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BENEFICIAL EFFECT OF FLAVONOID COMPOUND ON FEMALE REPRODUCTIVE SYSTEM EXPOSURED TO THE OXIDATIVE STRESS

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ABSTRACT

This paper aimed at investigate the effect of flavonoid which act as antioxidant on female reproductive system of rats that exposed to oxidative stress. Used (40) female mature rats divided as following: Control group was given drinking water only, T1 group was given flavonoid (quercetin) (300 mg/kg) for 60 days, T2 group was given leade acetate (10 mg/kg) for 60 days, and T3 group was given leade acetate (10mg/kg) for 30 day then treated by quercetin (300 mg/kg) for other 30 day. The results showed a significant increase ($p<0.05$) in FSH levels in T1 group compared with the other groups, and there were a significant increase in estrogen hormone levels in T1 group and a significant decrease in T2 group compared with the other groups, also there were a significant increase in T3 group compared with the control group. Ovarian sections in control group showed moderate follicular growth. While the results of T1group showed normal follicular, the results in T2 group showed there was inhibition of the follicular growth, hemorrhage in the ovarian stroma and presence of infiltration of inflammatory cells. In T3 group there was high follicular growth wave which characterized by primary and secondary follicles with mature graffian follicles contains prominent ova lined by theca interna and theca externa with profuse follicular fluid. The results of uterine sections of rats in control group showed normal uterine wall. According to results of T1 group there is thickening of uterine wall, high numbers of developed and mature uterine glands. T2 group showed thin uterine wall, higher magnification, also presence few number of uterine glands, degeneration and destruction of columnar epithelium which lining uterus. Finally in T3 group There was

thick uterine wall, presence of large numbers of uterine glands and mild degeneration in the uterine epithelium.

KEYWORDS: Flavonoid, Female Reproductive System, Oxidative stress, Quercetin.

INTRODUCTION

Oxidative stress: is a balance disturbance between free radicals and antioxidants in favour of the free radicals, lead to cells damage.[1] Heavy metals, like leade (Pb), are main causes over production of free radicals and subsequently enhance peroxidation of lipid, and overproduces the unsaturated fatty acids.[2] Leade is considered a cause of oxidative stress by producing free radicals such as hydroxyl radicals, hydrogen peroxide and lipid peroxides.[3] A different types of free radicals are produced during cell aerobic metabolism, exposure to X rays ,UV light and continuous stress.[4] Human is exposed to lead through the air, food and water. Also leade well known to exert toxicity on male and female reproductive system.[5] Several mechanisms in the human body counteract the oxidative stress by synthesis antioxidants, either endogenous that naturally produce in body or exogenous that externally supplied through dietary supplements. So exogenous and endogenous antioxidants scavenge the free radicals and preventing damage caused by it, therefore it can be enhance the immune system defense.[6] An antioxidants are a compounds able to prevent the oxidation of biological molecules.[7] Antioxidants scavenge free radicals to counteract potential for significant damage of the cells by excessive free radicals. Antioxidants also aid to create a balance between generation of useful oxidant (cells signaling molecules) and damaging oxidative stress.[8] Flavonoids which are a group of compounds distributed extensively in the plants as secondary metabolites.[9] Quercetin are importance type of flavonoids, its scavenge free radicals and prevents cells death through protecting against metals ions and lipid peroxidation.[10] The quercetin are a flavonol found naturally in fruits like apples, grapes and vegetables like onions so, it is commonly found in human foods.[11] Quercetin present in the roots, seeds, barks, stems, and flowers of several medical plant and already used in treating human disease.[12] Quercetin have biological activities such a antioxidant, anti-inflammatory, anticancer, antiviral, antimicrobial, and many more.[13] So the my study aims to investigate the beneficial effect of flavonoid in improving the female reproductive system efficiency that exposed to oxidative stress by leade acetate**.**

MATERIALS AND METHODS

Laboratory animals: Forty adult females wistar rats were used in my experiment, with about 8 months in age, and weights about (200±10 gm.). The rats housed in wire-plastic cages, and allowed to acclimated for 10 days before experimentation.

biological material: quercetin from onion with purity 95% provided by brightol company/ PRC.

Experiment design: forty adult female Wistar rats divided to the 4 equal groups as following-:

Control group (C) were given drinking water for 60 days, T1 group was given flavonoid(quercetin) (300 mg/kg) for 60 days, T2 group was given leade acetate (10 mg/kg) for 60 days, and T3 group was given leade acetate (10mg/kg) for 30 day then treated by quercetin (300 mg/kg) for other 30 day.

Samples collection: Blood collected by using heart puncture method for assessment of FSH and Estrogen hormone. The blood were centrifuged at (3000) rpm for (5) minutes, the serum were stored at (- 15 C°) until used for measurement of FSH and Estrogen hormones.[16] The reproductive organs (ovaries , uterus) were taken for histological study.

Hormonal assays in blood serum: FSH and estrogen hormone evaluated by using ELISA technique and done according to the company instruction.

Histological studies: Five samples of (Ovaries and uterus) from each group were taken and fixed 10% formalin for prepare histological sections (Luna, 1968).

Statistical analysis

A computerized program SPSS was used to calculated the statistics analysis .The statistical analysis of data had done by

1. Descriptive statistics :mean± stander error
2. statistical analysis of data was performed on the basis of with LSD was detected to compare between groups
3. the confidence limit was accepted at 95% ($p>0.05$).[17]

RESULTS AND DISCUSSION

1. Follicular Stimulating Hormone (FSH)

Table (1) revealed there were a significant increase ($p< 0.05$) in serum FSH levels in T1 group (7.85 ± 1.7) compared with other groups, and there were no significant difference between other groups(C,T2 andT3)

2. Estrogen hormone

Table (1) revealed there were a significant increase ($p< 0.05$) in serum estrogen levels in T1group (842.2 ± 42.7) compared with other groups and there were a significant decrease in T2 group (102 ± 4.6) compared with other groups. Also there were a significant increase in T3 group (681± 4.4) compared with control group(380.2 ± 70.3).

Table 1: Show Effect of Quercetin on FSH and Estrogen hormone of adult females Wistar rats exposured to the oxidative stress.

Groups	FSH mlU/ml	Estrogen pg /ml
Control Group	(4.4 ± 0.6) b	(380.2 ± 70.3) c
T1	(7.8 ± 1.7) a	(842.2 ± 42.7) a
T2	(3.6 ± 0.5) b	(102.0 ± 4.6) d
T 3	(4.4±0.6) b	(681.0± 4.4) b

Values refer to mean ± slandered error

Different letters refer to significant differences ($p<0.05$).

Same letters refer to no significant differences ($p>0.05$).

Control Group: animals received (standard food and drinking water) for 60 days.

T 1: animals received quercetin 300 mg/kg for 60 days.

T 2: animals received leade acetate 10mg/kg for 60 days.

T 3: animals received leade acetate 10 mg/kg for 30 days then treated by quercetin 300mg/kg for other 30 days.

Histopathological study

Ovary

The results of ovarian sections of rats in control group revealed there was moderate follicular growth wave characterized by few numbers of primary and secondary follicles **(**yellow arrow**)** figure (1). While the results of T1 group showed normal follicular growth characterized by high numbers of secondary follicles(yellow arrows) with few numbers of primary follicles(red arrow) with presence of corpus luteum (green arrow) Figure (2).The results in T2 group showed there was inhibition of the follicular growth wave which characterized by presence of primary follicle (red arrow) and secondary follicles (yellow arrows) with presence of corpus luteum (green arrow) and there is hemorrhage in the ovarian stroma and presence of infiltration of inflammatory cells (black arrow) figure (3).

In T3 group there is high follicular growth wave which characterized by primary and secondary follicles with mature graffian follicles contains prominent ova (blue arrow) lined by theca interna (red arrow) and theca externa (black arrow) with profuse follicular fluid (green arrow) figure (4).

Uterus

The results of uterine sections of rat in control group show normal uterine wall contain normal developed uterine glands (thin arrows) and there is normal epithelium which lining the uterus (blue arrow) figure (5). According to results of T1 group there is thickening of uterine wall with high numbers of developed and mature uterine glands (thin arrows), also there is normal columnar epithelium which lining uterine tissue(blue arrow) figure (6). The results in T2 group show There is thin uterine wall (yellow arrow) and Higher magnification, also presence few number of uterine glands (red arrows), degeneration and destruction of columnar epithelium which lining uterus(black arrows) figure (7). Finally in T3 group There are proliferation of smooth muscle fibers (green arrow) and presence of large numbers of developed uterine glands (thin arrows) and mild degeneration in the uterine epithelium(blue arrow) figure (8**).**

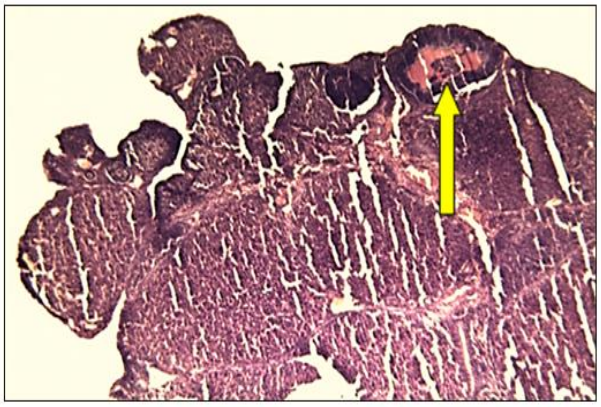

Fig. 1: Ovarian section of rat in control group There is moderate follicular growth wave characterized by few numbers of graffian follicles (yellow arrow)). 4X H&E.

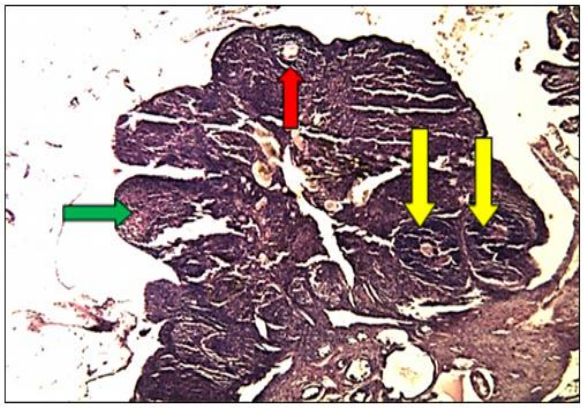

Fig. 2: Ovarian section of rat in (T1) group containing normal follicular growth characterized by high numbers of secondary follicles (yellow arrows) with few numbers of primary follicles (red arrow) with presence of corpus luteum (green arrow). 4X H&E.

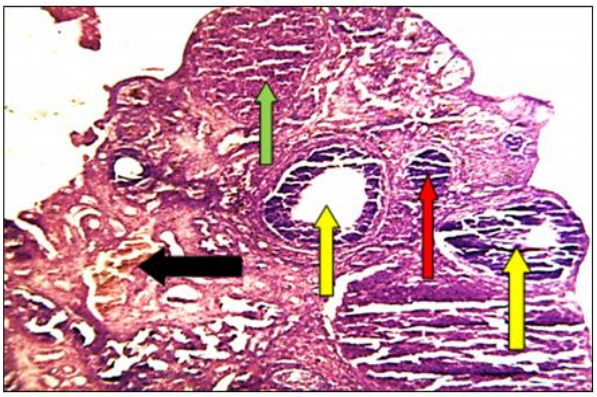

Fig. 3: Ovarian section of rat in (T2) group There is inhibition of the follicular growth wave which characterized by presence of primary (red arrow) and secondary follicles (yellow arrows) with presence of corpus luteum (green arrow) and there is hemorrhage in the ovarian stroma (black arrow). 4X H&E.

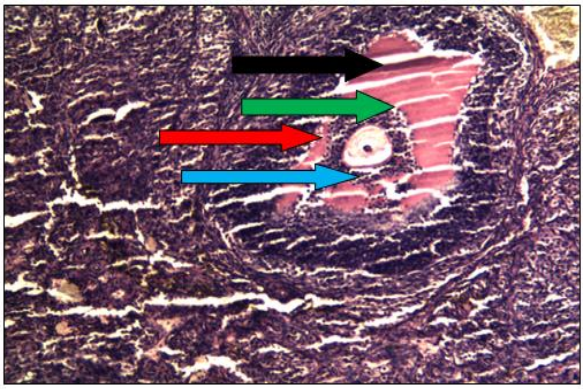

Fig. 4: Ovarian section of rat in (T3)group . Note mature graffian follicle contains prominent ova (blue arrow) lined by theca interna (red arrow) and theca externa (black arrow) with profuse follicular fluid (green arrow). 10X H&E.

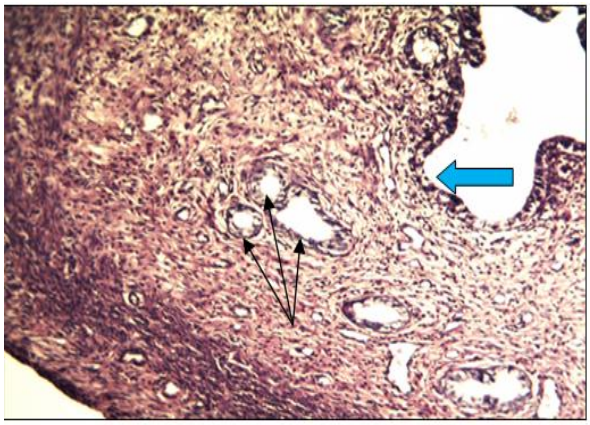

Fig. 5: Uterine section of rat in (control group). Normal uterine wall contain normal developed uterine glands (thin arrows) and there is normal epithelium which lining the uterus (blue arrow). 10X H&E.

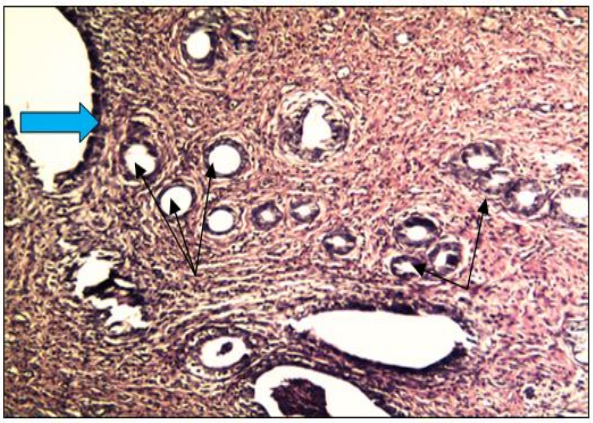

Fig. 6: Uterine section of rat in (T1) group. Thickening of uterine wall with high numbers of developed and mature uterine glands (thin arrows), also there is normal columnar epithelium which lining uterine tissue (blue arrow). 10X H&E

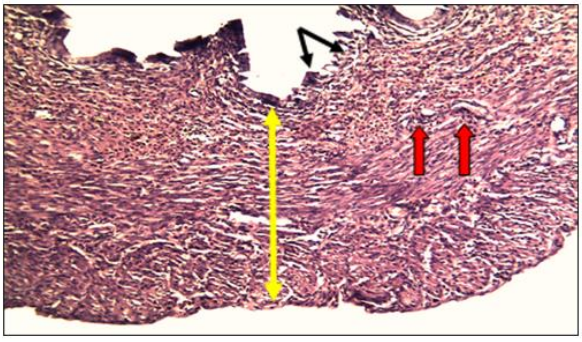

Fig. 7: Uterine section of rat in (T2) group. There is thin uterine wall (yellow arrow) and few number of uterine glands (red

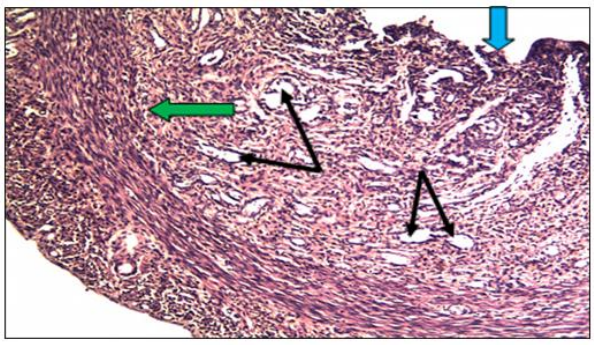

Fig. 8: Uterus of rat in (T3) group. There are proliferation of smooth muscle fibers (green arrow) and presence of large numbers of

arrows), degeneration and destruction of columnar epithelium which lining uterus (black arrows). 4X H&E.	**developed uterine glands (thin arrows) and mild degeneration in the uterine epithelium (blue arrow). 4X H&E.**

DISCUSSION

Quercetin are a polyphenol produced by a variety species of plant.[18] It have an antioxidant properties on injuries, so it is prevents oxidation and cells damage by several mechanisms, such as free radicals scavenging,[19,20] Oxidative stress caused by leade acetate caused decrease in the estrogen hormone levels in T2 groupe compared with other groups due to the harmful effects of leade acetate on female reproductive organs, so this result agreement with the.[21] which showed that leade salts can be decrease the estrogen concentration in the plasma.[22] reported that the activities of 17beta - HSD (estradiol-17beta -metabolizing enzyme) were increased in uterine extracts that treated by leade acetate ,this effect coincided with significant decreasing in the serum estrogen levels of. So the result agreed with,[23] who reported that females that exposed to low level of leade showed decrease estrogen level. Several studies showed that reproductive system deteriorations may be developed in women's even with low leade level, including early abortion.[24] fetal growth limitation,[25] and preterm delivery,[26] There were difference in the FSH plasma concentration experimental groups, the highest concentrations were for T1 group (given quercetin alone), and The lowest concentrations were for T2 group (given leade acetate alone) and control group. Alteration in serum concentration of sex hormones may cause reproductive system dysfunction through interfere with feedback mechanisms of the pituitary and hypothalamus glands,[27] my statistics supported this idea as the changed plasma levels of FSH and estrogen were detected in the leade exposed rats. Administration of leade acetate decreased plasma concentrations of FSH and estrogen hormone. Several studies showed the inhibitory effects of leade acetate on GnRH from hypothalamus Subsequently FSH concentration.[28] The results agreement with[29] that showed exposure to the leade caused significant decrease in FSH and estrogen hormone level. Exposure to leade at a time of organogenesis, interfering with the female germ cells development and caused decrease of fertility.[30] Previously, exposured the female to the leade caused alteration in the functions of reproductive system[31] The low concentration of FSH in T2 group may be due to The hypothalamic-pituitary axis is a main part that response to the stress.[32,33] reported that free radicals affect several physiological processes start from oocyte development, fertilization and pregnancy. Quercetin administration showed significant effect on estrogen. In similarity to my finding, some studies[34] reported that quercetin inhibited estrogen sulfotransferase this lead to increasing

estradiol level. A recent study showed that protective effect of dietary flavonoids through inhibition to estrogen sulfatase,[35] Previous study have suggestion that flavonoids can be strong inhibitors of sulfotransferase, so this fact demonstrate the quercetin effect in the high level of estrogen in T1.[36]

Antioxidant in the nutrients like minerals and vitamins may be play a role in decrease some dangerous effects of leade.[37] The antioxidant effects of quercetin may explain significant increasing in the level of estrogen in T3 group.

My data investigated a significant increase in estrogen level in T1 and T3 after two months oral administration of quercetin, this increase resulted from activation of the ovary cells (granulose and theca) from the quercetin treated female rats.

Histological sections

The ovary contain follicles and oocyte and produce the steroid hormones that necessary for continuance of the ovarian cycle, implantation and the secondary sex characteristics.[38] In the present finding, there was a normal histological appearance of ovary and uterus in control group while in T1 group that treatment with Quercetin (300mg /kg b.w) ovary showed high numbers of growing follicles with presence of corpus luteum. The results of uterine section showed there is thickening of uterine wall with high numbers of developed and mature uterine glands, also there is normal columnar epithelium which lining uterine tissue. Anti-oxidants are able to scavenge free radicals which are usually present in a human body cells.[39] While treatment (10 mg /kg) of lead acetate resulted in ovarian sections inhibition of the follicular growth wave and there is hemorrhage in the ovarian stroma and presence of infiltration of inflammatory cells.[40] Leade administration decreased the number of mature follicles and increased the number of atretic follicles, we can be observed that the effects of leade on reproductive hormones are complex, through several locations on the hypothalamic–pituitary–gonadal axis, confirming our results on female rats there is thin uterine wall and higher magnification, also with presence few number of uterine glands, degeneration and destruction of columnar epithelium that lining uterus.

Oxidative stress plays important role in induced the female reproductive system diseases like polycystic ovarian, tubal factor infertility and endometriosis pathogenesis.[41] Mechanisms of oxidative stress caused by leade include the effects of leade on antioxidant defense enzymes and DNA.[42] Researchers reported that low doses of leade affect sexual development in small

mammals.[43,44] reported that the several physiological processes affect by ROS starting from maturation of oocyte to fertilization, development of the embryo and pregnancy.

Finally in T3 group that treated from oxidative stress inducer by lead acetate showed high follicular growth wave and thick uterine wall and presence of large numbers of developed uterine glands and mild degeneration in the uterine epithelium there are proliferation of smooth muscle fibers, the effect of quercetin as antioxidant may reduce granulose cells damage induced by lead acetate.[45] which suggests that antioxidant may be act as fertility inducer treatment and decreased the harmful effects caused by leade acetate.

CONCLUSION

1. Quercetin have role in improvement the reproductive system efficiency, by increase of estrogen hormone, progesterone hormone and ovarian function.
2. That use of the quercetin at a dose of (300 mg/kg) did not causes any side effects along period of experiment.

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