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# Effect of Gossypol on Rat Ovarian Reserve and Folliculogenesis, The role of Quercetin and Curcumin

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GOSSYPOL is a poisonous yellow polyphenolic pigment found in cotton plants (*Gossypium spp.*), which inhibits animal reproduction. Gossypol also affects steroidogenesis, nuclear maturation, follicular size, granulosa cell proliferation, and steroidogenic activity. Therefore, we aimed to examine the effect of gossypol on rat ovarian physiology and detect the probable beneficial effects of quercetin and curcumin. Forty-eight female albino rats were divided into six groups: control, gossypol, quercetin, curcumin, (gossypol and quercetin), and (gossypol and curcumin) were administered orally at different doses for 35 days. The results showed that gossypol significantly decreased body, ovarian and uterine weights, whereas, neither quercetin or curcumin treatments with gossypol showed any significant improvement in body, ovarian, and uterine weight compared to the gossypol group. Gossypol group showed the highest number of growing ovarian follicles compared with the control group. The two groups of quercetin, curcumin with gossypol showed a significant increase in the antral ovarian follicles compared with gossypol treatment. This study concluded that gossypol had negative effects on body, uterus and ovaries which led to a decrease in their weights. In addition, the use of antioxidants (quercetin or curcumin) with these doses and duration of the treatment has minor effects to reverse or ameliorate gossypol harmful effects.

**Keywords:** Gossypol, Quercetin, Curcumin, Ovary, Rats.

## Introduction

The Chinese presented gossypol a yellow polyphenolic material found in the seeds, stems, and roots of the cotton plant, as a potential male contraceptive [1]. Although gossypol being recognized as toxic in non-ruminants animals, the Chinese specified that, in men, low doses of gossypol are an effective oral antifertility drug with only minor adverse effects [2]. Despite reports that gossypol alters reproductive cycle and impairs conception and reproductive performance in female rats, it is not considered effective contraceptive in females [3]. Studies on the influence of gossypol on serum hormone levels and the ultrastructure of female endometrium revealed that it has a direct effect on ovarian function [4]. The use of gossypol in rats leads to a decrease in the number of viable follicles and alterations in hormone levels, interfering with the estrous cycle [5].

Quercetin is a flavonoid glycoside produced from plants with a high flavonoid content [6]. Quercetin has long been utilized as a natural antioxidant to prevent or treat diseases such as cancer, cardiovascular disease, neurological and neurodegenerative disorders, obesity, chronic inflammation, gastritis, allergies, and asthma [7]. Furthermore, various *in vitro* and *in vivo* studies have evaluated its efficacy as a therapy for male infertility [8]. Quercetin may be useful in the

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treatment of reproductive problems because it regulates reproductive system activities such as folliculogenesis, oocyte maturation, and ovulation [9]. In rats, quercetin can increase the antioxidant capacity of the ovary by upregulating oxidative stress-related genes [10].

Curcumin, turmeric's principal bioactive component, is a natural antioxidant with anti-inflammatory, anti-apoptotic, antitoxic, and anticancer properties [11]. The ability of curcumin to reduce lipid peroxidation by scavenging superoxide anions and hydroxyl radicals has long been known [12]. Several studies have shown that dietary supplementation with curcumin or turmeric can improve meat quality and stability, liver enzyme activity, immunological responses [13], and sperm quality in birds [14]. Curcumin appears to have beneficial effects on the sexual glands, testes and ovaries, which may be due to its antioxidant properties [15], anti-inflammatory [16], and anti-apoptotic characteristics [17].

In this study, we examined the effects of gossypol on rat ovarian physiology by evaluating its effect on ovarian follicular storage. In addition, we detected the possibility of reversing these effects using the antioxidants, quercetin and curcumin.

## Material and Methods

*Material*

Gossypol acetate (WonderLand, China) was administered orally with a gavage needle at 40 mg/ kg body weight [18], quercetin (Samsara Herbs, USA) was orally administered at 100 mg/kg body weight [19] and curcumin (Bella Chemical, USA) was orally administered at 200 mg/kg body weight [20], all of which were dissolved in corn oil.

*Animals*

Female albino rats (n=48), 21 days old, weighing 28-32 g, were housed in plastic cages under controlled environmental conditions with a 12 h light/dark cycle and at a temperature of 30 ± 3 °C. Regular rodent chow and tap water were provided *ad libitum*.

*Experimental Design*

The experimental animals were randomly and equally distributed into six groups (n=8 each) and dosed orally using a gavage needle for 35 days as follows: control group (corn oil), gossypol group (gossypol 40 mg/kg/b.w.), quercetin group (Quercetin 100 mg/kg/b.w.), curcumin group (Curcumin 200 mg/kg/b.w.), gossypol + quercetin group and gossypol + curcumin group at the same doses as groups 2, 3, 4.

Rats were weighed on the first day then every 3 days to calibrate the dose and at the end of treatment. The ovaries and uteri were dissected and weighed relative to body weight.

On the day after the last dosing, all rats were deeply anesthetized by intraperitoneal injection of xylazine (5 mg/kg/ b.w.) and ketamine (50 mg/kg/ b.w.) to collect ovaries and uterus. Five ovaries were taken for each experimental group and placed in formalin 10% for fixation after passing them through a series of ethyl alcohol with a concentration of (70, 95,100) % to remove water (dehydration), and then xylol for clearing then embedded in paraffin. The blocks were sectioned at 5µm and were stained with hematoxylin-eosin stain (H&E). A light microscope (Novel, china) with a camera (Omax, china) was used to examine the ovarian sections. Serial sections were studied for each ovary (n=12). Two perpendicular diameters were measured for each follicle that appeared in each section using the Image J/Fiji 1.46 program [21]. Follicles were classified according to their different maturation stage growing, pre-antral or antral follicles [22].

*Statistical analysis*

Descriptive and inferential statistics were performed using JMP Pro16.1 software (2021 SAS Institute Inc., North Carolina, USA). Descriptive statistics included the mean and standard error. To determine the effect of the treatments on the animals, uterine and ovarian weights, the data were analyzed using analysis of variance (ANOVA). Duncan's multiple range test to find differences between the treatment groups. The chi-square test was used to determine whether there was a significant difference between the number of follicles and follicle diameters in the treatments. Results were considered significant at $P < 0.05$.

## Results

Treatment with gossypol alone led to a significant decrease ($P < 0.05$) in the body weight compared to the control group. The addition of quercetin or curcumin with gossypol did not show a significant difference in body weight compared with the gossypol group, as shown in Fig. 1.

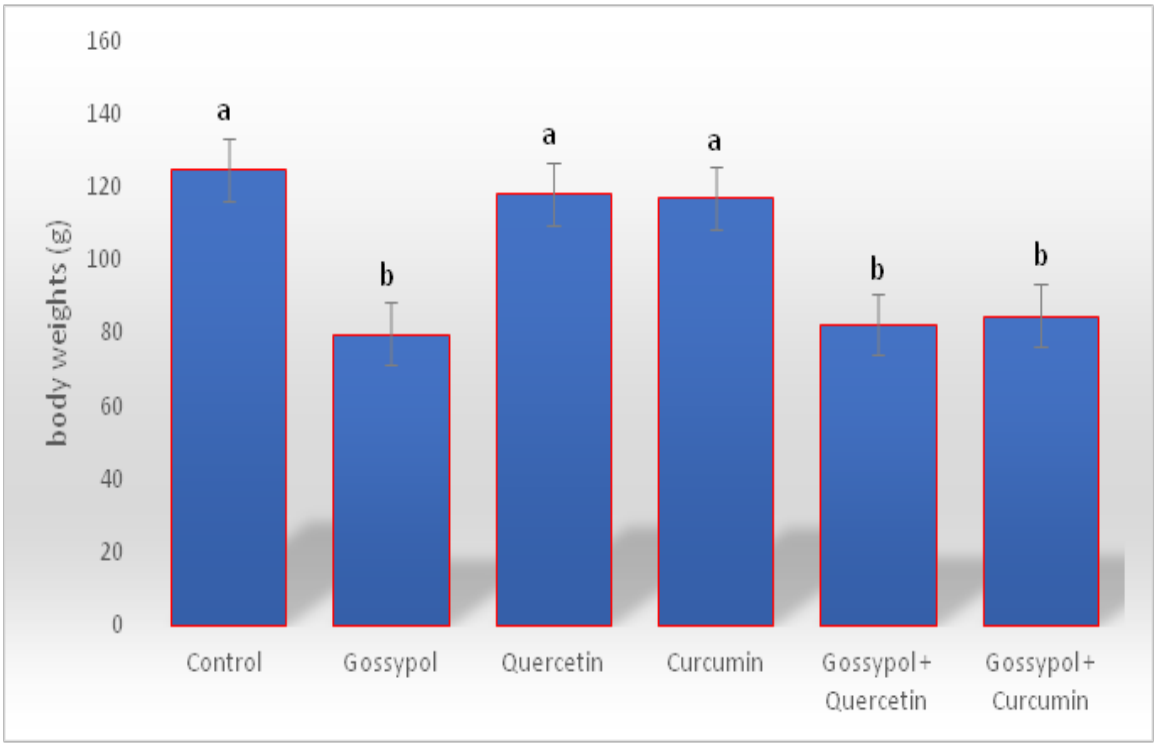


**Fig. 1. The effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on animal weights (mean ± standard error). Similar letters indicate no significant differences between groups at (P > 0.05), while different letters indicate a significant difference between groups at (P < 0.05).**

On the other hand, gossypol treatment significantly decreased relative uterine weight compared with the control group, while the addition of quercetin or curcumin with gossypol did not show a significant difference in uterine weight compared with gossypol alone, as shown in Fig. 2.

Gossypol alone demonstrated a significant decrease in relative ovarian weight compared to the control group, while the addition of quercetin with gossypol did not show significant differences in the ovarian weight compared with gossypol alone but the addition of curcumin to gossypol revealed to significant increase compared to gossypol alone as shown in Fig. 2.

Regarding the number of ovarian follicles, there was a variation in the numbers depending on the type of treatment. All treatments (except curcumin) demonstrated a significant increase ($P<0.05$) in the number of growing ovarian follicles compared to the control group, while there were no significant differences for the group treated with curcumin alone compared to the control group as well, as shown in Fig. 3. There were no significant differences in the number of preantral follicles in the group treated with gossypol compared to the control group, With a significant increase in quercetin and curcumin treatment compared with control group, the treatment of (gossypol + quercetin) revealed no significant differences in the number of preantral ovarian follicles compared with the gossypol group whereas the treatment with (gossypol + curcumin) demonstrated a significant increase in the number of preantral ovarian follicles compared to gossypol group . As for the antral ovarian follicles, there was a significant decrease in the number of follicles in the gossypol group alone compared to the control group ($P < 0.05$). The treatment with quercetin demonstrated no significant differences in antral ovarian follicles compared to the control group with a significant decrease in curcumin treatment compared to control group. The (gossypol + quercetin) and (gossypol + curcumin) treatments were significantly higher in antral follicle numbers compared to the gossypol group ($P < 0.05$) and returned to control values as shown in Fig. 3 and 4.

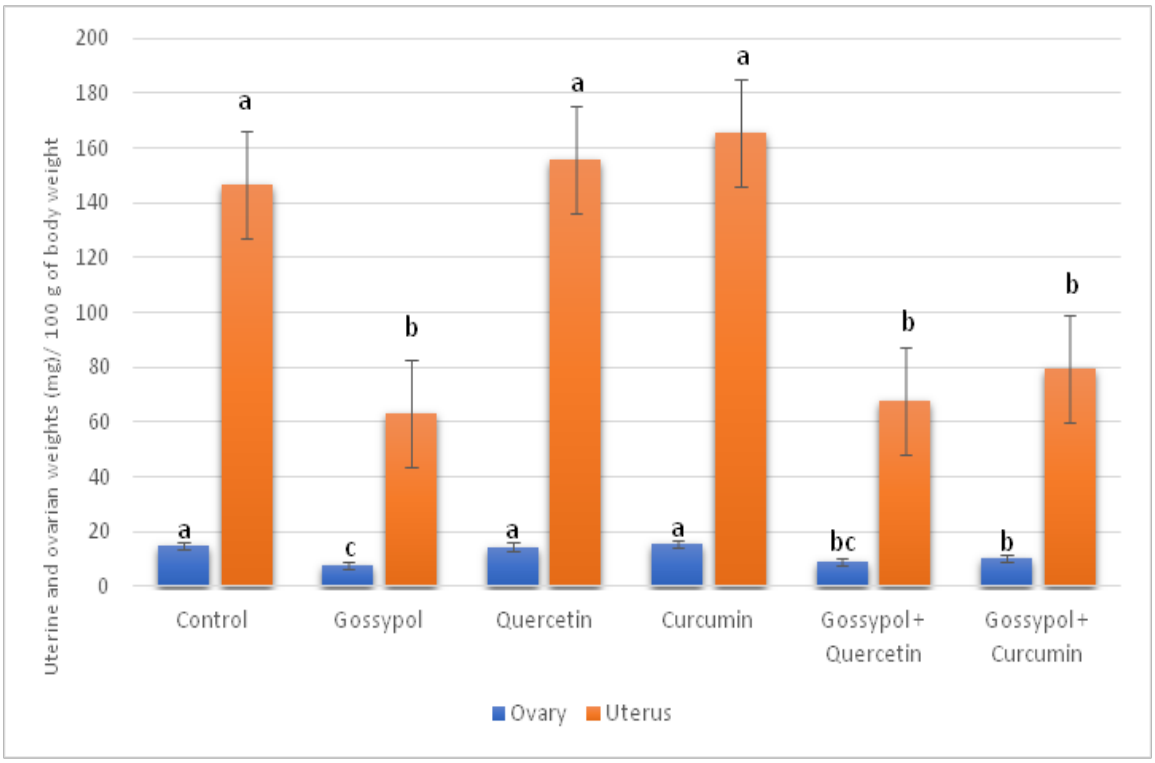


**Fig. 2. The effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on uterine and ovarian weights (mean ± standard error). Similar letters indicate no significant differences between groups at (P > 0.05), while different letters indicate a significant difference between groups at (P < 0.05).**

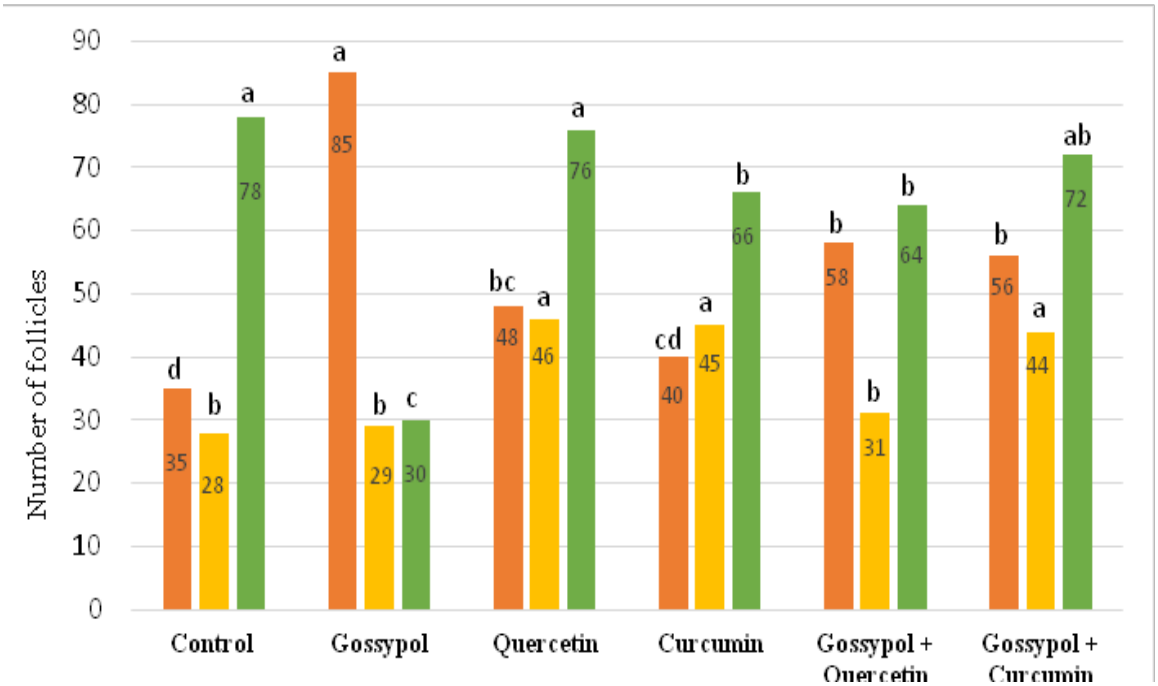


**Fig. 3. Effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on the number of ovarian follicles (mean ± standard error). Similar letters indicate no significant differences between groups (P > 0.05), while different letters indicate a significant difference between groups (P < 0.05).**

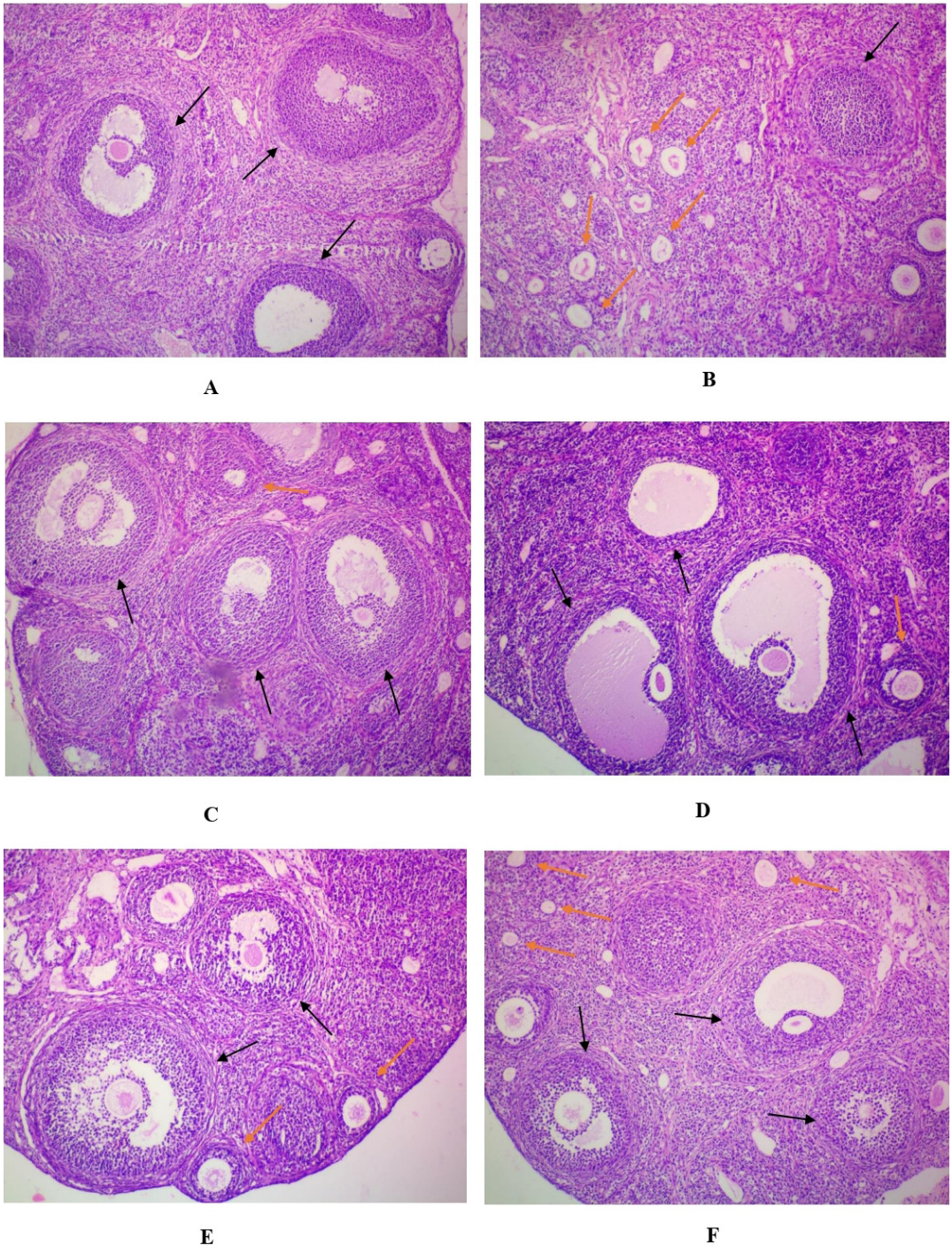


**Fig. 4. (A) Ovaries from the control group showed a normal number of antral follicles (H&E, X100). (B) Ovaries from the gossypol group showed an increased number of growing follicles, and decreased the number of antral follicles (H&E, X100). (C) Ovaries from the quercetin group showed a normal number of antral follicles (H&E, X100). (D) Ovaries from the curcumin group showed a normal number of antral follicles (H&E, X100). (E) Ovaries from (gossypol + quercetin) group showed an increased number of antral follicles compared to the gossypol group (H&E, X100). (F) Ovaries from (gossypol + curcumin) group showed an increased number of antral follicles compared to the gossypol group (H&E, X100). The orange arrow refers to growing follicles, black arrow refers to antral follicles.**

In addition, the ovarian follicle diameters were also varied depending on the type of treatment. The results indicated that gossypol treatment significantly decreased (P<0.05) the follicles diameter at growing and antral follicles compared to the control group. The addition of quercetin and curcumin revealed to significant increased the diameter of growing follicles compared to the gossypol group. As for the preantral follicles, the results showed there were no significant differences in the follicles diameter of the gossypol, quercetin and curcumin treatment compared to the control group, in addition to the (gossypol + quercetin) and (gossypol + curcumin) treatment revealed no significant differences compared to the gossypol group. As for the antral follicles, the treatment with gossypol led to significant decrease the diameter of the follicles (P > 0.05) compared to the control group, the treatment with quercetin and curcumin showed no significant differences in follicles diameter compared to the control group, in addition, the treatment with (gossypol + quercetin) showed no significant differences compared to the gossypol group while the treatment (gossypol + curcumin ) demonstrated to significantly increase compared to the gossypol group, as shown in Fig. 5.

## Discussion

Gossypol is a poisonous yellow polyphenolic pigment found in cotton plants (*Gossypium spp.*) which inhibits animal reproduction [23]. Gossypol has been shown to have harmful effects on reproduction in male cattle [24], rats [25] goats [26] sheep [27] and other animals. When gossypol is consumed, it inhibits spermatogenesis and causes declines in sperm motility and viability, as well as induces morphological damage to sperms, depending on the dose and reproductive stage [28].Gossypol has an effect on the estrous cycle in cows [29], and rodents [30].Gossypol also influences steroidogenesis, nuclear maturation, and follicular size [31], as well as granulosa cells proliferation and steroidogenic activity in pigs[32].Gossypol therapy causes oxidative stress, which leads to cell death [33]. The present study was conducted to determine gossypol effects on rat ovarian physiology and detect the probable beneficial effect of quercetin and curcumin. Gossypol treatment led to a significant decrease in body weight which coincides with Bender et al [34] who found a decrease in body weight with 40 and 60 mg/kg/b.w. for 30 days gossypol treatment, this decrease may be due to a drop in food intake after anorexia [35]. Our

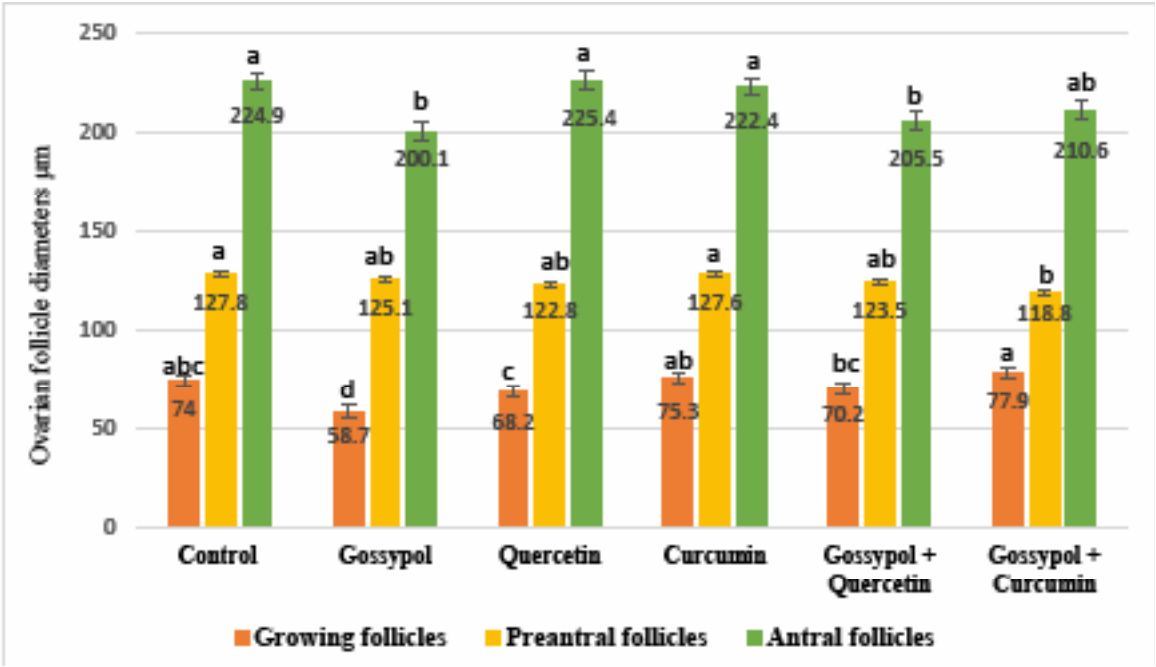


**Fig. 5. The effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on the ovarian follicle diameters (mean ± standard error). Similar letters indicate no significant differences between groups (P > 0.05), while different letters indicate a significant difference between groups (P < 0.05).**

results disagreed with Gadelha et al. [5], who found no significance in rat body weight with gossypol 25 mg/kg/b.w. subcutaneously for 15 days. The significant decrease in relative ovarian and uterine weights in our study coincides with Gu and Anderson [36] who found a decrease in the ovarian weight in rats treated with 5 or 10 mg gossypol/kg subcutaneously for 20 days. On the other hand, our results disagreed with Wu et al [37] who found no significant change in ovarian and uterine weights in rats treated with 10 or 20 mg/kg for 20 days. Gossypol treatment led to a significant increase in the number of growing follicles and a significant decrease in the number of antral follicles which coincided with the results of Randel et al [31] who found that heifers treated with 5 g free gossypol/day/animal have a smaller number of ovarian follicles >5mm. The mechanism by which gossypol promotes follicle damage is not yet known. Many investigations have shown that gossypol has cytotoxic activity [38, 23]. This cytotoxic effect can be enhanced by the production of reactive oxygen species leading to oxidative stress [39, 40] intercellular communication disruption [41] and apoptosis induction [42] and interference with ions transport via membranes [43, 44]. Interference with cellular energy metabolism is another proposed mechanism underlying gossypol toxicity [45]. Quercetin, a bioflavonoid present in a various fruits, vegetables, and plants [46], is known for its anti-cancer, anti-inflammatory, anti-thrombotic, and anti-hypertensive properties [47]. Quercetin has a considerable scavenging impact on free radical formation by enhancing the activities of GSH, SOD, CAT, GSH-px, and glutathione reductase [48]. Quercetin treatment did not show a significant effect on the body, relative ovarian and uterine weights compared to control which coincides with Yang et al [49], no significant change in the body, ovarian and uterine weights with quercetin addition 0, 0.2, 0.4 and 0.6 g/kg feed for 8 weeks. Quercetin caused a significant increase in growing and preantral ovarian follicles which is consistent with the findings Bolouki et al [50], a significant increase in the secondary and antral follicles with quercetin at 30 mg/kg/day for 30 days. Gossypol + quercetin did not succeed in returning body, uterine and ovarian weights control values this may be due to the short duration of treatment or may be due to the low dose. As for the number of ovarian follicles, there was a significant decrease in growing follicles and a significant increase for antral follicles with no significant differences in preantral follicles compared to the gossypol group and this may be due to the role of quercetin in inhibiting the reactive oxygen species [51]. As for the follicle's diameters, there was a significant increase in the growing follicles diameter compared to the gossypol group. Quercetin can reduce granulosa cells cytotoxicity by lowering lipid peroxidation and increasing antioxidant capacity [52]. Quercetin protects granulosa cell from oxidative stress by boosting the expression and activity of Nrf2 and thioredoxin genes [53]. Curcumin has antioxidant, anti-inflammatory, chemotherapeutic, radioprotective, and angiogenesis-regulating activities so curcumin protects tissues by acting as an antioxidant as a result of these activities [54, 55]. Curcumin treatment did not cause significant differences in the body, ovarian, uterine weights and diameter of ovarian follicle except a significant increase in the preantral and significant decrease in antral follicles. Gossypol + curcumin did not succeed in returning body and uterine weight to control values which may be due to the short duration of treatment or the low dose of curcumin. The significant increase in the ovarian weight may be caused by the significant increase in the number of pre-antral and antral follicles, this improvement by curcumin treatment may be due to it having strong antioxidant activity [56]. Curcumin reduces malondialdehyde levels and increases the activity of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase [57, 58]. Curcumin also reduces oxidative stress markers in rats that had been exposed to chronic stress [59]. Curcumin has also been shown to increase the expression of Nrf2, a transcription factor that regulates the expression of many genes, including those encoding antioxidant enzymes [60].

## Conclusions

Gossypol had negative effects on body weight and weights of the uterus and ovaries, which led to a decrease in these weights. In addition, the use of antioxidants (quercetin or curcumin) had minor effects on blocking the action of gossypol inside the body. Where the curcumin with gossypol group showed improvement in the weight of ovaries by reducing the effect of gossypol. Also, the curcumin with gossypol group showed improvement in the number of antral ovarian follicles. Furthermore, the use of antioxidants (quercetin or curcumin) had no effect on the diameters of ovarian follicles. The findings conclude that the dose concentrations of quercetin or curcumin may not be sufficient to

act against the action of gossypol or may need to Fig. out new antioxidants have a better action to prevent the effects of gossypol.

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*Conflict of interest*

The author of this manuscript stated there is no conflict of interest regarding the writing process or data analysis.

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# تأثير الجوسيبول على الخزين المبيضي و عملية تكوين الجريبات في الجرذان : دور الكورستين و الكركمين

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الجوسيبول صبغة صفراء من متعدد الفينول سامة في نبات القطن (*Gossypium spp*.) تثبط التكاثر في الحيوانات و توثر على عملية انتاج الستيرويدات، نضوج الانوية، حجم الجريبات، تكاثر الخلايا الحبيبية و فعالية الهرمونات الستيرويدية. هدفت الدراسة عن تاثير الجوسيبول في فسلجة و وظيفة المبايض و التحري عن الدور المفيد لكل من الكورستين و الكركمين. استخدم في التجربة ثمانية و اربعون من اناث الجرذان البيض قسمت الى ستة مجاميع مجموعة سيطرة، معاملة بالجوسيبول، بالكورستين، بالكركمين، معاملة بالجوسيبول + الكورستين و معاملة بالجوسيبول + الكركمين ، جميع المعاملات عن طريق الفم و بجرع مختلفة و لمدة ٣٥ يوم. اظهرت النتائج انخفاض معنوي ($p<0.05$) في اوزان الجسم، الرحم و المبايض في المجموعة المعاملة بالجوسيبول و لم تتمكن كل من مجموعة الكورستين، الكركمين مع الجوسيبول من تحسين هذه الاوزان معنويا. و اظهرت المعاملة بالجوسيبول اعلى عدد في الجريبات المبيضية النامية مقارنة مع مجموعة السيطرة بينما اظهرت مجاميع الجوسيبول مع الكورستين و مع الكركمين زيادة معنوية في اعداد الجريبات المبيضية الغارية مقارنة مع مجموعة الجوسيبول لوحده. استنتجت هذه الدراسة ان للجوسيبول تاثيرات سلبية على الجسم، المبايض و الارحام تمثلت بانخفاض اوزانها فضلا عن ذلك فقد اظهر استعمال مضادات الاكسدة ( الكورستين و الكركمين) بهذه الجرع ومدة المعاملة تاثيرات صغيرة في عكس او تحوير التاثيرات الموذية للجوسيبول.

الكلمات المفتاحية: جوسيبول، كورستين، كركمين، مبيض، جرذان.