Quercetin Reduces Vascular Permeability in an Experimental Rat Model of Ovarian Hyperstimulation Syndrome: A Comparative Histochemical and Immunohistochemical Study with Cabergoline

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Abstract

This study investigated the effects of quercetin and cabergoline on ovarian histomorphology, biochemical changes and the vascular endothelial growth factor (VEGF)–pigment epithelium-derived factor (PEDF)- cyclooxygenase-2 (COX-2) axis in an experimental rat model of ovarian hiperstimulation syndrome (OHSS).

Forty-two immature female Wistar rats were randomly divided into six groups: Control, OHSS, Quercetin, Cabergoline, OHSS+Quercetin, and OHSS+Cabergoline. Ovarian morphology was assessed by measuring ovarian weight and diameter. Histological examination was performed with hematoxylin and eosin (H&E) staining, and immunohistochemical analyses were conducted to determine VEGF, PEDF, and COX-2 expression in ovarian tissue. Vascular permeability was evaluated spectrophotometrically using Evans Blue dye extravasation, while serum TNF-α and estradiol levels were determined by ELISA.

The OHSS group showed significantly increased ovarian weight and diameter compared with the other groups. VEGF and COX-2 expression were increased, whereas PEDF immunoreactivity was reduced in granulosa cells. In the treatment groups, VEGF and COX-2 expression were similar patterns, but PEDF expression was higher in the OHSS+Cabergoline group. Vascular permeability was significantly lower in the OHSS+Quercetin group than in the OHSS+Cabergoline group, indicating a stronger protective effect of quercetin on vascular integrity. Quercetin reduced vascular permeability, although most histological and biochemical parameters did not differ significantly between the treatment groups.

These findings suggest that quercetin may exert protective effects on ovarian tissue, possibly through modulation of angiogenic balance and vascular permeability in experimantal OHSS.

Introduction

OHSS is a serious iatrogenic complication associated with ovarian stimulation during assisted reproductive technologies, particularly in vitro fertilization (IVF) treatment and is accompanied by enlarged ovaries, hemoconcentration, ascites, and increased vascular permeability (Delvigne and Rozenberg 2002; Elchalal and Schenker 1997). The incidence of moderate to severe OHSS has been reported to range between 0.5% and 5% of IVF cycles and may reach up to 20% in women considered to be at high risk (Nastri et al. 2010). The development of OHSS is largely triggered with the secretion of hCG, which induces a sustained luteinizing hormone-like effect and stimulates the release of vasoactive and inflammatory mediators in ovarian tissue (Abbara et al. 2018). Among these mediators, vascular endothelial growth factor (VEGF) is a key mediator that promotes angiogenesis and increasing vascular permeability, which contributes to fluid accumulation and ovarian edema (Ferrara et al. 1991; Ferrara and Davis-Smyth 1997). In contrast, pigment epithelium-derived factor (PEDF) acts as an endogenous anti-angiogenic factor that counterbalances VEGF activity and contributes to the maintenance of vascular homeostasis (Craword et al. 2013; Chuderland et al. 2013). Characterisation of VEGF and PEDF associated expression patterns in ovarian tissue may offer significant insight into the cellular and microvascular changes underlying OHSS from a histochemical and cell biology standpoint.

In addition to angiogenic dysregulation, oxidative stress and inflammatory signaling are known as contributing factors in the development and severity of OHSS (Blumenfeld 2018). These interrelated mechanisms may impair endothelial function, disturb microvascular homeostasis, and amplify vascular hyperpermeability within ovarian tissue. Accordingly, bioactive molecules with antioxidant and anti-inflammatory properties have attracted increasing attention as potential modulators of the cellular and vascular alterations associated with OHSS. Quercetin, a naturally occurring flavonoid widely present in fruits and vegetables, has been extensively studied because of its anti-inflammatory, antioxidant, and anti-angiogenic activities (Hertog and Hollman 1996). Experimental studies have shown that quercetin suppresses several inflammatory signalling molecules, including nitric oxide (NO), tumor necrosis factor-α (TNF-α), interleukins (IL-6, IL-1β), cyclooxygenase-2 (COX-2), and nuclear factor-κB (NF-κB), thereby reducing oxidative stress and limiting VEGF-mediated vascular permeability (Mrvová et al. 2015; Ramyaa et al. 2014; Zhang et al. 2022; Azeem et al. 2023). In addition, inhibition of COX-2 signaling by quercetin

may contribute to the attenuation of angiogenic pathways involved in OHSS progression (Soares 2012; Lamazou et al. 2011; Xiao et al. 2011).These characteristics imply that quercetin may affect the ovarian tissue response to OHSS by regulating inflammatory activity, vascular permeability, and angiogenic marker expression from a histochemical and cell bıology standpoint.

Cabergoline, a selective dopamine D2 receptor agonist, has been used as a pharmacological approach to reduce the incidence of OHSS. Its protective effect is mainly attributed to the inhibition of VEGF receptor-2 phosphorylation, which limits vascular leakage without compromising reproductive outcomes (Carizza et al. 2008; Seow et al. 2013; Rubenfeld and Dahan 2021). Although the preventive role of cabergoline in OHSS has been investigated in several studies, the potential effects of natural bioactive compounds such as quercetin on ovarian angiogenesis and vascular permeability remain insufficiently explored. In particular, limited data are available regarding the comparative effects of quercetin and cabergoline on histomorphological changes and angiogenic markers associated with OHSS.

Considering these mechanisms, the present study aimed to comparatively evaluate the structural and biochemical effects of quercetin and cabergoline in an experimental OHSS model. Particular emphasis was placed on histomorphological alterations and the regulation of angiogenic markers associated with ovarian vascular permeability.

Materials and Methods

Experimental OHSS Model Development

The experimental protocol was approved by the Local Ethics Committee for Animal Experiments of Muğla Sıtkı Koçman University (Approval No. 07/23, February 7, 2023) and supported by the Scientific Research Projects Coordination Unit of Aydın Adnan Menderes University (Project No. TPF-23025).

A total of 42 immature female Wistar albino rats (22 days old, 30–50 g) were obtained from the Muğla Sıtkı Koçman University Experimental Animal Research Center (MUDEM-HADYEK). Animals were housed in standard conditions (21–24°C, 45–55% humidity, 12-h light/dark conditions with ad libitum access to standard chow and water). Wistar albino rats were grouped in cages (3–4 per cage), which were cleaned every other day. Immature rats were selected due to their uniform hormonal background and suitability for ovarian hyperstimulation, as previously established in the literature (Kitajima et al. 2004). To induce OHSS, animals received daily intraperitoneal injections of 10 IU pregnant mare serum gonadotropin (PMSG) for four consecutive days starting on postnatal day 22, followed by a single dose of 30 IU human chorionic gonadotropin (hCG) on day 26 (Ferrero et al. 2014). This protocol is widely recognized for effectively modeling OHSS pathophysiology and evaluating potential therapeutic agents.

Experimental Groups

A total of 42 immature female Wistar albino rats were randomly allocated into six experimental groups (n = 7 per group) as outlined below:

Group I (Control)

Received daily intraperitoneal (i.p.) injections of 0.1 mL 0.9% NaCl from postnatal day 22 to 26.

Group II (OHSS)

Treated with 10 IU of PMSG in 0.1 mL 0.9% NaCl via i.p. route for four consecutive days, followed by a single 30 IU dose of human chorionic gonadotropin (hCG) on day 26 to induce OHSS.

Group III (Quercetin)

Administered quercetin orally (via gavage) at the dose of 20 mg/kg/day for six days starting on day 22.

Group IV (Cabergoline)

Received cabergoline at 100 µg/kg/day orally for six days, beginning on day 22.

Group V (OHSS + Quercetin)

Underwent the same OHSS induction protocol as Group II and concurrently received quercetin (20 mg/kg/day, oral gavage) for six days starting on day 22.

Group VI (OHSS + Cabergoline)

Subjected to the OHSS protocol (as in Group II) and simultaneously treated with cabergoline (100 µg/kg/day, oral gavage) for six days from day 22.

Table 1
Experimental groups and treatment schedule in the rat model of OHSS.

Groups	22th Day	23th Day	24th Day	25th Day	26th Day	27th Day	28th Day
GROUP I (Control) N = 7	0,1 ml % 0.9 NaCl(ip)	0,1 ml % 0.9 NaCl (ip)	0,1 ml % 0.9 NaCl (ip)	0,1 ml % 0.9 NaCl (ip)	0,1 ml % 0.9 NaCl (ip)		SACRIFICE
GROUP II (OHSS) N = 7	10IU/0,1 ml PMSG/ % 0,9NaCl (ip)	10 IU/0,1ml PMSG/ % 0,9NaCl (ip)	10 IU/0,1ml PMSG/ % 0,9NaCl (ip)	10 IU/ 0,1ml PMSG/ % 0,9NaCl (ip)	30 IU/0,1ml hCG/ % 0,9NaCl (ip)		
GROUP III (Quercetin) N = 7	20 mg/kg/day (oral gavage)	20 mg/kg/day (oral gavage)	20 mg/kg/day oral gavage)	20 mg/kg/day (oral gavage)	20 mg/kg/day (oral gavage)	20 mg/kg/day (oral gavage)	
GROUP IV (Cabergolin) N = 7	100 µg/kg/day (oral gavage)	100 µg/kg/day (oral gavage)	100 µg/kg/day (oral gavage)	100 µg/kg/day (oral gavage)	100 µg/kg/day (oral gavage)	100 µg/kg/day (oral gavage)	
GROUP V (OHSS+ Quercetin) N = 7	10 IU/0,1ml PMSG/ % 0,9NaCl (ip) + 20 mg/kg/day (oral gavage)	10 IU/0,1ml PMSG/ %0,9NaCl (ip) + 20 mg/kg/day (oral gavage)	10 IU/0,1ml PMSG/ %0,9NaCl (ip) + 20 mg/kg/day (oral gavage)	10 IU/0,1ml PMSG/ % 0,9NaCl (ip) + 20 mg/kg/day (oral gavage)	30 IU/0,1ml hCG / % 0,9 NaCl (ip) + 20 mg/kg/day (oral gavage)	20 mg/kg/day (oral gavage)	
GROUP VI (OHSS+ Cabergolin N = 7	10 IU/ 0,1mlPMSG/% 0,9NaCl (ip) + 100 µg/kg/day (oral gavage)	10 IU/ 0,1mlPMSG/% 0,9NaCl (ip) + 100 µg/kg/ day (oral gavage)	10 IU/ 0,1mlPMSG/% 0,9NaCl (ip) + 100 µg/kg/ day (oral gavage)	10 IU/ 0,1mlPMSG/% 0,9NaCl (ip) + 100 µg/kg/ day (oral gavage)	30 IU/ 0,1 ml hCG % 0,9NaCl (ip) + 100 µg/kg/ day (oral gavage)	100 µg/kg/ day (oral gavage)	

Evaluation of Vascular Permeability via Peritoneal Lavage

To assess vascular permeability, rats received an intravenous injection of 0.2 mL 5 mM Evans Blue dye via the jugular vein under brief anesthesia, following cervical area shaving (Fig. 1). After a 30-minute circulation period, 5 mL of 0.9% NaCl (at 21°C) was gently instilled into the peritoneal cavity. The abdomen was agitated for 30 seconds and the lavage fluid was carefully collected to avoid tissue damage. Samples were collected in experimental tubes containing 0.05 mL of 0.1 N NaOH for spectrophotometric analysis.

Assessment of Vascular Permeability

Peritoneal lavage samples were centrifuged at 900 × g for 12 min to obtain the supernatant. The concentration of Evans Blue (EB) dye in the supernatant was determined spectrophotometrically at 600 nm using a Shimadzu UV-1601 UV–Visible spectrophotometer (Shimadzu, Japan). Vascular permeability was quantified by measuring the amount of extravasated EB dye and was expressed as millimoles (mM) per 100 g body weight.

Ovarian Weight and Diameter Measurement

The left ovaries were carefully dissected and weighed, then fixed in 10% neutral buffered formalin for histological analysis. Ovarian diameter was measured from digital images of ovarian tissue sections using ImageJ software version 1.52p (NIH, Bethesda, MD, USA). For each ovary, six separate measurements were taken, and the mean value was calculated. Ovarian diameter was expressed in millimeters (Fig. 2).

Serum TNF-α and Estradiol Measurements

Serum TNF-α and estradiol levels were determined using commercially available rat-specific ELISA kits (Sunred Biological Technology Co., Ltd., Shanghai, China) in accordance with the manufacturer's instructions. Absorbance values were measured using a microplate reader (Multiskan GO, Thermo Scientific, Rockford, IL, USA). All samples were analyzed in duplicate to ensure measurement reliability.

Ovarian Collection and Histomorphological Analysis

Following dissection, the left ovaries of the rats were carefully excised and weighed. The ovarian tissues were fixed in 10% neutral buffered formalin for 24 h. After fixation, the samples were rinsed and dehydrated through a graded ethanol series, cleared in xylene, and embedded in paraffin blocks according to standard histological procedures.

Serial sections of 4 μm thickness were obtained at 50-μm intervals to avoid repeated evaluation of the same structures. Ten sections from each ovary were selected for analysis. The sections were mounted on glass slides, dried at 60°C, and stained with hematoxylin–eosin (H&E) for general histomorphological evaluation (Sun et al. 2017).

For follicle quantification, ten sections from each experimental group were analyzed. Only follicles with clearly visible nuclei were included in the counting to avoid duplicate assessment of the same follicle. The total number of follicles in each section was recorded and classified according to follicle type. The proportion of each follicle category was then calculated as a percentage of the total follicle count for each group.

Immunohistochemical Analysis

Paraffin-embedded ovarian sections were incubated with 10% hydrogen peroxide (H_2O_2) for 30 min to block endogenous peroxidase activity and then treated with 10% normal goat serum (Invitrogen, Camarillo, CA, USA) for 1 h at room temperature to prevent non-specific binding.

Sections were incubated overnight at 4°C with primary antibodies against VEGF (orb11553, Biorbyt, UK), COX-2 (orb10450, Biorbyt, UK), and PEDF (BT LAB, Jiangsu Korain Biotech, China) at a dilution of 1:100. Information on antibody reactivity and application was obtained from the manufacturers datasheets, and negative controls were included by omission of the primar antibody. Immunoreactivity was detected using the Histostain-Plus Bulk kit (Bioss Inc., Woburn, MA, USA) according to the manufacturer's instructions, and 3,3'-diaminobenzidine (DAB) was used as the chromogen. Sections were examined and photographed using with an Nikon Eclipse Ci microscope (Nikon, Japan) and Nikon Camera adaptor Y-TV55 TV intermediate tube for C-0.55x (Nikon, Japan).

Immunoreactivity Evaluation

Staining intensity was evaluated using the H-score method. For each group, ten randomly selected fields were analyzed at ×20 magnification. Staining intensity was evaluated on a four-point scale: negative (0), weak (1), moderate (2), or strong (3). The H-score was calculated using the formula H-score = Σ (1 + d) × h, where d represents staining intensity and h indicates the percentage of positive cells. Evaluations were performed independently by two histologists to minimize observer bias (Yilmaz et al. 2018).

Statistics Analysis

Normality was assessed with the Shapiro–Wilk test. Variables with normal distribution and homogeneous variances were analyzed by one-way ANOVA followed by Tukey's HSD test. Vascular permeability, which showed unequal variances, was analyzed using Welch's ANOVA followed by Games–Howell post hoc testing. Non-normally distributed variables were analyzed using the Kruskal–Wallis test followed by Dunn's multiple comparison test. Data are presented as mean ± standard deviation or median with interquartile range, as appropriate. Statistical analyses were performed using R software (version 4.4.2), and $p < 0.05$ was considered statistically significant.

Results

Histomorphological Analysis

In the control, QUR, and CAB groups, ovarian sections showed a normal histological appearance with numerous developing follicles. In the OHSS group, the ovaries were largely occupied by cystic structures and abundant corpora lutea, indicating marked luteinization. Similar luteinized structures were also observed in the OHSS + QUR and OHSS + CAB groups. However, the number of corpora lutea appeared lower in the OHSS+Quercetin group than in the OHSS group, whereas the OHSS+Cabergoline group showed comparable findings (H&E, ×10) (Fig. 3A). VEGF expression was low in the control, QUR, and CAB groups, but markedly increased in the OHSS and OHSS+Quercetin groups. This increase was statistically significant in the OHSS group compared with the control, QUR, and CAB groups (VEGF, ×10) (Fig. 3B). The same pattern was detected for COX-2. Minimal staining was detected in the control, QUR, and CAB groups, whereas strong immunoreactivity was found in the OHSS and OHSS+Quercetin groups (COX-2, ×10) (Fig. 3C). PEDF expression showed the opposite pattern. Strong immunoreactivity was observed in the control, QUR, and CAB groups, while markedly reduced staining was found in the OHSS and OHSS+Quercetin groups (PEDF, ×10) (Fig. 3D). Overall, OHSS induction was associated with marked morphological changes and altered expression of angiogenic and inflammatory markers. Quercetin and cabergoline appeared to differ in their effects on ovarian structural and biochemical changes.

Table 2. Percentage distribution of ovarian follicle types in the experimental groups (mean ± SD).

	Control	OHSS	QUR	CAB	OHSS + QUR	OHSS+CAB
Primordial Follicle	15,57 ± 11,28	4,14 ± 2,54	9,71 ± 7,56	13,85 ± 10,31	8,14 ± 1,34	9,85 ± 8,64
Early Primary Follicle	5 ± 2,5	3 ± 2,5	11 ± 7,5	10 ± 6	7 ± 1,5	6 ± 4,5
Late Primary Follicle	5,57 ± 5,59	3,42 ± 2,22	4,14 ± 3,84	4,42 ± 2,69	4,71 ± 1,11	6,85 ± 4,59
Secondary Follicle	7,71 ± 5,46	3,85 ± 1,21	7,28 ± 5,64	5,85 ± 3,62	5 ± 0,81	3,71 ± 2,81
Graaf (Antral) Follicle	2,28 ± 1,25	1,71 ± 0,95	3,57 ± 2,63	3,71 ± 1,88	3,14 ± 1,77	2,14 ± 1,21
Atretic Follicle	2 ± 3,5	2 ± 2	6 ± 3.5	4 ± 2	5 ± 2	4 ± 5,5
Cystic Follicle	3 ± 2	10 ± 6	2 ± 1$_a$	1 ± 1$_a$	2 ± 1	5 ± 2
Corpus Hemorrhagicum	0 ± 0,5	0 ± 0	0 ± 0	0 ± 0	1 ± 0,5	0 ± 1,5
Corpus Luteum	0 ± 0	7 ± 3,5*	0 ± 0$_a$	0 ± 0$_a$	5 ± 2	7 ± 3**

Statistical significance was accepted at *p < 0.05 and ** p < 0.01 compared with the control group; a: p < 0.05 compared with the OHSS group.

Table 3
TNF-α and Estradiol table of the experimental groups (mean ± SD).

TNF-α (ELISA)	**CONTROL**	**OHSS**	**QUR**	**CAB**	**OHSS + QUR**	**OHSS + CAB**	**P**
ng/L	**175,5 ± 39,1**	**212,6 ± 21,15**	**175,6 ± 20,25**	**121,9 ± 19,49**	**159 ± 18,92**	**79,4 ± 8,06**	**p < 0.0001**
Estradiol (ELİSA) ng/L	151,6 ± 8,65	186,5 ± 10,9	138,7 ± 9,59	135,6 ± 23,25	150 ± 7,55	308,7 ± 43	p < 0.0001

Regarding estradiol levels, the OHSS group (186.5 ± 10.9 ng/L) showed higher values than the control group (151.6 ± 8.65 ng/L), although the difference was not statistically significant. Estradiol concentrations in the Quercetin (138.7 ± 9.59 ng/L) and Cabergoline (135.6 ± 23.25 ng/L) groups were lower than those of the control group. In the OHSS + Quercetin group (150 ± 7.55 ng/L), estradiol levels were close to control values. In contrast, the OHSS + Cabergoline group exhibited a marked and significant increase in estradiol levels (308.7 ± 43 ng/L). A significant difference was observed between the OHSS and Quercetin groups (p = 0.0457). Estradiol levels in the OHSS + Cabergoline group were significantly higher than those in the Quercetin group (p = 0.0002) and the OHSS + Quercetin group (p = 0.0012). Furthermore, estradiol levels in the Cabergoline-alone group were significantly lower than those in the OHSS+ Cabergoline group (p = 0.0063).

Serum TNF-α levels were elevated in the OHSS group (212.6 ± 21.15 ng/L) compared to the control group (175.5 ± 39.1 ng/L); however, this increase did not reach statistical significance. TNF-α levels in the Quercetin group (175.6 ± 20.25 ng/L) remained comparable to those of the control group. Cabergoline administration alone resulted in lower TNF-α levels (121.9 ± 19.49 ng/L) compared to the OHSS group, showing a significant reduction (p = 0.0027). Notably, the OHSS + Cabergoline group demonstrated the lowest TNF-α concentration among all groups (79.4 ± 8.06 ng/L). This decrease was statistically significant when compared with the control (p = 0.0045), OHSS (p = 0.0001), and Quercetin groups (p = 0.0145).

Discussion

This study provides an integrated evaluation of the structural, biochemical, and immunohistochemical effects of quercetin and cabergoline in an experimental model of OHSS. The findings show that OHSS is associated with marked

histomorphological alterations together with increased expression of angiogenic and inflammatory markers, particularly VEGF and COX-2, and reduced PEDF immunoreactivity. These observations are consistent with previous reports indicating that VEGF plays a central role in OHSS by promoting angiogenesis and increasing vascular permeability in ovarian tissue (Ferrara et al. 1991; Ferrara and Davis-Smyth 1997).

Quercetin treatment was associated with a reduction in cystic and atretic follicles and a relative increase in developing follicles, suggesting a supportive effect on ovarian tissue organization. These changes were accompanied by a clear decrease in vascular permeability, which appeared more pronounced than that observed with cabergoline. This finding is particularly relevant, as increased vascular permeability is a key feature of OHSS pathophysiology and is directly linked to fluid shift and ovarian edema (Delvigne and Rozenberg 2002; Elchalal and Schenker 1997).

Although both quercetin and cabergoline reduced VEGF and COX-2 expression to some extent, neither agent fully normalized these markers. This suggests that angiogenic and inflammatory pathways activated during OHSS may persist despite pharmacological intervention. In addition, OHSS is known to involve multiple mediators, including cytokines and vasoactive systems, which may contribute to the incomplete suppression of these pathways (Nastri et al. 2010; Blumenfeld 2018). This may also explain the limited differences observed between treatment groups in some histological findings.

An important aspect of the present study is the evaluation of the VEGF–PEDF balance. Increased VEGF expression together with reduced PEDF immunoreactivity in the OHSS group indicates a disruption of angiogenic homeostasis. PEDF is recognized as a potent endogenous anti-angiogenic factor that counteracts VEGF activity and contributes to vascular stability (Craword et al. 2013; Chuderland et al. 2013). The partial modulation of this imbalance in the treatment groups suggests that quercetin may influence angiogenic regulation not only through suppression of pro-angiogenic signals but also through interaction with endogenous inhibitory mechanisms.

Cabergoline is known to reduce vascular permeability mainly through inhibition of VEGF receptor-2 phosphorylation, thereby limiting vascular leakage (Carizza et al. 2008). In contrast, the effects of quercetin on ovarian angiogenesis and vascular permeability remain less clearly defined. Experimental studies have shown that quercetin can suppress inflammatory mediators such as TNF-α, COX-2, and NF-κB, which are closely associated with angiogenic signaling pathways (Mrvová et al. 2015; Ramyaa et al. 2014; Azeem et al. 2023). In addition, COX-2 activity has been linked to increased VEGF expression and angiogenesis, suggesting a potential mechanistic link between inflammation and vascular changes in OHSS (Soares 2012; Lamazou et al. 2011). In line with these findings, the present results indicate that quercetin exerts a measurable effect on vascular permeability and ovarian morphology in this experimental model. However, since most molecular parameters did not differ significantly between treatment groups, these findings should be interpreted with caution.

The possible involvement of PEDF-related mechanisms is of particular interest, as this pathway has not been extensively studied in relation to quercetin in OHSS. However, the current results do not allow a definitive conclusion regarding the exact role of PEDF in mediating these effects, and further mechanistic studies are required.

Some limitations should be taken into consideration. The study was carried out in an experimental animal model with a relatively limited sample size, and treatment effects may depend on dose and duration. Therefore, further research is required to better understand dose-response relationships and to better define the underlying mechanisms.

In conclusion, quercetin showed a noticeable effect on vascular permeability and ovarian morphology in experimental OHSS. While both quercetin and cabergoline influenced angiogenic and inflammatory markers, their effects were not identical. These findings suggest that quercetin may have a modulatory role in ovarian vascular responses; however, further experimental and clinical studies are necessary to verify its potential relevance.

Declarations

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Author contributions O.U.G.: Performed the experiment, data collection and analysis, conceptualization, writing draft manuscript, final editing and proofreading of the manuscript. A.G.: Design of the experiment, supervision, final editing and proofreading of the manuscript. M.E., Ö.Ç.: Design of the experiment.

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Data availability The data used in the study are included in the manuscript.

Conflict of interest The authors declare no conflict of interest.

Ethical approval The experiment protocols was conducted in accordance with institutional guidelines and Muğla Sıtkı Koçman University Animal Experiments Local Ethics (Approval No. 07/23, February 7, 2023) and supported by the Scientific Research Projects Coordination Unit of Aydın Adnan Menderes University (Project No. TPF-23025).

Consent for publication Not applicable.

References

1. Abbara A, Clarke SA, Dhillo WS (2018) Novel concepts for inducing final oocyte maturation in in vitro fertilization treatment. Endocr Rev 39:593–628. https://doi.org/10.1210/er.2017-00236
2. Azeem M, Hanif M, Mahmood K, Ameer N, Chughtai FRS, Abid U (2023) An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: a review. Polym Bull (Berl) 80:241–262. https://doi.org/10.1007/s00289-022-04091-8
3. Blumenfeld Z (2018) The ovarian hyperstimulation syndrome. Vitam Horm 107:423–451. https://doi.org/10.1016/bs.vh.2018.01.018
4. Carizza C, Abdelmassih V, Abdelmassih S, Ravizzini P, Salgueiro L, Salgueiro PT, Jine LT, Nagy P, Abdelmassih R (2008) Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study. Reprod Biomed Online 17:751–755. https://doi.org/10.1016/S1472-6483(10)60401-4
5. Chuderland D, Ben-Ami I, Kaplan-Kraicer R, Grossman H, Ron-El R, Shalgi R (2013) The role of pigment epithelium-derived factor in the pathophysiology and treatment of ovarian hyperstimulation syndrome in mice. J Clin Endocrinol Metab 98: E258-E266. https://doi.org/10.1210/jc.2012-3037
6. Craword SE, Fitchev P, Veliceasa D, Volpert OV (2013) The many facets of PEDF in drug discovery and disease: a diamond in the rough or split personality disorder? Expert Opin Drug Discov 8:769–792. https://doi.org/10.1517/17460441.2013.794781
7. Delvigne A, Rozenberg S (2002) Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update 8:559–577. https://doi.org/10.1093/humupd/8.6.559
8. Elchalal U, Schenker JG (1997) The pathophysiology of ovarian hyperstimulation syndrome–views and ideas. Hum Reprod 12:1129–1137. https://doi.org/10.1093/humrep/12.6.1129
9. Ferrara N, Davis-Smyth T (1997) The biology of vascular endothelial growth factor. Endocr Rev 18:4–25. https://doi.org/10.1210/edrv.18.1.0287
10. Ferrara N, Houck KA, Jakeman LB, Winer J, Leung DW (1991) The vascular endothelial growth factor family of polypeptides. J Cell Biochem 47:211–218. https://doi.org/10.1002/jcb.240470305
11. Ferrero H, García-Pascual CM, Gómez R, Delgado-Rosas F, Cauli O, Simón C, Gaytán F, Pellicer A (2014) Dopamine receptor 2 activation inhibits ovarian vascular endothelial growth factor secretion in vitro: implications for treatment of

ovarian hyperstimulation syndrome with dopamine receptor 2 agonists. Fertil Steril 101:1411–1418. https://doi.org/10.1016/j.fertnstert.2014.01.031

12. Hertog MG, Hollman PC (1996) Potential health effects of the dietary flavonol quercetin. Eur J Clin Nutr 50:63–71
13. Kitajima Y, Endo T, Manase K, Nishikawa A, Shibuya M, Kudo R (2004) Gonadotropin-releasing hormone agonist administration reduced vascular endothelial growth factor (VEGF), VEGF receptors, and vascular permeability of the ovaries of hyperstimulated rats. Fertil Steril 81(Suppl 1):842–849. https://doi.org/10.1016/j.fertnstert.2003.11.012
14. Lamazou F, Legouez A, Letouzey V, Grynberg M, Deffieux X, Trichot C, Fernandez H, Frydman R (2011) Le syndrome d'hyperstimulation ovarienne: physiopathologie, facteurs de risque, prévention et prise en charge. J Gynecol Obstet Biol Reprod (Paris) 40:593–611. https://doi.org/10.1016/j.jgyn.2011.06.008
15. Mrvová N, Škandík M, Kuniaková M, Račková L (2015) Modulation of BV-2 microglia functions by novel quercetin pivaloyl ester. Neurochem Int 90:246–254. https://doi.org/10.1016/j.neuint.2015.09.005
16. Nastri CO, Ferriani RA, Rocha IA, Martins WP (2010) Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet 27:121–128. https://doi.org/10.1007/s10815-010-9387-6
17. Ramyaa P, Krishnaswamy R, Padma VV (2014) Quercetin modulates OTA-induced oxidative stress and redox signalling in HepG2 cells-up regulation of Nrf2 expression and down regulation of NF-κB and COX-2. Biochim Biophys Acta 1840:681–692. https://doi.org/10.1016/j.bbagen.2013.10.024
18. Rubenfeld, E. S., Dahan, M. H. (2021). Does the timing of cabergoline administration impact rates of ovarian hyperstimulation syndrome?. *Obstetrics & gynecology science*, *64*(4), 345–352. https://doi.org/10.5468/ogs.21067
19. Seow KM, Lin YH, Bai CH, Chen HJ, Hsieh BC, Huang LW, Tzeng CR, Hwang JL (2013) Clinical outcome according to timing of cabergoline initiation for prevention of OHSS: a randomized controlled trial. Reprod Biomed Online 26:562–568. https://doi.org/10.1016/j.rbmo.2013.03.002
20. Soares SR (2012) Etiology of OHSS and use of dopamine agonists. Fertil Steril 97:517–522. https://doi.org/10.1016/j.fertnstert.2011.12.046
21. Sun HY, Li Q, Liu YY, Wei XH, Pan CS, Fan JY, Han JY (2017) Xiao-Yao-San, a Chinese medicine formula, ameliorates chronic unpredictable mild stress induced polycystic ovary in rat. Front Physiol 8:729. https://doi.org/10.3389/fphys.2017.00729
22. Xiao, X., Shi, D., Liu, L., Wang, J., Xie, X., Kang, T., & Deng, W. (2011). Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. *PloS one*, *6*(8), e22934. https://doi.org/10.1371/journal.pone.0022934 Ovarian Res 11:51. https://doi.org/10.1186/s13048-018-0421-0
23. Yilmaz E, Gul M, Melekoglu R, Koleli I (2018) Immunhistochemical analysis of Nuclear Factor Kappa Beta expression in etiopathogenesis of ovarian tumors. Acta Cir Bras 33:641–650. https://doi.org/10.1590/s0102-865020180070000009
24. Zhang J, Li H, Wang W, Li H (2022) Assessing the anti-inflammatory effects of quercetin using network pharmacology and in vitro experiments. Exp Ther Med 23:301. https://doi.org/10.3892/etm.2022.11230

Figures

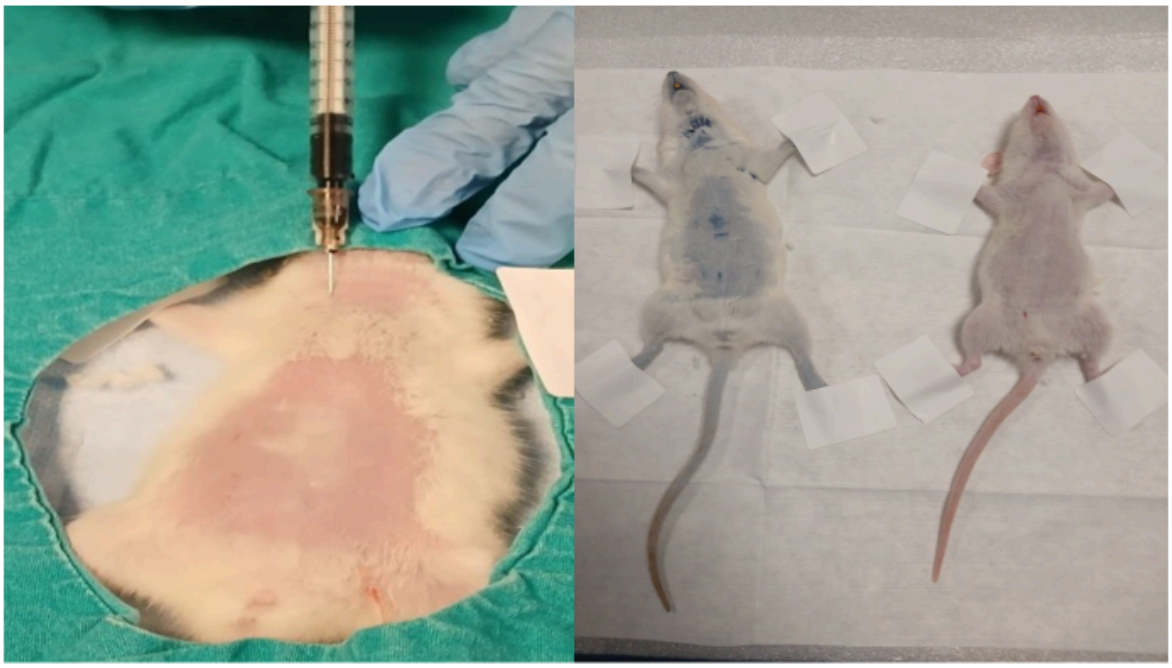

Figure 1

Evans Blue application in the jugular vein.

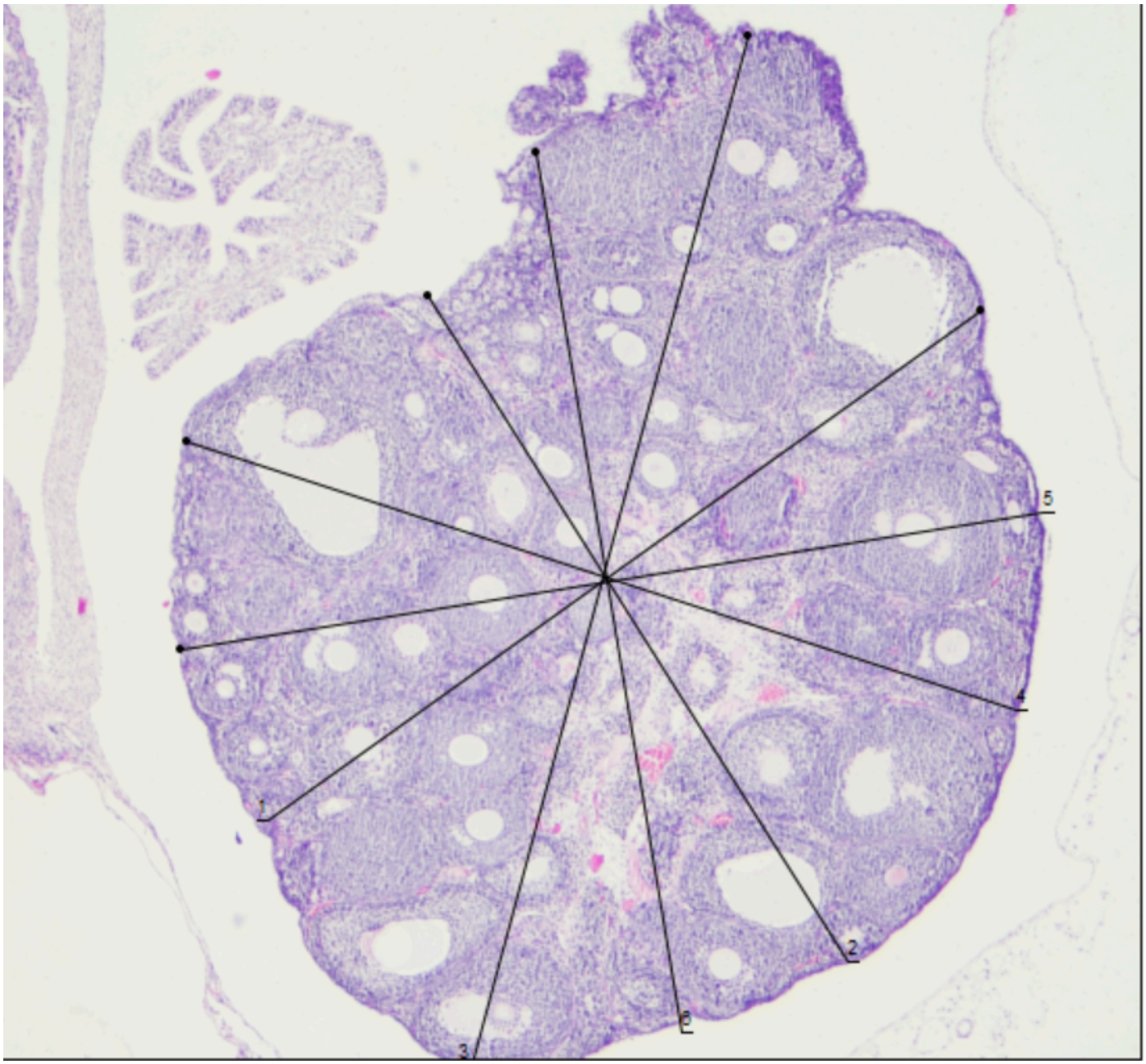

Figure 2

Ovarian sections showing diameter measurement using ImageJ (H&E, ×4).

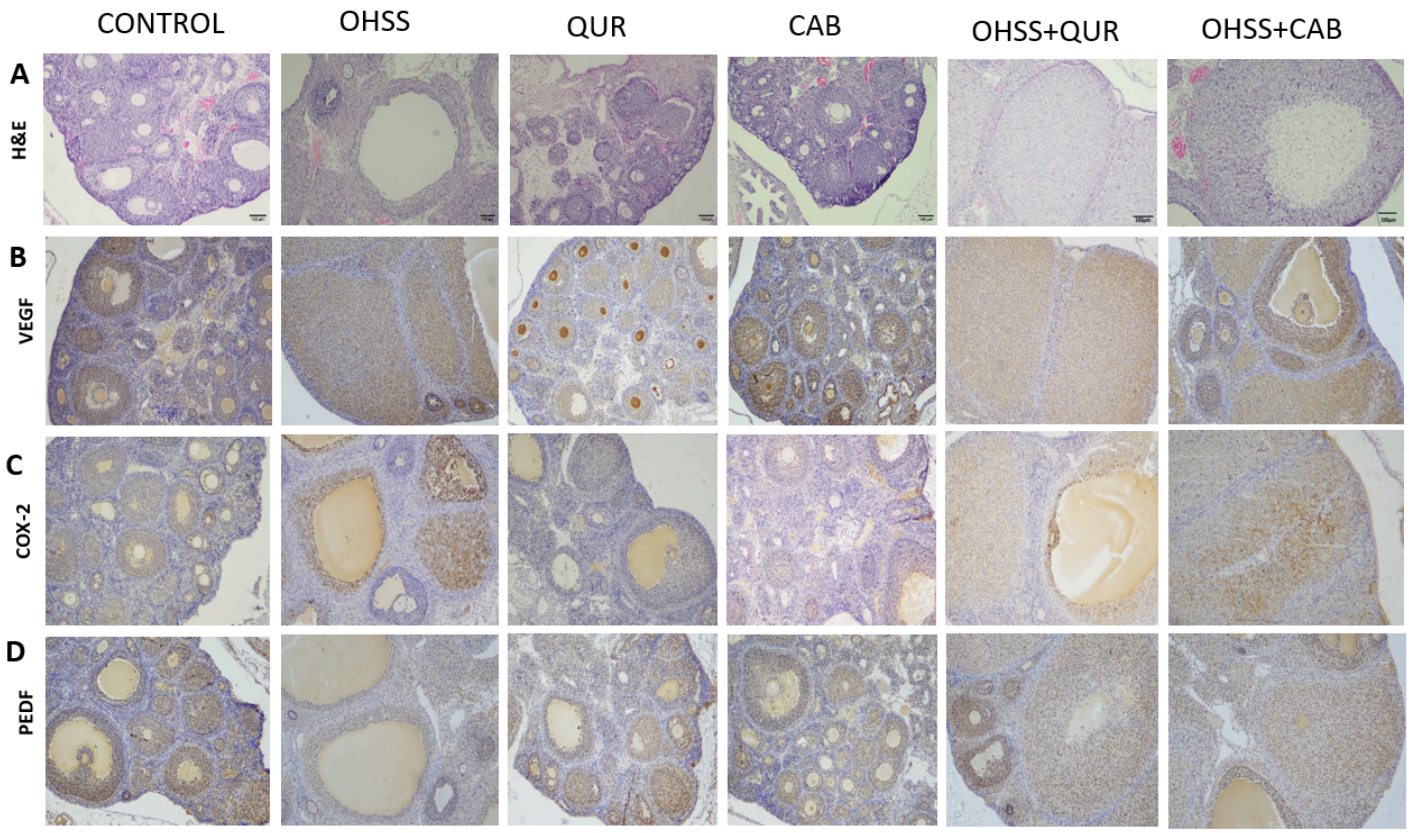

Figure 3

Immunohistochemical evaluation of experimental groups.

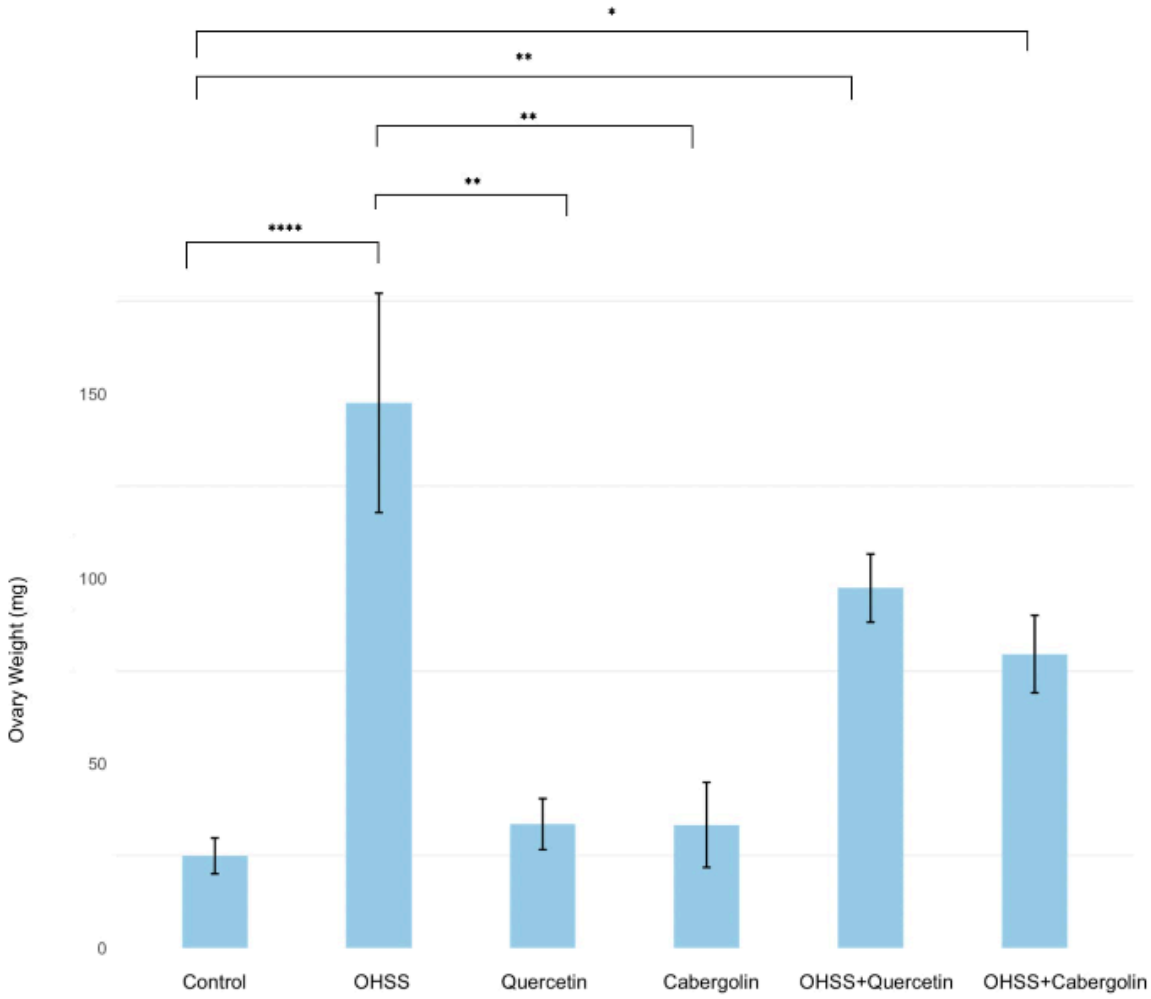

Figure 4

Ovarian weight graph of the experimental groups.

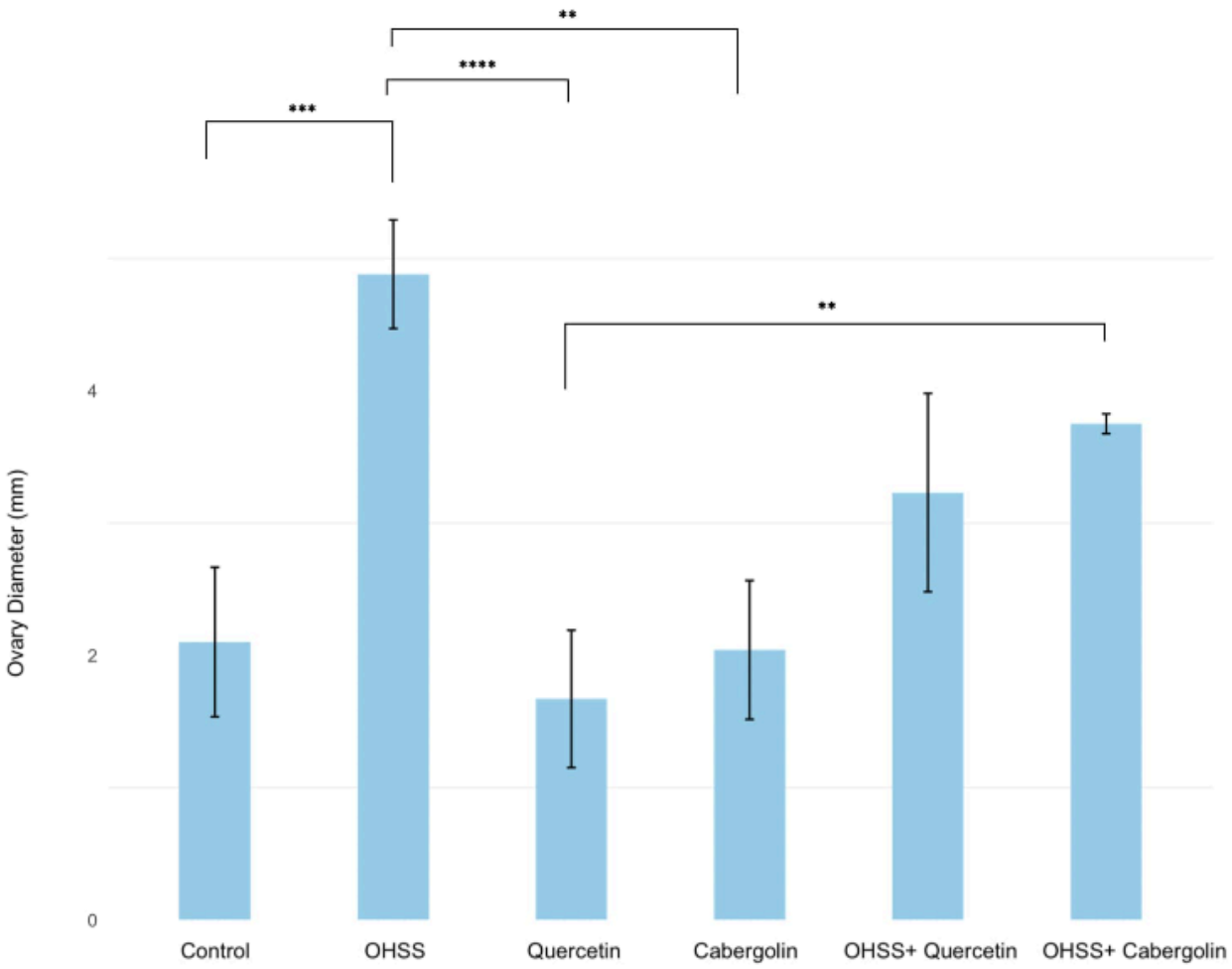

Figure 5

Graph of ovarian diameter in the experimental groups.

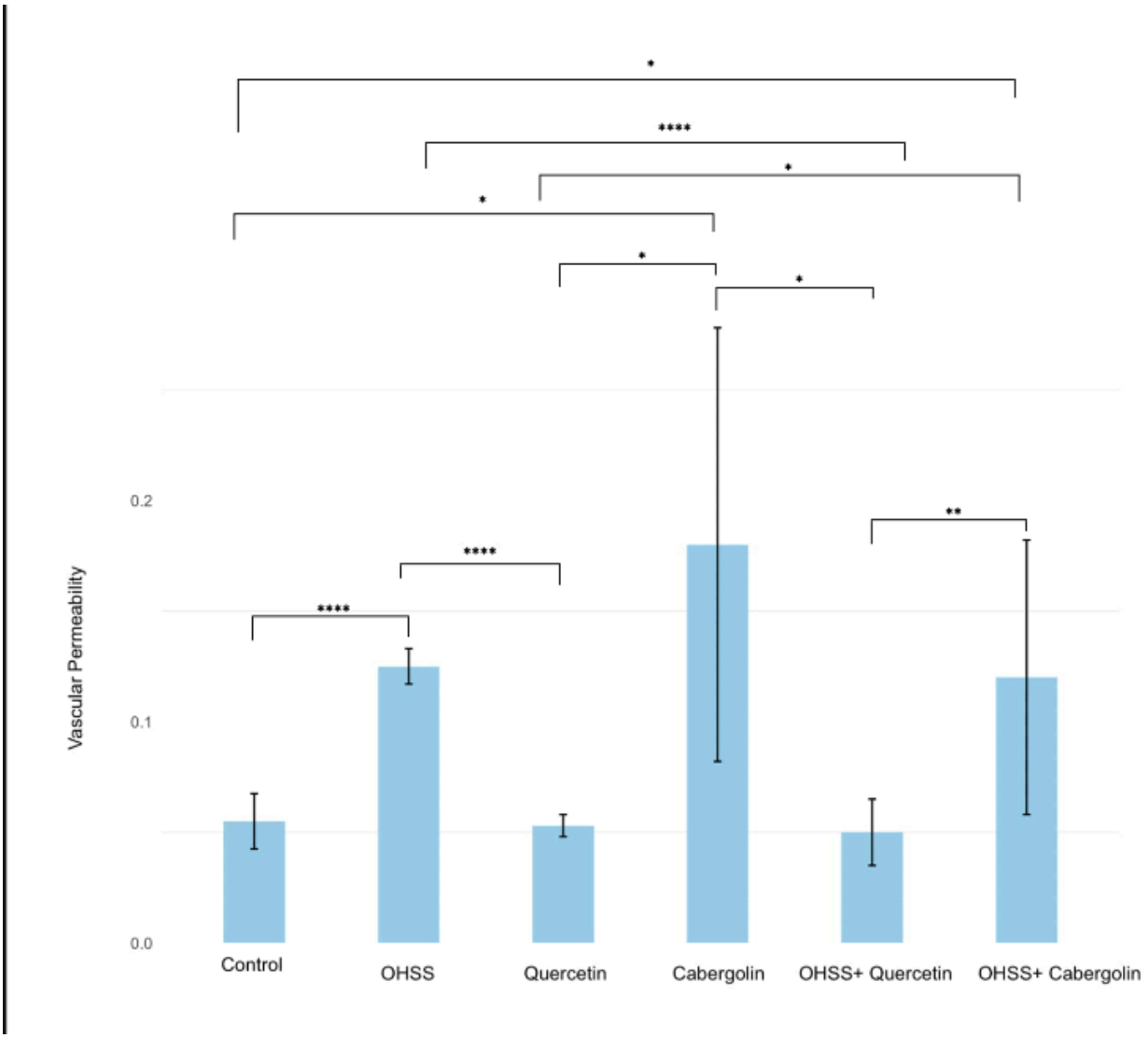

Figure 6

Vascular permeability graph of the experimental groups.

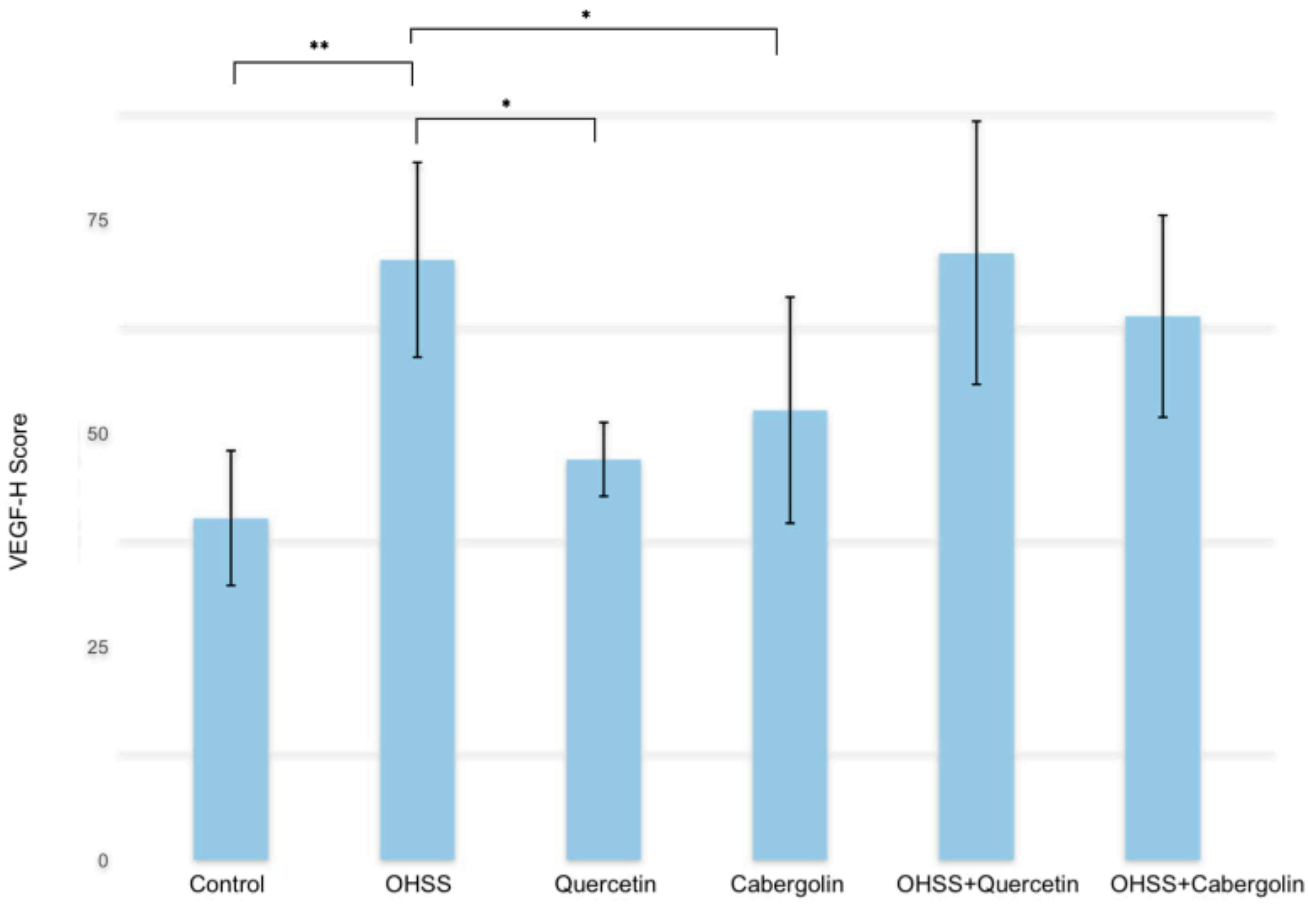

Figure 7

Comparison of VEGF immunohistochemical H-score values among the experimental groups. Data are presented as mean ± SD. *p < 0.05 compared with the control group; a p < 0.05 compared with the OHSS group.*