ORIGINAL ARTICLE

Effect of chamomile capsule on lipid- and hormonal-related parameters among women of reproductive age with polycystic ovary syndrome

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Background: According to traditional herbal medicine, chamomile has been considered as one of the herbal remedies for patients with polycystic ovary syndrome (PCOS). The study aimed to investigate the effect of chamomile on lipid and hormonal parameters in women of reproductive age with PCOS. **Materials and Methods:** This study is a randomized clinical trial which was conducted on 80 women (40 patients in each group) of childbearing age with PCO. The intervention group received 370 mg oral capsules of chamomile three times a day for 3 months. The control group did receive starch capsule (three times a day). Hormonal and lipid parameters were examined before and 3 months after the intervention. **Results:** The mean age of the patients was 22.40 ± 5.10 and 24.38 ± 6.14 years in the intervention and control groups, respectively. Decreased level of testosterone was observed in the intervention group (in women with PCOS) who received chamomile capsules (P = 0.017). A significant difference was not seen in low-density lipoprotein cholesterol level (P = 0.249), high-density lipoprotein cholesterol (P = 0.073), triglycerides (P = 0.603), the hormone dehydroepiandrosterone sulfate (P = 0.423), and the ratio of luteinizing hormone/follicle-stimulating hormone (LH/FSH) in the experimental and control groups after the intervention (P = 0.420). **Conclusion:** According to the findings, oral administration of chamomile capsule caused a significant decrease in total testosterone levels in these patients. However, no significant change was reported with lipid parameters, the ratio of LH/FSH, and dehydroepiandrosterone sulfate level.

Key words: Chamomile herb, dyslipidemia, hirsutism, polycystic ovary syndrome

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age (for almost 6%–18%).[1,2] The prevalence of PCOS in Iran, according to the NIH, is 7%; according to the Rotterdam criteria it is 15.2%, and finally, according to the criteria of polycystic ovary association and androgen excess, it is 7.92%.[3] Its clinical symptoms include reproductive disorders, metabolic disorders such as dyslipidemia, hypertension, insulin resistance (IR), compensatory hyperinsulinemia, gestational and type 2 diabetes, increased risk of cardiovascular morbidity, and mental signs.[2,4] This syndrome has been associated with various symptoms of dyslipidemia and more than 70% have at least one abnormal level of fatty acid.[5] Increased level of lipids was reported among women with PCOS in the study of Wild *et al*.[6] as well as Valkenburg *et al*.[7] This increase was reported in the study conducted by Akbarzade *et al*.[8] No treatment has been reported for this syndrome.[9] The treatment of PCOS depends on its symptoms.[10] Weight loss,[11] oral contraceptives pills, cyclic progestin,[12] spironolactone, and finasteride

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are used to improve the symptoms by androgen rise.[11] Oral contraceptives can increase the IR, heart, and endocrine-related side effects[13,14] in addition to its positive effects. Metformin also has side effects such as nausea and vomiting, diarrhea, bloating and abdominal pain, loss of appetite and metallic taste, deficiency of vitamin B12, and lactic acidosis.[14-17] Complementary medicine is one of the most common treatments for a variety of diseases, including PCOS.[10,18] The use of complementary medicine has been rising during the last 10 years for about 26%–91% and includes many items such as herbal remedies, reflexology, and acupuncture.[10,19] Chamomile plant has been used as a medicine for decoction in stomach upset, indigestion, diarrhea, nausea and urinary inflammation, and painful menstruation.[20] There are two main types of chamomile, Roman and German. Both types are used in traditional medicine though the German type is much more common in medical sciences.[21] The main ingredients of chamomile are amino acids, polysaccharides, fatty acids, essential fats, minerals, flavonoids, and other phenolic as well as coumarone compounds and phytoestrogens.[22,23] The effect of flavonoids on the central nervous system has been studied for the past 10 years. In particular, the study conducted by Medina in 1989 indicated the ability of some flavonoids in connection with central benzodiazepine receptors.[24] Rafraf *et al*. indicated the effect of chamomile tea, which significantly reduces HbA1c (P = 0.03), serum insulin levels (P = 0.001), total cholesterol, triglycerides (TGs), and low-density lipoprotein (LDL) cholesterol compared to the control group.[25] Romualdi *et al*. evaluated the effects of soy isoflavone on 12 women with PCOS, obesity, dyslipidemia, and hyperinsulinemia. The results showed that adjuvant phytoestrogen significantly improved the level of total cholesterol, LDL, and TG. It also decreased the LDL/high-density lipoprotein (HDL) ratio.[26] According to the study conducted by Khani *et al*. (2011) on the influence of phytoestrogens on hormonal and metabolic parameters in women of reproductive age who have PCOS, genistein led to improved lipid- and hormonal-related parameters, which hurtled metabolic and coronary heart disease.[27] Chamomile has phytoestrogen as well as those herbs. Therefore, considering the importance of menstrual and metabolic disorders in patients with PCOS, most studies have been conducted on the prevalence of syndrome and these disorders. The researcher decided to use chamomile regimen (effective on menstruation), by making possible changes in hormonal hormones and also possibly by creating positive estrogen feedback on pituitary, hypothalamus, and luteinizing hormone (LH), and menstrual disorders decrease. The aim of the study was to investigate the effect of chamomile capsule on lipid- and hormonal-related parameters among women of reproductive age who have PCOS.

MATERIALS AND METHODS

This study is a randomized clinical trial. According to a previous study,[28] and considering the study purpose and hypotheses, the sample size was calculated to be 45 for each group, Confidence interval: 95%, significance level (alpha) of 0.05 and effect size of 0.6 and power = 1 − β = 80, by applying the following formula. But until the end of the study, 40 people remained in each group [Figure 1].

$$n = \frac{2\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 SD^2}{(\mu_2 - \mu_1)^2}$$

The samples were selected through convenience sampling and randomly allocated using stratified block randomization in the two intervention (chamomile capsules) and control groups. Since the participants were divided into 2 groups in this study, two-therapy method was used and classification was performed as follows: (a) chamomile capsules group and (b) control group. The study used a single-blind design; to keep the study blind from the participants, we marked the drug and placebo with the same weight, shape, and the same manner of consumption. The study population included all women of reproductive age who referred to Shiraz Clinics of Medical Science. A sample of 90 women with a diagnosis of PCOS was obtained through medical records (chemical and clinical criteria, sonography record by specialized endocrinologist). Patients were categorized into two groups by single-blind technique, intervention group (chamomile capsules) and the second group which included 45 patients (placebo). However, only 80 patients remained at the end of the study. Inclusion criteria were women of childbearing age (15–45)[29,30] who were willing to cooperate in this study, written consent, approved diagnosis of PCOS, no history of liver, gastrointestinal and renal disease, and no history of seizure, asthma, allergy, cancer (particularly breast cancer), and hormonal drugs since 1 month ago, and besides, PCO patients received any therapy like metformin during the study. Exclusion criteria included allergic reaction to medications, inability to continue taking the drug (for any reason), and lack of willingness to cooperate. The study tool was a demographic form, which contained information about menstruation, measured lipid parameters (TGs, cholesterol, HDL and LDL cholesterol, the ratio of LH/follicle-stimulating hormone (FSH), and testosterone–total testosterone, and dehydroepiandrosterone sulfate (DHEAS). Both chamomile and placebo capsules were produced in the Pharmacology Department in Shiraz University of Medical Sciences under the supervision of a pharmacology professor and research project consultant. According

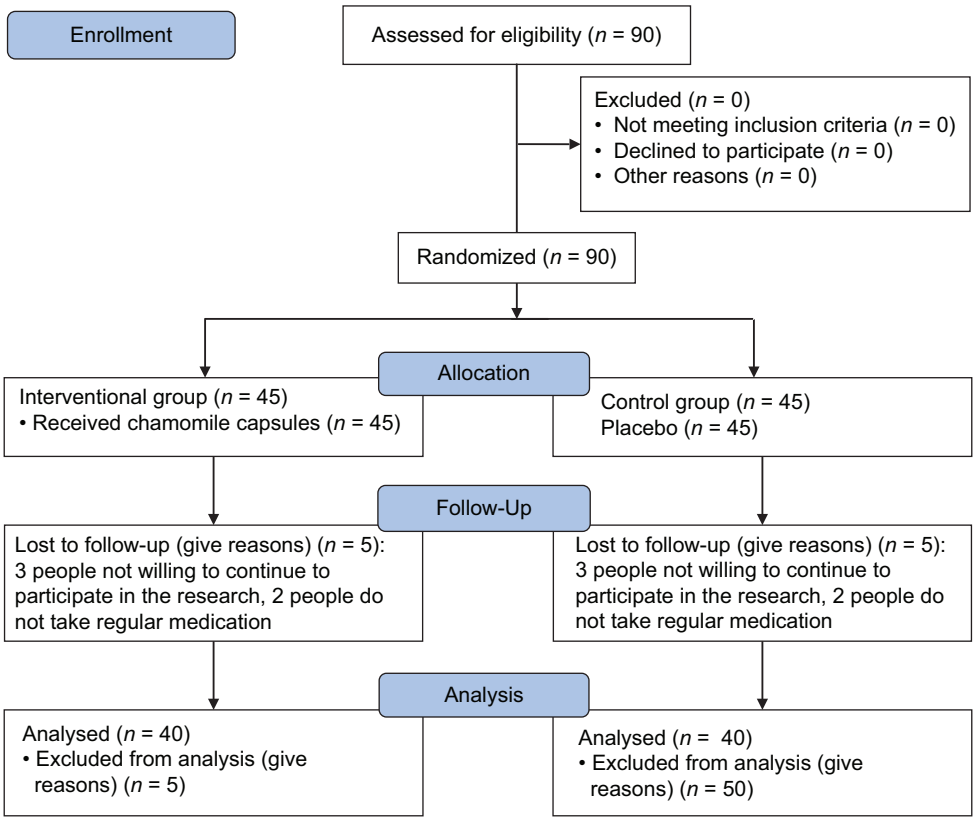

Figure 1: Flowchart of the participants throughout the intervention

to previous studies and a pharmacologist's views, the chamomile capsules containing 370 milligrams were produced (derived from dried flowers of German chamomile by Barij companies of oil essence). Placebo capsules, also weighing 370 mg, were similar to chamomile capsules in appearance and weight, but they contained starch-based inert material. After informed written consent was taken, demographic data form was completed. Blood sampling (10 ml) was performed to measure the lipid and hormonal components including TGs, cholesterol, HDL and LDL cholesterol, the ratio of LH/FSH, and testosterone–total testosterone, and DHEAS. Blood samples were kept in proper condition (at a temperature of below 70-Celsius degree). In the intervention group, chamomile capsules containing 370 mg were prescribed three times a day (morning, afternoon, and evening) for 12 weeks. The prescription time and route was the same as the control group with placebo. The patients received a phone call weekly, which reminded them about their regular drug consumption. The second blood sampling was done after 12 weeks. The last blood analysis was done at the end of the study. Blood analysis was done in Namazi Hospital laboratory. Pars photometric diagnostic kits were used to measure HDL cholesterol (normal value ≥35 mg/dl), TGs (normal <200 mg/dl, borderline: 200–400 mg/dl, abnormal value >400 mg/dl) and LDL cholesterol (normal value ≥130 mg/dl, borderline: 130–160 mg/dl, the abnormal >160 mg/dl). DRG kit was used to measure DHEAS with ELISA method. DiaSource kit was used to measure both testosterone and LH/FSH ratio with radioimmunoassay and immunoradiometric methods, respectively.

After the approval process by Shiraz University of Medical Sciences Ethics Committee (6989) and clinical trial registration (IRCT2014060217958N1), written consent was obtained. A proper time and place were set for the participants' interview and study tool distribution. They were assured of the researcher's respect for their right for withdrawal from the study at any stage and their identity which would remain confidential.

Statistical analysis

Finally, SPSS statistical software (version 16; SPSS Inc., Chicago, IL, USA) was used to analyze the data. Independent *t*-test was used for comparing body mass index (BMI) and age in both groups before the intervention. Normality was assessed by Shapiro–Wilk test. Repeated measure ANOVA was applied to analyze the laboratory data. The assumption of repeated measure ANOVA was evaluated and confirmed. Furthermore, paired *t*-test was used in testosterone calculation due to the significant interaction between time and group. Besides, $P < 0.05$ was considered as statistically significant.

RESULTS

The mean age of the patients was 22.40 ± 5.10 and 24.38 ± 6.14 years and the mean of BMI patients were 24.68 ± 3.68 and 24.80 ± 4.87 kg/m^2 in the intervention and control groups, respectively. BMI and age in both groups were homogeneous before the intervention [Table 1]. LDL level was reduced after 3 months of intervention in both intervention and control groups. However, the difference between the two groups was not statistically significant (P = 0.249).

The average level of HDL cholesterol was 39.20 ± 8.12 mg/dl before the intervention, and it reached 41.57 ± 10.43 mg/dl after the intervention. This difference was not statistically significant (P = 0.073).

The average level of TG was 117.05 ± 58.53 mg/dl before the intervention, and after treatment, it reached 108.77 ± 60.87 mg/dl. This difference was not statistically significant in both groups after 3 months of the intervention (P = 0.603) [Table 2].

According to hormonal parameters analysis, the average level of LH/FSH ratio was 1.85 ± 1.51 MIu/Ml before the intervention and 1.70 ± 0.72 MIu/Ml after it. Despite the fact that a slight increase was reported after the intervention from 1.60 ± 0.93 MIu/Ml (preintervention) to 1.64 ± 0.85, this difference was not statistically significant in both groups (P = 0.420) [Table 2].

In the intervention group, a decrease was found in the average level of testosterone from 0.67 ± 0.430 (preintervention) to 0.58 ± 0.33 ng/ml. However, no change was observed from 0.54 ± 0.10 (preintervention levels) to 0.54 ± 0.15 ng/dl in the placebo group. Since the interaction of time/groups in the testosterone variable was significant, analysis was done by groups. The results showed that testosterone decreased in the intervention group (P = 0.017); F (1, 38) = 6.285). However, no significant changes were observed in the control group (P = 0.901) [Table 2].

The average level of DHEAS hormone increased from 1.82 ± 0.83 (preintervention) to 1.90 ± 0.81 µg/dl (postintervention). In addition, this increase was observed in the placebo group from 1.69 ± 0.78 (preintervention) to 1.75 ± 0.84 µg/dl. This difference was not statistically significant (P = 0.423). Thus, according to the study results, chamomile consumption leads to a significant decrease of serum testosterone hormone in women with PCOS. The slight increase of DHEAS was not significant in both groups [Table 2].

Table 1: General characteristics of patients with polycystic ovary syndrome at baseline (n=40)

Group characteristic	Mean±SD		P
	Control	Intervention	
Age (year)	24.38±6.14	24.38±6.14	0.122
BMI (kg/m^2)	24.80±4.87	24.68±3.68	0.888

SD=Standard deviation; BMI=Body mass index

DISCUSSION

According to the study results, chamomile consumption caused a decrease in the serum LDL cholesterol and TGs and an increase in the HDL cholesterol in women with PCOS although this change was not significant compared to the control group. Rafraf *et al*. conducted a study to evaluate the effect of chamomile tea on glycemic control and serum lipid parameters in 64 patients with type 2 diabetes. The level of total cholesterol, serum LDL cholesterol, and TGs significantly decreased compared to the control group. However, no significant change was found on HDL cholesterol levels in both groups.[25] Thus, the result of this study was inconsistent with Rafraf M (2015) about LDL cholesterol and TGs. Johary *et al*. (2011) conducted a study to evaluate the effect of chamomile hydroalcoholic extract on hormonal changes and ovarian tissue of 45 rats. Although there was a difference in weight loss between the control and intervention groups, the weight loss was not significant in the intervention group and decreased body weight was only found in high doses of chamomile. Another study

Table 2: Lipid and hormonal profiles of the two groups before and after intervention

Group characteristic	Mean±SD				Repeated measurement		
	Control		Intervention				
	Before	After	Before	After	Time* (P)	Interaction time × group (P)	Group (P)
LDL (mg/dL)	91.30±22.64	88.95±20.54	97.77±27.58	94.15±22.17	0.042	0.660	0.249
HDL (mg/dL)	43.47±10.43	44.67±10.28	39.20±8.12	41.57±10.43	0.002	0.297	0.073
TG (mg/dL)	109.82±59.76	103.40±48.58	117.05±58.53	108.77±60.87	0.083	0.826	0.603
LH/FSH (MIU/ML)	1.60±0.93	1.64±0.72	1.85±1.51	1.70±0.72	0.705	0.536	0.420
TES (ng/ml)	0.54±0.10	0.54±0.15	0.67±0.43	0.58±0.33	0.029	0.022	0.199
P**	0.901		0.017				
DHEAS (µg/dl)	1.69±0.78	1.75±0.84	1.82±0.83	1.90±0.81	0.253	0.921	0.423

*Repeated measurement, **Paired t-test. SD=Standard deviation; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; TG=Triglycerides, FSH=Follicle-stimulating hormone; LH=Luteinizing hormone; TES=Testosterone; DHEAS=Dehydroepiandrosterone sulfate

was done by Johary to explain the effects of chamomile on lipid oxidation rise and its absorption control, which was consistent with this study for its effect on lipid parameters. So, in the study of Johary and colleagues Phytoestrogens exist in the hydroalcoholic extract and carried by lipoproteins in the mice plasma. These compounds reduce the level of cholesterol and LDL cholesterol by 10% and 20%, respectively.

In addition, phytoestrogen leads to inhibition of progesterone metabolizing enzyme, 20-alpha-hydroxysteroid dehydrogenase and increase the progesterone hormone. Some phytoestrogen compounds that control this enzyme contain 3-alpha7-hydroxy flavon, 3- and 7-dihydroxyflavone and flavones. Progesterone increase leads to an increase in basal metabolism and it can be the possible reason of weight loss in the experiment group. The sterols in chamomile plant stimulate lipid catabolism in the mice cells. It can finally reduce and control the cholesterol absorption. The mice treated by chamomile hydroalcoholic extract had weight loss. Phytosterols presented in the extracts of chamomile enhance dehydroepiandrosterone, which is slightly produced in the liver. The chamomile hydroalcoholic extract contains ascorbic acid, which promotes weight loss, prevents weight gain, and reduces the amount of cholesterol.[22] Phytosterols have some compounds similar to cholesterol, which can interfere with the cholesterol absorption to decrease LDL cholesterol and TG levels 31).

In addition, phytoestrogens can regulate cholesterol homeostasis by increasing the secretion of fecal bile acid, modifying bile acid synthesis, and increasing the secretion of the liver cholesterol.

Recent evidence suggests that phytoestrogens can significantly decrease the cardiovascular disease by its impact on lipid profiles. A double-blind study showed that phytoestrogens can improve the blood pressure and lipid profile.[31] Flavonoids inhibit the oxidation of LDL; thus, it inhibits the synthesis of atherosclerosis plaque.[22] According to the result of the current study on hormonal parameters, the difference of the LH/FSH was not statistically significant in both intervention and control groups ($P = 0.420$).

According to Karampour *et al*. results in 2014, in a study on the effect of fennel extract on rats with PCOS, fennel increased the serum levels of FSH and decreased the LH hormones. Fennel plant treats to the same as chamomile for its estrogenic properties, the active ingredients of phytoestrogens and coumarin.[32] In this study, we used LH/FSH ratio due to the patients' oligomenorrhea and their interrupting follicular or luteal phase at blood sampling time. After the intervention, although an improvement was reported in this ratio, it was not statistically significant.

According to the results of Johari *et al*., hydroalcoholic extract of chamomile had no effect on the LH and FSH hormones.[22] Daniel Romualdi *et al*. evaluated the effects of soy isoflavone (which has the same active phytoestrogens as chamomile) on patients with the polycystic ovary. It showed that no change was reported in the gonadotropin level after 6 months of treatment with phytoestrogens.[26]

According to the above studies, the following conclusions are made: long-term use of herbal extracts with phytoestrogens ingredient can have negative feedback on LH and testosterone levels, respectively. Thus, reduced androgen leads to less generation of LH and lower dominant influence of LH to FSH.[32] Endocrine studies on mice have shown that some neuronal compounds are responsible for the height of LH secretion in the preoptic area (POA). GnRH neurons in the POA are responsible for regulating the secretion of LH. Gamma-aminobutyric acid (GABA) neurotransmitter plays an important role in the control of gonadotropin secretion. Evidence suggests that reduced inhibitory effect of GABA on GnRH neurons leads to LH hormone secretion peak. Flavonoids, as benzodiazepines legend binding site, are proper drugs on GABA-amino butyric acid receptors to cause the beneficial effects on the central nervous system. Chamomile extract improves induced symptoms of PCOS in mice. Its potential mechanism is through the counter performance of GABA along with chamomile on LH secretion and regulation.[24]

In this study, chamomile consumption caused a significant decrease in the serum testosterone levels in women with PCOS.

The slight increase in the DHEAS hormone was not significant in both groups. According to the study conducted by Karampoor *et al*., fennel extract significantly reduced the testosterone levels in rats with PCOS.[32] Furthermore, Grant *et al*. (2010) investigated the antiandrogenic effect of mint tea on patients with PCOS. It revealed a significant reduction in levels of testosterone.[33] On the contrary, Romualdi *et al*. evaluated the effects of soy isoflavone on adrenal and ovarian androgens in patients with PCOS. After 6 months of intervention with phytoestrogens, no change was reported in the SHBG values.[26] The results of the present study are consistent with those of the study conducted by Romualdi on the unchanged level of DHEAS after the intervention. Unlike Romualdi's study, the current study revealed a significant fall in testosterone after 3 months of intervention with chamomile. Flavonoids, phytoestrogens, and coumarin are reported as the compounds in chamomile.[22,23]

Phytosterols can reduce the synthesis of androgen hormones, especially testosterone. Phytoestrogens reduce cytochrome P450 (cholesterol desmolase enzyme), which suppresses

the pregnenolone conversion from cholesterol. It finally reduces the synthesis of steroids, including testosterone. Phytoestrogens and coumarin, impose their function through the inhibition of anti-androgenic receiver complex, which reduces testosterone. The long-term use of herbal extracts that contain phytoestrogens can reduce the testosterone levels by a mechanism of negative feedback on LH.[32]

The limitations of this study included the participants' negligence about the proper use of capsules, so they were called to be reminded of the importance of accurate and timely medication. There was a risk of improper use of drugs, so sufficient explanation was done for prevention, but if the participants tried not to treat or obey according to the mentioned protocol in drug consumption, they were removed and replaced. Besides, based on the test repeated measurement, power analysis was performed using PASS software, which has the ability to perform repeated measurement for LDL, HDL, DHEAS, LH/FSH, and TG data between 0.59 and 0.88. Based on the power analysis (0.59), the number of samples for the LH/FSH parameter was not sufficient. However, the insignificant result of other variables was not related to the number of samples in the two groups. It is suggested that future research should focus on the impact of chamomile on the number of ovarian follicles growing in every cycle and ovulation in women with PCOS, and improvement of mature follicles' number per cycle. In addition, the impact of chamomile on anxiety in women with PCOS is suggested. Therefore, according to the results of the power analysis and the inadequacy of the sample size for one of the variables, it is recommended that subsequent studies should be done with a larger sample size.

CONCLUSION

The results showed that the chamomile consumption was effective and caused a significant decrease in total testosterone levels in women with PCOS. However, no significant change was reported with lipid parameters, the ratio of LH/FSH and DHEAS level.

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Conflicts of interest

There are no conflicts of interest.

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