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Comparing the therapeutic effects of 6-gingerol and hydro-alcoholic extract of ginger on polycystic ovary syndrome in Wistar rat

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ABSTRACT

Background and aims: PCOS (polycystic ovary syndrome) is the most common endocrine and metabolic disorder characterized by amenorrhea, hyper androgens, hirsutism, chronic anovulation and infertility. The aim of the present study was determining the effects of ginger extract, and 6-gingerol on hormonal levels and ovarian follicles in induced PCOS rats, and comparing the ameliorating effects of these two substances for treatment of PCOS.

Methods: In this experimental research, 42 adult female Wistar rats weighting between 160 g-180 g were divided into six groups of 7 animals. PCOS control that received no injection. PCOS received intraperitoneal injections of 100 mg/kg of ginger extract (for 28 days). Statistical analyses with SPSS, one-way ANOVA, T-test and Duncan test were used to compare groups.

Results: In comparison with PCOS control, the treatment of PCOS rats with ginger extract (100 and 200 mg/kg) and 6-gingerol (200 and 400 µg/kg) led to significant decrease in LH levels. There was a decrease in FSH levels, but the significant one was only in the 6-gingerol treated group (400 µg/kg). In PCOS treated groups with ginger extract and 6-gingerol, the serum levels of estradiol decreased significantly compared to control and PCOS control groups ($P<0.001$). Progesterone levels in PCOS groups injected with ginger extract and 6-gingerol showed a significant increase ($P<0.05$). In PCOS treated groups with ginger extract and 6-gingerol, testosterone levels decreased significantly ($P<0.001$, $P<0.01$, $P<0.05$).

Conclusion: 6-gingerol and ginger extract may be a useful treatment for improving the PCOS through reduction of estrogen, testosterone, LH and FSH, and improvement of ovulation. In fact, because of anti-inflammatory and antioxidant properties of ginger components, especially 6-gingerol, they can cause to improve PCOS.

Keywords: 6-Gingerol, Ginger, Polycystic Ovary Syndrome, Hormonal levels.

Original article

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INTRODUCTION

PCOS (polycystic ovary syndrome) is the most common endocrine and metabolic disorder characterized by amenorrhea, hyper androgens, hirsutism, chronic anovulation and infertility. In this syndrome, ovarian morphological abnormalities such as polycystic ovaries with small ovarian follicles producing predominantly androgens in thecal cells consider.

All PCOS women are at risk of insulin resistance, metabolic syndrome, endometrial hyperplasia and cardiovascular diseases. The exact etiology of PCOS is not entirely clear, although hypersecretion of LH and insulin resistance are known to be responsible for the pathogenesis of the syndrome. In PCOS women, insulin resistance and subsequent hyperinsulinemia may contribute to hyperandrogenism and abnormal gonadotropin levels.[1,2]

Ginger is the rhizomes of the plant *Zingiber officinale* belonging to the family zingiberaceae and has been cultivated for a thousand years as a cooking spice and flavoring agent in many Asian and African countries. Moreover, ginger possesses medical properties and widely used in the treatment of various disorders including headaches, vomiting, asthma, rheumatism, arthritis, gastrointestinal disturbances and diabetes. In addition, anti-tumor, anti-inflammation, anti-hepatotoxicity and anti-microbial properties that have been shown in recent.[3,4] The mechanism of chemo preventive effects of ginger is attributed to its antioxidant activities, free radical scavenging, alteration of gene expressions and induction of apoptosis resulting decrease in tumor promotion and progression.[5] 6-Gingerol is one of the major components of ginger which is responsible for its pungent taste (Figure 1), as well as ginger's most anti-oxidative and anti-inflammatory component.[6]

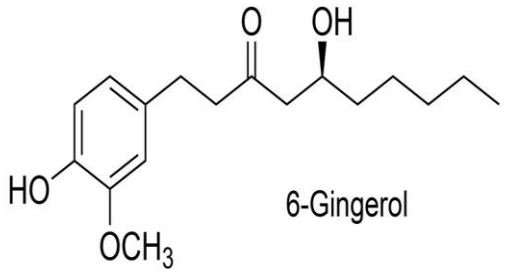

Figure 1: Chemical structure of 6-gingerol

Infertility is a widespread medical problem, defined as the inability to conceive without contraception after one year of regular intercourse. Approximately 30% of infertilities are due to female fertility problems. The most common causes of female infertility are ovulation problems often caused by PCOS. In fact, this is a disorder with hormonal imbalance affecting the normal ovulation.[7] Given the importance of the infertility treatment and the main role of PCOS in the pathogenesis of anovulation and infertility, the aim of the present study was determining the effects of ginger extract, and 6-gingerol on hormonal levels and ovarian follicles in induced PCOS rats, and comparing the ameliorating effects of these two substances for treatment of PCOS.

METHODS

Estradiol valerate and 6-Gingerol were purchased from Abraham Co. (Iran) and Sigma- Aldrich Co. (USA), respectively. Rat Estradiol and Progesterone ELISA kits were purchased from Monobind Co. (USA), and serum concentration of Testosterone, FSH and LH were measured using rat/mouse testosterone, FSH and LH ELISA kits from Cosmo Bio Co. (Japan).

42 adult female Wistar rats weighting between 160 g-180 g were purchased from the Pasteur Institute of Tehran, Iran. The rats were kept in temperature controlled room (23 °C), exposed to a 12-hour light/dark cycle, and they fed with normal diet and sufficient water. To adapt to the environment, the rats were kept under the above conditions for 14 days. To control, regular estrous cycle, daily vaginal smear was prepared for 2 weeks. After 14 days of acclimatization, the rats were divided into 6 groups of control and PCOS treated groups.

The rats were divided into 6 groups of 7 animals as follows: Group C: Control without treatment. PCOS control that received no injection. Group PCOS-G_{100}: PCOS received intraperitoneal injections of 100 mg/kg of ginger extract (for 28 days); Group PCOS-G_{200}: PCOS received intraperitoneal injections of 200 mg/kg of ginger extract (for 28 days); Group PCOS-$6g_{200}$: PCOS received intraperitoneal injections of 200 µg/kg of 6-gingerol (for 14 days); Group PCOS-$6g_{400}$: PCOS received intraperitoneal injections of 400 µg/kg of 6-gingerol (for 14 days).

4 mg estradiol valerate (EV) in 0.4 ml oil/rat is injected subcutaneously for 28 days. To confirm the induction of syndrome at the end of injection course, blood samples was taken via heart puncture and two rats of PCOS group were sacrificed, then, hormonal and morphological studies were performed.

The fresh rhizomes of ginger were purchased from the local markets of Tehran, Iran. The ginger rhizomes were cleaned, washed, dried at room temperature and powdered by electric grinder. To prepare hydro-alcoholic extract, 150 grams of ginger powder were soaked with 1500 ml of 70% ethanol in the Soxhlet apparatus for 48 hours. Then the rotary evaporator was used to concentrate and dry the extract. Afterwards, in order to dissolve the extract and prepare the specified concentrations distilled water was used. 6-gingerol also was dissolved in distilled water to prepare treatment doses.

At the end of treatment duration, the rats were anaesthetized and blood samples were taken via heart puncture. To separate the serum, blood samples were allowed to clot and centrifuged at 12000 RPM for 5 min. The serum concentrations of estradiol, progesterone, testosterone, LH and FSH were measured by ELISA kits according to the manufacturer's instruction.

Ovaries were dissected apart and fixed in 10% formaldehyde. The fixed samples were kept in alcohol solutions for dehydration and cleared in xylene, and then embedded in paraffin. The samples were sectioned serially in 7 micron thickness by microtome and finally stained with hematoxylin and eosin.

Statistical analyses with SPSS, one-way ANOVA, T-test and Duncan test were used to compare groups ($P<0.05$). The results were expressed as the mean ± standard deviation (SD). Finally, graphs were plotted by Excel software.

RESULTS

In PCOS control group, the LH, FSH, estradiol and testosterone hormones showed a significant increase compared to control group ($P<0.01$). Progesterone levels decrease in the PCOS group compared to control group, but this reduction was not significant. Histological studies showed that, in the PCOS control group the number of corpora lutea decreased, and the number of cystic follicles, increased significantly, while in the control group the ovaries were lacking cystic follicles, and possessed a great number of corpora lutea. These observations indicated that EV injection led to decrease in the number of active follicles and subsequently decreased ovulation (Figure 2).

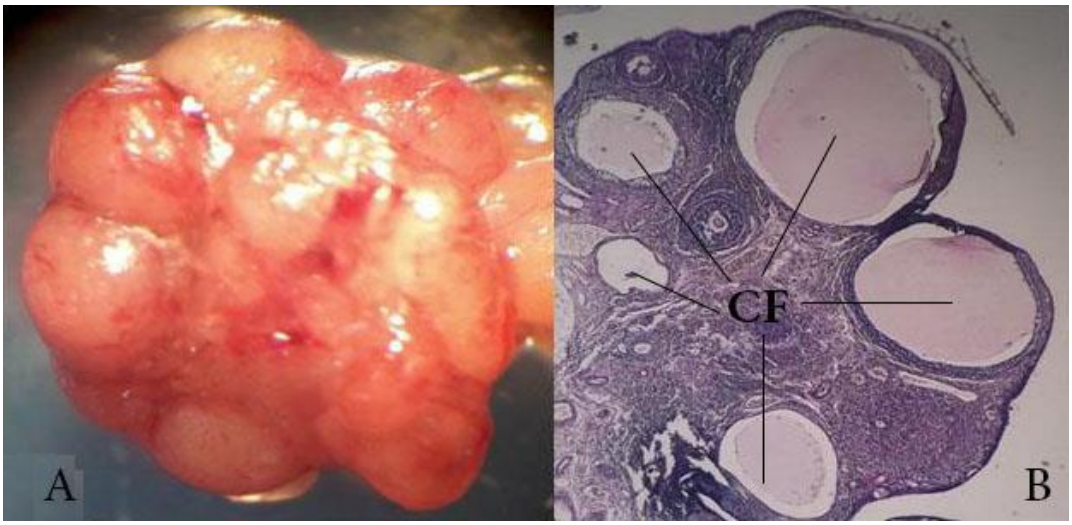

Figure 2: The macroscopic (A) and microscopic (B)

View of rat ovary, that induced by subcutaneous injection of EV. Increase of cystic follicles (CF) and decrease of corpus luteum is observed. The ovary sections were stained by haematoxylin and eosin.

In comparison with PCOS control, the treatment of PCOS rats with ginger extract (100 and 200 mg/kg) and 6-gingerol (200 and 400 µg/kg) led to significant decrease in LH levels. There was a decrease in FSH levels, but the significant one was only in the 6-gingerol treated group (400 µg/kg). In PCOS treated groups with ginger extract and 6-gingerol, the serum levels of estradiol decreased significantly compared to control and PCOS control groups ($P<0.001$). Progesterone levels in PCOS groups injected with ginger extract and 6-gingerol showed a significant increase ($P<0.05$). In PCOS treated groups with ginger extract and 6-gingerol, testosterone levels decreased significantly ($P<0.001$, $P<0.01$, $P<0.05$). These results have shown in Table 1.

Table 1: The values of estradiol, progesterone, testosterone, LH and FSH in the studied groups

Groups	E2 (ng/ml)	P4 (ng/ml)	T (ng/ml)	LH (ng/ml)	FSH (ng/ml)
Control	0.0386±0.003	2.29±0.015	3.1±0.1	3.24±0.41	18±1.62
PCOS control	0.0465±0.004 (+++)	2.12±0.181	4±0.26 (+++)	4.27±0.83(+++)	22.5±2.43(+++)
PCO-G100	0.0461±0.003 (+++)	2.25±0.056	3.83±0.11 (+++)	3.95±0.66(+++)	21.15±1.89
PCO-G200	0.0451±0.001 (+++)	2.24±0.0137	3.8±0.1 (+++)	3.78±0.42(+++)	20.27±1.13
PCO-6g200	0.0430±0.005 (+++**)	2.34±0.076	3.6±0.1 (+++*)	3.73±0.55 (+++***)	18.45±1.62(**)
PCO-6g400	0.404±0.002(***)	2.48±0.036 (***)	3.36±0.15 (***)	3.55±0.6(***)	17.1±1.67(***)

*Values are Mean ± Standard deviation (Mean ± SD); PCOS induction led to a significant increase in FSH, LH, E2 and T versus control rats; These treatments led to a significant decrease in T, E2, FSH and LH, also a significant increase in P4 levels in PCOS treated groups, compare to PCOS control group. E2: Estradiol, P4: Progesterone, T: Testosterone, LH: Luteinizing hormone, FSH: Follicle stimulating hormone; +: P<0.05, ++: P<0.01, +++: p<0.001; Differences between PCOS control group and PCOS treated groups with the control group. *: P<0.05, **: P<0.01, ***: P<0.001; Differences between PCOS treated groups with ginger extract and 6-gingerol and PCOS control group.*

In PCOS groups treated with ginger extract and 6-gingerol, the number of ovarian cysts showed a significant decrease compared to PCOS control group which means no cysts were observed in PCOS groups treated with doses of 6-gingerol (200 and 400 µg/kg). Comparing to PCOS control, moreover, the number of primary, preantral, antral follicles as well as corpus luteum increased in PCOS treated groups with ginger extract and 6-gingerol. Therefore, these changes indicated relative improvement of ovarian function in PCOS treated groups (Figure 3).

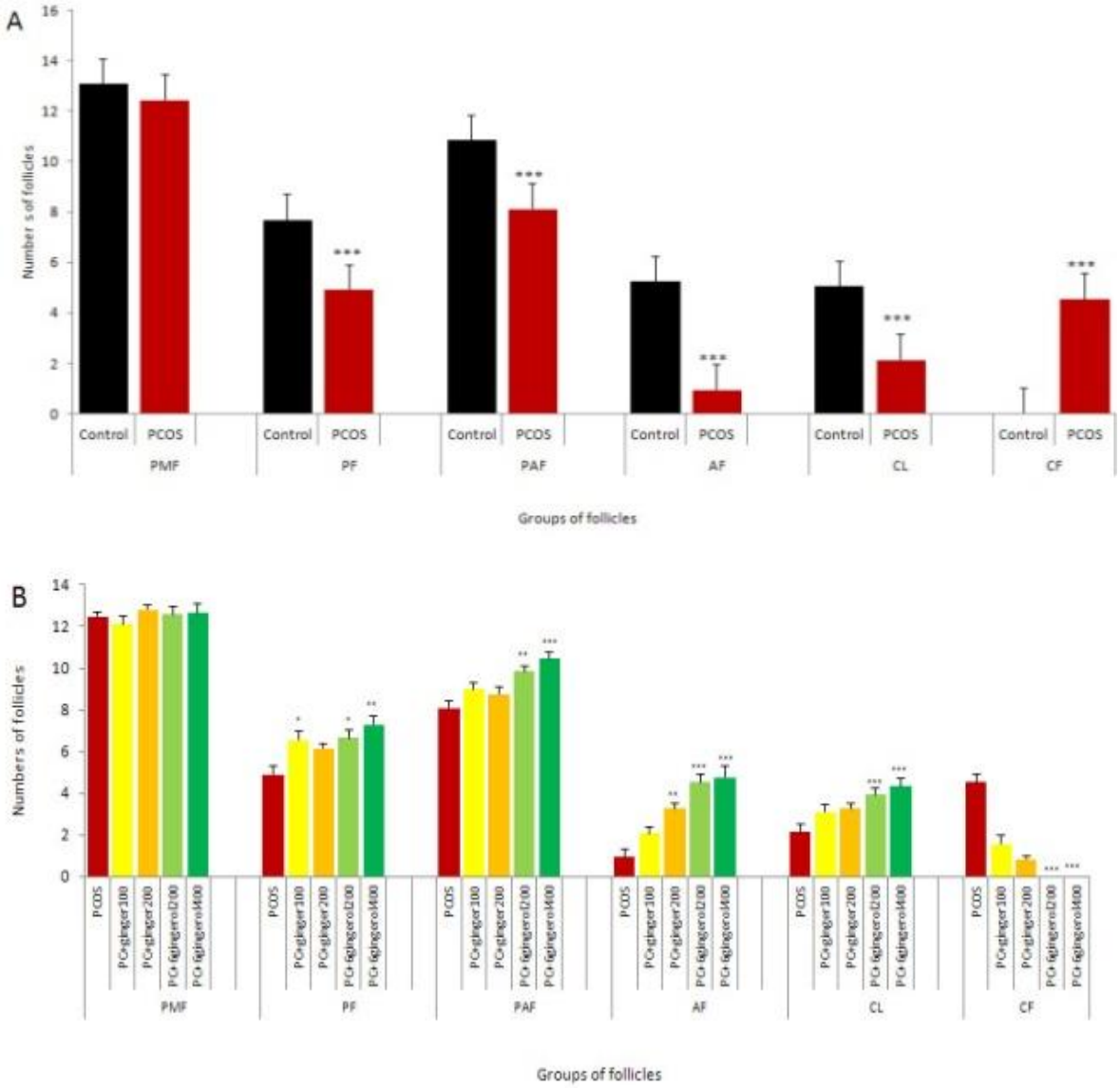

Figure 3: Diagrammatic comparison of follicles in control, PCOS control and PCOS treated groups with ginger extract and 6-gingerol

*PMF: Primordial follicle; PF: Primary follicle; PAF: Parenteral follicle; AF: Antral follicle; CL: Corpus luteum; CF: Cystic follicle; A: Differences between PCOS group and control group; B: Differences between PCOS treated groups with ginger extract and 6-gingerol, and PCOS control group. *: P<0.05, **: P<0.01, ***: P<0.001.*

DISCUSION

In this research, PCOS was induced in adult female Wistar rats by intraperitoneal injection of EV for 28 days. Data showed that after induction of PCOS, serum testosterone, estradiol, FSH and LH levels increased, while progesterone levels were decreased in the PCOS groups compared to those in control. Microscopic studies showed an increase in the number of cystic follicles and a decrease in corpora lutea in polycystic ovaries. These findings also corroborated with the findings of Kargar Jahromi et al, Ghafurniyan et al and Zafari et al.[8-10]

In PCOS groups, the elevated LH levels are explained by an increased pituitary sensitivity to hypothalamic gonadotropin releasing hormone (GnRH), and increased pulse frequency of GnRH which may cause the production of LH over the FSH.[11] Increasing amount of insulin in PCOS lead to the decrease of liver production of two important proteins: Insulin-like growth factor–binding proteins (IGFBP I, II) and Sex hormone binding globulin (SHBG) and consequently led to an increase in the concentrations of IGF I, II and sex steroid level, thus IGF I and II augment androgen production by LH stimulation via ovarian IGF receptors. On the other hand, a decrease of SHBG led to an increase of free estradiol. The excess of estrogen in PCOS is also caused by peripheral conversion of androgens to estrogens, especially by fat tissue. In addition, increased levels of LH lead to an increase in the production of androgens from the theca cells.[12,13] In fact the LH stimulation caused the thickness of the theca cell layer leading to androgen hypersecretion by increasing the expression of the key enzymes in androgen synthesis. In addition, elevated insulin levels are common in PCOS bringing about an increase in LH-stimulated androgen production in polycystic ovaries.[14] According to the previous studies, it was stated that in PCOS women, high levels of FSH caused to form the ovarian cysts, in fact, elevated androgens in this condition lead to increase in GnRH neurons activities via the changes in gamma amino butyric acid ergic (GABA ergic) transmission and finally causes to increase of FSH secretion from pituitary.[15,16]

Low serum progesterone levels in PCOS were associated with reduction of corpora lutea because the follicles don't release the egg and become cysts in these ovaries.[17] In polycystic ovaries, the number of antral follicles is lower than normal ovaries. In fact, there is a positive correlation between high levels of androgen and preventing small follicles to become mature.These high androgen levels and follicular cell stimulation by LH and insulin might produce high levels of cyclic adenosine monophosphate (CAMP) in the granulosa cells, which causes premature terminal differentiation and arrest follicular growth.[18] The serum concentrations of FSH, LH, estradiol and testosterone in the PCOS groups treated with ginger extract and 6-general show significant decrease compared to PCOS control group; however, the level of progesterone significantly increased in the PCOS treated groups.

The obtained results showed reduction in the number of ovarian cysts, and increase in corpora lutea and antral follicles. It's worthy to mention that all changes in this research were dose dependent, and the effects of 6-gingerol treatment in comparison to ginger extract were more significant in all parameters. The reason which can be stated for a decrease of gonadotropins by ginger extract and 6-gingerol is that ginger and its compounds reduce the secretion of FSH and LH via an effect on pituitary-gonadal axis.[19] Researchers suggested that gingerols and sesquiterpens in ginger via inhibition of cyclooxygenase

and lipooxygenase pathways cause to inhibition of the arachidonic acid and prostaglandin synthesis. Considering the role of prostaglandins in gonadotropin synthesis, gingerol can decrease gonadotropin levels in this way.[20,21] Other studies showed that, due to its action as a serotonin receptor antagonist, ginger can decrease the secretion of gonadotropin. Previous studies indicated that serotonin mediates the secretion of GnRH by direct stimulation of hypothalamus to release GnRH through the phospholipase C (PLC) pathway.[22] On the other hand, many studies showed that GABA regulation of GnRH neurons affects the regulation of LH surge.[15] Many studies showed that some flavonoids bind to the benzodiazepine site of the GABAA receptor.[23,24] Thus we can say the flavonoids of ginger act as GABA receptor agonists, and cause to a decrease in LH secretion. Ginger and its active components like 6-gingerol cause to decrease in testosterone levels via reduction of blood glucose and insulin levels, and also through the decrease of LH levels and changes in pituitary-ovaries axis.[25] Biosynthesis of estrogens from androgens are done by Aromatase enzyme. In fact, Aromatase is a cytochrome P450 enzyme, and inhibited by 6-gingerol causing to the reduction of estrogen levels.[26]

Since PCOS is one of the inflammatory response in the body, it is shown that ginger and its active components like 6-gingerol decrease the levels of proinflammatory cytokines (IL-1β, IL-6, TNFα).[27] In addition, one of the anti-inflammatory effects of ginger and gingerol is inhibition of NF-kβ (Nuclear factor kappa β). NF-kβ is the most important factor in causing inflammation in the body that controls the production of other cytokines (TNFα, IL-1, IL-6), and important inducer of NF-kβ is oxidative stress.[28-30]

CONCLUSION

The present study is the first comparing the effects of 6-gingerol and ginger extract on recovery of PCOS. The results showed that 6-gingerol and ginger extract may be a useful treatment for improving the PCOS through reduction of estrogen, testosterone, LH and FSH, and improvement of ovulation. In fact, because of anti-inflammatory and antioxidant properties of ginger components, especially 6-gingerol, they can cause to improve PCOS. Their effects are dose dependent and the therapeutic potential of 6-gingerol is more effective than the ginger extract.

AUTHORS'CONTRIBUTION

Pournaderi and Yaghmaei designed the study and executed the experiments, Hejazi prepared and studied the tissue samples, Khodaei analyzed the sera, Noormohammadi analyzed the data.

CONFLICT OF INTEREST

The authors state no conflict of interest regarding the content of this article.

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