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Protective Effect of Quercetin and Curcumin against Ovarian Oxidative Stress Induced by Gossypol in Albino Female Rats

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ABSTRACT

This study aimed to investigate the effect of gossypol on ovarian physiology, which includes oxidative stress, hormone levels, and ovarian apoptosis, and detect the positive role of quercetin and curcumin against gossypol's effect. Forty-eight albino female rats were used in the experiment, divided into six groups that included the control group (corn oil), gossypol (40 mg / kg/ b.w), quercetin (100 mg / kg /b.w), curcumin (200 mg / kg / b.w), gossypol + quercetin (40 and 100 mg / kg /b.w), gossypol + curcumin (40 and 200 mg / kg /b.w). All treatments were administered orally using a gavage needle for 35 days. The results showed that gossypol significantly decreased glutathione levels compared to the control group. However, the control group showed a significant increase in malondialdehyde levels and caspase-3 levels in ovarian tissue. In addition, treatment with curcumin (alone) significantly increased the anti-Müllerian hormone level compared to the control group. Furthermore, it was observed that in treatment with the gossypol and quercetin, there were no significant differences in caspase-3 levels compared with the gossypol group. However, there was a significant increase in glutathione levels compared with the gossypol group. As well as a significant decrease in malondialdehyde levels compared to the gossypol group. More research using different concentrations of these antioxidants (quercetin and curcumin) is needed to determine their effectiveness against gossypol effects. In conclusion, gossypol causes harmful effects on the ovaries of rats by inducing oxidative stress, decreasing glutathione levels, and increasing malondialdehyde levels.

Keywords: Albino female rats, Curcumin, Gossypol, Oxidative stress, Quercetin.

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INTRODUCTION

Cottonseed meal, a byproduct of cotton high in protein and oil, is used for animal feeding; gossypol is a phenolic chemical produced by pigment glands in cotton stems, leaves, seeds, and flower buds (Gossypium spp.) (**Gadelha *et al.*, 2014**). Gossypol increases embryo defects and has an impact on both male and female gametogenesis (**Gadelha *et al.*, 2011**). Gossypol effects in females have been connected to early embryo development, pregnancy, and estrous cycle disturbance **(Randel *et al.*, 1992; 1996; Gadelha *et al.*, 2011).** Direct embryonic cytotoxicity is the most likely mechanism by which gossypol induces embryotoxicity **(Li *et al.*, 1989).** This cytotoxic effect is caused by reactive oxygen species generation, which causes oxidative stress (**Kovacic, *2003)***, disruption of cell-to-cell communication (**Herve *et al.*, 1996**), induction of apoptosis (**Moon, *et al.*, 2011**), and interference with membrane ion transport, which increases intracellular calcium (**Cheng *et al.*, 2003).**

One flavonoid widely found in fruits, vegetables, olive oil, and tea is quercetin. **(Hollman and Katan, 1999)**. Due to its powerful antioxidant capabilities, it has recently been demonstrated as cardioprotective, anti-inflammatory, anti-proliferative, and anticancer actions **(Boots *et al*., 2008; Altundag *et al*., 2016)**. The impact of quercetin on ovarian functions in different *in vivo* models has been well explained in a number of papers **(Algandaby, 2021)**. Quercetin supplementation resulted in a noticeable improvement in follicular growth and reduced granulosa cell death in rabbits **(Naseer *et al*., 2017)**. Quercetin has also been linked to increased ovarian antioxidant capacity in menopausal rats and *in vitro* ovarian granulosa cells **(Wang *et al*., 2018)**.

Turmeric rhizomes contain 3-5% curcumin, the active ingredient. **(Zhang *et al*., 2013)**. The antioxidant, anti-inflammatory, anti-apoptotic, and antibacterial effects of curcumin have been demonstrated by scientific investigations (**Augustyniak *et al*., 2010; Mun *et al*., 2013; Ueki *et al*., 2013; Geng *et al*., 2017**). Curcumin can significantly reduce the formation of reactive oxygen species (ROS) *in vitro* and *in vivo* as a free radical scavenger **(Gupta *et al*., 2012)**. Recent investigations have demonstrated that curcumin possesses a potent oxygen-free radical scavenger that raises intracellular glutathione content to prevent lipid peroxidation **(Ciftci *et al*., 2011)**. Curcumin promotes steroidogenesis **(Pandey and Sairam, 2009)** and folliculogenesis **(Alekseyeva *et al*., 2011)** in mouse ovarian tissue.

The aim of the study is to determine the effects of gossypol on rat ovarian physiology, including apoptosis, hormone levels and oxidative stress indicators and detect the possibility of reversing these effects by using the antioxidants (quercetin and curcumin).

MATERIALS AND METHODS

Materials

Gossypol (WonderLand, China), quercetin (Samsara Herbs, USA) and curcumin (Bella Chemical, USA) were dissolved in corn oil and administered orally with a gavage needle **(Santana *et al*., 2015; Sengul *et al*., 2017; El-Din *et al*., 2019)**.

Animals

Female albino rats (n=48), 21 days old, weighing 28-32 g, were kept in plastic cages under carefully monitored environmental conditions, including a 12 h light/dark cycle and a temperature of 30 ± 3 °C. Regular rodent food and tap water were freely available.

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) **(de Carvalho *et al*., 2013)**, quercetin group (Quercetin 100 mg/kg/b.w) **(Almaghrabi, 2015)**, curcumin group (Curcumin 200 mg/kg/b.w) **(El-senosi, 2017)**, gossypol + quercetin group and gossypol + curcumin group at the same doses as groups 2, 3, 4. To collect ovaries and blood for biochemical tests and to estimate hormone levels, all rats were given intraperitoneal injections of xylazine (5 mg/kg/b.w) and ketamine (50 mg/kg/b.w) the day after the final dose.

Blood samples

Blood samples were collected from the choroid venous plexus of the rats. The blood sample was placed in tubes and centrifuged at 3000 rounds/min for 15 minutes, after which the serum was separated and distributed to small volumes in Eppendorf tubes and kept in the freezer at -20 C˚ until the GSH, MDA, FSH and AMH were measured.

Ovary sample

The ovaries were taken, wrapped in aluminum foil, and frozen at -20 ˚C until the tests were carried out.

Biochemical assays

1. Estimation of glutathione (GSH) level in serum

The level of glutathione was estimated using the modified method adopted by the researchers **(Sedlk and Lindsay, 1968; Tietz, 1999)**, and the method depends on the use of Elman's reagent containing DTNB reagent [5, 5-dithiobis (2-nitrobenzoic acid)] (HiMedia, India), as the reagent reacts rapidly with glutathione and reduced by the sulfhydryl group (-SH) of glutathione to form a colored product whose absorbance was measured using a spectrophotometer at a wavelength of 412 nm.

2. Estimation of Malondialdehyde (MDA) level in serum

The level of lipid peroxidation in the blood was determined by estimating the amount of malondialdehyde (MDA) as a final product of lipid peroxidation, the intensity of its absorption is measured at a wavelength of 532 nm **(Wierusz-Wysocka *et al*., 1995)**. (HiMedia, India).

3. Estimation of Caspase-3 level in ovarian tissue

A colorimetric assay was used to estimate the level of caspase-3 using a ready-made kit from Solarbio Life Sciences (Beijing, China). Sample preparation and determination were made according to the kit instructions (**Catalog**: BC3830).

4. Estimation of follicle-stimulating hormone (FSH) level in serum

The microplate reading (ELISA) technique was used to estimate the level of follicle-stimulating hormone using a ready-made kit from BT Lab (Shanghai Korean Biotech Co., Ltd). Sample preparation and determination were made according to the kit instructions (**Catalog**: **EA0015Ra**).

5. Estimation of anti-Müllerian hormone (AMH) level in serum

Microplate reading technique was used to estimate the level of anti-Müllerian hormone using a ready-made kit from BT Lab (Shanghai Korain Biotech Co., Ltd). Samples were prepared and determined according to the kit instructions (**Catalog**: EA0083Ra).

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, the data were analyzed using analysis of variance (ANOVA). Duncan's multiple range test to find differences between the treatment groups. Results were considered significant at $P < 0.05$.

RESULTS

1. Serum glutathione and malondialdehyde levels in treated groups compared to the control group of albino female rats

The results showed a significant ($P < 0.05$) decrease in glutathione level in gossypol-treated group compared to the control group. There were no significant differences in glutathione levels in groups treated with quercetin and curcumin alone compared to the control group. While glutathione level significantly ($P<0.05$) increased in the groups treated with gossypol, quercetin and gossypol with curcumin compared to the gossypol group, it did not reach its level in the control group (Fig.1). Also, the results in Fig. 1 showed a significant ($P<0.05$) increase in malondialdehyde level in the gossypol-treated group compared to the control group. There were no significant differences in malondialdehyde levels in groups treated with quercetin and curcumin alone compared to the control group. While malondialdehyde levels significantly ($P<0.05$) decreased in the groups treated with gossypol with quercetin and gossypol with curcumin compared to the gossypol group.

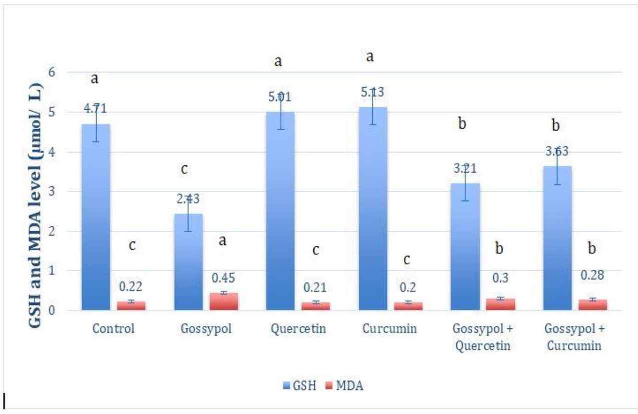

Fig. 1: The effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on GSH and MDA levels in serum (mean ± standard error). Similar letters indicate no significant differences between groups at ($P > 0.05$), while different letters indicate a significant difference between groups at ($P < 0.05$).

2.Caspase-3 level in ovarian tissue in the treated groups compared to the control group in albino female rats

The results did not show any significant differences in groups that treated gossypol with quercetin and with curcumin compared to the gossypol group (Fig.2). Treatment with gossypol alone showed a significant ($P<0.05$) increase in caspase-3 level compared to the control group. At the same time, there were no significant differences in caspase-3 levels in the groups treated with quercetin and curcumin alone compared to the control group.

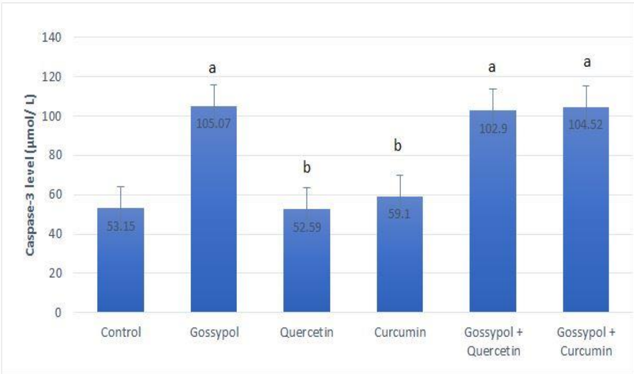

Fig. 2: The effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on Caspase-3 level in ovarian tissue (mean ± standard error). Similar letters indicate no significant differences between groups at ($P > 0.05$), while different letters indicate a significant difference between groups at ($P < 0.05$).

3.Serum FSH levels in the treated groups compared to the control group in albino female rats

The results showed no significant differences in FSH levels in the groups treated with gossypol alone, quercetin alone and curcumin alone compared to the control group. Also, there were no significant differences in groups treated with gossypol with quercetin and gossypol with curcumin compared to the gossypol group, and its level was significantly ($P<0.05$) decreased in the group treated with gossypol with quercetin compared to the control group, as shown in Fig. 3.

4.Serum AMH level in the treated groups compared to the control group in albino female rats

The results in Fig.ure (4) indicate no significant differences in AMH levels in groups treated with gossypol alone and quercetin alone compared with the control group. In contrast, there was a significant ($P<0.05$) increase in AMH level in the group treated with curcumin compared to the control group. There were no significant differences in groups treated with gossypol with quercetin and gossypol with curcumin compared to the gossypol group and the control group.

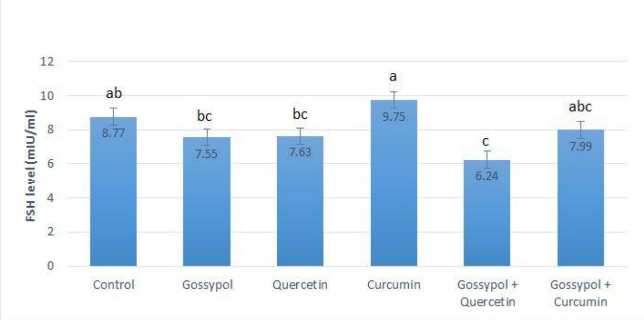

Fig. 3: The effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on FSH level in serum (mean ± standard error). Similar letters indicate no significant differences between groups at (P > 0.05), while different letters indicate a significant difference between groups at (P < 0.05).

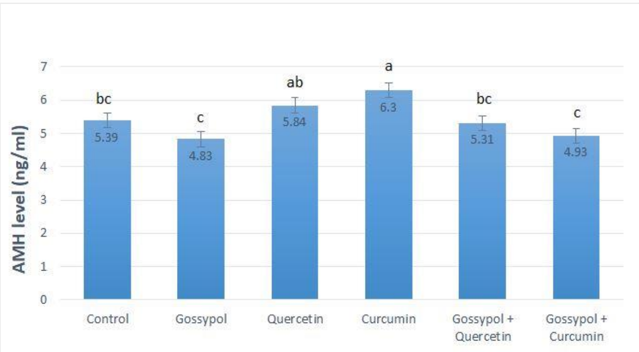

Fig. 4: The effect of treatment with gossypol, quercetin, curcumin, gossypol + quercetin and gossypol + curcumin on AMH level in serum (mean ± standard error). Similar letters indicate no significant differences between groups at (P > 0.05), while different letters indicate a significant difference between groups at (P < 0.05).

DISCUSSION

Gossypol interferes with reproduction by harming sperm, interfering with the estrous cycle, and killing embryos. Gossypol treatment in females accelerates the degradation of ovarian follicles, but it is unclear whether this action is direct or indirect **(luz *et al*., 2018)**. Glutathione levels significantly decreased after treatment with gossypol, and malondialdehyde levels significantly increased. This result coincides with that of **Santana *et al*. (2015)**. They recorded a significant decrease in glutathione levels accompanied by an increase in rat serum malondialdehyde level treated with gossypol for 14 days at 5 mg/kg/b.w has taken orally.

On the other hand, our results disagreed with **El-Sharaky *et al*. (2010)**, who found that when rats were given gossypol intraperitoneally at doses of 5, 10, and 20 mg/kg/b.w for two weeks, their levels of glutathione significantly increased and their levels of malondialdehyde significantly decreased. In our study, the low level of glutathione and high level of malondialdehyde may be caused by the increased reactive oxygen species produced by gossypol and the occurrence of oxidative stress **(Santana *et al*., 2015)**.

Also, our study result demonstrated a significant increase in caspase-3 levels in the ovaries of the group treated with gossypol, and this result is consistent with **Haasler *et al*. (2021)**. They recorded a 5-fold increase in caspase-3 level after 24 hours of treating melanoma cells with gossypol at a concentration of 2.5 µmol. The reason for the high level of caspase-3 may be attributed to the cytotoxicity caused by gossypol, which led to an increase in programmed cell death **(Nowzari *et al*., 2021)**.

The findings demonstrated that the group receiving gossypol treatment had no detectable variations in FSH levels, which agrees with **Nowzari *et al*. (2021)**, who noted there were no significant differences in FSH levels in serum of female rats fed on pellets containing 20% cottonseed ***shell*** flour for 35 days, and disagrees with **Oyewopo *et al*. (2012)**, who recorded a significant decrease in FSH levels in females treated with cotton seed extract at 20 and 60 mg/kg/ b.w intraperitoneally for 21 days.

Our results also showed an ***insignificant reduction*** in AMH levels in the gossypol group contrasted with the control group. The reason for the decrease may be the gossypol granulosa cell cytotoxicity which is responsible for its secretion **(Hong *et al*., 2021)**. There are no previous studies on the effect of the gossypol on AMH and their relationship.

Compared to the gossypol group, the gossypol + quercetin treatment significantly increased glutathione levels while significantly lowering malondialdehyde levels, which agrees with **Elkady *et al*. (2019)**, who found that mice treated with cyclophosphamide at 90 mg/kg/b.w + quercetin at 100 mg/kg/b.w intraperitoneally for 8 days had higher glutathione levels and lower malondialdehyde levels.

On the other hand, the findings indicated that there were no significant differences in caspase-3 levels in the group treated with gossypol + quercetin compared to the gossypol group. This result is consistent with **Algandaby, (2021),** who found that rats were given cisplatin at a dose of 6 mg/kg/b.w and quercetin at a dose of 5 mg/kg/b.w orally every day for 17 days showed no discernible variation in the amount of caspase-3 in the ovaries. The repair of quercetin for ovarian damage is due to quercetin's ability to reduce the granulosa cell cytotoxicity, which was reflected by reducing malondialdehyde levels and increasing the antioxidant activity by raising glutathione levels **(Jia *et al*., 2011)** and may be due to increasing the expression and activity of genes Nrf2 which is a transcription factor that controls the expression of numerous genes, including those of the antioxidant enzymes and thioredoxin **(Rashidi *et al*., 2019)**.

When compared to the gossypol group, the gossypol + curcumin treatment significantly increased glutathione levels while significantly lowered malondialdehyde levels, which agrees with **Cheraghi and Roshanaei, (2019)**, who found that rats given the combination of 10 mg/kg/b.w of aluminum chloride and 10 mg/kg/b.w of curcumin intraperitoneally for 28 days had higher levels of glutathione and lower levels of malondialdehyde. The reason for increased glutathione and decreased malondialdehyde levels may be due to the effectiveness of curcumin as an antioxidant for its ability to scavenge reactive oxygen species and nitrogen free radicals **(Gabr *et al*., 2014)**.

Treatment with curcumin alone led to a significant increase in AMH levels compared to the control group, which agrees with **Azami *et al*., (2020)**, who observed a significant increase in AMH levels in female mice treated with curcumin at 100 mg/kg/b.w intraperitoneally for 12 weeks, the increase may be due to curcumin regulation of reproductive endocrine function and promote growth follicles **(Yan *et al*., 2018)**. Curcumin repairs the effect of gossypol may be due to its increased expression of Nrf2 **(Scapagnini *et al*., 2011)**.

CONCLUSION

We conclude from the current study that gossypol caused harmful effects on the ovaries of rats by inducing oxidative stress, decreasing glutathione levels, and increasing malondialdehyde levels. However, female rats' hormone levels were unaffected by gossypol. While treatment with quercetin and curcumin caused a mild improvement in some parameters, it was not able to improve other parameters when administered with gossypol at these doses and duration of treatments.

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Declaration of Conflicting Interests

No conflict of interest existed during the writing or data analysis, according to the manuscript's author.

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