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Estimation of Quercetin Treatment Effects in Polycystic Ovarian Syndrome (PCOS) Induced Rats

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Abstract

PCOS is a complex hormonal disorder characterized by infertility, irregular menstrual cycle and hirsutism. Different therapeutic agents are used to treat PCOS, but they have several drawbacks and cannot effectively cure the condition. The flavonoid quercetin has been proven to have health-promoting properties due to its strong antioxidant activity, anti-obesity, anti-inflammation, and other actions; the purpose of this study was to assess quercetin's impact activity in the treatment of PCOS-induced rats. 24 Wistar female rats weighing (170-180) g divided into three groups each with 8 animals ; the control group (Negative control) received vehicle propylene glycol (PG) 0.5ml/day given by subcutaneous (S.C) injections for 28 days then given orally by oral gavage for 35 days while group II which is Polycystic Ovary Syndrome (PCOS) animal model induced by testosterone propionate (TP) 10mg/kg/day dissolved in propylene glycol given by subcutaneous (S.C) injections for 28 days followed by propylene glycol orally for 35 days and considered as positive control group and quercetin group (QU) received testosterone propionate (TP) 10mg/kg/day dissolved in propylene glycol given by subcutaneous (S.C) injections for 28 days then given Quercetin extract at dose of 25 mg/kg/day (Hong) orally by oral gavage for 35 days . Administration of TP leads to a significant increase ($P < 0.05$) in body weight, fasting blood glucose, fasting insulin, cholesterol, LDL, VLDL and triglyceride levels at 4wk, 6wk and 9wk compared to control. Oral administration of Quercetin resulted in significant decrease ($P < 0.05$) in body weight, fasting blood glucose, fasting insulin, cholesterol, LDL, VLDL and triglyceride levels at 6wk and 9wk compared to PCOS-treated rats. An increase of HDL level was observed in quercetin - treated group compared to PCOS group. Thus, these results show that quercetin plays a positive role in alleviate the metabolic disturbances occurring in PCOS.
Keywords. PCOS, Quercetin, Testosterone propionate, Biochemical analysis, lipid profile.

Introduction

Polycystic ovary syndrome (PCOS) is a complex reproductive, glandular, and metabolic disorder it is a common heterogeneous disorder that appears around the time of puberty years, furthermore, it is a common complex multifaceted disorder associated with genetic and environmental influences [1, 2]. Outspread complications of PCOS lead to endometrial cancer, diabetes mellitus, cardiovascular disease, amenorrhea/oligomenorrhea, and obesity [3, 4]. PCOS etiology and causative factors are not well remain till now therefore, the researchers reviewed several possible reasons such as Glycogen synthesis reduced glucose uptake and insulin resistance along with exhibiting steroidogenic effect in ovaries during PCOS, on the other hand, obesity disrupts the steroidogenic pathway, which increases androgen synthesis while decreasing the levels of sex hormone binding globulin (SHBG) production and raising free androgen levels [5, 6].

Several metabolic disorders as including insulin resistance, obesity, hyperglycemia, hyperlipidemia, and type 2 diabetes brought on by PCOS can all be prevented by polyphenols [7]. Plant extracts are commonly used to treat diseases related to female reproduction like plant flavonoids due to their broad medicinal benefits [8, 9]. Quercetin is a common flavonoid found mostly in fruits and vegetables such as grapes, blueberries apples, broccoli, lettuce, tomato, onion, and such many others [10]. Quercetin have antioxidant effect, protection of cardiovascular, potential anticancer, anti-diabetic, anti-inflammatory influence, prevention of bone loss in postmenopausal women, antioxidant enzymes, decrease in the surplus growth of hairs on the body, helps in balancing the hormonal levels and inhibit lipids peroxidation [11-15].

Quercetin can decrease the expression of ERα, ERβ, thereby inhibiting estrogen binding to their

receptors to play the role of antiestrogen [16, 17]. Additionally, quercetin improves ovarian functions by modulating cell steroidogenic activity through inhibition of PI3K which attributes to a decrease in the expression of CYP17A1 gene, having a key role in steroidogenesis, decreased the activity of steroidogenic enzymes (3β-HSD and/or 17β-HSD), reduced granulosa cell nuclear translocation of NF-κB and reducing Resistin levels, it is the hormone that responsible for of androgens by increasing theca cells thickness and 17α-hydroxylase activity [18, 19] stimulates the synthesis .This study aims to estimate the possible Quercetin effects in PCOS rat model induced by testosterone propionate.

Materials and Methods

Chemicals and kits

Testosterone Propionate (TP) (Sustanon 250mg, 1ml from Aspen®, Jena, Germany). Quercetin (100mg/kg Chengdu Biopurify Phytochemicals Ltd. China). Diethyl Ether (Alpha Chemika, India) and Propylene glycol (PG) (Santa Cruz biotechnology/USA) were used in the study. The diagnostic kits used were obtained from (Randox Laboratories Ltd) for the estimation of cholesterol, HDL, LDL, and VLDL, while, an enzyme-linked immunosorbent assay (ELISA) Mercodia kit was used for the estimation of fasting insulin serum in the current study.

Animal

Twenty-Four wistar female rats weighing (170-180) g were obtained from Animal house, College of Pharmacy, University of Baghdad between February and April 2023. Animals were kept in stainless steel cages (8 rats/cage) at room temperature 23 ± 5 °C. Rats were kept under (10/14 h dark/light) cycle and supplied with fresh standard laboratory food and daily fresh water was acquirable ad libitum. The University of Baghdad's College of Pharmacy's Department of Pharmacology and Toxicology gave approval, which was followed in experimenting.

Experimental protocol

Three groups each of 8 animals ; the control group received vehicle propylene glycol (PG) 0.5ml/day given by subcutaneous (S.C) injections for 28 days then given orally by oral gavage for 35 days while Polycystic Ovary Syndrome (PCOS) animal model induced by testosterone propionate (TP) 10mg/kg/day (18) dissolved in propylene glycol given by subcutaneous (S.C) injections for 28 days (induction stage) then given propylene glycol orally by oral gavage for 35 days (treatment stage) and considered as positive control group and quercetin group (QU) received testosterone propionate (TP) 10mg/kg/day dissolved in propylene glycol given by subcutaneous (S.C) njections for 28 (induction stage) days then given Quercetin extract at dose of 25 mg/kg/day (20) orally by oral gavage for 35 days (treatment stage) and considered as test group. During these periods, body weight changes were estimated and fasting blood glucose tests were estimated in blood samples withdrawn from tail vein to get the basal sugar level of all rats by using Accu-Chek® device. At the end of the study, all animals were weighed and then anesthetized with diethyl ether and 5 mL blood was drawn by using cardiac puncture, blood clotted then serum collected by centrifugation at 3000 rpm for 15 minutes used for biochemical. Fasting insulin estimated by enzyme-linked immunosorbent assay (ELISA), while triglycerides and differential cholesterol (HDL, LDL, and VLDL) were measured by spectrophotometric method.

Statistical analysis

Data was analyzed using IBM SPSS Statistical Package for the Social Sciences software version 27. The data were analyzed using IBM SPSS statistics means of groups were compared using one-way ANOVA followed by Post hoc (Tukey). All data are expressed as mean ± Standard Error (SE) and were considered as significant when the p-value < 0.05.

Results

Insulin level and lipid profile

There was a significant decrease ($P < 0.05$) in fasting serum insulin, total serum cholesterol, and triglyceride levels in the quercetin treatment group compared to the control and PCOS groups (figure 1A, B, C). A significant ($P < 0.05$) increase in the levels of LDL and VLDL, while a decrease in HDL was observed in PCOS-induced rats when compared to control and quercetin rats (figure 1D, E, F). Moreover, quercetin therapy resulted in a significant elevation in serum HDL levels while there is a significant reduction of serum LDL and VLDL levels.

Body weight and Fasting blood glucose in PCOS and Quercetin rats

During PCOs induction periods, there is a gradual increase in rat's body weight of PCOS and quercetin than the control ($P < 0.05$) (Table 1, Fig 2). PCOS rats showed a 40%, 51%, and 44% increase in mean body weight as compared to the control group at 4wk, 6wk, and 9wk respectively (Table 1). On the other hand, quercetin rats showed 43% and 20% increases in main body weight as compared to the control group at 4wk and 6wk respectively, while, no significant differences in mean body weight when compared with the control group at 9wk (Table 1). Results showed a decrease in the mean body weight of quercetin rats compared with PCOS rats at 6wk and 9wk ($P < 0.05$) (Table 1). In PCOS induced group, fasting blood glucose significantly increased ($P < 0.05$) compared to the control group. However, treatment with quercetin significantly decreased ($P < 0.05$) in fasting blood glucose level of the Qu group unlike PCOS induced group (Table 1, Figure 3).

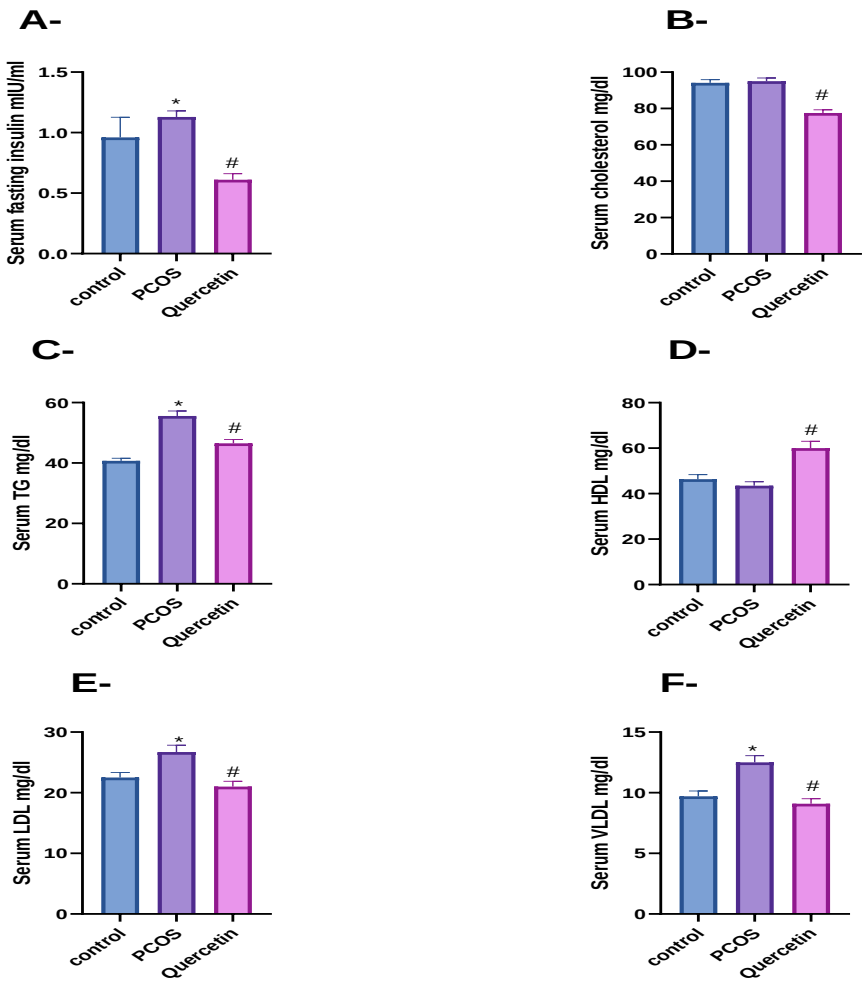

Figure1. Quercetin effect on a biochemical parameter in testosterone-induced PCOS Serum levels of: (A) fasting insulin, (B) cholesterol, (C) TG, (D) HDL, (E) LDL, (F) VLDL. Data Represented as mean ± SEM., n=8 animals. *P<0.05 vs. control; #P < 0.05 vs. the PCOS rats.

Table 1. Mean of Body Weight and Fasting blood glucose of Control, PCOS model, and QU treated groups during 63 days of experiment

Parameters	Control	PCOS	QU
Starting B.W (gm)	175 ±1.52	173 ± 0.93	170 ± 0.48
B.W After 4wk (gm)	190 ± 4.68	230 ± 6.57*	233 ± 4.35*
B.W After 6wk (gm)	207± 4.06	258 ± 5.20*	227 ± 2.01*#
B.W After 9wk (gm)	226 ± 1.83	270 ± 5.72*	223 ± 2.88#
Starting FGT (mg/dl)	95 ±2.36	93 ± 2.15	97 ± 2.84
FBG After 4wk (mg/dl)	99 ± 1.40	110 ± 2.04*	112 ± 2.82*
FBG After 6wk (mg/dl)	100 ±3.02	125 ± 3.27*	103 ±2.81#
FBG After 9wk (mg/dl)	97 ± 2.26	144 ± 1.60*	99 ± 1.95#

Values are expressed as Mean ± SEM, n=8. Control; PCOS: polycystic ovary; QU: Quercetin
* P<0.05 as compared to control group
# P<0.05 as compared to PCOS group

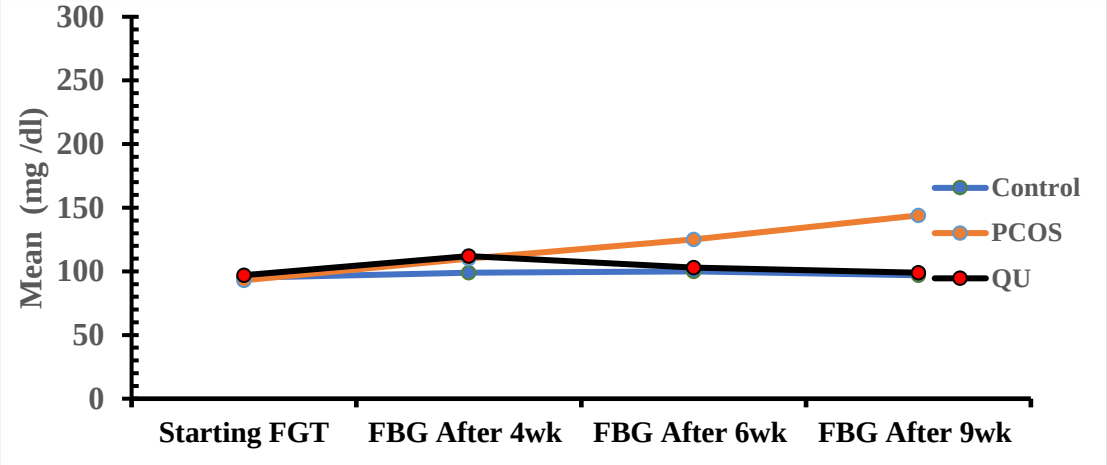

Figure 2. Mean of Body Weight of experimental group during Qu treatment.

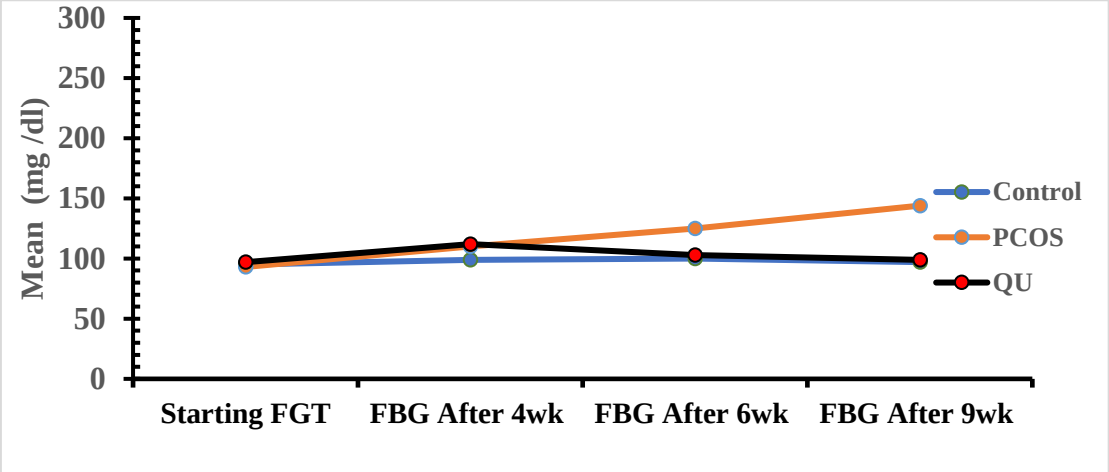

Figure 3. Mean of FBG of experimental group during Qu treatment.

Discussion

In this study, PCOS model shows increased in body weight and FBG level compared to control rats. The current study results come in accordance with some previous studies [21]. On the other hand, rats treated with quercetin have a considerable loss in weight at 6wk and 9wk compared to PCOS model, which may be demonstrating quercetin's capacity to suppress the adiposity-causing genes [22], quercetin may regulate physical activity [23] and may be related to the role of quercetin in lowering uterus and ovary weights through decreased cystic follicles and increased in corpus luteum and normal follicles [24, 25].Quercetin also acts as a blocker of adipogenesis, impeding the mitogen-activated protein kinase (MAPK) signal pathway [26]. Furthermore, increased levels of the MAPK were found to be related with an increase in body weight and a reduction in energy expenditure [27].

In contrast to the treated groups, glucose levels were extremely high in the PCOS-positive group, demonstrating the capacity of quercetin to decrease plasma glucose level [28, 29, 30]. Furthermore, quercetin promotes glucose absorption by activating adenosine monophosphate-activated protein kinase AMPK-dependent and insulin-independent mechanisms to enhance GLUT-4 content [31, 32] and also controls the pathway by which glucose is formed from non-hexose precursors such as glycerol, lactate, pyruvate, glucogenic amino acid and protects the β-cell function of the islet [33].

Hyperglycemia is a well-known consequence of the insulin resistant (IR) state. Also, there is a close relation between hyperinsulinemia and IR and that means insulin level is the major factor in all these states. In the current study, our results showed the therapeutic effects of quercetin in insulin levels when compared between quercetin-treated rats and TP-induced PCOS rats [28], and Quercetin's anti-inflammatory, anti-diabetic, and antioxidant qualities may be connected to this action [11, 21, 34, 35].

In this study, Quercetin significantly improved the levels of cholesterol and triglycerides in quercetin – treated rats compared to PCOS animals. Some previous studies showed similar improving serum levels of total cholesterol and triglycerides by protects cellular injury directly by scavenging free radicals and inhibiting LDL from

oxidation, correction of hyperinsulinemia may improve dyslipidemia through decreased insulin resistance. Insulin resistance may also result in increased catecholamine induced lipolysis and release of fatty acids from visceral adipose tissue into the circulation [36]. Additionally, Quercetin intake may activate AMP-activated protein kinase (AMPK) and prevent lipid accumulation in the liver [37]. AMPK subsequently inhibits the activity of Acetyl-CoA carboxylase and carbohydrate response element-binding protein, and the gene expression of sterol regulatory element-binding transcription factor 1c [38]. Furthermore, quercetin intake may increase the gene expression of peroxisome proliferator-activated receptor-gamma (PPAR-c) [39]. PPAR-c plays main functions in the metabolism of lipid and insulin [40]. Quercetin works primarily on leukocytes to reduce inflammation and resistance and concentrates on numerous intracellular signaling phosphatases and kinases, enzymes, and membrane proteins, which are frequently essential for a biological function and, as a result of this role, quercetin is considered to be a one of important phenolic compounds prevent from degenerative illnesses such as fat peroxidation in different tissues [41, 42] and this may help to interpretation the results found in this study.

Moreover to its anti-oxidant impact, there is an amazing variety of enzymes whose action is modulated (mostly inhibited) by quercetin.Hoek-van den Hil EF, et al. 2013 found that quercetin-fed mice reduced triglycerides serum with 14% and positively improved with 13% in total polyunsaturated fatty acids levels [43]. Studies have shown that quercetin may reduce the likelihood of problems with lipid metabolism by increasing the expression of lipid droplet proteins in fat cells and this is done by reducing the level of fasting insulin which leads to a reduction of IR state in PCOS, and the results of our study indicated that quercetin treated rats showed significant reduce in the level of fasting insulin [44, 45].

The lipid profile measured in this study showed that quercetin increased HDL and decreased the LDL and VLDL serum levels in quercetin-treated rats compared to PCOS model and this may be due to its anti-hyperlipidemic potential role and this role can be attributed to its capacity in correcting hyperinsulinemia and hyperandrogenemia [11, 18, 46, 47, 48] or, may be related to the roles of quercetin in the regulation of Paraoxonase 1 (PON1) expression, PON1 protects the oxidative modification of low-density lipoprotein (LDL) and is a major anti-atherosclerotic protein component of high-density lipoprotein (HDL) [49].

Tremellen and Pearce, 2013 proposed the idea that dysbiosis of the intestinal (gut) microbiome is a causative factor of metabolic and reproductive manifestations of PCOS in women and in female rodent models of the disorder [50]. Dysbiosis of Gut Microbiota (DOGMA) theory of PCOS can account for all three components of the syndrome-anovulation/menstrual irregularity, hyper-androgenism and the development of multiple small ovarian cysts [51]. Overall, all the previously mentioned references have proven that quercetin has the therapeutic ability of Polycystic Ovary Syndrome and its Complications, including weight gain and obesity resulting from an excess of androgens in PCOS female.

Conclusion

The current results indicate that quercetin gradually ameliorates PCOS complications by reducing weight gain, improving glycemic status and lipid profile. Thus, Quercetin exerts satisfactory therapeutic effects on PCOS rats.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any conflict of interest.

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Ethics Statements

The study protocol was approved by the Graduate Studies and Ethics Committees of the College of Pharmacy/ University of Baghdad (approval # 7876 \12\2022).

Author Contribution

Conception and Design of the study by Lecturer. Ammar A. Fadhil, Dr. Shihab H. Mutlaq and Dr. Ali J. Abd-Alhussain. Conducted animal experiment and manuscript writing by Lecturer. Ammar A. Fadhil. All authors reviewed the results and approved the final version of the manuscript.

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تقدير تأثيرات العلاج بالكويرستين في الجرذان المستحثة بمتلازمة المبيض المتعدد الكيسات (PCOS)

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الخلاصة

متلازمة المبيض المتعدد التكيسات هي اضطراب هرموني معقد يتميز بالعقم وعدم انتظام الدورة الشهرية والشعر الزائد . تُستخدم عوامل علاجية مختلفة لعلاج متلازمة المبيض المتعدد الكيسات ولكن لها عدة عيوب ولا يمكنها علاج الحالة بشكل فعال، وقد ثبت أن الفلافونويد كويرستين له خصائص معززة للصحة بسبب نشاطه القوي المضاد للأكسدة ومضاد للسمنة ومضاد للالتهابات وغيرها من الإجراءات، وكان الغرض من هذه الدراسة هو تقييم نشاط تأثير الكويرستين في علاج الجرذان التي تسببها متلازمة المبيض المتعدد الكيسات. تم تقسيم ٢٤ من إناث الجرذان الويستاروالتي تزن (١٧٠-١٨٠) جرامًا إلى ثلاث مجموعات كل منها ٨ حيوانات؛ المجموعة الضابطة (كروب السيطره) تلقت بروبيلين جلايكول ٠,٥٠ مل/يوم تعطى عن طريق الحقن تحت الجلد (S.C) لمدة ٢٨ يومًا ثم تليها عن طريق الفم لمدة ٣٥ يومًا بينما المجموعة الثانية وهي نموذج حيواني لمتلازمة المبيض المتعدد الكيسات (PCOS) المستحثة بواسطة بروبيونات التستوستيرون وتم اعطاء التستوستيرون بجرعة ١٠ ملجم/كجم/يوم مذاب في بروبيلين جلايكول تعطى عن طريق الحقن تحت الجلد (S.C) لمدة ٢٨ يوماً ثم أعطي البروبيلين جلايكول عن طريق الفم لمدة ٣٥ يوماً واعتبرت مجموعة التحكم الإيجابي، وتلقت مجموعة الكويرستين (QU) بروبيونات التستوستيرون ١٠ ملجم/كجم/يومياً مذابة في البروبيلين جلايكول تعطى عن طريق الحقن تحت الجلد (S.C) لمدة ٢٨ يوماً ثم أعطي مستخلص الكويرستين بجرعة ٢٥ ملجم/كجم/يومياً عن طريق الفم لمدة ٣٥ يوماً. وأدى إعطاء بروبيونات التستوستيرون إلى زيادة كبيرة ($P < 0.05$) في وزن الجسم، وجلوكوز الدم ، والأنسولين ، والكوليسترول، والبروتين الدهني منخفض الكثافة ، والبروتين الدهني منخفض الكثافة جدا، ومستويات الدهون الثلاثية في الاسبوع الرابع والسادس والتاسع مقارنةً مع مجموعة السيطرة. وأدى تناول الكويرستين عن طريق الفم إلى انخفاض ملحوظ ($P < 0.05$) في وزن الجسم والجلوكوز في الدم والأنسولين والكوليسترول والبروتين الدهني منخفض الكثافة والبروتين الدهني منخفض الكثافة جدا والدهون الثلاثية عند الاسبوع السادس والتاسع مقارنة بجرذان متلازمة المبيض المتعدد التكيسات. ولوحظت زيادة في مستوى البروتين الدهني مرتفع الكثافة في المجموعة المعالجة بالكويرستين مقارنة بمجموعة متلازمة المبيض المتعدد التكيسات وبالتالي، تظهر هذه النتائج أن الكويرستين يلعب دورًا إيجابيًا في التخفيف من الاضطرابات الأيضية التي تحدث في متلازمة تكيس المبايض.

الكلمات المفتاحية : متلازمة المبيض المتعدد الكيسات، كويرستين، بروبيونات التستوستيرون، اختبارات بيوكيميائية، دهنيات الدم.