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Original Research Article

The protective role of antioxidants extracted from spirulina against hormonal disruption in rabbit ovaries

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Abstract: The study was conducted on 24 adult female local rabbits, which were divided into four groups (6 rabbits per group) and treated as following: the first group received normal saline solution (0.9% sodium chloride) as a control; the second group received valproic acid (400 mg/kg); the third group was treated with spirulina extract only (500 mg/kg); and the fourth group received valproic acid (400 mg/kg) and spirulina extract (500 mg/kg). All treatments were administered for 21 days. Ovarian hormones levels (estrogen and progesterone), as well as anterior pituitary hormones (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)), were assessed using ELISA technique, and histological sections of the ovaries were examined. The results showed a significant decrease in LH, FSH, estrogen, and progesterone levels, and an increase in testosterone levels in the valproate group compared to the control group. Spirulina also had a protective effect against the effects of valproate on the hormone levels under investigation, furthermore, the results showed that spirulina extract reduced ovarian tissue damage caused by valproate. We conclude that spirulina acts as a natural antioxidant, which may reduce reproductive hormonal imbalances and improve damaged ovarian tissue.

Keywords: spirulina,Valproic acid, Reproductive hormones, female rabbits.

Aim of study

to assess if an aqueous extract of *Spirulina* algae can lessen the negative effects on the hormonal and histological characteristics of rabbit ovaries.

INTRODUCTION

Valproic acid (VPA) is an eight-carbon simple branched-chain carboxylic acid synthesized by Burton in 1882, also called 2-propyl pentanoic o (Safdar and Ismail, 2023). It is a broad-spectrum antiepileptic drug and is generally used as monotherapy or in combination with other antiepileptic drugs (Singh *et al.*, 2021).

A series of studies reported that hyperandrogenism, menstrual disorders, polycystic ovary and other reproductive endocrine abnormalities were more prevalent in women taking VPA (Wood *et al.*, 2005 ; De vries *et al.*,2007).

The study of microalgae has gained importance in recent years, because microalgae are considered as raw materials for chemical compounds that result from their primary and secondary treatment (Chun *et al.*,2011). Microalgae biomass presents remarkable commercial interest in the food, nutraceutical,

cosmetic and pharmaceutical fields due to its high value-added bioactive components (Khan *et al.*, 2018). The discovery of high levels of natural antioxidants in microalgae has triggered the nutraceutical industries to use microalgaederived metabolites as a replacement for synthetic antioxidants (Azaman *et al.*, 2017).

Antioxidants are substances that limit the effects of free radicals, which are compounds that damage living cells and may cause their death. (Venables *et al.*, 2008; Ahlam & Alaa, 2021). Spirulina is a free-floating filamentous microalgae with the helical properties of its filaments. It is officially called Arthrosporia powder and is related to the class of cyanobacteria with the ability to photosynthesize (Sapp, 2005)Spirulina is known for its wide-ranging biological and antioxidant activities (Miranda *et al.*, 1998), so spirulina is considered a valuable source of antioxidants such as phycocyanin, carotenoids, and phenolic compounds (Ismaiel *et al.*, 2016). These biologically active compounds in Spirulina reduce the risk of chronic diseases such as cardiovascular diseases, inflammatory diseases, type 2 diabetes, and cancer (Rodriguez *et al.,* 2018)

This study was designed to determine the effect of spirulina extract on reproductive hormones and related hormones in female rabbits treated with valproate and its effect on ovarian tissue.

MATERIAL AND METHODS

Preparation of the aqueous extract of *spirulina*:

The cold aqueous extract of ***spirulina*** algae was prepared by taking 50 grams of dried algae powder and adding 500 ml of distilled water to it and placing the mixture in a magnetic stirrer for 24 hours, then filtering it using filter paper, then pouring the liquid after filtration into Petri dishes and leaving it to dry at laboratory temperature. Then the algae extract was collected in sterile opaque glass containers and placed in the refrigerator at a temperature of (4) $_{o}$ C until use (Harborn,1984 ;Ahmed & Marwa, 2020).

Depakine (valproic acid)

Depakine tablets were powdered, dissolved in distilled water, and administered orally to animals in the form of an emulsion.

Experimental Animals

The study was conducted on female rabbits aged 24 weeks, with an average body weight ranging from 2000 to 2500 g. The rabbits were housed in special cages with specified dimensions. The cages were cleaned and provided with appropriate environmental conditions, including a fixed lighting regimen (12 h light / 12 h dark), a ventilation cycle, and a temperature ranging from 22 to 25 °C. Adequate amounts of water and feed were supplied in the feeding area inside the cages.

Experimental design:

In the present study, 24 female rabbits were divided into four groups according to the following order:

1. Control group: Consisting of (six) rabbits treated with normal saline NaCl (0.5 ml).

2. Valproate group:Consisting of (six) rabbits given Valproate at a dose of (400 mg/kg) of body weight (Elwakkad et al .,2008) .

3. The Third group:Consisting of (six) rabbits treated with *Spirulina* algae extract at a dose of (500mg/kg) of body weight.

4. The Fourth group: consisting of (six) rabbits was Valproate is given as (400mg/kg) of body weight that were treated with *Spirulina* extract (500mg/kg) of body weight .

Blood collectionand laboratory tests

After the experimental period, the animals were dissected and blood was collected using a fine needle (5 cc) via cardiac puncture. The collected blood samples were placed in a gel tube for blood collection and allowed to coagulate at room temperature. They were then separated by centrifugation for 15 minutes at 3000 rpm. The serum was then collected and stored in a plain tube at -20°C until use.Hormonal tests were performed using ELISA technology (Aliah et al., 2025), which includes:estrogen,progesterone, luteinizing hormone and follicle-stimulating hormone levels by using (kits of FineTest**,** China). During the dissection of experimental laboratory animals, we took sections of the ovaries and fixed them with a 10% formalin solution for preservation purposes, and the tissue sections of the ovaries were prepared according to the method (AL-Salmi, 2021).

Statistical analysis:

The results were represented as mean ± standard deviation (M±SD), and the experiments were analyzed using one-way analysis of variance (ANOVA) with SPSS and the LSD test, with a p-value <0.05.

RESULT

1-Hormonal profile :

1- Follicle-stimulating hormone (FSH)

Figure 1 shows a significant decrease ($p<0.05$) in follicle-stimulating hormone (FSH) level in the valproic acid group compared to the control group and other groups. However, the spirulina extract (500 mg/kg) group and the valproic

acid + spirulina (500 mg/kg) group showed no significant difference ($p<0.05$) compared to the control group.

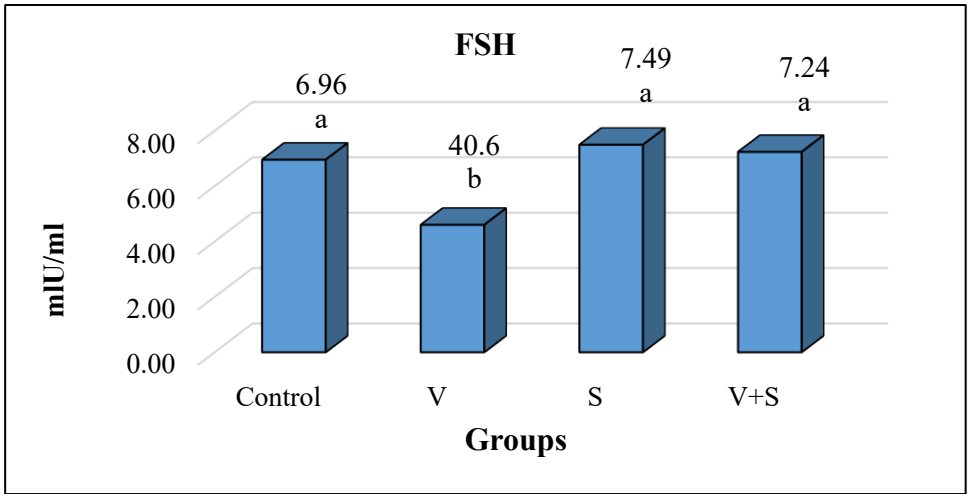

Figure 1: Effect of spirulina extract on FSH level in female rabbits treated with valproic acid.

[a–b] Different letters indicate significant difference (P< 0.05)

2- Luteinizing hormone (LH)

Results showed a significant decrease ($p<0.05$) in luteinizing hormone (LH) level in the valproic acid group compared to the control group and other groups. However, the valproic acid group combined with spirulina (500 mg/kg) showed no significant difference ($p<0.05$) compared to the control group. The results also showed a significant increase in LH levels in the spirulina extract group (500 mg/kg) alone (Figure 2).

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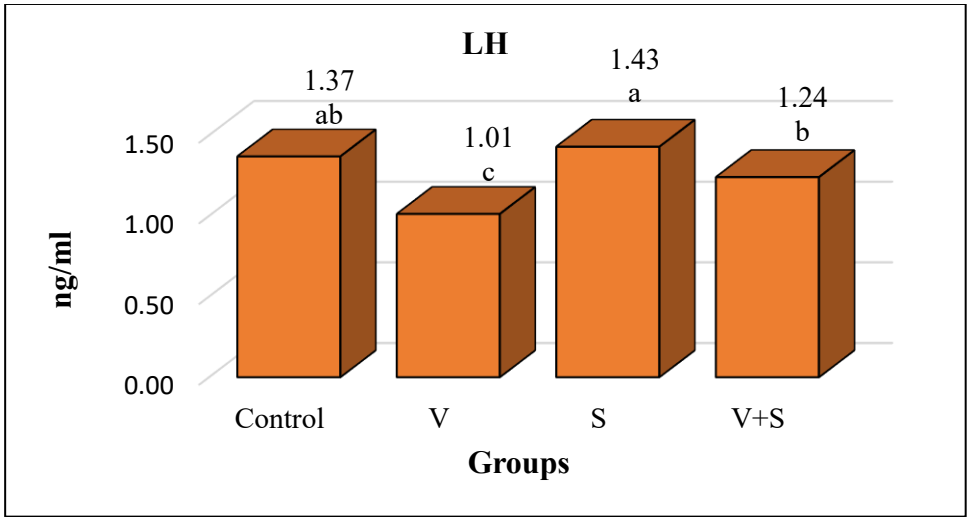


Figure 2: Effect of spirulina extract on LH level in female rabbits treated with valproic acid.

[a–c] Different letters indicate significant difference (P< 0.05)

3- Estrogen hormone (E2)

Figure 3 shows a significant decrease ($p<0.05$) in estrogen (E2) level in the valproic acid group compared to the control group and other groups. There was a significant increase ($p<0.05$) in both the spirulina extract (500 mg/kg) group alone and the valproic acid with spirulina (500 mg/kg) group compared to the control group. The greatest increase in hormone levels was observed in the spirulina extract (500 mg/kg) group alone.

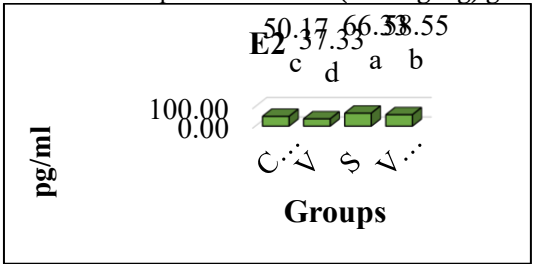


Figure 3: Effect of spirulina extract on E2 level in female rabbits treated with valproic acid.
[a–d] Different letters indicate significant difference (P< 0.05)

4- progesterone hormone
Results showed a significant decrease (p<0.05) in progesterone levels in the valproic acid group compared to the control group and other groups. However, the spirulina extract (500 mg/kg) group and the valproic acid with spirulina (500 mg/kg) group showed no significant difference (p<0.05) compared to the control group (Figure 4).

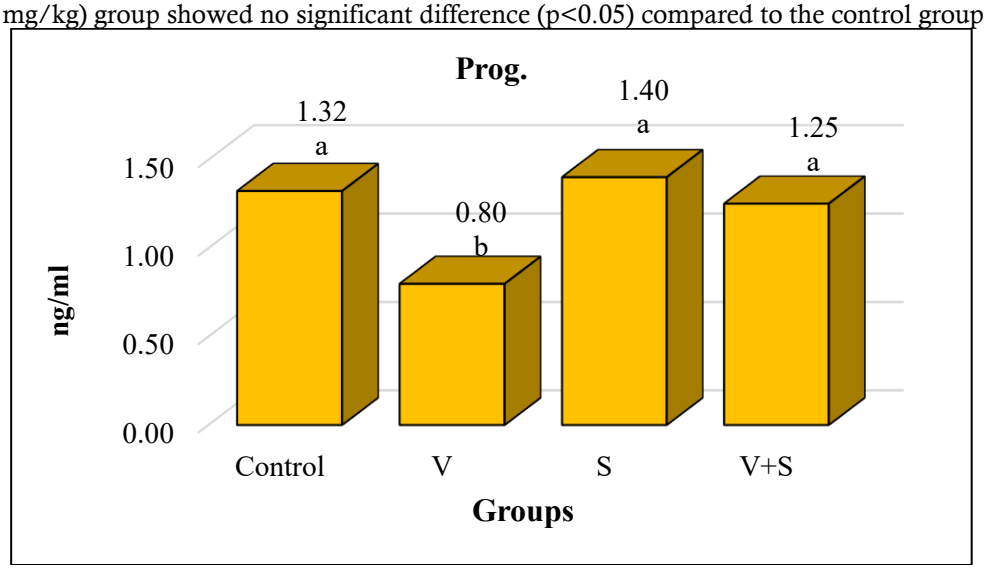


Figure 4: Effect of spirulina extract on Progesterone level in female rabbits treated with valproic acid.
[a–b] Different letters indicate significant difference (P< 0.05)

5- Testosterone hormone
Figure 5 shows a significant increase (p<0.05) in testosterone level in the valproic acid group compared to the control group and other groups. while, the spirulina extract (500 mg/kg) group and the valproic acid with spirulina (500 mg/kg) group showed no significant difference (p<0.05) compared to the control group.

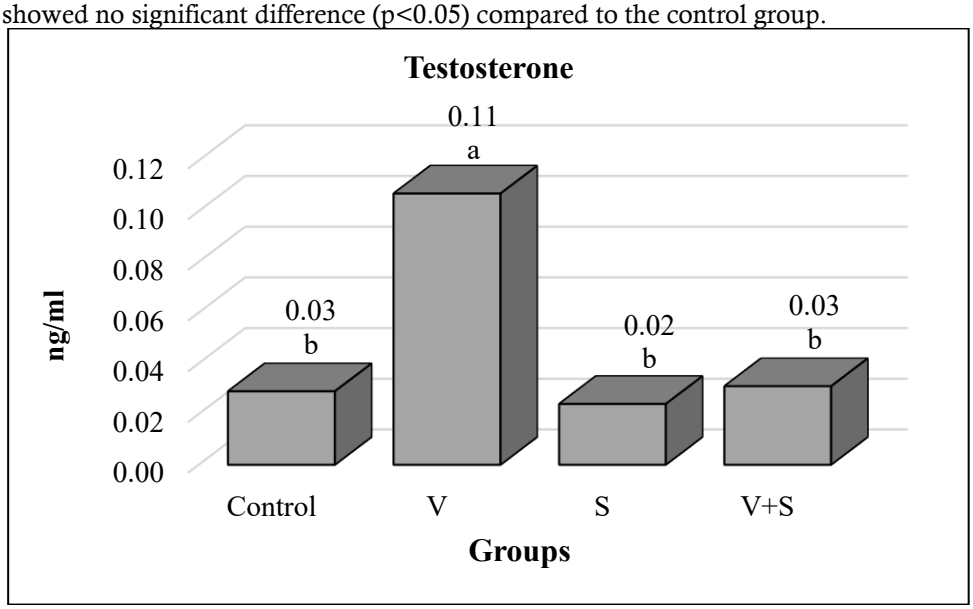
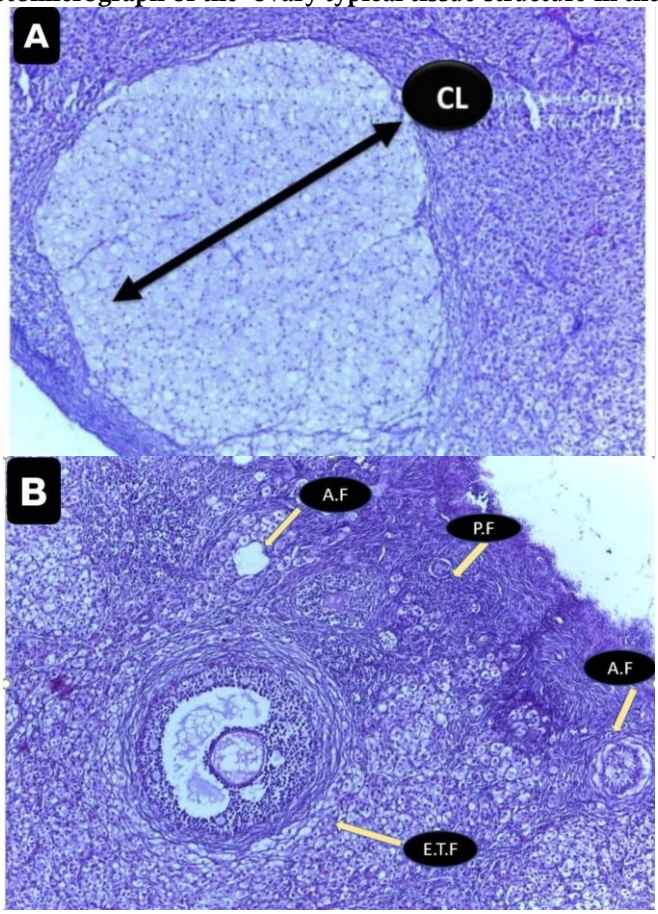


Figure 5: Effect of spirulina extract on Testosterone level in female rabbits treated with valproic acid.
[a–b] Different letters indicate significant difference (P< 0.05)

2-**Histological examination:**
The histological sections of the ovaries in the control group showed normal follicles at various growth stages, including primordial, primary, secondary, and well-developed graafian follicles corpora lutea were present with normal structure, and the ovarian stroma appeared normal follicles were enclosed with a thin layer of surrounding cells ovaries were covered with a simple cuboidal epithelial tissuegraafian follicles were surrounded by mural granulosa cells enclosing the oocyte, with several antral cavities (antra) visible. The sections also displayed stromal fibroblasts and smooth muscle cells. Oocytes were surrounded by a corona radiata, and follicles were embedded within internal and external theca layers, intermixed with fibroblast-like cells the medulla (**Figure 1)**.

Figure 1: A photomicrograph of the ovary typical tissue structure in the control group.

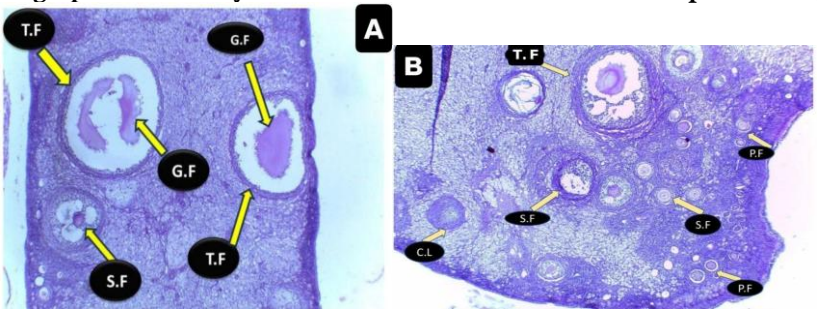


A: showing the Corpus Luteum (C.L). H&E : 100 x
B: Showing the Early Tertiary Follicle (E. T. F) ; Atretic Follicle (A. F) ; Early Atretic Follicle (EA. F) and Primary Follicle (P. F). H&E : 100 x.

The histological examination of rabbit ovaries treated with VPA showed marked degenerative changes.These changes included a decrease in the number of follicles at different developmental stages (primary and secondary follicles), accompanied by an increase in ovarian follicular atresia, additionally, there was evidence of hyperplasia and vascular congestion, along with a reduction in the number of corpora lutea (CL) in the ovarian sections (as seen in figure 2). Degenerated oocytes and atretic follicles were observed, as well as degeneration of granulosa cells showing pyknotic nuclei within the follicular cavity, moreover, connective tissue appeared intermingled with the theca interna, and the zonapellucida was disrupted.The blood vessels were dilated and congested between the stromal cells

The main histological changes in the ovaries of the VPA group indicated aclear impairment of follicular activity, manifested by a small number ofdeveloping follicles and a high number of atretic and degenerative follicles,withlysedoocytes

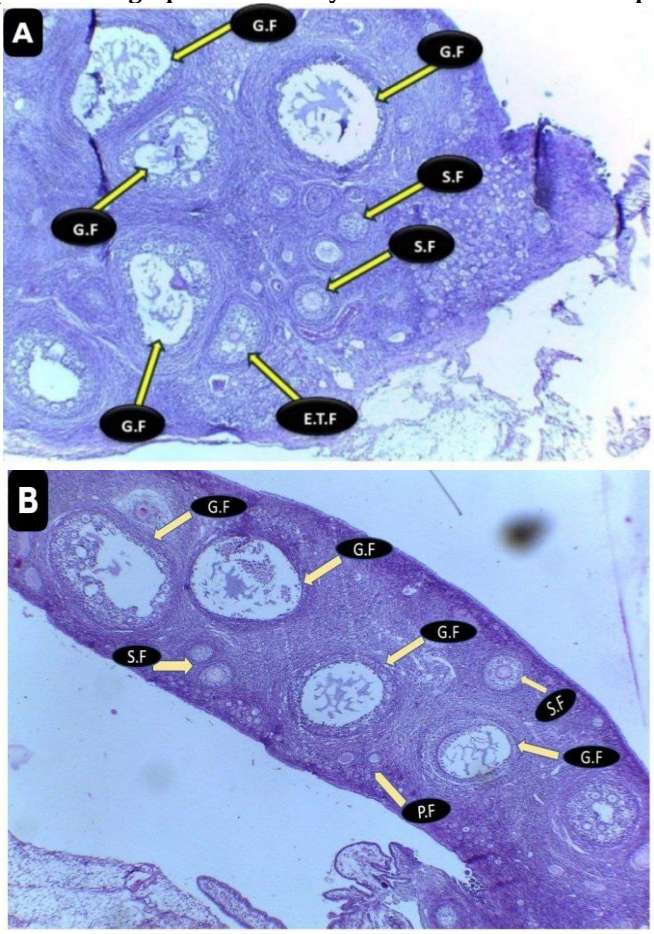
Figure 2: A photomicrograph of the ovary's abnormal tissue structure in the valproic acid group



A: Showing the Graafian Follicle (G. F) ; Tertiary Follicle (T. F) and Secondary Follicle (S. F) . H&E : 100 x
B: Showing the Corpus Luteum (C. L) ; Tertiary Follicle (T. F) ; Secondary Follicle (S. F) and Primary Follicle (P. F) . H&E : 100x

The histological sections of the female ovaries treated with Spirulina extract showed a noticeable number of primary and secondary follicles, as well as a few atretic follicles, when compared to the VPA-treated group , generally, the results of our study revealed that there were no significant histological alterations in the ovaries of rabbits administered with Spirulina extracts no vascular congestion was observed, and the histological architecture appeared close to normal, showing well-organized follicles and corpora lutea the morphology of the follicles appeared mature and well-developed (figure 3).

Figure 3: A photomicrograph of the ovary's tissue structure in the spirulinagroup.

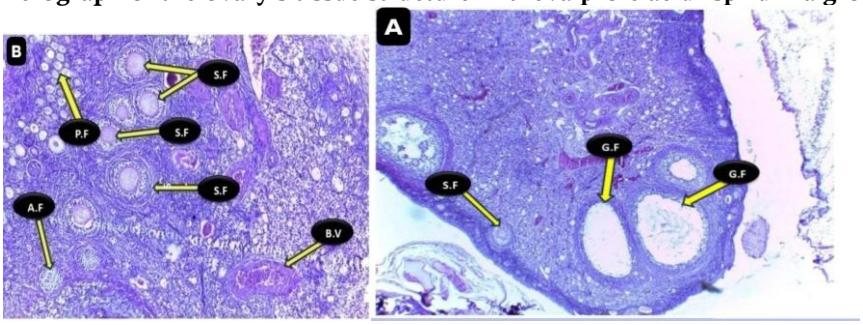


A : Showing the Graafian Follicle (G. F) ; Secondary Follicle (S. F) and Early Tertiary Follicle (E. T. F) . H&E : 100x

B : Showing the Graafian Follicle (G. F) ; Secondary Follicle (S. F) and Primary Follicle (P. F) . H&E : 100x

In summarized description, the section of the female ovaries treated with (Spirulina+ VPA)showed a reduction in congestion of blood vessels, the section also revealed light activity of folliculogenesis, moreover, the ovarian tissue appeared to contain many follicles varying in size and developmental stages, as shown in (figure 4).

Figure 4: A photomicrograph of the ovary's tissue structure in thevalproic acid+spirulina group.



A: Showing the Graafian Follicle (G. F) ; Secondary Follicle (S. F) . H&E : 100x

B : Showing the Secondary Follicle (S. F) and Primary Follicle (P. F) ; Atretic Follicle (A. F) and Blood Vessel (B. V) . H&E : 400x

DISCUSSION

The results of this study showed a clear decrease in the levels of FSH and LH in the VAP group compared to the control group. This agrees with (Ibrahim et al., 2019), who reported a significant decrease in FSH and LH levels in female rats treated with VAP.

This potential decrease in hormone levels is attributed to the fact that VPA may lead to an increase in the neurotransmitter gamma-aminobutyric acid (GABA). An increase in GABA can affect the hypothalamus by altering the secretion of gonadotropin-releasing hormone (GnRH), which in turn may affect gonadotropic secretion decreased, FSH and luteinizing hormone levels (Ernst and Goldberg, 2002) . In contrast, the spirulina extract group and the spirulina + VAP group showed a noticeable improvement and increase in FSH and LH levels compared to the VAP-treated group. This is consistent with(Hanafi et al., 2025), who reported the supportive effects of Spirulina extract in increasing FSH and LH levels and supporting reproductive function in female rabbits. This is because spirulina is a source of antioxidants and biologically active compounds (Ismaiel et al., 2016).This extract may contain bioactive compounds or amino acids similar to a general central nervous system stimulatory neurotransmitter that triggers the pulsatile release of GnRH from the hypothalamus, leading to the pulsatile release of pituitary hormones Garreau and De Rochambeau, 2003) Also, the results showed a clear decrease in its levels of E2 hormonein the VAP group compared to the control group. This decrease is consistent with the study of (Gregoraszczuk et al., 2000), which reported a similar decrease in E2 levels in wistar female rats treated with VAP, and decrease in levels progesterone hormone in the VAP group compared to the control group.This agrees with the study of (Røste et al.,2002), which reported a similar decrease in levels of progesterone in female rats treated with VAP. While regarding testosterone hormone, the results showed a marked increase in the VAP group compared to the control group, this agrees with the study of (Røste et al., 2002), which reported a clear increase in testosterone levels in female rats treated with VAP.Steroid synthesis and ovulation are key functions of the mammalian ovary, and these processes are closely related to follicular formation (Ahn et al., 2021).The inhibitory effect of valproate on cytochrome P450 and glucuronide systems leads to elevated serum testosterone concentrations, the effect of valproate on the ovaries may be due to its effect on the activity of the P450 aromatase enzyme. (Verrotti et al., 2016).

The follicles in women with polycystic ovary syndrome (PCOS) were negative for the P450 aromatase enzyme, thus reducing the conversion of testosterone to estrogen (Tamura et al. ,1993)

In contrast, the spirulina extract group and the spirulina + VAP group showed an increase in E2 levels compared to the VAP group. This agrees with the study of (Embabyet al., 2025), and this effect is attributed to the antioxidant compounds present in Spirulina.

Also, the spirulina extract group and the spirulina + VAP group showed a noticeable improvement in progesterone levels compared to the VAP group. This agrees with the study of (Hussin et al., 2022), and this is due to the direct effect of spirulina on hormone secretion from the follicles and its content of essential amino acids, fatty acids, vitamins, and minerals, which is attributed to its antioxidant activity (Hoswini et al.,2013; Farag et al., 2019).

In contrast, the results of the spirulina group and the spirulina + VAP group showed a noticeable improvement in testosterone levels compared to the VAP group. This agrees with the studies of (Bobescu et al., 2020 ; EL Leithy et al.,2022), which reported that spirulina has an effective role in significantly reducing testosterone levels in female rats, due to the active role of spirulina and its anti-androgenic effect. spirulina is an algae rich in vitamins and minerals, thus exhibiting strong antioxidant activity. It is rich in flavonoids and phenols, which are reflected in its role in improving hormone levels(Hanafi et al., 202 5)

Our histological studies of the ovaries confirmed that the improvement in hormone levels due to spirulina showed a moderate effect on ovarian tissue, especially in ovaries treated with valproate, in terms of the growth of mature follicles and corpus luteum, consistent with normal conditions compared to control animals. Perhaps a longer treatment period with spirulina is needed for its positive effect on the ovary tissue to be fully apparent, which is consistent with (Hanafi et al. 2025) who demonstrated the effect of administering an aqueous extract of spirulina on the reproductive capacity of female rabbits; an increase in serum luteinizing hormone and estradiol concentrations was observed.

Conclusion

Research findings indicate that valproic acid exerts significant effects on hormonal balance and ovarian tissue in female rabbits. Notably, the combined administration of valproic acid and Spirulina algae extract resulted in a significant increase in the levels of several reproductive hormones, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone (P4), and estradiol (E2), accompanied by a marked decrease in testosterone levels. These findings suggest a potential role of spirulina extract in mitigating the hormonal disturbances induced by valproic acid. Furthermore, statistical analyses,

particularly analysis of variance (ANOVA), demonstrated significant differences in hormone levels among the different treatment groups.

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