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Amelioration by quercetin of insulin resistance and uterine *GLUT4* and *ERα* gene expression in rats with polycystic ovary syndrome (PCOS)

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Abstract. Insulin resistance (IR) and infertility are two major complications of polycystic ovary syndrome (PCOS), which are the results of changes in certain parts of the reproductive and metabolic systems. We aimed to observe the effect of quercetin on dehydroepiandrosterone (DHEA)-induced PCOS and insulin resistance in rats. All animals were divided into five groups and DHEA was used to induce PCOS. Bodyweight and ovarian morphology of all groups were observed. Fasting blood glucose and insulin levels were analysed. The homeostasis model assessment of insulin resistance (HOMA-IR) method was used for IR level determination. The expression of oestrogen receptor α (*ERα)* and glucose transporter 4 (*GLUT4*) genes in the uterus was examined by real-time polymerase chain reaction. Liver hexokinase (HK) and glucokinase (GK) activity was determined using spectrophotometry. Quercetin significantly improved the IR state in PCOS rats. PCOS resulted in a decrease in liver GK and an increase in liver HK specific activity, whereas quercetin increased both liver HK and GK activity. Our data also showed a significant reduction in uterine *ERα* and *GLUT4* expression in the PCOS group, which was increased by quercetin. A remarkable effect of quercetin was the intensive reduction of PCOS-IR and significant induction of uterine *GLUT4* and *ERα* gene expression; it could thus be a possible effective treatment for PCOS and its complications, IR and infertility.

Additional keywords: glucokinase, hexokinase , HOMA index, infertility.

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Introduction

In 1980 Burghen *et al.* (1980) reported that women with polycystic ovary syndrome (PCOS) have basal hyperinsulinaemia, suggesting the possibility of insulin resistance (IR; Burghen *et al.* 1980). PCOS is a complex hormonal disorder with many unsought aspects comprising infertility, irregular menstrual cycle and hirsutism as the symptoms (Shah and Patel 2016). The patients are prone to long-term consequences including diabetes and endometrial cancer, which are usually caused by high levels of androgens and IR (Goodarzi *et al.* 2015). The exact mechanism of PCOS-IR and, more importantly, its association with hyperandrogenaemia has not so far been discovered. Both genetic factors and defects in intracellular signalling pathways can cause IR but there is some evidence indicating that androgen excess could contribute to PCOS-IR (Bremer and Miller 2008). Under IR circumstances, disruption of the entire glucose haemostasis system is probable; this may include changes in the activity of liver hexokinase (HK) and glucokinase (GK) enzymes or alteration of uterine glucose transporter 4 (GLUT4) gene expression, which are intensively dependent on insulin action. The GK and HK enzymes catalyse the first step of glucose metabolism reaction with different affinities for glucose (Aleshin *et al.* 1998). Transcription of the GK gene is strongly dependent on the insulin effect (Foretz *et al.* 1999). In the case of diabetes or prolonged fasting, during which serum insulin levels decrease, liver GK activity is also greatly reduced (Magnuson *et al.* 2004). More interestingly, IR with contrary effects on the HK enzyme decreases the relative activity of HK in the muscles (Vestergaard 1999) and increases it in the pancreas (Cockburn *et al.* 1997). However, the activity of these two enzymes in terms of PCOS-IR has not yet been studied.

The expression of insulin receptors in the uterus is proven (Strowitzki *et al.* 1993) and adequate glucose metabolism has also been reported to be vital for uterine cell differentiation

(Sheets *et al.* 1985). GLUT4 is the most important glucose transporter isoform in insulin-dependent tissues and mediates insulin-stimulated glucose transport in the uterus (Mioni *et al.* 2004). Recently, several investigations have shown a reduction in GLUT4 expression in the uterus of PCOS patients (Zhai *et al.* 2012; Carvajal *et al.* 2013) and, for the first time, we aimed to examine the therapeutic effect of quercetin on uterine GLUT4 expression under PCOS conditions.

In the fertility process, uterine oestrogen receptors, particularly oestrogen receptor α (ERα), have an essential role (Hulchiy *et al.* 2016), such that ER-knockout rats are completely infertile and this has been repeatedly evaluated and endorsed over many years (Meyer *et al.* 2011; Quaynor *et al.* 2013). Therefore, it's very likely that infertility occurs as a consequence of changes in ERα gene expression. Thus, we also aimed to assess the changes in ERα gene expression in the PCOS uterus. Also for the first time, we investigated the effects of quercetin on ERα expression, as it may be considered as an alternative way to reduce the complications of PCOS or even treat it.

Quercetin, also known as 3,3′,4′,5,7-pentahydroxyflavone, is a flavonoid found in herbal medicines and the most ubiquitous one, which is usually present in glycosylated form (Anhê *et al.* 2012; Yarahmadi *et al.* 2017). In the present study, we appraised the amelioration effects of quercetin as an anti-inflammatory, antioxidant and antidiabetic compound on PCOS-IR, liver HK and GK enzyme activities and the expression of GLUT4 and ERα in the uterus, after PCOS induction with dehydroepiandrosterone (DHEA).

Materials and methods

Animals

All animal experiments were approved by the ethics committee of the Shiraz University of Medical Sciences. Thirty-five Sprague–Dawley female rats (180 g average weight) were provided by the Shiraz University of Medical Sciences Animal Centre. All rats were housed in a 25°C environment under a 12 : 12 h light:dark cycle. The rats were fed with conventional feed pellets and given free access to food and water. Animals were weighed at the beginning of the study and on the final day. All rats were randomly divided into five groups at the start: (1) Control group, didn't receive any treatment for 30 days; (2) quercetin (Q) group, treated with quercetin gavage (15 mg kg^{-1} quercetin (Sigma) dissolved in 0.5 mL 10% ethanol) for 30 days (Vessal *et al.* 2003; Santi *et al.* 2014); (3) ethanol vehicle group, received 0.5 mL 10% ethanol gavage for 30 days; (4) PCOS group, prior to the start of the experiment rats were subcutaneously injected with 6 mg DHEA per 100 g day^{-1} (DHEA dissolved in 0.2 mL sesame oil) for 21 consecutive days to induce PCOS and then didn't receive any treatment for 30 days (Endo *et al.* 2001; Honnma *et al.* 2006; Misugi *et al.* 2006; Kavitha *et al.* 2016); (5) PCOS+Q group, prior to the start of the experiment rats were subcutaneously injected with 6 mg DHEA per 100 g day^{-1} (DHEA dissolved in 0.2 mL sesame oil) for 21 consecutive days to induce PCOS and then were treated with 15 mg kg^{-1} quercetin dissolved in 0.5 mL 10% ethanol for 30 days.

Briefly, after 30 continuous days, all the animals were killed and all required tissues, including liver, ovaries, uterus and serum, was collected and kept in proper storage conditions.

IR occurrence assessment

After 12 h of fasting all rats were anesthetised and 2 mL blood was drawn from the orbital vein and tested for fasting blood glucose (FBG) and fasting insulin serum (FIS) levels. FBG was calculated with the glucose oxidase method and FIS was measured with a direct competitive enzyme-linked immunosorbent assay (ELISA) Mercodia kit (Miladpour *et al.* 2017). The optical density values were read at 450 nm using a microplate reader and the induction of IR was appraised with the homeostasis model assessment of insulin resistance (HOMA-IR) method. HOMA-IR was calculated using the following formula:

$$\text{HOMA-IR} = \text{FBG}\,(\text{mmol}\,\text{L}^{-1}) \times \text{FIS}\,(\text{mU}\,\text{L}^{-1})/22.5. \quad (1)$$

Rat ovarian morphology

All rat ovaries were obtained by surgery, fixed in 10% formalin and embedded in paraffin. Sections were prepared and stained with haematoxylin and eosin then assessed by two pathologists who were not aware of the sample type for ovarian morphological features.

Hepatic GK and HK specific activity assay

For liver HK and GK activity assays 1 g frozen liver tissue from each sample was homogenised in 9 mL cold buffer (including 50 mM Na-HEPES, 1 mM ethylendiamine tetraacetic acid (EDTA), 5 mM MgCl2, 100 mM KC1 and 2.5 mM dithiothreitol (DTT), adjusted to pH 7.4) using a glass–Teflon Potter homogeniser (Vessal *et al.* 2003). The suspension obtained was centrifuged at 12 000*g* at 4°C for 1 h and the clear supernatant was utilised for enzyme activity assessment by the coupled enzyme assay procedures. The incubation mixtures for the assay of these enzymes in both control and test tubes contained the following ingredients in a final volume of 1.0 mL: incubation buffer, pH 7.4 containing HEPES, 50 µmol; KC1, 100 µmol; MgC12, 7.5 µmol and dithiothreitol, 2.5 µmol; fatty acid free bovine serum albumin, 10 mg; NAD+, 0.5 µmol; glucose-6-phosphate dehydrogenase (G6PD), 4 units; liver supernatant, 100 ml for hexokinase assay or 10 mL for total hexokinase and glucokinase assays; and D-glucose, 0.5 µmol for hexokinase and 10 µmol for total enzyme activities. Tubes were pre-incubated at 25 8C for 5 min. To the control tubes, 0.2 mL of H2O were added and to start the reactions in the test tubes, 0.2 ml of a solution containing 0.5 µmol of ATP was addedThe changes in the absorbance at 340 nm were followed for 10 min. Total enzyme activities (GK+HK) and HK activities were calculated in terms of mU mL^{-1} of the liver supernatant. For calculating GK activity, HK activity was subtracted from the total HK+GK activities. Biuret reagent was used for liver protein concentration measurement (Gornall *et al.* 1949) and bovine serum albumin (BSA) was used as standard. Enzyme specific activities were expressed as mU per mg protein.

Table 1. List of primers and real-time PCR conditions

Genes	Primer sequence	Annealing temperature (°C)	Cycle number
β-Actin	F: 5′-AAGGCCAACCGTGAAAAGAT-3′	58.0	35
	R: 5′-ACCAGAGGCATACAGGGAC-3′	58.0	35
ERα	F: 5′-CCAAAGCCTCGGGAATGG-3′	56.1	35
	R: 5′-AGCTGCGGGCGATTGAG-3′	56.1	35
GLUT4	F: 5′-GGGCTGTGAGTGAGTGCTTTC-3′	56.0	35
	R: 5′-CAGCGAGGCAAGGCTAGA-3′	56.0	35

Endometrium RNA isolation and real-time polymerase chain reaction (PCR)

Total endometrium RNA was isolated using Trizol reagent (GIBCO) followed by an overnight precipitation at −20°C, then the final pellet was dissolved in 25 μL nuclease-free water. Complementary DNAs were made by cDNA synthesis kit (Thermoscientific). Complementary DNA templates were subjected to fluorometric semiquantitative real-time PCR in duplicate, using an ABI 7500 (Applied Biosystems) with SYBR Green PCR master mix (Applied Biosystems). B-actin was used as an internal control for all samples. The real-time results were analysed by the $^{\Delta\Delta}$CT method (Robker *et al.* 2009; Totonchi *et al.* 2016). The sequences of all the primers used in this study are summarised in Table 1.

Statistical analyses

SPSS 22.0 (IBM Corp.) was used to perform statistical analysis. All values are expressed as mean ± standard deviation (s.d.). Differences between two groups were analysed by the non-parametric Mann–Whitney test and differences between more than two groups were performed by the Kruskal–Wallis test followed by Dunn's test. The level of statistical significance was set at $P < 0.05$.

Results

Effect of PCOS and Q on ovarian morphology

Pathological assessment and light microphotography of ovarian morphology are presented in Fig. 1. In the control and ethanol groups the ovary and follicles were normal (Fig. 1*a*, *b*). More remarkably, under normal conditions quercetin significantly improved folliculogenesis and luteinisation in the quercetin group compared with control group (Fig. 1*c*). As seen in Fig. 1*d*, the ovaries of rats in the PCOS group showed an increase in ovarian volume, significant reduction in corpus luteum and theca layer hypertrophy and thickening compared to the normal control. Follicular enlargement and cystic follicles were also observed. This therefore suggests the successful induction of PCOS (Fig. 1*d*). The results of ovarian morphological comparisons in all five groups showed that quercetin had an ameliorating effect on the PCOS+Q group compared to the PCOS group. The PCOS+Q group had fewer cystic follicles, a significant increase in corpus luteum and normal follicles (Fig. 1*e*) and a significant decrease in ovarian weight compared with the PCOS group, thus showing the effect of quercetin therapy .

Effects of PCOS and Q on bodyweight and fasting insulin and glucose levels

As shown in Fig. 2, PCOS induced an increase in mean bodyweight in rats ($P < 0.05$) that was not decreased by treatment with Q. Fasting insulin and glucose levels in addition to HOMA-IR value of all groups are shown in Fig. 3*a*–*c*. HOMA-IR >2.5 is considered as IR. The HOMA-IR value in the PCOS group was significantly higher (~five times) than the normal group and also more than 2.5 ($P < 0.05$; Fig. 3*c*), indicating that IR has occurred. Treatment with 15 mg kg^{-1} quercetin for 30 days dramatically reduced IR and insulin levels in the PCOS+Q group (Fig. 3*a*) compared to the PCOS group ($P < 0.05$) but the duration of the treatment was not enough to completely eliminate IR (Fig. 3*c*).

Liver HK and GK specific activity

The results of HK and GK specific activity are presented in Fig. 4*a* and Fig. 4*b* respectively. PCOS conditions decreased liver GK specific activity (Fig. 4*a*) but, by contrast, liver HK specific activity was elevated compared with normal control ($P < 0.05$; Fig. 4*b*). Quercetin treatment for 30 days in PCOS+Q rats significantly increased liver GK and HK activities in this group compared with the PCOS group, but quercetin had no influence on liver HK and GK specific activity in normoglycaemic conditions ($P < 0.05$; Fig. 4*a*, *b*).

Expression of uterine GLUT4 and ERα genes

The results of the real-time PCR demonstrated a significant reduction in the expression of uterine GLUT4 and ERα genes in PCOS rats compared to the control group ($P < 0.05$). As shown in Fig. 5, 30 days of quercetin treatment in the PCOS+Q group dramatically increased the expression of both desired genes in this group compared with the PCOS group and even more than the control group, such that the expression of ERα and GLUT4 gene reached 5 and 4.4 times higher, respectively, in PCOS+Q animals than in controls ($P < 0.05$). Furthermore, GLUT4 and ERα gene expression in the quercetin group was remarkably increased compared with the control group ($P < 0.05$).

Discussion

In the present study we successfully created a PCOS model with elevated FBG levels and, most importantly, insulin resistance. The results of our study have shown that quercetin has noteworthy and ameliorative effects in PCOS-IR reduction.

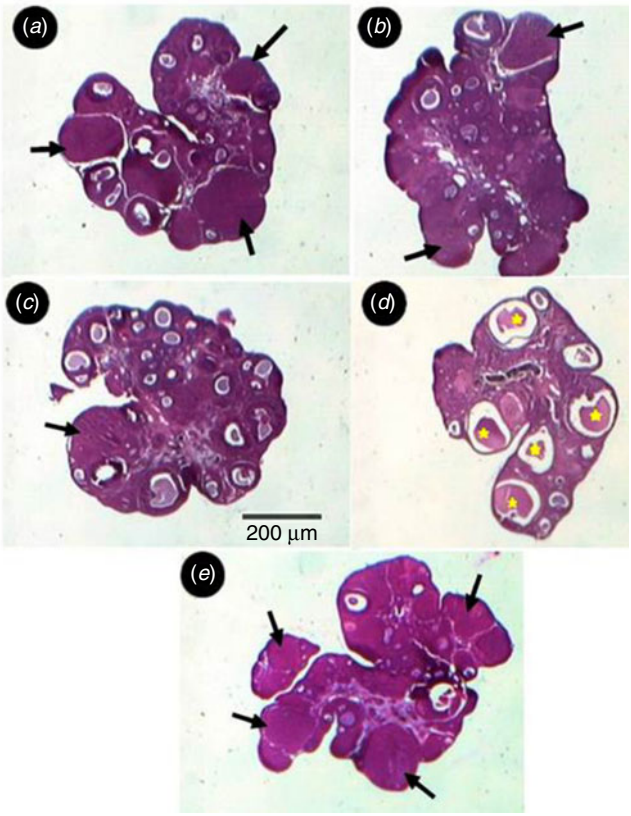

Fig. 1. Light photomicrograph of ovarian tissue in five groups of rats. Haematoxylin and eosin staining, 40× magnification. (*a*) Control group, (*b*) ethanol group, (*c*) quercetin group (healthy rats under treatment with 15 mg kg^{-1} quercetin), (*d*) PCOS group, (*e*) PCOS+Q group (PCOS rats treated with 15 mg kg^{-1} quercetin). The black arrows shows corpora lutea and the yellow stars in (*d*) show cystic follicles. In (*c*) elevated folliculogenesis in the ovary under the effect of quercetin can be observed. In the PCOS+Q ovary (*e*), treatment with quercetin has increased corpora lutea in this group compared with the PCOS group (*d*).

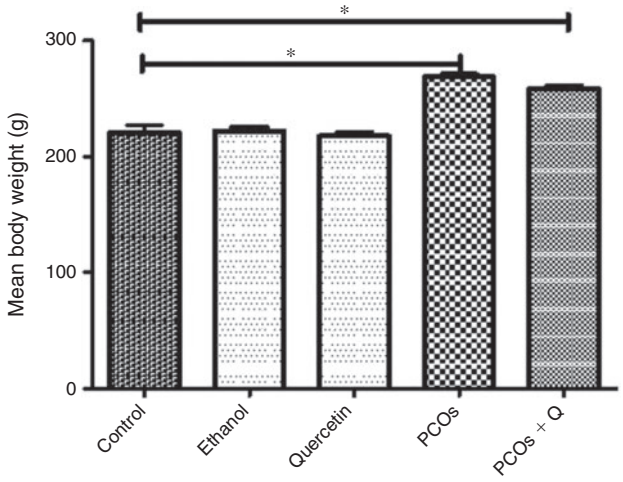

Fig. 2. Mean bodyweight in five groups of rats: control, ethanol (10% ethanol as vehicle), quercetin (15 mg kg^{-1} quercetin), PCOS, PCOS+Q (PCOS treated with 15 mg kg^{-1} quercetin). Data presented are mean ± s.d. $^*P < 0.05$; significant difference compared with the control group.

Also, the effects of quercetin on the reproductive system, including the uterus and ovaries, as well as liver enzymes is not well understood, and here we found that under the significant stimulatory effects of quercetin, ERα and GLUT4 gene expression not only improved but was raised even more than expected. Furthermore, the activities of both liver enzymes, GK and HK, were also restored to normal levels with quercetin treatment.

Undoubtedly, hyperglycaemia is a direct result of the IR state, but the notable question is: what conditions can drive PCOS-IR? The exact mechanism of PCOS-IR has not yet been found. Previous studies suggested that impairment in insulin intracellular signalling pathways, especially changes in insulin receptor substance-1 (IRS-1) phosphorylation, could be a possible reason for PCOS-IR (Catena *et al.* 2003; Diamanti-Kandarakis *et al.* 2008) but the role of hyperandrogenaemia, which is also not yet properly identified, should not be overlooked (Karakas 2017). All studies that have been able to induce PCOS-IR by using DHEA as androgen can somehow be an assertion for this hypothesis that hyperandrogenaemia may contribute to PCOS-IR induction (Misugi *et al.* 2006). It has already been proven that increased androgen levels induce fat accumulation and weight gain (Yildirim *et al.* 2003), which we also observed in the PCOS rats. Adipose tissue accumulation causes release of tumour necrosis factor α (TNFα) as an adipokine and inflammatory factor (Winkler *et al.* 2003) and switches IRS-1 tyrosine phosphorylation to serine phosphorylation, which can be one of the possible reasons for IR initiation. In fact, under the influence of TNFα, IRS-1 autophosphorylation is disrupted and it is no longer able to trigger the intracellular signalling pathway (Nieto-Vazquez *et al.* 2008; De Pergola *et al.* 2009), leading us to hypothesise that this could be one of the possible mechanisms of how hyperandrogenaemia leads to IR. In this study a sharp decrease in IR state in the PCOS+Q group as a result of quercetin usage was seen. This effect of quercetin might be related to its anti-inflammatory properties (Wang *et al.* 2016), as it inhibits TNFα as has been shown by Lin *et al.* (2004).

The results of our study indicate that GK enzyme activity significantly decreased and HK activity unexpectedly increased in the PCOS rats. These results raise the possibility that increases in HK activity is a compensatory mechanism of liver cells in IR state, in cases of lowered GK activity. It is probable that lowering the amount of glucose influx to less than glucokinase Km compelled the HK, with its high affinity for glucose, to be more active to keep liver glucose metabolism at normal levels as much as possible. In fact, this behaviour is observed in pancreatic cells during diabetes-IR (Becker *et al.* 1996; Cavaghan *et al.* 2000). We thought it may be effective for explaining what we have seen in the liver in terms of PCOS-IR. Similarly, Lowes *et al.* (1998) reported a 7-fold increase in HK activity in a cirrhotic and alcoholic liver compared to a normal liver. Quercetin was found to increase the activity of both enzymes and return GK activity to normal levels in PCOS+Q liver. Based on this result, the improvement of GK and HK activities could be a result of a reduction in IR by quercetin and

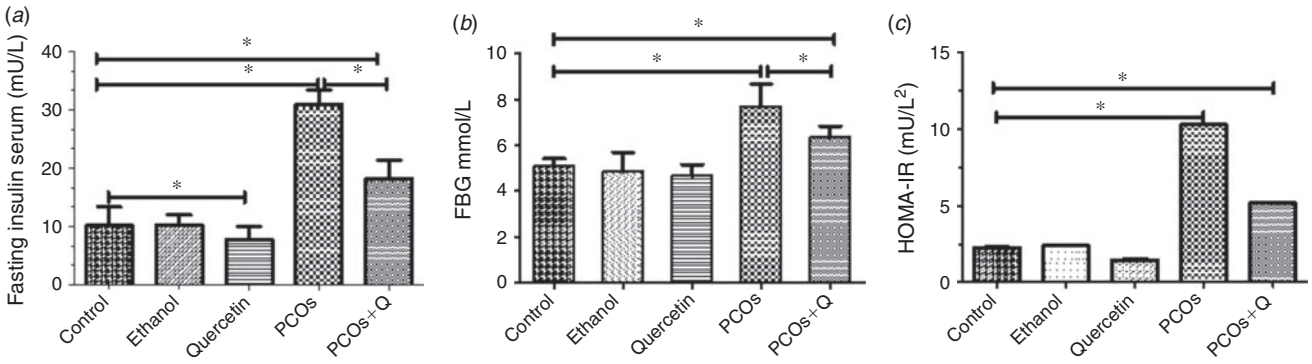

Fig. 3. (*a*) Fasting insulin serum (FIS), (*b*) fasting blood glucose levels (FBG), (*c*) homeostasis model assessment of insulin resistance (HOMA-IR). $*P < 0.05$; significant differences between groups are marked with an asterisk. Insulin, glucose levels and HOMA-IR in the PCOS group are significantly raised compared to the control. Quercetin therapy reduced all three factors in PCOS+Q compared with PCOS.

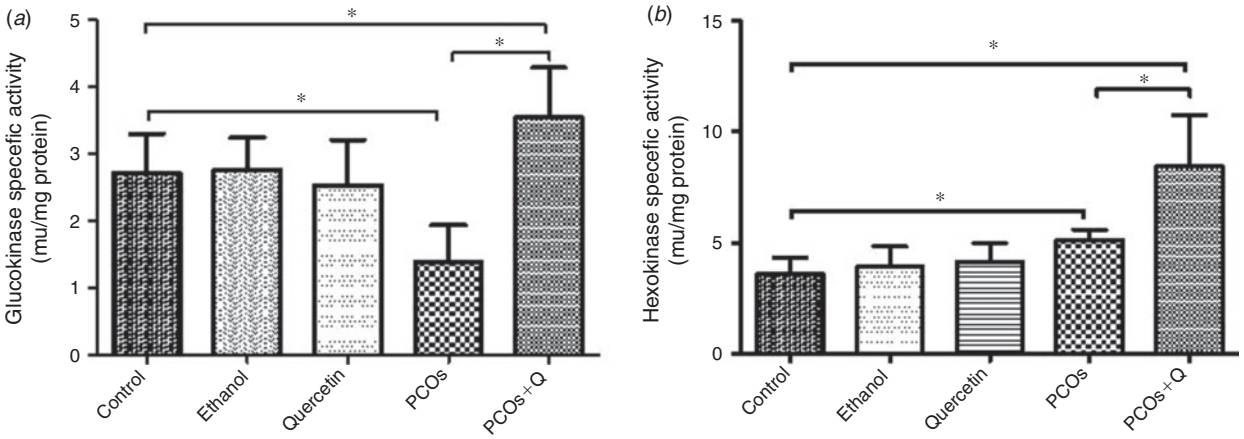

Fig. 4. The specific activity of liver enzymes. (*a*) glucokinase (GK) specific activity, (*b*) hexokinase (HK) specific activity. Data are presented as mean ± s.d. $*P < 0.05$; significant differences between groups are marked with an asterisk. quercetin treatment for 30 days led to improvement and increase in both liver-specific enzyme activities in PCOS+Q rats.

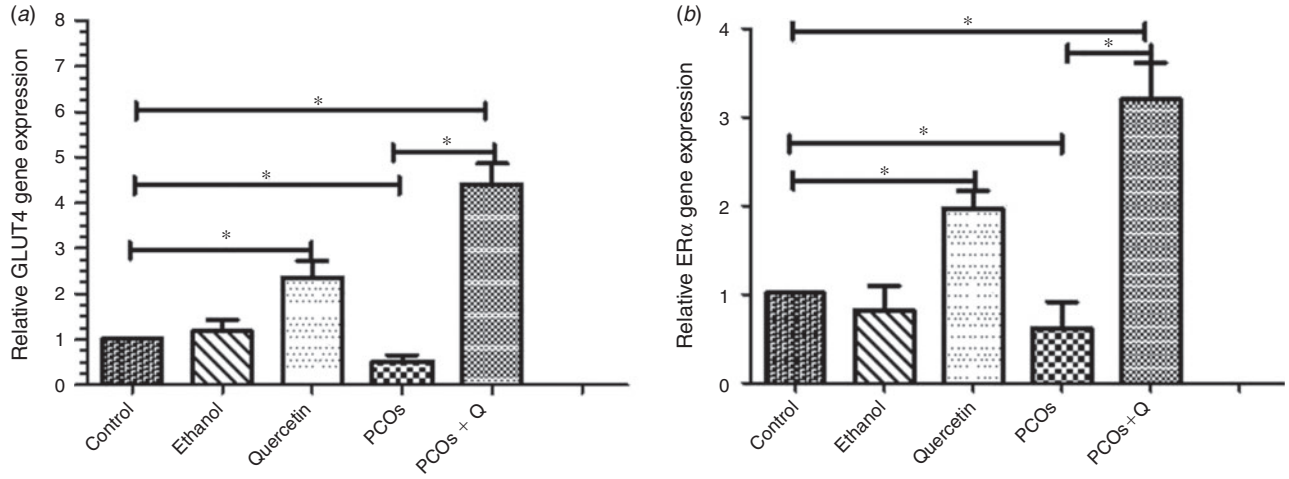

Fig. 5. Relative expression of uterine GLUT4 and ERα genes expressed as mean ± s.d. (*a*) GLUT4 expression, (*b*) ERα expression. $*P < 0.05$; significant differences between groups are marked with an asterisk. Expression of both uterine genes under PCOS conditions decreased dramatically to almost half of the normal expression in the control group ($*P < 0.05$). Quercetin enhanced the expression of both genes in PCOS+Q compared to both PCOS and control group rats.

would thus be an indirect effect of quercetin; since a similar study is not available in this area, it is not possible to conclude with certainty about this issue.

One interesting finding is that for the first time we showed that quercetin can enhance and increase uterine ERα gene expression. A reduction in ERα mRNA levels was reported in PCOS women by Hughes *et al.* (2006). It has also been determined that ERα-knockout male and female rats become completely infertile (Villavicencio *et al.* 2006; Shang *et al.* 2012). We observed extreme reduction in uterine ERα expression in the PCOS group, which matches those observed in earlier studies as expected. The definitive causes of diminished ERα expression in this condition are not yet clear. In the ovary, under the influence of FSH hormone, oestrogen is produced. Conversion of cholesterol to androstenedione (A2) is the first step of oestrogen synthesis. A2 should convert to oestrogen, which is catalysed by the aromatase enzyme (Nelson and Bulun 2001). Therefore, the factors (such as testosterone (T)) that can decrease aromatase activity or result in a deficiency of this enzyme can indirectly reduce the production of oestrogen and ERα expression (Chen *et al.* 2015). Also, the inhibitory role of androgens, especially T, on aromatase activity have been proven by Jiang *et al.* (2010). Elevated T levels in the estradiol/testosterone (E2/T) fraction has an inhibitory effect on aromatase activity (Jiang *et al.* 2010) so it can be considered as a possible reason for ERα downregulation. Quercetin is also known as a phytoestrogen component (Mueller *et al.* 2004). According to the results of van der Woude *et al.* (2005) it seems that quercetin has the ability to induce cell divisions in the MCF-7 cell line through the induction of ERα and ERβ expression and has a similar and synergistic effect with oestrogen so it is therefore likely that such conditions existed in our study.

The results of our study indicate that the expression of uterine GLUT4 in the PCOS group is significantly lower than normal, which is similar to the results of Mioni *et al.* (2004) and Mozzanega *et al.* (2004). GLUT4 transporting to the cell surface depends on the insulin signalling pathway (Patel *et al.* 2006) and the role of IR in reducing GLUT4 expression is well understood (Fornes *et al.* 2010). The role of both ER receptors in determining the expression of GLUT4 in skeletal muscle (Barros *et al.* 2006) as well as the regulation of insulin sensitivity in the liver (Bryzgalova *et al.* 2006) have also been identified. It has been reported that the induction of ERα expression could increase the sensitivity of skeletal muscle cells to insulin and thus lead to glucose uptake (Riant *et al.* 2009). Hence, considering the effects of oestrogen and its receptors with regard to insulin sensitivity and GLUT4 expression in skeletal muscle as well as the results of our investigation, which showed decreased expression of uterine ERα in PCOS, it is possible that reducing the effect of oestrogen in the uterus induces or exacerbates the reduction of GLUT4 expression in PCOS.

Our study also showed that the oral administration of quercetin for 30 days could enhance the expression of the GLUT4 gene in the PCOS+Q group significantly, even more than its value in the normal control. Comparison of HOMA-IR values in the PCOS+Q group and normal group also revealed that IR was not fully vanished in the PCOS+Q rats. So, quercetin must be able to enhance the expression GLUT4 through an insulin-independent mechanism. Otherwise, the expression values of the GLUT4 gene in the PCOS+Q group could not be more than the amount expressed in the normal control, with full sensitivity to insulin. Studies conducted by Eid *et al.* (2010) on skeletal muscle have shown that quercetin can increase the expression and transfer of GLUT4 to the cell surface and increase the level of glucose clearance in these cells even in the IR state in a manner independent of insulin by activating AMP-activated protein kinase (AMPK). The same mechanism might be happening in the uterus. AMPK is recognised as a key energy sensor and regulates cellular metabolism to maintain the energy homeostasis pathway (McInnes *et al.* 2006). Studies on the effects of quercetin on the elimination of IR in skeletal muscle have also shown that it can increase the expression of GLUT4 in skeletal muscle by inhibiting TNFα activity and inducing the overall somatic sensitivity to insulin (Anhê *et al.* 2012). Wang *et al.* (2012) also showed that quercetin increased the expression of GLUT4 through eliminating uterine inflammation. Quercetin has also been able to increase the expression of GLUT4 by improving the expression of ERα and oestrogen effects in the uterus. In addition, the effect of quercetin on improving ERα expression and increasing oestrogen effects in the uterus might be another probable mechanism for increasing GLUT4 expression that should not be ignored.

Metformin is a medication often prescribed for women with PCOS to help prevent diabetes. Some studies have shown that metformin improves carbohydrate metabolism, reduces proliferation and decreases Cytochrome P450-17 (CYP-17) expression in the follicular structures of androgenised rats (Mahamed *et al.* 2018). Metformin treatment also reduces the area taken up by degenerating ovarian follicles, the number of interstitial cells and the thickness of the endometrium, whereas it increases the number of endometrial glands (Mahamed *et al.* 2011) and could decrease the serum levels of androstenedione (Macedo *et al.* 2015). We showed that the therapeutic effects of quercetin on glucose metabolism in liver and endometrial gene expression operate by a different mechanism.

Conclusion

In conclusion, our data suggest that quercetin has a strengthening protective effect in PCOS and the results represent an actual success in PCOS therapy in both diabetes prevention and increasing fertility. A remarkable advantage of quercetin usage was the sharp reduction in IR and induction of GLUT4 and ERα expression, which was evident in gene studies, as well as the increase of folliculogenesis in the ovaries. Our results also showed a decrease in liver GK activity and an increase in HK activity. The ameliorative effect of quercetin improved the specific activity of these liver enzymes.

Conflicts of interest

The authors declare no conflicts of interest.

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