D), and combined duloxetine hydrochloride and L-carnitine treated group (DL). Throughout their pregnancy and for two weeks following birth, each female in the corresponding groups were given daily oral doses of 0.96ml, 2.06ml of purified water, 36mg L-Carnitine, 1.44 mg of duloxetine hydrochloride and combined 1.44 mg of duloxetine hydrochloride with 36 mg of L-carnitine once daily. At two weeks of age, samples were collected from each group for morphometric, light and electron microscopic analyses.

Results: Studies using morphometric analysis, light and electron microscopy demonstrated a variety of degeneration, necrosis, inflammation, and fibrosis. However, L-carnitine mitigated most of the adverse effects.

Conclusion: Duloxetine hydrochloride induced various deleterious changes in the testes. These changes were improved to a large extent by L-carnitine.

JRAM 2024; 5 (2): 96- 110

Keywords: Duloxetine hydrochloride; L-Carnitine; rat; testes.

Submission Date: 15 March 2024 **Acceptance Date:** 3 September 2024

Corresponding author: Samia Ahmed Ismael, Anatomy department, faculty of medicine for girls, Cairo, Al-Azhar university, Egypt. **Tel:** 01152330897. **E-mail:** samiaahm1357@gmail.com

Please cite this article as: Ismael SA, Maleek SA, Abo-Ouf M. Effect of duloxetine hydrochloride on the testes of albino rat offspring and possible protective effect of L-carnitine (histological study). JRAM 2024; 5 (2): 96-110. DOI: 10.21608/jram.2024.226611.1229

INTRODUCTION

Pregnant women are predicted to have a depression incidence of 7–19%. Negative outcomes like low birth weight, premature birth and inadequate prenatal care have been related to untreated depression [1]. Postpartum depression is common, occurring in about 10 to 20 percent of women after giving birth. 1 to 8 percent of women take antidepressants during pregnancy [2].

Duloxetine hydrochloride (Cymbalta) is a drug from the class of antidepressants called serotonin-norepinephrine reuptake inhibitors (SNRIs). SNRIs block serotonin and norepinephrine transporters and cause increased serotonergic or noradrenergic neurotransmission [3]. Duloxetine is classified as a Category C pregnancy drug by the United States (US) Food and Drug Administration (FDA) and was first authorized in US in August 2004 [4]. Duloxetine hydrochloride taken orally is well absorbed by the body [5]. Duloxetine is metabolized primarily by two hepatic cytochrome P450 isoenzymes; CYP2D6 and CYP1A2 [3]. In the US, duloxetine received approval in 2004 for the medical treatment of diabetic neuropathy and depression. These drugs are suitable for the treatment of these pathologies during pregnancy and breastfeeding. [6] A report found that the concentration of duloxetine in the umbilical cord is low (12%) compared to maternal blood [7].

Taking this drug while breastfeeding is probably safe as only a small amount passes into breast milk [8]. Duloxetine is an antidepressant that has toxic effects on many organs, particularly the male reproductive system. It causes sexual dysfunction in men by causing

a significant decrease in androgen levels. In rat testes, it causes oxidative stress, apoptosis, and adverse effects on sperm parameters [9]. The antioxidant L-carnitine is soluble in water. It is made in the liver and kidneys from two types of amino acids called lysine and methionine. L-carnitine's primary job is transporting long-chain fatty acids from the cytoplasm to the mitochondrial matrix, where they are oxidized for energy. It also removes toxic compounds produced by these cell organelles to prevent their accumulation. This helps sperm grow up in the epididymis. Studies have shown that taking carnitine supplements can help sperm move better and increase their number [10]. Therefore, the purpose of this study was to explore the impact of duloxetine hydrochloride administration on the histological structure of testes in the offspring of male albino rats and the protective function of L-carnitine.

MATERIALS AND METHODS

Drugs: Duloxetine hydrochloride (Trade name Cymbalta) produced in Cairo by the Eli Li Organization for Chemical and Pharmaceutical Industries and was sold as capsules. Duloxetine hydrochloride was prescribed to humans at a therapeutic dose of 40 to 120 mg per day. **[11]** The average therapeutic dose (80 mg/day) was utilized in this work. The equivalent therapeutic dose for an adult albino rat was calculated using the Paget and Barnes formula [12] to be 80*18/1000 = 1.44 mg/rat. 20 milliliters of purified water were used to dissolve a 30-milligram duloxetine hydrochloride tablet, and the adult rat was given 1.44 mg of duloxetine hydrochloride in 0.96 ml of purified water. One daily dosage of distilled water and distilled water mixed with the medication was given orally by gavage to controlled and treated albino rats, respectively. Arab Organization for Pharmaceuticals and Medicinal plants (MEPACO- MEDIFOOD), Sharkeya- Egypt produced L-carnitine in pill form. L-carnitine has a therapeutic dosage of 1000–3000 mg per day for humans. [13]**.** In this experiment, the average therapeutic dose of 2000 mg/day was employed. Using Paget and Barnes formula **[12]**, the adult albino rat equivalent therapeutic dose was determined to be 2000* 18/1000 = 36 mg/rat.20 milliliters of purified water were used to dissolve a 350 mg L-carnitine tablet. Then, the adult rat was given L-carnitine from distilled water that contained 36 mg of L-carnitine. Purified water alone or in combination with the drug was administered orally by gavage as a single daily dose to control and treated albino rats respectively.

Animals: An experimental study was conducted on 38 mature albino rats (25 females, 13 males) and 100 of their young were utilized. The mature albino rats weighed an average of 180–200 grams. They were acquired and given veterinary treatment at the Al-Azhar university faculty of medicine for girls, animal house. They kept in clean properly ventilated cages with a 12-hour light/dark cycle and were given a balanced diet of rat chow and water (standard food pellets- El-Nasr Company, Abo-Zaabal- Egypt).

Two weeks prior to the commencement of the experiment, mature males and females were separated for the purpose of acclimatization, then each male was kept in a separate cage (40 x 27.5 x 19.5 cm) with two females to allow mating. Only one cage had one male and one female. The adult female rats were considered to be in their first day of pregnancy if they had vaginal plug. The 25 pregnant albino rats were divided equally among the following 5 groups:

I. **First control group (Group CA):** Every pregnant rat was given daily 0.96 milliliters of purified water throughout pregnancy and for 2 weeks after delivery.
II. **Second control group (Group CB):** Every pregnant rat received 2.06 milliliters of purified water daily throughout pregnancy and for 2 weeks following delivery.
III. **L-carnitine treated group (Group L):** Every pregnant rat was received 36 milligrams of L-carnitine throughout pregnancy and for 2 weeks following delivery once daily.
IV. **Duloxetine hydrochloride treated group (Group D):** Every pregnant rat received 1.44 milligrams/ day of duloxetine hydrochloride once daily for the course of the pregnancy and for two weeks following delivery.
V. **Combined duloxetine hydrochloride and L-carnitine treated group (Group DL):** Throughout pregnancy and for two weeks following delivery, every pregnant rat received 1.44 milligrams of duloxetine hydrochloride as well as 36 milligrams of L-carnitine once daily.

Collection of the specimens and preparation for examination:

Two weeks following birth, samples from every group were gathered. Two-week-old offspring lightly anaesthetized by diethyl ether inhalation. Each rat's testes were removed and utilized for histological studies (the testes of ten offspring were prepared for light microscopy and morphometric studies, while the remaining ten offspring were prepared for electron microscopy).

Histological analysis

1. **Light microscopic analysis:** Testes embedded in Bouin solution and processed for paraffin blocks. Paraffin blocks were sliced into 5 µm transverse sections and stained with Haematoxylin and Eosin [14] to examine the testicular structure, Masson's trichrome [15] to demonstrate collagen fibers and immunohistochemistry **[14]** using caspase-3 for detecting apoptotic cells. Images were captured in anatomy department, faculty of medicine for girls, Al-Azhar university, Cairo, Egypt, using a Leica DM750 microscope that was connected to a digital camera.
2. **Transmission electron microscopic analysis:** Specimens were fixed in glutaraldehyde, washed with phosphate buffer, and preserved with osmium tetroxide. Specimens underwent phosphate buffer

washing, alcohol dehydration, and epoxy resin embedding. To find the ultrathin section area, 1micrometer thick sections were cut using an ultratome, stained, and analyzed. Lead citrate and uranyl acetate were used to stain 60 nm ultrathin slices, which were then placed on copper grids [14]. Sections were inspected at Al-Azhar university's regional mycology and biotechnology center, Cairo, Egypt, using an electron microscope for transmission (JEOL1010 EX II, Japan). Additionally, at the histology department of the Faculty of Medicine for Girls at Al-Azhar University in Cairo, Egypt.

3. **Morphometric study:** The department of oral and dental pathology, Al-Azhar university, faculty of dental medicine for girls, Cairo, Egypt, used a Leica Qwin 500 image processing computer system to measure collagen fiber percentage in testicular sections stained with Masson's trichrome stain, and to evaluate immune reactivity by estimating the area filled with positive immunostained cells from the total number of cells. Ten rats from each group were photographed at a power field of x 100 (2.3 mm field`s diameter) on ten slides.

Statistical analysis

The SPSS statistical program was used to analyze collagen fibers and immunohistochemical staining (IHC) of the analyzed groups. After analyzing the data (which were presented as means ± standard deviation), one-way ANOVA was used for comparison between groups, and a Tuckey post-Hoc test was used for multiple comparisons. *P* value of less than 0.05 was considered statistically significant [16].

RESULT

I-Control group (Group C): Light and electron microscopic analysis of groups; CA, CB and L revealed insignificant variations, so their data were combined as (GC).

Light microscopic analysis of the control group **(GC)** testes demonstrated that the testicular capsule was consisted of an outer layer, the tunica albuginea, which was a fibrous coat consisted of connective tissue fibers and spindle shaped cells with elongated deeply stained basophilic nuclei and an inner layer, the tunica vasculosa, which consisted of loose connective tissue containing blood vessels [figure 1 a, b and c]. The ***Sertoli cells*** appeared pyramidal-shaped and had elongated faintly stained basophilic nuclei with prominent nucleoli. Their long axes were perpendicular to the basal laminae. Note the pseudostratified appearance of ***Sertoli cells***, which was due to rapid expansion of them with limited increase in tubular diameter in this age [figure 1 b]. The ***spermatogonia A*** cells appeared few and lied along the basal lamina in-between the Sertoli cells. They appeared large and had large oval lightly stained basophilic nuclei, and their long axes were parallel to the basal laminae [figure 1 b]. The ***spermatogonia B*** appeared as small round cells between the Sertoli cells and had small rounded deeply stained basophilic nuclei [figure 1 b]. The ***primary spermatocytes*** appeared few, large and rounded cells lied near the centers of many seminiferous tubules. They had rounded deeply stained basophilic nuclei [figure 1 b]. The ***interstitial tissue*** of the testes was scanty and the ***interstitial cells of Leydig*** were few and appeared singly scattered between the seminiferous tubules. They were irregular in shape and had small rounded vesicular basophilic nuclei [figure 1 a, b, c and d]. Fine collagen fibers in the testicular capsule; tunica albuginea and tunica vasculosa, seminiferous tubules' basal lamina, blood vessels wall and the interstitial tissue were distributed normally in sections of the testis stained with

Masson's trichrome stain [figure 1 c]. The sections of the testis showed a weak positive Caspase 3 immunoreaction as cytoplasmic faint brown color in the interstitial tissue, as well as in some germ cells [figure 1 d].

Electron microscopic analysis of the testes of the control **(GC)** found that the seminiferous tubules were surrounded by ***basal laminae*** composed of the basement membranes and inner cellular layer. The basement membrane appeared as thin homogenous layer enclosing the seminiferous tubule. One layer of myoid cells made up the inner cellular layer, which had euchromatic nuclei with periphery arranged heterochromatin. There was a gap, separating the myoid cells from the basement membrane and contained considerable amount of collagen fibers and another narrow gap containing few collagen fibers outside them [figure 4 a, b]. The ***Sertoli cells*** appeared pyramidal and lied perpendicular to the basement membrane. It had irregular nuclei, which were euchromatic and had prominent nucleoli. Their cytoplasm had rough endoplasmic reticulum, free ribosomes and small, rounded and elongated mitochondria [figure 4 a].

Spermatogonia A possessed a wide area of contact with the basement membrane. They appeared oval-shaped and contained oval euchromatic nuclei with prominent eccentric nucleoli. Their cytoplasm had rough endoplasmic reticulum, free ribosomes and few round and oval mitochondria [figure 4 b]. The ***spermatogonia B*** appeared round in form and had large clumps of peripherally located heterochromatin in euchromatic nuclei. Oval or rounded mitochondria, rough endoplasmic reticulum and free ribosomes in their cytoplasm [figure 4 c]. ***Primary spermatocytes*** appeared round or oval with heterochromatic nuclei. Small oval mitochondria, free ribosomes, and few rough endoplasmic reticula in their cytoplasm [figure 4 d]. The ***interstitial tissues*** formed of interstitial cells of Leydig and few collagen fibers. The ***interstitial cells of Leydig*** had an oval euchromatic nuclei with notable nucleoli. Well-developed highly distended smooth endoplasmic reticulum, oval mitochondria, free ribosomes, fat droplets, and secondary lysosomes were found in their cytoplasm contained [figure 4e].

Morphometric analysis showed insignificant differences in the collagen fibers and immune reaction between the **CA, CB and L groups** [table 1 and figure 7].

II- Duloxetine hydrochloride treated group (Group D):

Light microscopic analysis of the testes of **group D** revealed that testicular capsules were consisted of tunica albuginea, which appeared irregular and widely separated from the seminiferous tubules and the tunica vasculosa, which appeared loose and had congested blood vessel. The interstitial tissue contained a homogenous eosinophilic material [figure 2 a, b]. Some cells of the seminiferous tubules had cytoplasmic vacuoles and nuclear alterations include shrunken deeply stained nuclei, nuclear fragmentation and fading of their basophilia. Some ***Leydig interstitial cells*** had shrunken deeply stained nuclei [figure 2 b]. A noticeable increase in the collagen fibers distribution in the testicular capsule; tunica albuginea and tunica vasculosa, the seminiferous tubules' basal lamina, blood vessels walls and the interstitial tissue in comparison to the control groups was noted in the testis sections stained with ***Masson's trichrome stain*** [figure 1 c] and [figure 2 c]. The immune stained sections of the testis with *Caspase 3* ***stain*** showed a strong positive reaction as a brown color in the interstitial connective tissue, the follicular lumen, and the germ cells in comparison to the control groups [figure 1 d] and [figure 2 d].

Electron microscopic examination of **group D** testes showed that the ***basal lamina'*** basement membrane appeared slightly irregular in some seminiferous tubules. There were in the gap between myoid cells and the basement membrane a slight increased collagen fiber, while fewer in other parts. Some myoid cells exhibited chromatin-fading regions and asymmetric euchromatic nuclei. [figure 5 a, b, c]. Some ***Sertoli cells*** had irregular euchromatic nuclei with prominent nucleoli. Their cytoplasm contained vacuoles, cristae-destructed mitochondria and degraded mitochondria [figure 5 a]. Some ***spermatogonia A*** appeared pyramidal and possessed euchromatic nuclei with notable nucleoli. Vacuoles, degraded mitochondria, cristae-destructed mitochondria, and dilated rough endoplasmic reticulum were all present in their **cytoplasm. [figure 5 b].** Some ***spermatogonia B*** appeared round and included heterochromatic nuclei with presence of condensed clumps of heterochromatin and patches of chromatin fading. They had degraded mitochondria and vacuoles in their cytoplasm [figure 5 c]. Some ***primary spermatocytes*** nearly appeared round and had large heterochromatic central nuclei with ill-defined outlines. Their cytoplasm had rough endoplasmic reticula and cristae-destructed mitochondria [figure 5 d]. The ***interstitial tissue*** contained abundant collagen fibers bundles cut in different directions and ***Leydig interstitial cells*** with poorly defined boundaries and irregular nuclei with more peripheral heterochromatin clumps, and chromatin fading [figure 5 e].

Morphometric analysis showed a significant increase in the collagen fibers and immune response in group ***D*** when compared with that of **CA, CB and L groups** [table 1 and figure 7].

III- Combined duloxetine hydrochloride and L-Carnitine treated group (Group DL):

Light microscopic analysis of group **DL** testes showed thin, wavy testicular capsule and consisted of tunica albuginea and tunica vasculosa which resembled the control group [figure 1 a, b, c] and [figure 3 a, c]. The spermatogenic cells were improved and appeared to be roughly the same as the control group. But few cells had cytoplasmic vacuoles and shrunken deeply stained nuclei as compared with **D** group [figure 1 b], [figure 2 b] and [figure 3 b]. The ***interstitial tissue*** consisted of blood vessels and ***interstitial cells of Leydig*** with normal appearance as contrasted with the control group [figure 1 a, b] and [figure 3 a, b].

Masson's trichrome stained sections when compared with group **D,** the testicular capsule; tunica albuginea and tunica vasculosa, the basal lamina surrounding seminiferous tubules, the walls of blood vessels, and the interstitial tissue all appeared to have less collagen fibers distributed throughout them. However, the collagen fibers showed a mild increase in contrast to the control group [figure 1 c], [figure 2 c] and [figure 1 c]. ***Caspase 3 stained*** sections of the testis showed that the testis was more or less resembled the control group and less than group **D** with weak positive reaction as a brown color in the interstitial connective tissue, the follicular lumen and the germ cells [figure 1 d], [figure 2 d] and [figure 1 d].

Electron microscopic analysis of **DL group** showed that the seminiferous tubules were surrounded by ***basal laminae*** which appeared more or less resembled the control group **[**figure 4 a, b] and [figure 6 a, b]. The ***Sertoli cells*** had characteristic irregular euchromatic nuclei with notable nucleoli. Their cytoplasm still had very small vacuoles and mitochondria in contrast to those in the control group and group **D** [figure 4 a], [figure 5 a] and [figure 6 a]. The ***spermatogonia A*** exhibited euchromatic nuclei with prominent nucleoli. Their cytoplasm still had few vacuoles and mitochondria with destroyed cristae as opposed to the control group and group **D [**figure 4 b], [figure 5 b] and [figure 6 b]. The ***spermatogonia B*** looked to be roughly the same as the control group. However, their cytoplasm contained few cytoplasmic vacuoles and mitochondria with destroyed cristae [figure 4 c] and [figure 6 c]. The ***primary spermatocytes*** appeared much the same as the control group. However, their cytoplasm had few mitochondria with destroyed cristae as opposed to group **D** [figure 4 d], [figure 5 d] and [figure 6 d]. The ***interstitial tissue*** consisted of ***interstitial cells of Leydig*** and collagen fibers. Most of interstitial cells of Leydig appeared more or less

similar to the control group while others still had nuclei with chromatin fading. The collagen fibers appeared more than the control group and less than group **D** [figure 4 e], [figure 5 e] and [figure 6 e].

Morphometric analysis showed significant reduction in the immune response and collagen fibers in ***DL*** *group* relative to the group ***D***. However, it showed insignificant increase in collagen fibers and immune response in group ***DL*** when compared with ***CA, CB and L*** groups **[table 1 and figure 7]**.

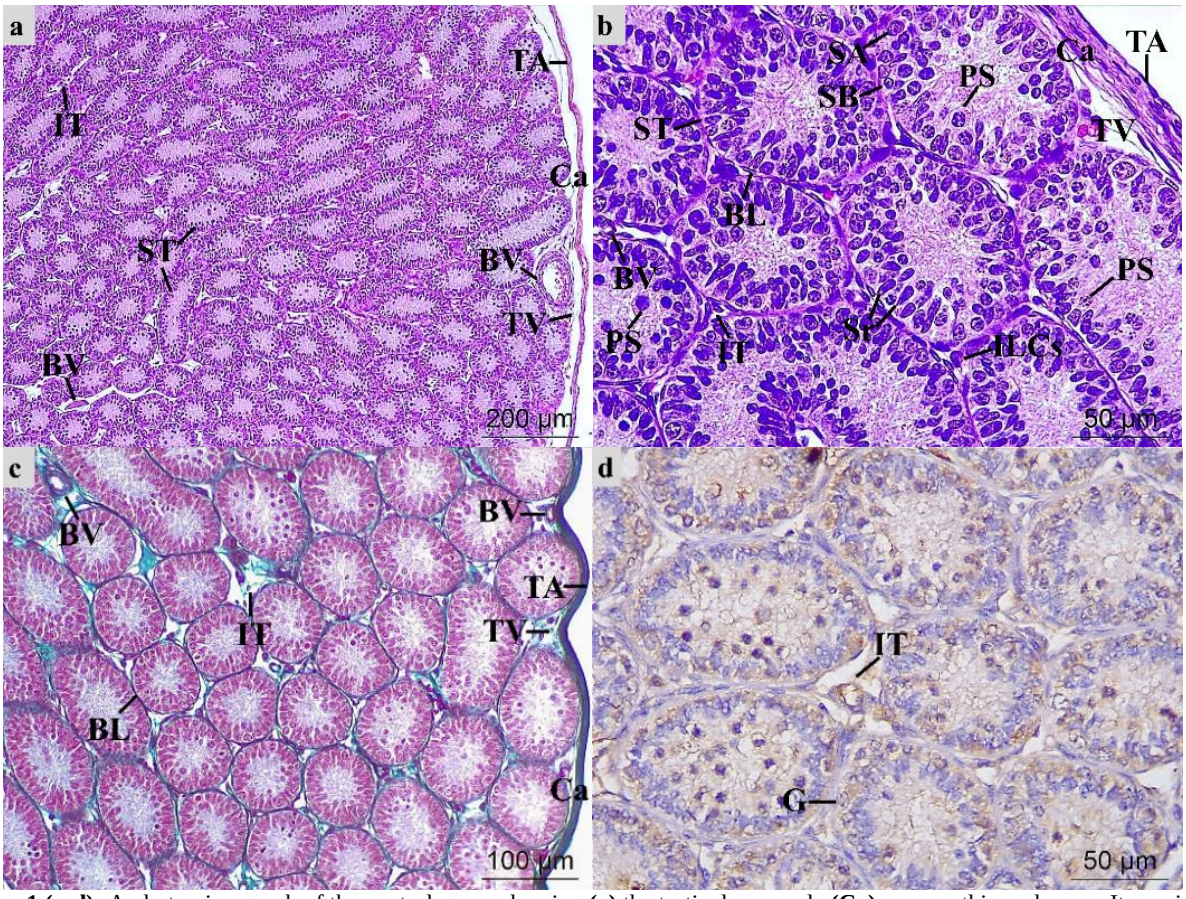
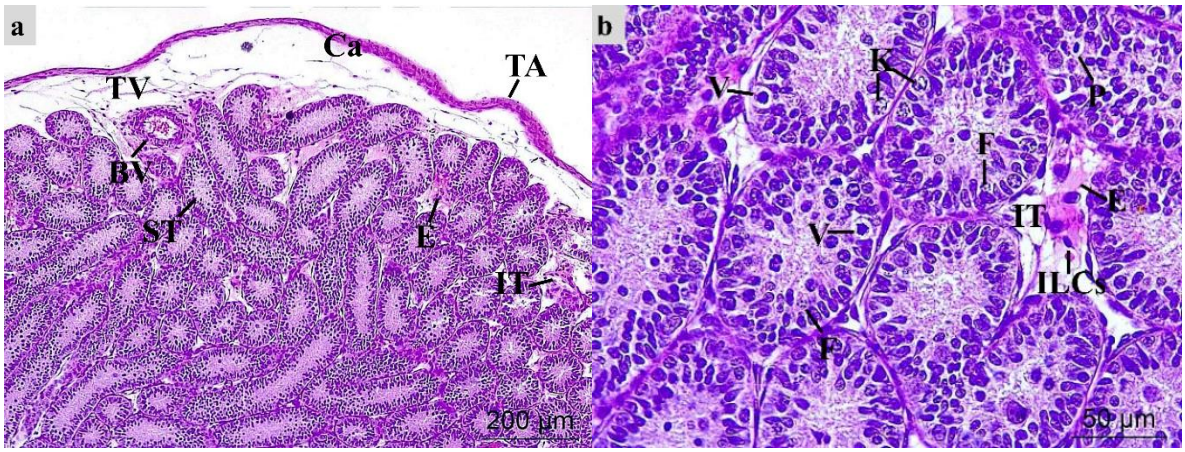


Figure 1 (a-d): A photomicrograph of the control group showing **(a)** the testicular capsule **(Ca)** appears thin and wavy. It consists of tunica albuginea **(TA)** and tunica vasculosa **(TV)**, which consists of loose connective tissue containing blood vessels **(BV)**. The seminiferous tubules **(ST)** are separated by scanty interstitial tissue **(IT)** containing blood vessel **(BV) (H and E X 100). (b)** The testicular capsule **(Ca)** consists of tunica albuginea **(TA)** and tunica vasculosa **(TV)**. The seminiferous tubules **(ST)** are surrounded by thin basal laminae **(BL)**. The Sertoli cells shows pseudostratified appearance and have elongated lightly stained basophilic nuclei **(Sr)**. The spermatogonia A have oval lightly stained basophilic nuclei **(SA)**. The spermatogonia B have small rounded deeply stained basophilic nuclei **(SB)**. The primary spermatocytes have deeply stained basophilic nuclei **(PS)**. The interstitial tissue **(IT)** consists of blood vessel **(BV)** and interstitial cells of Leydig **(ILCs)** which have vesicular basophilic nuclei **(H and E X 400). (c)** Normal distribution of collagen fibers in the testicular capsule **(Ca)**; tunica albuginea **(TA)** and tunica vasculosa **(TV)**, the basal lamina **(BL)** around the seminiferous tubules, the wall of blood vessels **(BV)** and the interstitial tissue **(IT) (Masson's trichrome X 200). (d)** A weak positive reaction as cytoplasmic faint brown color in the interstitial tissue **(IT)** as well as in some germ cells **(G) (Caspase 3 X 400)**.



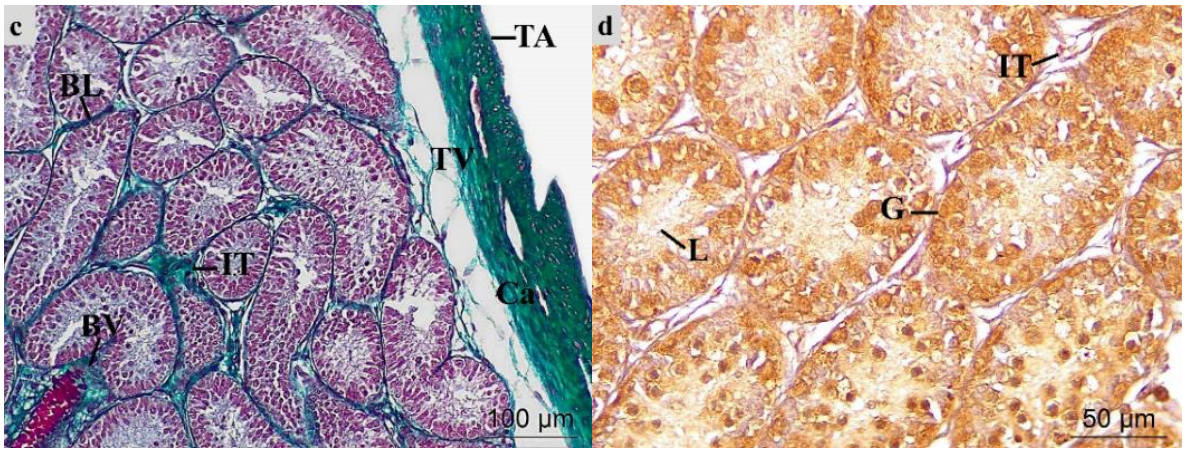


Figure 2 (a-d): A photomicrograph of duloxetine hydrochloride treated group showing **(a)** The testicular capsule **(Ca)** consists of irregular tunica albuginea **(TA)**, which is widely separated from the seminiferous tubules and tunica vasculosa **(TV)**, which has congested blood vessels **(BV)**. The seminiferous tubules **(ST)** are separated from each other by the interstitial tissue **(IT)** which contains a homogenous eosinophilic material **(E) (H and E X 100). (b)** The seminiferous cells have cytoplasmic vacuoles **(V)**, nuclei with fading of their basophilia **(K)**, shrunken deeply stained nuclei **(P)** and nuclear fragmentation **(F)**. The interstitial tissue **(IT)** contains interstitial Leydig cells with shrunken deeply stained nuclei **(ILCs)** and homogenous eosinophilic material **(E) (H and E X 400). (c)** An apparent increase in the distribution of collagen fibers in the testicular capsule **(Ca)**; the tunica albuginea **(TA)** and tunica vasculosa **(TV)**, the basal lamina **(BL)** around the seminiferous tubules, the walls of blood vessels **(BV)** and the interstitial tissue **(IT) (Masson's trichrome X 200). (d)** A strong positive reaction as a brown color in the interstitial connective tissue **(IT)**, the tubular lumen **(L)** and the germ cells **(G) (Caspase 3 X 400).**

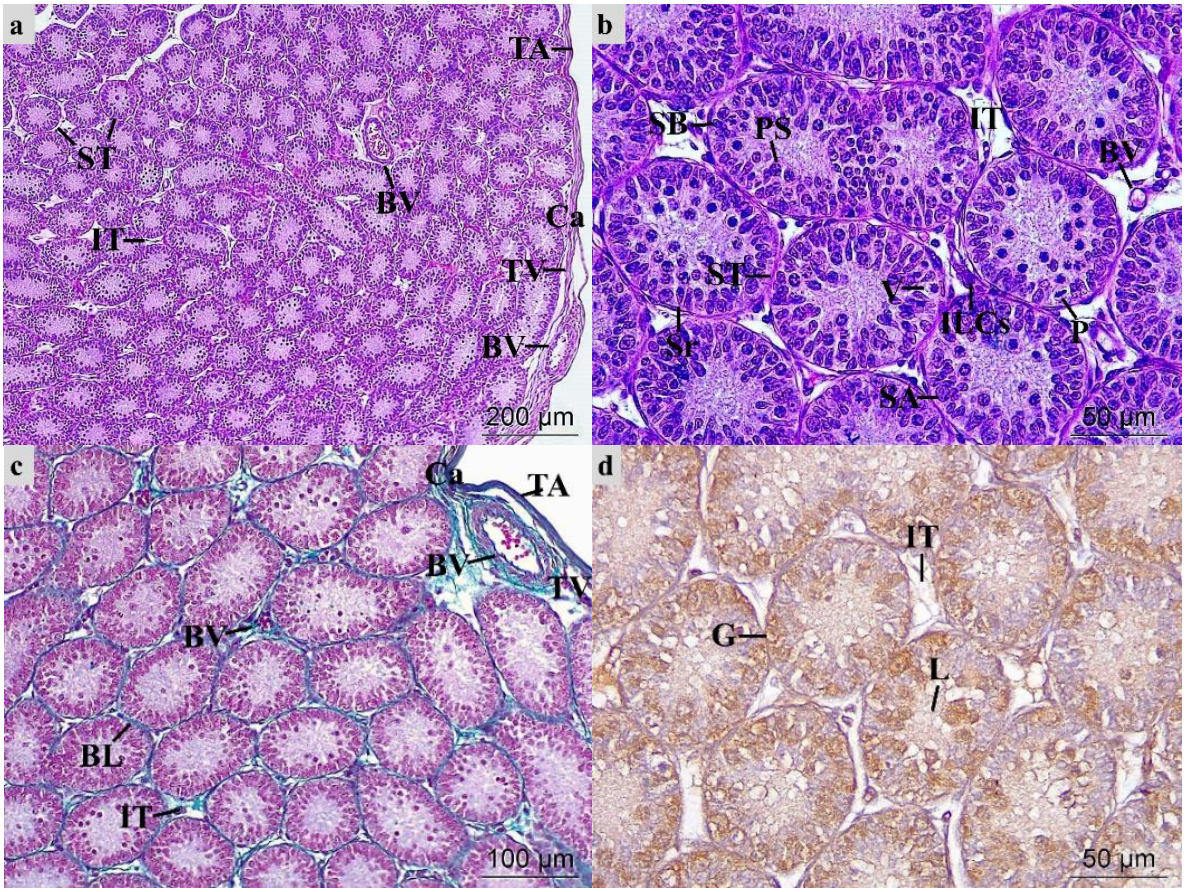


Figure 3: (a-d) A photomicrograph of combined duloxetine hydrochloride and L-carnitine treated group showing **(a)** The testicular capsule **(Ca)** appears thin, wavy and consists of tunica albuginea **(TA)** and tunica vasculosa **(TV)** containing blood vessels **(BV)**. The seminiferous tubules **(ST)** are separated by the interstitial tissue **(IT)** containing blood vessel **(BV) (H and E X 100). (b)** Most of the seminiferous cells; Sertoli **(Sr)**, spermatogonia A, B **(SA) (SB)** and primary spermatocytes **(PS)** appear normal. Scanty cells have cytoplasmic vacuoles **(V)** and shrunken deeply stained nuclei **(P)**. The interstitial tissue **(IT)** consists of blood vessel **(BV)** and interstitial cells of Leydig **(ILCs)** with normal appearance **(H and E X 400). (c)** A mild increase in the distribution of collagen fibers in the testicular capsule **(Ca)**; the tunica albuginea **(TA)** and tunica vasculosa **(TV)**, the basal lamina **(BL)** around the seminiferous tubules, the walls of blood vessels **(BV)**, and the interstitial tissue **(IT) (Masson's trichrome X 200). (d)** A weak positive reaction as a faint brown color in the interstitial connective tissue **(IT)**, the tubular lumen **(L)** and the germ cells **(G) (Caspase 3 X 400).**

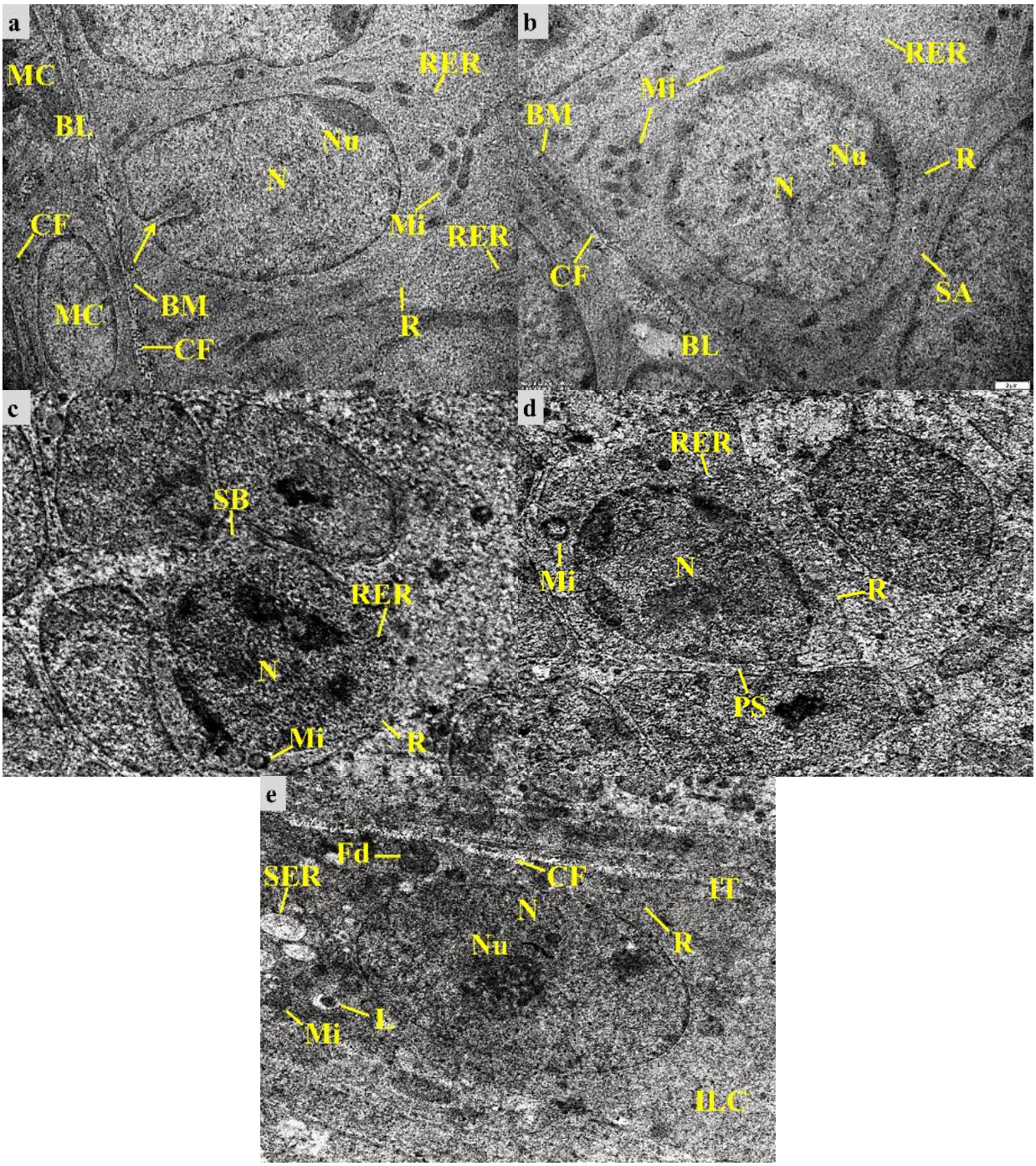


Figure 4: (a-e) An electron micrograph of the control group showing **(a)** The basal lamina **(BL)** consists of basement membrane **(BM),** myoid cells **(MC)** and collagen fibers **(CF)** between them. The Sertoli cell has an irregular **(arrow)** euchromatic nucleus **(N)** with prominent nucleolus **(Nu)**. Its cytoplasm contains small rounded and elongated mitochondria **(Mi)**, rough endoplasmic reticulum **(RER)** and free ribosomes **(R) (EM X 10000). (b)** The spermatogonium A **(SA)** has euchromatic nucleus **(N)** with prominent eccentric nucleolus **(Nu)**. Its cytoplasm contains round and elongated mitochondria **(Mi)**, and free ribosomes **(R)**. Notice the basal lamina **(BL)** consists of thin basement membrane **(BM)** and collagen fibers **(CF) (EM X 10000). (c)** The spermatogonium B **(SB)** appears spherical in shape and has euchromatic nucleus **(N)** with peripherally located heterochromatin. Its cytoplasm contains round mitochondria **(Mi)**, free ribosomes **(R)** and rough endoplasmic reticulum **(RER) (EM X 10000). (d)** The primary spermatocyte **(PS)** has heterochromatic nucleus **(N)**. Its cytoplasm contains oval mitochondria **(Mi)**, free ribosomes **(R)** and few rough endoplasmic reticula **(RER) (EM X 10000). (e)** The interstitial tissue **(IT)** consists of few collagen fibers **(CF)** and interstitial cell of Leydig **(ILC)** having euchromatic nucleus **(N)** with prominent nucleolus **(Nu)** and its cytoplasm contains well-developed highly distended smooth endoplasmic reticulum **(SER)**, oval mitochondria **(Mi)**, free ribosomes **(R)**, fat droplets **(Fd)**, and secondary lysosomes **(L) (EM X 10000).**

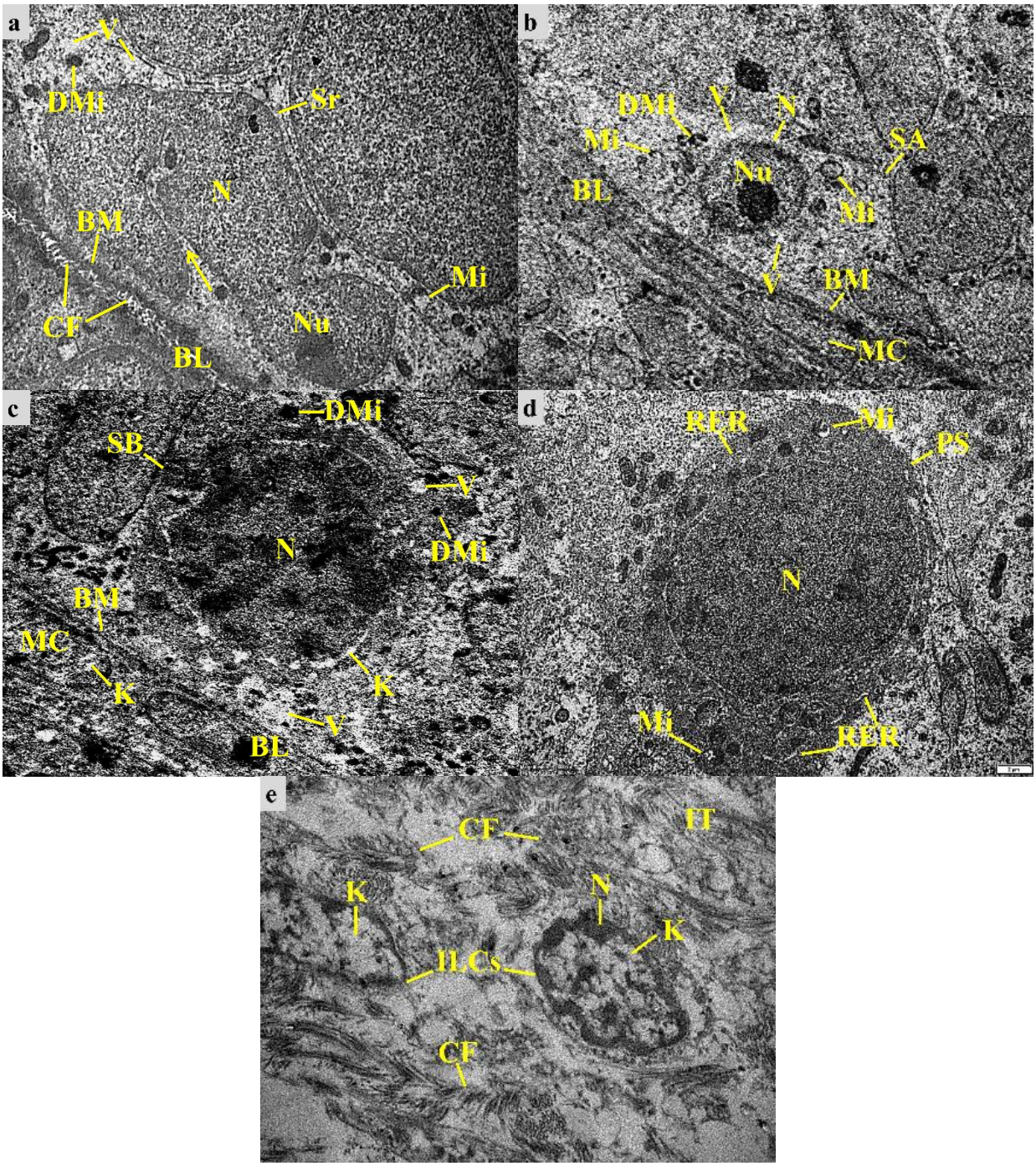


Figure 5: (a-e) An electron micrographs of duloxetine hydrochloride treated group showing **(a)** The Sertoli cells **(Sr)** have irregular **(arrow)** euchromatic nuclei **(N)** with prominent nucleoli **(Nu)**. Their cytoplasm contains vacuoles **(V)**, mitochondria with destructed cristae **(Mi)** and degenerated mitochondria **(DMi)**. The basal lamina **(BL)** has slightly irregular basement membrane **(BM)** and a slight increased collagen fiber **(CF) (EM X 10000). (b)** The spermatogonia A **(SA)** are pyramidal in shape and have euchromatic nuclei **(N)** with prominent nucleoli **(Nu)**. Their cytoplasm contains vacuoles **(V)**, mitochondria with destructed cristae **(Mi)**, degenerated mitochondria **(DMi)**, and dilated rough endoplasmic reticulum **(RER)**. The basal lamina **(BL)** consists of basement membrane **(BM)**, myoid cells **(MC)**, and collagen fibers **(CF) (EM X 10000). (c)** The spermatogonia B **(SB)** has heterochromatic nucleus with condensed clumps of heterochromatin **(N)**. The nucleus has areas of chromatin fading **(K)**. Its cytoplasm contains vacuoles **(V)** and degenerated mitochondria **(DMi)**. The basal lamina **(BL)** consists of basement membrane **(BM)** and myoid cells **(MC)**, which have euchromatic nuclei with areas of chromatin fading **(K) (EM X 10000). (d)** The primary spermatocyte is nearly round **(PS)**. It has a large heterochromatic central nucleus **(N)** with ill-defined outlines. Its cytoplasm contains mitochondria with destructed cristae **(Mi)** and rough endoplasmic reticula **(RER) (EM X 10000). (e)** The interstitial tissue **(IT)** contains abundant collagen fibers **(CF)** bundles cut in different directions and two interstitial cells of Leydig **(ILCs)** with ill-defined outlines and having irregular nuclei with increased peripheral clumps of heterochromatin **(N)** with presence of chromatin fading **(K) (EM X 10000)**.

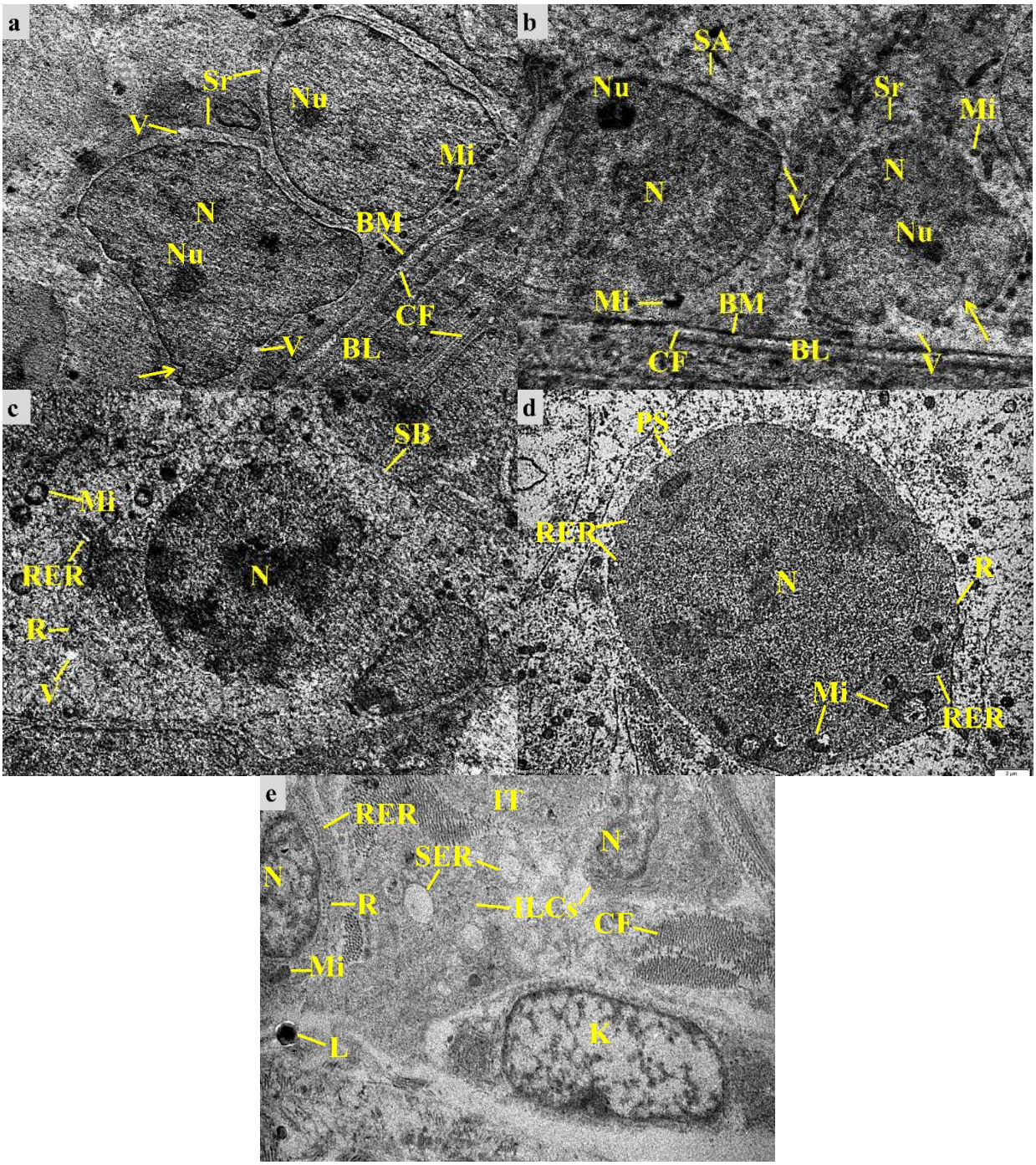


Figure 6: (a-e) An electron micrograph of combined duloxetine and L-carnitine treated group showing **(a)** The Sertoli cells **(Sr)** have irregular **(arrow)** euchromatic nuclei **(N)** with prominent nucleoli **(Nu)**. Their cytoplasm contains very small cytoplasmic vacuoles **(V)** and mitochondria **(Mi)**. The basal lamina **(BL)** consists of basement membrane **(BM)**, and collagen fibers **(CF) (EM X 10000). (b)** The spermatogonium A **(SA)** has euchromatic nucleus **(N)** with prominent eccentric nucleolus **(Nu)**, few cytoplasmic vacuoles **(V)** and mitochondria with destructed cristae **(Mi)**. Notice also, the Sertoli cell **(Sr)** has irregular **(arrow)** euchromatic nucleus **(N)** with prominent nucleolus **(Nu)**, few cytoplasmic vacuoles **(V)** and oval or elongated mitochondria **(Mi)**. The basal lamina **(BL)** consists of basement membrane **(BM)** and collagen fibers **(CF) (EM X 10000). (c)** The spermatogonium B **(SB)** has euchromatic nucleus with peripherally located heterochromatin **(N)**, rough endoplasmic reticulum **(RER)**, free ribosomes **(R)**, few cytoplasmic vacuoles **(V)** and mitochondria with destructed cristae **(Mi) (EM X 10000). (d)** The primary spermatocyte **(PS)** has heterochromatic nucleus **(N)**, rough endoplasmic reticula **(RER)**, free ribosomes **(R)** few mitochondria with destructed cristae **(Mi) (EM X 10000). (e)** The interstitial tissue **(IT)** consists of collagen fibers **(CF)**, which were fewer than duloxetine hydrochloride treated group and three interstitial Leydig cells. Two interstitial Leydig cells **(ILCs)** have normal appearance. They have euchromatic nuclei **(N)** with small clumps of heterochromatin, rough **(RER)** and smooth **(SER)** endoplasmic reticulum, oval mitochondria **(Mi)**, secondary lysosomes **(L)** and free ribosomes **(R)**. The third cell has nucleus with chromatin fading **(K) (EM X 10000).**

Table (1): Comparison of measurements of collagen fibers percentage and area filled by immune in the offspring of all studied groups

	Collagen fibers (%)		Immune	
Groups	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
CA	33.4 ± 3.647	8.00	0.152 ±0.053	0.28
CB	31 ± 3.391	9.13	0.152 ±0.053	0.17
L	31.7 ± 3.24	11.619	0.152 ±0.053	0.193
D	65.63 ± 2.28	8.138	1.33 ± 0.28	1.005
DL	42.8 ± 5.03	18.008	0.45 ± 0.206	0.742
Stat. test	F =87.34		F = 50.219	
p-value	p= 0.05*		p =0.05*	
Post Hoc analysis				
	Parameters			
Compared groups	**Collagen fibers (%)**		**Immune**	
CA vs. CB	<0.05		<0.05	
CA vs. L	<0.05		<0.05	
CA vs. D	0.003*		0.04*	
CA vs. DL	<0.05		<0.05	
CB vs. L	<0.05		<0.05	
CB vs. D	0.002*		0.03*	
CB vs. DL	<0.05		<0.05	
L vs. D	0.001*		0.05*	
L vs. DL	<0.05		<0.05	
D vs. DL	0.015*		0.051*	

F: One Way ANOVA, CA: First control group, CB: Second control group, L: Protective group, D: Treated group, DL: Recovery group, *: Significant p-value (<0.05).

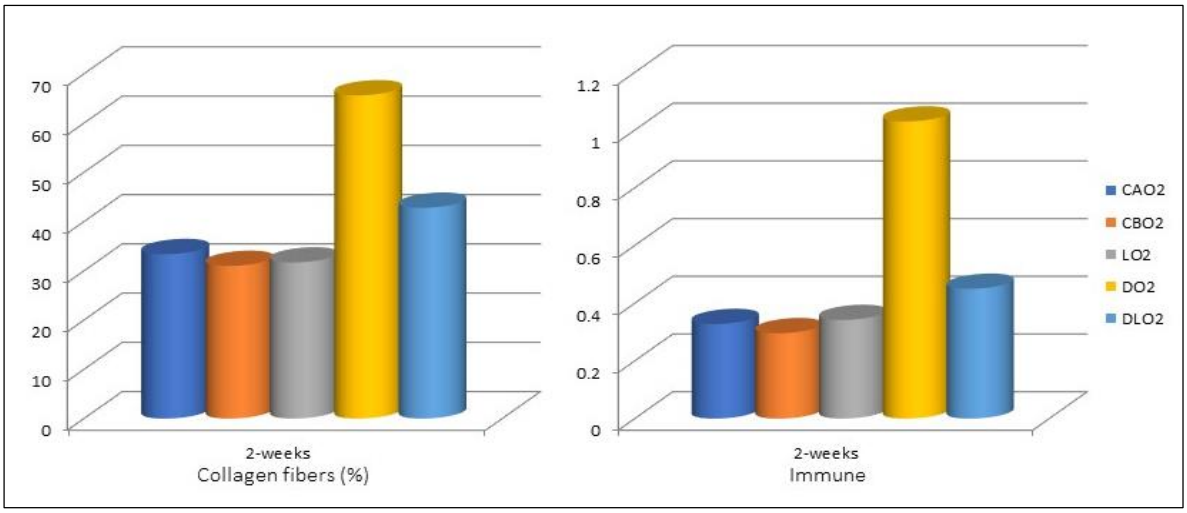


Figure (7): Mean values of area percentage of collagen fibers and area filled by immune in the offspring of all studied groups

DISCUSSION

In this study, light and electron microscopic examinations as well as testicular morphometric analysis of the offspring of duloxetine hydrochloride treated group displayed a range of necrosis and degeneration indicators, including cytoplasmic vacuoles, mitochondria with destroyed cristae, degraded mitochondria, dilated rough endoplasmic reticulum and nuclear alterations in the form of karyolysis, pyknosis and nuclear fragmentation. A significant increase in Caspase-3 protein expression in the germinal epithelium and interstitial tissue was detected. A noticeable rise in the testicular capsules' collagen fiber content, basal laminae and interstitial tissue, interstitial oedema, and dilated and congested blood vessels were among the several indications of inflammation and fibrosis. These findings agreed with El-Din and Abd-El Aty [17] who reported that rats' testicles suffered cell damage and death because of

duloxetine. The germ cells were disorganized, disrupted and had pyknotic nuclei. Many Leydig's interstitial cells appeared pyknotic. Also, there was a noticeable growth of collagen fibers in the group that received duloxetine treatment. Also, Atli et al. [18] found that, fluoxetine caused significant testicular damage and germ cell apoptosis. Some germ cells showed cytoplasmic vacuolation and strongly stained pyknotic nuclei. The intertubular space containing damaged Leydig cells and homogenous acidophilic hyaline material. There was increased collagen fibers deposition in the capsule, the seminiferous tubules, blood vessels walls. Also, dilatation and congestion of blood vessels in the intertubular spaces. Also, Câmara et al. [19] and Elsedawi et al. [20] showed that fluoxetine had deleterious effects on testicular tissue in treated rats, including nuclear apoptosis of spermatogenic cells and large cytoplasmic vacuoles. In addition, the perifollicular blood vessels were congested. Moreover, Elsedawi et al. [20] and Bezerra et al. **[21]** discovered that rats treated with fluoxetine and sertraline during pregnancy and lactation experienced adverse effects on the testes and liver, manifested by cell degeneration and blood vessels congestion. Additionally, Kaur et al. **[22]** mentioned that mice treated with venlafaxine hydrochloride had increased levels of certain proteins in their bodies. These proteins are called caspase-3, caspase-9 and Bax. Also, Atli et al. [18] and Khaksar et al. [23] found that rats treated with fluoxetine had more of a protein called caspase-3 in spermatogenic cells and Leydig cells, leading to DNA fragmentation and germ cell apoptosis. Also, Youssef [24] reported that fluoxetine administration to rats was associated with increased inflammation and fibrosis of the interstitial tissue of the testis, between the acini of the parotid gland and around pancreatic ducts. Also, Youssef et al. [25] demonstrated that duloxetine had a negative impact on the salivary glands and oral mucosal histological structure in rats. In adult rats, they discovered that the lamina propria had a significant dilatation of blood vessels. Duloxetine dosing over an extended period resulted in significant atrophic and degenerative alterations to the tongue's deep and superficial layers, as well as aberrant cytoplasmic vacuolization, nuclei pyknosis, and karyolysis. All regions of the tongue were also shown to contain high concentrations of a protein known as Bax (brown cytoplasmic staining). In addition, Paulis et al. [26] found that rats treated with venlafaxine showed signs of damage and inflammation in the liver, stomach, and kidneys. The liver tissue degeneration, inflammatory cell infiltration, and cortical distortion led to lobular loss. Degenerated cells, apoptotic hepatocytes, and fragmented nuclei were found. Gastrointestinal mucosa showed ulcers, deteriorated gastric cells, and swelling. Renal sections showed interstitial bleeding and glomeruli hyperemia.

The potential causes of duloxetine hydrochloride's negative effects were disturbance of the hormonal axis and could also damage the testes by producing harmful compounds called free radicals **[17].** Also, Tinkel et al. [27] revealed increased cellular damage caused by oxidative stress which linked to a certain type of molecule called reactive oxygen species (ROS). Membrane lipids, in a process known as lipid peroxidation, was the major targets of ROS. Oxidative stress is a problem in many disease states. Additionally, de Oliveira et al. [28] mentioned that the exposure to increased serotonergic activity induced by the administration of the serotonin reuptake inhibitors, caused seminiferous tubules degeneration. Also, Solek et al. **[29]** found that antidepressant (venlafaxine) toxicity on the reproductive cells was mediated by increased reactive nitrogen and oxygen species generation, and failure of the cellular defense systems, both enzymatic and non-enzymatic, as well as impairment of mitochondrial function. Erdemir et al. [30] mentioned that reactive oxygen species (ROS) and antioxidant defenses were out of balance during oxidative stress, which could lead to lipid, protein, and DNA deterioration. In living cells, this could result in necrosis or apoptosis. Oxidative stress caused by several factors, including medications.

Also, Ahmed and Shaheen [31] explained that expansion of the spaces between the seminiferous tubules in the testes of rats was due to the accumulation of a substance called hyaline material in these spaces. This clear substance can result from excessive fluid loss from unhealthy lymph vessels as well as increased vascular permeability due to the accumulation of free radicals and reactive oxygen species. Also, Atli et al. [18] mentioned that lipid peroxidation causes the cytoplasm of spermatogenic cells to vacuolate. This, in turn, damages the cell membrane through the action of sertraline and increases the permeability of the cell organelle membranes. Additionally, they demonstrated how oxidative stress caused by selective serotonin reuptake inhibitors led to DNA fragmentation and an excess of reactive oxygen species, which inflicted cell damage in the male rats' reproductive organs. In addition, El-Beltagi et al. [32] reported that the transparent vacuoles in the cytoplasm reflect elongated and compressed segments of the endoplasmic reticulum. The absence of energy-dependent ion pumps in the cell membrane can cause cellular swelling and make it difficult to maintain fluid and ion homeostasis and they called this nonlethal damage pattern as hydropic injury or vacuolar degeneration. Also, Saleem et al. [33] stated that testicular degeneration, seminiferous tubules vacuolization and basement membrane detachment by venlafaxine and pramipexole occurred when the drug crossed the blood testes barrier (BTB) and possibly had effect on the Sertoli cells. Also, Soliman et al. [34] reported that lipid peroxidation caused by the production of hydroxyl radicals and other extremely reactive oxidative molecules damaged proteins and nucleic acids. Collagen fibers and the creation of ground substance increased because of those interactions. Furthermore, the production of free radicals from lipid peroxidation resulted in membrane disorganization, a reduction in fluidity, and ultimately substantial tissue damage. Also, Abo-Ouf **[35]** reported that the Increased oxidative stress may be the cause of the degenerative impact of

fluoxetine. and reduced activity of antioxidant enzymes.

Also, Soliman et al. [34] found that the degenerative effects in germ and interstitial cells in rats treated with fluoxetine could be due to reduced blood supply and tissues ischemia caused by inflammation and fibrosis of the interstitial tissue. Also, dilated and congested blood vessels in some areas of dilated interstitium could be attributed to a compensatory mechanism of reduced testicular blood flow after fluoxetine administration. Also, Aitken et al. [36] discovered that the testes' oxidative stress (OS) could harm cell membranes and impair testicular cell function and testosterone production. Decreased testosterone level not only affected spermatogenesis but also libido and sexual function. Therefore, OS might have had more than one mechanism of action leading to loss of spermatogenesis and fertility.

Also, Álvarez-González et al. [37] found that venlafaxine and duloxetine damaged liver cells by producing too many harmful chemicals called reactive oxygen species (ROS). This led to problems such as damaged proteins and lipid peroxidation. Also, provided evidence that the primary targets were mitochondria and lysosomes, leading to loss of lysosomal membrane integrity, mitochondrial membrane potential collapse and finally cell death. Also, hepatotoxicity caused by oxidative stress could induced by hydroxylated and epoxide metabolites, which could release free radicals or reactive oxygen species. Also, Álvarez-González et al. [37] and Ziegler et al. [38] revealed that during a crucial stage of brain development, prenatal exposure to equivalent therapeutic doses of venlafaxine and duloxetine raised the levels of reactive oxygen species and pro-apoptotic protein (Bax) in the fetal brain, causing apoptotic neurodegeneration that affects brain cell migration, proliferation, and differentiation. That led to serious and long-term damage to the embryo and fetus. Increased induction of lipid peroxidation and oxidized proteins in brain cells was found. Mishra et al. [39] mentioned that the molecular oxidation could be due to the involvement of duloxetine epoxide in duloxetine metabolism or to some changes that happen in some parts of the duloxetine molecule. It was known that epoxides could cause harmful changes in cells, including mutations, deletions, chromosomal abnormalities, genetic changes, tumors and viral infections. Duloxetine could also cause liver damage by releasing harmful substances called free radicals or (ROS) produced by its metabolites.

CONCLUSION

Duloxetine hydrochloride caused various deleterious changes in the histological structure of the testis. L-carnitine made significant improvements in these changes. Pregnant and breast-feeding mothers who will take antidepressants should try to take antioxidants with them to alleviate their dangerous effects on them and their offspring.

Funding: No fund

Conflicts of interest: The authors declare no conflicts of interest regarding the publication of this paper.

REFERENCES

1. **Norris MM.** Use of antidepressants during pregnancy and lactation: Mental Health Clinician. 2013; 3(2):58-2.
2. **Lassen D, Ennis ZN, and Damkier P.** First-trimester pregnancy exposure to venlafaxine or duloxetine and risk of major congenital malformations: A systematic review. Basic and Clinical Pharmacology and Toxicology. 2016; 118(1):32-4.
3. **Brunton LL, Chabne BA, and Knollmann BC.** In: "Goodman and Gilman, the Pharmacological basis of therapeutics". 13th ed. United States of America: McGraw-Hill Education; 2018, pp. 268-69.
4. **Andrade C.** The safety of duloxetine during pregnancy and lactation. Clinical and practical psychopharmacology. Journal clinical psychiatry. 2014; 75(12): e1423-4.
5. **Onuţu AH.** Duloxetine, an antidepressant with analgesic properties – a preliminary analysis: Romanian Journal of Anesthesia and Intensive Care. 2015; 22(2):123-5.
6. **BNF (British national formulary).** In: "British national formulary". 76th ed. Pharmaceutical Press. BMJ Group and the Royal Pharmaceutical Society of Great Britain; 2018, pp. 364-65.
7. **Jimenez-Solem E.** Exposure to antidepressants during pregnancy prevalence's and outcomes: Danish medical journal. 2014; 61(9): B4916.
8. **Huybrechts KF, Bateman BT, Pawar A, Bessette LG, Mogun H, Levin R, et al.** Maternal and fetal outcomes following exposure to duloxetine in pregnancy: cohort study. British Medical journal. 2020; 368 (m237):1-10.
9. **Beeder LA and Samplaski MK.** Effect of antidepressant medications on semen parameters and male fertility. International Journal of Urology.2020; 27(1):39-7.
10. **Armstrong D and Stratton RD.** In: "Oxidative Stress and antioxidant protection, the science of free radical biology and disease". 1st ed. John Wiley and Sons, Inc, Hoboken, New Jersey, Canada; 2016, pp. 239-40.
11. **Katzung BG.** In: "Basic and Clinical Pharmacology". 14th ed. McGraw-Hill Education, USA; 2018, pp. 546-551.
12. **Paget GC, and Barnes JM.** In: "Toxicity in evaluation of the drug activities". 1st ed. Pharmacometric. Vol. I edited by: Laurence DR and Bacharach AL. Academic Press, London, New York, 1964 pp. 1-13.
13. **Armstrong D and Stratton RD.** In: "Oxidative stress and antioxidant protection, the science of free radical biology and disease". 1st ed. John Wiley and Sons, Inc, Hoboken, New Jersey, Canada; 2016, pp. 239-40.

14. **Suvarna SK, Layton C, and Bancroft JD.** In: "Bancroft's theory and practice of histological techniques". 8th ed. Elsevier Health Sciences, China; 2019, pp. 126-137 and 353-389.
15. **Bancroft JD and Gamble M.** In: "Theory and practice of histological techniques". 6th ed. Elsevier, Health Sciences, Churchill Livingstone, London, Edinburgh, New York, Philadelphia, St. Louis Sydney, Toronto; 2013, pp. 125-27 and 150-58.
16. **Knapp S, Lawner S, and Abramowitz W.** In: "Statistic Using SPSS: An Integrative Approach". 1st ed. Cambridge University Press, USA; 2014, p. 373.
17. **El-Din SB and Abd-El Aty OA.** Biochemical and immunocytochemical studies of the testicular changes after treatment with duloxetine hydrochloride and the possible protective effects of omega 3 in adult rat model of depression. Al-Azhar Assiut Medical Journal. 2012; 11(3): 255-98.
18. **Atli O, Baysal M, Aydogan-Kilic G, Kilic V, Ucarcan S, Karaduman B, et al.** Sertraline-induced reproductive toxicity in male rats: evaluation of possible underlying mechanisms. Asian Journal of Andrology. 2017; 19(6): 672-79.
19. **Câmara ML, Almeida TB, de Santi F, Rodrigues BM, Cerri PS, Beltrame FL, et al.** Fluoxetine-induced androgenic failure impairs the seminiferous tubules integrity and increases ubiquitin carboxyl-terminal hydrolase L1 (UCHL1): Possible androgenic control of UCHL1 in germ cell death? Biomedicine and pharmacotherapy. 2019; 109: 1126-39.
20. **Elsedawi BF, Hussein Y, Sabry MA, and Aziz JA.** Effect of fluoxetine on the testes of adult albino rats and the possible protective role of curcumin. Anatomical Science International. 2021; 96(2):187-96.
21. **Bezerra MS, Martins ABM, Trajano FMG, Pontes THA, Gomes LTDC, Gavioli EC, et al.** Fluoxetine and sertraline effects on rat distal cauda epididymis contraction, sperm count and sperm transit time trough epididymis. European journal of pharmacology. 2019; 865: 172774.
22. **Kaur S, Kaur A, Jaswal N, Aniqa A, Sadwal S, and Bharati S.** Selenium attenuates venlafaxine hydrochloride-induced testicular damage in mice via modulating oxidative stress and apoptosis. Andrologia. 2021; 53(6): 1-10.
23. **Khaksar M, Oryan A, Sayyari M, Rezabakhsh A, and Rahbarghazi R.** Protective effects of melatonin on long-term administration of fluoxetine in rats. Experimental and toxicologic pathology. 2017; 69(8): 564-74.
24. **Youssef S.** Effect of fluoxetine on the pancreas of adult male albino rats and the possible protective role of Omega-3: light and electron microscopic study. International Journal of Clinical and Developmental Anatomy. 2017; 3(6): 45-56.
25. **Youssef M, Korraah A, and Hegazy E.** Apoptotic effect of long-term administration of antidepressant duloxetine on the tongue of albino rats: Histological and immuno-histochemical study. Egyptian Dental Journal. 2020; 66(1): 213-23.
26. **Paulis MG, Hafez EM, El-Tahawy NF, and Aly M.** Toxicological assessment of venlafaxine: Acute and subchronic toxicity study in rats. International Journal of Toxicology. 2018; 37(4): 327-34.
27. **Tinkel J, Hassanain H, and Khouri SJ.** Cardiovascular antioxidant therapy: a review of supplements, pharmacotherapies, and mechanisms. Cardiology in Review. 2012; 20(2): 77-83.
28. **de Oliveira WM, de Sá IR, de Torres SM, de Morais RN, Andrade AM, Maia FC, et al.** Perinatal exposure to fluoxetine via placenta and lactation inhibits the testicular development in male rat offspring. Systems Biology in Reproductive Medicine. 2013; 59(5): 244-50.
29. **Solek P, Mytych J, Tabecka-Lonczynska A, Sowa-Kucma M, and Koziorowski M.** Toxic effect of antidepressants on male reproductive system cells: evaluation of possible fertility reduction mechanism. Journal of physiology and pharmacology: an official journal of the Polish Physiological Society. 2021; 72(3): 1-13.
30. **Erdemir F, Atilgan D, Firat F, Markoc F, Parlaktas BS, and Sogut E.** The effect of sertraline, paroxetine, fluoxetine and escitalopram on testicular tissue and oxidative stress parameters in rats. International official journal of the Brazilian Society of Urology. 2014; 40(1):100-08.
31. **Ahmed FE and Shaheen AM.** Histological study of effect of food contaminant semicarbazide on testis of albino rats and possibility of recovery. British Journal of Science. 2016; 14(1): 2047-3745.
32. **El-Beltagi EM, Elwan WM, Mohsen El-Bakry NA, and Salah EF.** Histological and immunohistochemical study on the effect of gibberellic acid on the seminiferous tubules of testis of adult albino rat and the possible protective role of grape seeds proanthocyanidin extract. Tanta Medical Journal. 2017; 45(2):79-91.
33. **Saleem U, Zubair S, Riaz A, Anwar F, and Ahmad B.** Effect of venlafaxine, pramipexole, and valsartan on spermatogenesis in male rats. American Chemical Society Omega. 2020; 5(32): 20481-90.
34. **Soliman ME, Mahmoud BL, Kefafy MA, Yassien RI, and El-Roghy ESA.** Effect of antidepressant drug (fluoxetine) on the testes of adult male albino rats and the possible protective role of omega-3. Menoufia Medical Journal. 2017; 30(4): 1135-42.
35. **Abo-Ouf AM.** Effect of fluoxetine hydrochloride on the histological structure of the cerebellar cortex of albino rat offspring of treated mothers. Al-Azhar Medical Journal. 2018; 47(3): 24-27.
36. **Aitken RJ, Smith TB, Jobling MS, Baker MA, and De Iuliis GN.** Oxidative stress and male

reproductive health. Asian Journal of Andrology. 2014; 16(1): 31-38.

37. **Álvarez-González I, Camacho-Cantera S, Gómez-González P, Barrón M, Morales-González J, Madrigal-Santillán E, et al.** Genotoxic and oxidative effect of duloxetine on mouse brain and liver tissues. Scientific Reports. 2021; 11(1): 6897.
38. **Ziegler M, Eckstein H, Ottmann S, Reinelt L, Stepinski S, Kohler H, et al.** Biochemical and cellular biomarkers in brown trout (Salmo trutta f. fario) in response to the antidepressant's citalopram and venlafaxine. Environmental Sciences Europe. 2020; 32(158): 5-12.
39. **Mishra A, Keshari AK, Singh AK, Maity S, Nandy B, and Saha S.** Oxidative stress-based hepatotoxicity of duloxetine in wistar rats. International Journal of Pharmacy and Pharmaceutical Sciences. 2016; 8(11): 28-32

الملخص العربي

تأثير الدولوكستين هيدروكلورايد على خصي نسل الفئران البيضاء والتأثير الوقائي المحتمل للإل -كارنيتين (دراسة نسيجية)

سامية أحمد إسماعيل [1]، سمير أحمد مليك[1]، أماني مصطفى أبو عوف[2,1]

[1] قسم التشريح وعلم الأجنة، كلية طب بنات، القاهرة، جامعة الأزهر، جمهورية مصر العربية.

[2] علم التشريح والأجنة، قسم العلوم الطبية الأساسية، كلية الطب، جامعة الأمير سطام بن عبد العزيز، الخرج، المملكة العربية السعودية.

ملخص البحث

الخلفية: دولوكستين هيدروكلورايد أحد مضادات الاكتئاب المستخدمة على نطاق واسع. وقد تمت الموافقة عليه في عام 2004 لاستخدامه في علاج اضطراب الاكتئاب الشديد، والاعتلال العصبي السكري، والألم العضلي الليفي، واضطراب القلق العام.كما أن له تأثيرات ضارة للجهاز التناسلي الذكري. قد قام إل- كارنيتين بتحسين معايير مختلفة للإجهاد التأكسدي.

الهدف: اكتشاف تأثير إعطاء عقار الدولوكستين هيدروكلورايد والتأثيرات الوقائية المحتملة للإل-كارنيتين على التركيب النسيجي لخصي ذكور الجرذان البيضاء المولودة للأمهات المعالجة.

الطرق: في هذه الدراسة تم استخدام 100 جرذ من نسل 25 أنثى بالغة من الفئران البيضاء. تم تقسيم إناث الفئران بالتساوي إلى 5 مجموعات. طوال فترة الحمل ولمدة أسبوعين بعد الولادة، تم اعطاء كل أنثي في المجموعات; المجموعة الضابطة الاولي، المجموعه الضابطه الثانيه، مجموعة ال- كارنتين ، المجموعة المعالجة بالدولوكستين هيدروكلورايد، والمجموعة المعالجة بالدولوكستين هيدروكلورايد والإل- كارنيتين معا . و قد تم اعطاء كل انثى فى المجموعات على التوالى و ذلك يومياعن طريق الفم 0.96 مل من الماء المقطر، 2.06 مل من الماء المقطر، 1.44 مجم من دولوكستين هيدروكلورايد،36 مجم من إل-كارنيتين ثم (1.44مجم من دولوكستين هيدروكلورايد مع 36 مجم من إل-كارنيتين معا). استمر العطاء طوال فترة الحمل ولمدة أسبوعين بعد الولادة مرة يوميا. تم جمع العينات من كل مجموعة في عمر أسبوعين واستخدمت للفحص المجهري الضوئي والإلكتروني النافذ والدراسة المورفومترية.

النتائج: أظهر الفحص المجهرى الضوئي والإلكتروني النافذ بالإضافة إلى الدراسة المورفومترية علامات مختلفة من التنكس، والنخر، والالتهاب، والتليف. من ناحية أخري حسّن إل-كارنيتين غالبية هذه الآثار الضارة.

الإستنتاجات: أدي إعطاء عقار دولوكستين هيدروكلورايد إلى تغيرات ضارة متنوعة في الخصية، والتي قد تحسنت إلى حد كبير بتناول عقار إل-كارنيتين.

الكلمات المفتاحية: دولوكستين هيدروكلورايد، إل-كارنيتين، الجرذ، الخصية.

الباحث الرئيسي

الاسم: سامية أحمد علي أحمد، قسم التشريح وعلم الأجنة، كلية طب بنات، القاهرة، جامعة الأزهر، جمهورية مصر العربية .

الهاتف: 01152330897

البريد الإلكتروني: samiaahm1357@gmail.com