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Research article

Therapeutic potential of *Glycyrrhiza glabra* (licorice) in modulating metabolic and inflammatory parameters in women with PCOS

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Abstract

Aim: This study evaluated *Glycyrrhiza glabra* (licorice) supplementation's therapeutic efficacy in polycystic ovarian syndrome (PCOS) by assessing its impact on clinical and biochemical parameters, including metabolic and inflammatory markers.

Materials and methods: This randomized clinical trial evaluated Diane-35 plus crude licorice extract for improving symptoms in PCOS. Seventy five participants were randomly assigned to three groups: Diane-35 monotherapy (n=25), Diane-35-plus-licorice (450 mg twice daily; n=25), and health controls (n=25). Treatment lasted three months, with biochemical and clinical parameters assessed before and after therapy to determine therapeutic efficacy.

Results: Before treatment, PCOS patients showed higher body mass index (BMI; p=0.004), insulin resistance (p<0.001), fasting insulin, glucose, total cholesterol, and LDL (all p<0.001), with lower HDL. Furthermore, HbA1c was slightly reduced (p=0.012). IL-1β and TNF-α were elevated (p<0.001), while total antioxidant capacity (TAC) was unchanged. In the post-treatment, BMI was similar between the Diane-35 and Diane-35-plus-licorice group (p=0.07). The Diane-35-plus-licorice group showed greater reductions in insulin resistance, fasting insulin, total cholesterol, and IL-1β, with increased HDL and TAC, while TNF-α and LDL showed minimal change.

Conclusion: Licorice improved metabolic and inflammatory markers in PCOS, reducing insulin, HOMA-IR, glucose, lipids, IL-1β, and TNF-α, supporting its potential as adjunctive PCOS therapy.

Keywords

HOMA-IR, *Glycyrrhiza glabra*, IL-1β, PCOS, TNF-α, total antioxidant capacity

Introduction

Polycystic ovarian syndrome (PCOS) is the commonest endocrine disease in females. The condition is highly expressed through occasional menstruation, failure to get children in reproductive age, and other reproductive health issues. In its etiology, both hormonal imbalance and genetic predisposition are involved.[1] Information about the pathogenesis of PCOS is vital due to its multifactorial nature, which results from a variety of clinical manifestations and intricate interactions between genetic, hormonal, environmental, and lifestyle factors. A principal characteristic of the disorder comprises insulin resistance (IR), which is referred to as an inadequate and improper response to insulin.[2] Insulin resistance is independent of androgen levels, body fat distribution, and adiposity[3], and could occur in lean patients, also[4]. In PCOS women, insulin resistance is tissue-specific, and most of their tissues, such as skeletal muscles, adipocytes, and hepatocytes, are losing insulin sensitivity.[5,6]

Increasing evidence also highlights the role of chronic low-grade inflammation in PCOS. Inhibition of FSH and LH receptors is another effect of IL-1 that inhibits follicle development and ovulation.[7] TNF-α, as well as IL-1β, inhibits stimulation of hepatic nuclear factor (HNF) in several possible ways. Using the broader Rotterdam 2003 criteria (requiring any two of hyperandrogenism, oligo-anovulation, or polycystic ovaries on ultrasound), prevalence of PCOS rises to 12–18% in many populations.[8] Women affected by PCOS have experienced an increase in endometrial cancer, cardiovascular disease, dyslipidemia, and type-2 diabetes mellitus.[9] According to recent diagnostic data, there appears to be an odd correlation between the manifestation of PCOS and autoimmune activities.[10] Current pharmacological management, such as combined oral contraceptives (e.g., Diane-35) and insulin-sensitizing agents like metformin, provides symptomatic relief but is limited by side effects, incomplete symptom control, or lack of long-term effectiveness.[6] These limitations underscore the need for complementary or adjunctive approaches that target both metabolic and inflammatory pathways.

Glycyrrhiza glabra, also known as licorice, forms the trademark of the family of Fabaceae and has played a significant role as the basis of traditional medicine. Its use in the treatment of cuts, in the reduction of pain, in the symptomatology of the cough, and in gastrointestinal problems is documented in literature. Numerous bioactive substances found in the plant's roots, including flavonoids, sterols, gums, starches, and essential oils, have been described by the biochemical profile. The sterols, or the so-called phytoestrogens, have been found to support the hypolipidemic effect, hence reducing the circulating triglycerides and cholesterol.[11] World Health Organization (WHO) confirms that the licorice has low toxicity profile and lists it as a demulcent in the therapeutic use of sore throats and bronchial catarrh.[12] Phytoestrogens, flavonoids, and anti-inflammatory agents are all abundant in licorice, which is linked to its medicinal properties.[13] Some of these constituents have been shown to possess biological properties, such as antibacterial, antiviral, anti-inflammatory, and antioxidant properties. Furthermore, licorice exhibits anticancer, hepatoprotective, and antiproliferative properties in addition to its ability to cure wounds and prevent ulcerative colitis and mucosal damage in gastric ulcers. Skin lightening, depigmentation, antiaging, and cognitive improvement are additional biological implications that have been noted.[14,15]

Aim

The present study aimed to evaluate the therapeutic potential of *Glycyrrhiza glabra* (licorice) in combination with Diane-35 in improving clinical, metabolic, antioxidant, and inflammatory parameters in women with PCOS.

Materials and methods

Patients

Between February 2023 and March 2025, a therapeutic randomized control study was carried out in the Department of Gynecology, Obstetrics, and Infertility of the Al-Imamain Al-Kadhimain and Baghdad Teaching Hospitals. The study involved a sample of 75 females, 25 of whom were found to be healthy and 50 were diagnosed with PCOS by a specialist gynecologist using the Rotterdam criteria 2003 (ESHRE/ASRM, 2004).[15] The participants were enlisted in the study following fulfillment of the following requirements: age range (20–40 years), marital status, and single status. Patients over 40 and under 20 years old, those with chronic illnesses (heart failure, diabetes mellitus), those with congenital adrenal hyperplasia, and those with Cushing syndrome tumors that secrete androgen, those with thyroid and autoimmune diseases were excluded from the study.

Data collection

To collect information through direct patient interviews, a structured questionnaire comprising four sections was created. The demographic information of patients, their medical history, obstetric and gynecological history, menstrual cycle pattern history (amenorrhea, oligomenorrhea, or polymenorrhagia), family history of PCOS, and any medications taken are included in the first section. The second section involved assessing the patients' body mass index. The third section contained ultrasound detection for preliminary information and tracking. Section four included laboratory analyses of HOMA-IR, HbA1c, insulin, fasting glucose, lipid profile (cholesterol, LDL, HDL, and TG), oxidative stress, and inflammatory markers (IL-1β, TNF-α), and total capacity antioxidant profile.

Study design and treatment

Three groups of participants were formed. The 25 women in Group 1 appeared to be in good health and showed no symptoms of PCOS. Group 2 consists of 25 patients who met the Rotterdam criteria for PCOS, which included two out of polycystic ovarian morphology, clinical or biochemical hyperandrogenism, and oligo/anovulation.[16] Diane-35® (ethinyl estradiol + cyproterone acetate 1 tab/day) was administered starting on the third day of the menstrual cycle for 21 days (repeated for 3 months). Group 3 consisted of 25 PCOS-diagnosed patients who were treated with Diane-35® (ethinyl estradiol + cyproterone acetate) once daily starting on the third day of their menstrual cycle for 21 days plus one capsule twice daily of crude extract of licorice (450 mg in each capsule) taken for 3 months.

Biochemical analysis

Enzyme-linked immunosorbent assay (ELISA) was employed to quantify serum insulin, IL-1β, TNF-α, and total antioxidant content, following the manufacturer's protocol. The level of fasting glucose, HbA1c, and lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) were measured using enzyme-based colorimetric tests on an automated analyzer (Selectra Pro; Elitech, France).

Ethical approval

On February 6, 2023, the Institutional Review Board (IRB) approved the study's protocol for revision of research ethics approval obtained from the College of Medicine, Al-Nahrain University (No.: 20221167). Before being included in this study, all participants provided informed consent. Patient privacy and anonymity were guaranteed, and patient data was used exclusively for research purposes. The Declaration of Helsinki's guidelines served as the study's foundation.

Statistical analysis

Microsoft Excel 365 and Statistical Package for the Social Sciences (SPSS; version 26) were used in data entry and analysis. The chi-square test was utilized in the presentation of categorical variables in the form of frequencies and percentages. An independent t test was utilized to compare the means. The results of the various parameters are presented in mean ± standard deviation (SD), and significance level was denoted as $p \leq 0.05$ or highly significant level denoted as $p \leq 0.001$.

Results

A comparative study on the apparently healthy controls and PCOS untreated patients was conducted. The findings provided evidence that there are considerable disparities in a number of anthropometric and metabolic values between both groups. As shown in **Table 1**, there is a statistically significant difference ($p=0.004$) in body mass index (BMI) between untreated PCOS patients and the control group (apparently healthy women). Also, fasting blood glucose, fasting insulin, and HOMA-IR significantly increased in PCOS compared to the control patients ($p<0.001$ in each of the parameters), indicating the presence of insulin resistance in PCOS patients. On the contrary, between the two groups, no statistically significant difference was observed in the level of HbA1c ($p=0.12$).

Table 1. Comparing the BMIs and insulin resistance parameters of an apparently healthy control group and patients with PCOS before treatment

Parameter	Group		*P*-value
	Apparently healthy control	Patients with PCOS	
	Mean ± SD	Mean ± SD	
BMI (kg/m^2)	24.32±3.73	28.00±4.80	0.004
HbA1c	5.49±0.23	5.38±0.24	0.12
HOMA-IR	1.78±0.28	6.17±1.13	<0.001
Insulin (mIU/l)	9.56±1.45	29.98±17.22	<0.001
FBS (mg/dl)	75.84±9.73	93.08± 9.69	<0.001

$p<0.05$: significant using independent t test; $p<0.001$: highly significant using independent t test; PCOS: polycystic ovarian syndrome; BMI: body mass index; HbA1c: hemoglobin A1C; HOMA-IR: homeostatic model assessment for insulin resistance; FBS: fasting blood sugar

In the meantime, the comparison of the inflammatory markers and lipid profiles of healthy controls and untreated PCOS patients prior to treatment showed that PCOS patients had significantly higher total cholesterol and LDL levels than the seemingly healthy control group ($p<0.001$ and $p<0.001$, respectively), as shown in **Table 2**. However, the HDL level in the PCOS group was abnormally low ($p=0.023$). The level of triglycerides in the two groups did not differ significantly ($p=0.76$). When inflammatory factors were taken into account, PCOS patients showed significantly higher levels of TNF-α and IL-1β than control subjects ($p<0.05$). However, there was no statistically significant difference in the groups' total antioxidant capacity (TAC) ($p=0.45$).

With the exception of the two-tailed p-value of 0.07, which indicates no significant difference, there was no significant difference in the BMI between the Diane-35-treated group and the Diane-35-plus-licorice-treated group, as depicted in **Table 3**. Regarding insulin resistance parameters, the Diane-35-plus-licorice-treated group significantly decreased both fasting insulin and HOMA-IR compared to the Diane-35-only group ($p<0.001$ for both), which indicated a greater degree of improvement in insulin sensitivity. Furthermore, it was observed that while there was no significant difference between the cohorts' HbA1c levels ($p=0.12$), the fasting blood glucose (FBS) levels of the Diane-35-plus-licorice group cohort did exhibit significant changes ($p=0.028$).

Table 4 shows that the Diane-35-plus-licorice-treated group significantly reduced the total cholesterol level compared to the group that received only Diane-35 ($p=0.005$). Furthermore, the Diane-35-plus-licorice-treatment group's HDL level increased ($p=0.005$), and their triglyceride levels significantly increased as well ($p=0.018$). The LDL levels in

Table 2. Comparing the lipid profiles and inflammatory markers of an apparently healthy control group and patients with PCOS before treatment

Parameter	Group		***P*-value**
	Apparently healthy control	Patients with PCOS	
	Mean ± SD	Mean ± SD	
Lipid profile			
Cholesterol (mg/dl)	129.60±15.34	153.68±17.15	<0.001
TG (mg/dl)	76.43±23.63	74.32±25.35	0.76
LDL (mg/dl)	73.60±13.80	93.56±19.82	<0.001
HDL (mg/dl)	40.76±7.60	36.60±4.57	0.023
Inflammatory markers			
IL-1β (pg/ml)	20.75±7.07	141.61±55.27	<0.001
TNF-α (pg/ml)	26.23±8.50	44.56±8.07	<0.001
Total antioxidant capacity profile (u/ml)	4.25±0.93	3.50±4.89	0.45

p<0.05: significant using independent t test; *p*<0.001: highly significant using independent t test; PCOS: polycystic ovarian syndrome; TG: triglycerides; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IL: interleukin; TNF: tumor necrosis factor

Table 3. Comparing the BMIs and insulin resistance parameters of the Diane-35-treated and Diane-35-plus-licorice-treated PCOS groups after treatment

Parameter	Group		***P*-value**
	Diane-35-treated	Diane-35-plus-licorice-treated	
	Mean ± SD	Mean ± SD	
Clinical parameter			
BMI (kg/m^2)	26.61±4.45	28.80±4.07	0.07
Insulin resistance parameter			
HbA1c	5.39±0.29	5.26±0.26	0.12
HOMA-IR	3.00±0.40	2.18±0.28	<0.001
Insulin (mIU/l)	12.96±1.75	10.13±1.20	<0.001
FBS (mg/dl)	90.11±3.97	87.36±4.57	0.028

p<0.05: significant using independent t test; *p*<0.001: highly significant using independent t test; PCOS: polycystic ovarian syndrome; BMI: body mass index; HbA1c: hemoglobin A1C; HOMA-IR: homeostatic model assessment for insulin resistance; FBS: fasting blood sugar level.

the two groups did not differ significantly (*p*=0.75). Regarding the inflammatory markers, the levels of IL-1β showed a significant reduction in the Diane-35-plus-licorice group compared with the Diane-35-only group (*p*<0.001). TNF-α levels in the Diane-35-plus-licorice-treatment group showed a decreasing trend, but this trend was not statistically significant (*p*=0.08). Additionally, compared to the Diane-35 group, the total antioxidant capacity of the Diane-35-plus-licorice group showed highly significant improvements (*p*=0.04), as presented in **Table 4**.

Discussion

The current research showed that the difference between the mean BMI of women having PCOS before the treatment and of the healthy control group was statistically significant. This increased BMI prevalence among PCOS patients is consistent with existing research that consistently shows a strong link between PCOS and being overweight or obese.[17,18] Obesity, especially central or visceral obesity, contributes to the worsening of clinical symptoms of

Table 4. Comparing the lipid profiles and inflammatory markers of the Diane-35-treated and Diane-35-plus-licorice-treated PCOS groups after treatment

Parameter	Group		*P*-value
	Diane-35-treated	Diane-35-plus-licorice treated	
	Mean ± SD	Mean ± SD	
Lipid profile			
Cholesterol (mg/dl)	194.96±11.85	186.72±7.64	0.005
TG (mg/dl)	74.40±9.06	81.00±10.02	0.018
LDL (mg/dl)	131.32±10.75	130.60±4.04	0.75
HDL (mg/dl)	46.56±2.16	50.52±6.30	0.005
Inflammatory markers			
IL-1β (pg/ml)	99.92±18.38	53.31±25.20	<0.001
TNF (pg/ml)	49.30±8.16	48.70±13.23	0.08
Total antioxidant capacity profile (μ/ml)	5.55±4.45	6.23±2.25	0.04

$p<0.05$: significant using independent t test; $p<0.001$: highly significant using independent t test; PCOS: polycystic ovarian syndrome; TG: triglycerides; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IL: interleukin; TNF: tumor necrosis factor

PCOS, such as insulin resistance, hyperandrogenism, and ovulatory dysfunction.[19]

These findings demonstrated the importance of weight control as a fundamental component of PCOS treatment and long-term medication. The group that received Diane-35 and licorice in our study showed a significant improvement in BMI after therapy, which may have been caused by the mineralocorticoid effect of licorice. Given that licorice tends to cause water retention rather than an increase in body fat, the amount was not statistically significant, but it is consistent with other studies that have demonstrated that licorice consumption may result in mild weight gain.[20,21] Glycyrrhizic acid found in *Glycyrrhiza glabra* inhibits 11β-HSD2, and this leads to the inhibition and blocking of the loading of cortisol, enhancing the activity of mineralocorticoid receptors and possibly raising weight and BMI values. It causes pseudo aldosteronism, fluid retention, hypertension, and hypokalemia as reported in a previous study.[22]

The study found that women with PCOS displayed significant metabolic dysregulation prior to therapy, indicating a significant correlation between insulin resistance and PCOS pathophysiology.[23] Elevated insulin levels indicate compensatory hyperinsulinemia, caused by diminished insulin sensitivity in peripheral tissues, which contributes to hyperandrogenism and ovulatory dysfunction.[24] The Diane-35-plus-licorice group showed positive changes in glycemic and insulin-resistance markers, including a slight decrease in HbA1c, improved insulin sensitivity, and a modest decrease in fasting blood glucose. These findings are consistent with those of Hooshmandi et al.[25] In the same vein, a 2018 trial conducted on overweight individuals (both sexes) revealed a substantial decrease in insulin and HOMA-IR as a result of the supplementation of desiccated licorice extract with dietary modifications.[26]

These clinical observations are substantiated by mechanistic insights from animal models. For instance, in a mouse model of PCOS, glycyrrhizin reversed insulin resistance and enhanced glucose tolerance.[27] A 2023 systematic review suggests that licorice, a fruit with mineralocorticoids, may improve glucose homeostasis and insulin secretion, potentially aiding hormone-based treatment in PCOS. However, more extensive trials are needed to confirm these findings.[28] Women with PCOS exhibit significant dyslipidemia, primarily due to insulin resistance, which increases total cholesterol and LDL-C levels and reduces HDL-C levels.[29,23] Lipid metabolism exhibited a multifaceted response pattern in the Diane-35-plus-licorice group. A favorable shift in cardiovascular risk markers was indicated by a significant reduction in total cholesterol levels ($p=0.005$) and a significant increase in HDL ("good" cholesterol) ($p=0.005$). It was also observed that LDL ("bad" cholesterol) levels decreased, although the difference was not statistically significant ($p=0.75$).

Diane-35, an estrogenic component, significantly increased triglyceride levels ($p=0.018$) by stimulating the production of very-low-density lipoproteins (VLDL) in the liver.[30,31] The treatment's ability to balance antiandrogenic and estrogenic effects may be indicated by the concurrent increase in HDL and decrease in total cholesterol. These results are consistent with prior research that has indicated that Diane-35 may enhance certain lipid parameters while potentially deteriorating others, particularly TG.[32] Moreover, the literature is inconsistent regarding the impact of licorice on lipid metabolism; some studies report cholesterol-lowering effects, while others demonstrate minimal or even adverse effects on TG.[25,33]

In the current study, both IL-1β and TNF-α were significantly elevated in women with PCOS compared to the control group (p=0.001 for both). These findings support the growing evidence that chronic low-grade inflammation is a key component of PCOS pathophysiology.[34,35] Similarly, IL-1β is involved in the inflammatory response and has been implicated in ovarian dysfunction by disrupting folliculogenesis and steroidogenesis.[36] Increased IL-1β can also exacerbate oxidative stress and worsen systemic inflammation, further contributing to endocrine and metabolic derangements in PCOS. The current study has attempted to examine the anti-inflammatory effects of both Diane-35 and licorice in women with PCOS. The finding of the post-intervention demonstrated a statistically significant decrease in IL-1β levels (p<0.001), indicating a successful anti-inflammatory effect. This is consistent with earlier research showing that glycyrrhizin, the active component of licorice, can inhibit the NF-κB signaling pathway and prevent pro-inflammatory cytokines.[37,38]

A notable increase in the total antioxidant concentration was observed in the Diane-35 + licorice-treated group compared to that of Diane-35-only (p=0.04). Such a finding shows that there might be some antioxidant effect of *Glycyrrhiza glabra* as a supplementary therapy in PCOS management. The PCOS is associated with an increase of oxidative load and the breakdown of antioxidant defense, which contributes to metabolic and reproductive dysfunction.[39,40] Due to licorice extract's potent antioxidant qualities, which have been previously shown in animal studies, it can improve the ovarian morphology, oocyte quality, and reproductive outcomes of PCOS models produced in these studies.[38-41] According to the study conducted by Kalantari-Hesari et al. (2020),[42] the treatment of ovarian tissue with licorice was associated with histological improvements and implied the ability to reduce oxidative damage. Moreover, in-depth reviews and clinical examinations assume that the supplementation of antioxidants can benefit the level of insulin resistance, lipid evaluation, or female sexual hormone balance with PCOS.[43] As a result, the TAC trend observed in this study may also be proof of the synergistic effects of licorice as a medicinal ingredient that strengthens antioxidant machinery and helps PCOS patients overcome problems associated with oxidative stress.

Conclusion

The present research demonstrated that Diane-35-plus-licorice improved metabolic, inflammatory, and antioxidant parameters in women with PCOS compared to Diane-35 alone. Licorice reduced insulin resistance, glucose, cholesterol, and IL-1β, while enhancing HDL and antioxidant capacity, suggesting potential as an adjunctive therapy. However, the study was limited by its modest sample size, short intervention period, and absence of a licorice-only treatment arm. Future research should include larger, multi-center randomized trials with longer follow-up durations to validate these findings, establish optimal dosing, and assess licorice as a standalone therapy.

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None.

Ethical statements

On February 6, 2023, the Institutional Review Board approved the study's protocol for revision of research ethics approval obtained from the College of Medicine, Al-Nahrain University (No.: 20221167). The authors declared that all participants provided informed consent. Patient privacy and anonymity were guaranteed, and patient data was used exclusively for research purposes.

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

Data availability

All data used are referenced or included in the article.

Conflict of interest

The authors declare that they have no conflict of interest and no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Author contributions

R.A.A., F.D., and I.R.A contributed to the design and implementation of the research; R.A.A., A.R.L, and I.R.A - to the analysis of the results and to the writing of the manuscript; R.A.A. conceived the original and supervised the project.

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