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Review Article

The Therapeutic Effects of Cinnamon on Polycystic Ovary Syndrome: A Review

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Abstract

Polycystic Ovarian Syndrome (PCOS) is a common female gynecological endocrinopathy disorder with ages ranging from 18 to 45 years. PCOS significantly increases the risk of infertility, cardiovascular diseases, and type II diabetes in women. Cinnamon has a strong history of decreasing insulin resistance and treatment of PCOS. Therefore, we aim to review the effects of the cinnamon herb and extract on changes in the serum levels of sex hormones and ovarian tissue, metabolic activity, lipid profile, and insulin resistance.

Keywords: Cinnamon, Insulin resistance, Lipid profile, Polycystic ovary syndrome.

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Background

Polycystic Ovarian Syndrome (PCOS) is a common female gynecological endocrinopathy disorder with ages ranging from 18 to 45 years (1-3).

Patients with PCOS present different problems, including reproductive abnormalities (4), atherogenic dyslipidemia (5,6), coronary heart disease (7), increased risk for type 2 diabetes mellitus (8), marked insulin resistance (9), eating and sleeping disorders (10), and anxiety and depression (11).

The symptoms of PCOS include metabolic disorders (dyslipidemia, insulin resistance, and type 2 diabetes), changes in endocrine hormones (decreased level of progesterone versus increased levels of prolactin, estrogen, and androgen), and clinical ones (baldness, acne, hirsutism, menstrual disorders, and infertility) (12). A meta-analysis was conducted on 30 studies with a total sample size of 19, 226 women with PCOS that listed prevalence rates of its clinical symptoms (Table 1) (13).

In people with PCOS, the blood levels of androgens increase (14). Moreover, compared to healthy women, conversion of androgenic precursors into testosterone is more in patients with PCOS. Subsequently, the high levels of androgens, especially testosterone in PCOS, cause several problems, including lack of ovulation, disrupted synthesis of sex hormones, and dysfunction of the genital tract in the patients. They can lead to infertility in women of reproductive age (15,16).

The rates of PCOS prevalence, according to the diagnostic criteria of National Institutes of Health (NIH), Rotterdam, and AE-PCOS Society in the world were 6, 10, and 10%, respectively (17). In Europe, the prevalence rate of PCOS is 5.6–8%, while it is 6.8, 19.5 and 4.41% according to NIH, Rotterdam, and ultrasound methods, respectively, in the United States. Also, it is 6.8% and 19.5% based on the NIH and Rotterdam, respectively, in Iran (13). Among PCOS women, infertility occurs in approximately 75% of the cases (18).

Table 1. Prevalence rates (%) of clinical symptoms in Iranian women.

Clinical symptom	Prevalence rate (%)
Menstrual disorders	28
Infertility	8
Androgenic alopecia	9
Hirsutism	13
Obesity	19
Overweight	21
Acne	26

The three most widely used drugs, including tamoxifen, clomiphene citrate, and metformin, are currently applied to treat PCOS (19). They have side effects, and treatment of PCOS by them is relative; therefore, it is essential to identify and develop alternative and novel drugs or approaches for the treatment of PCOS (2).

Based on many previous studies, a wide spectrum of herbs can be applied to improve various aspects of PCOS. Several herbs can improve some adverse effects of PCOS, such as menstrual and ovulatory dysfunctions, lipid-metabolism dysfunction, insulin resistance, obesity, and androgen excess-related conditions (20). Among these, *Cinnamon spp.* showed promising effects on PCOS by various mechanisms. There are several studies that have shown the beneficial application of cinnamon extract to the treatment of PCOS side effects. Due to the increasing prevalence of PCOS and its association with physical and mental problems, this study aimed to review and document the effects of cinnamon extract on serum levels of lipid profile, insulin resistance, and sex hormones as well as ovarian tissue in women with PCOS.

Cinnamon extract

Cinnamon is one of the oldest known herbs; the four major economic species are *C. cassia*, *C. burmannii*, *C. loureiroi*, and *C. verum* (21). Cinnamon is mainly produced in China, Sri Lanka, Seychelles, and Madagascar and little scale in Vietnam and India (about 27,000-35,000 annual tons) (22).

Cinnamon is the traditional folk herb used for diabetes mellitus in Korea, China, Russia, and Iran (23). The chemical composition of cinnamon has been characterized previously (24,25). Cinnamaldehyde is the principal constituent of the bark (65-80%) (26), and eugenol is the primary component in extracts from the leaf (70-95%) (24). Other constituents in cinnamon comprise phenolic acids, coumarin, cinnamyl alcohol, tannins, carbohydrates, and terpenes (25). Table 2 shows the nutrient content of cinnamon.

Table 2. Nutrient content of cinnamon (22).

Nutrient Types	Constituent	Value
Macronutrients (per 100 *gm*)	Energy	247 *kcal*/ 1035 *KJ*
	Protein	3.99 *g*
	Total fat	1.24 *g*
	Carbohydrate	3.6 *g*
	Ash	80.59 *g*
Minerals	Calcium	1002 *mg*
	Iron	8.32 *mg*
	Magnesium	60 *mg*
	Phosphorus	60 *mg*
	Potassium	431 *mg*
	Zinc	1.83 *mg*
	Copper	0.339 *mg*
	Manganese	17.466 *mg*
Vitamins	A	295 IU
	B1 (Thiamine)	0.002 *mg*
	B2 (Riboflavin)	0.041 *mg*
	B3 (Niacin)	1.332 *mg*
	B5 (Pantothenic acid)	0.558 *mg*
	C	3.8 *mg*

Cinnamon has benefits in improving problematic blood glucose regulation resulting from type 2 diabetes and obesity, improved insulin resistance, lower blood cholesterol concentrations, and blood pressure (27). Also, cinnamon's antioxidant, anti-inflammatory, and antimicrobial activity have been shown previously (27). *Cinnamon spp* can reduce the adverse effects of PCOS. There are several review papers about cinnamon benefits (28,29), but in this article, we review the benefits of cinnamon treatment, particularly in women with PCOS.

Metabolic dysfunction

The treatment of metabolic dysfunction by herbs represents promising results in women with PCOS. Previous studies showed that cinnamon and its active ingredients (*e.g.* eugenol, cinnamic acid, cinnamate, and cinnamaldehyde) have several therapeutic effects on the metabolic syndrome factors, such as dyslipidemia and obesity (22), high blood glucose, and insulin resistance (30).

Anti-insulin resistance

Insulin resistance (found in 50–70% of the patients with PCOS) is one of the factors found in the development of PCOS (31).

According to a follow-up that lasted over ten years, the prevalence of diabetes was 5.0% in controls compared with 39.3% in PCOS patients of similar age (32). Also, insulin resistance has increased rates in women with PCOS compared to controls, and the absolute rates of insulin resistance were 65% in normal-weight women with PCOS and 95% in obese women with PCOS (33, 34). Insulin sensitizing agents (*e.g.* metformin and thiazolidinediones) have been used to treat patients with PCOS (35). Insulin sensitizing agents have been shown to significantly reduce insulin resistance and androgen levels and improve menstrual irregularity, ovulatory function, and some inflammatory markers in women with PCOS (36-38). However, they have

multiple safety concerns. For example, in patients at risk for fractures, bladder cancer, congestive heart failure, or other adverse cardiovascular effects, it is recommended that thiazolidinediones be used cautiously according to current treatment guidelines [American Diabetes Association (ADA) 2014] (39). Also, metformin, the most widely used drug in PCOS, is often poorly tolerated due to gastrointestinal side effects of nausea (61%), vomiting (30%), and diarrhea (65%) (39-41). Several clinical trial studies show that metformin treatment reduces the absorption of the B12 vitamin, and subsequently, causes anemia (42,43).

Wang *et al* showed that oral administration of ~1000 *mg*/day of cinnamon extract for eight weeks to fifteen women with PCOS improved insulin sensitivity in nondiabetic women with PCOS (44).

A double-blind, randomized, controlled trial conducted by Jain *et al* revealed that administration of 3 *g*/day of the cinnamon extract can significantly reduce fasting blood glucose (p=0.001) and glycosylated hemoglobin (p=0.023) in comparison with the placebo group (2500 *mg*/day of wheat flour) (45).

Eighty women with PCOS were treated with cinnamon powder capsules 1500 *mg*/day and placebo group for 12 weeks. The results showed that fasting insulin and insulin resistance were significantly reduced in the treated group with cinnamon (30).

One hundred and twelve girls (12.6-17 years old) with PCOS were treated with the cinnamon extract (1000 *mg*/day), metformin (1000 *mg*/day), or placebo (46). The results indicated that cinnamon, as well as metformin, significantly improved both quantitative insulin sensitivity check index (p<0.01) and homeostasis model insulin resistance index (p<0.005) in comparison to placebo (46).

More, Borzoei *et al* demonstrated that cinnamon extract (1500 *mg*/day) significantly decreased serum fasting blood glucose, insulin, and homeostatic model assessment for insulin resistance at sample group compared to the placebo group (all p<0.05) (47).

Cinnamon supplementation in patients with PCOS caused significantly reduced fasting insulin (p=0.024) and HOMA-IR (p=0.014) of the participants after the intervention in comparison with the placebo group (48).

Improving the lipid profile

In particular, alterations of the lipid profile affect up to 70% of the patients with PCOS. Several interrelated pathological processes seem to contribute to dyslipidemia instauration: among others, obesity, insulin resistance, and hyperandrogenism.

A clinical trial was conducted on 84 overweight or obese patients with PCOS aged 20-38 years that were treated with 1500 *mg*/day cinnamon or placebo for eight weeks. The results indicated that cinnamon extract significantly improved serum level of total cholesterol, Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL)- cholesterol (p<0.05) (49). In another similar study with this team, administrating cinnamon extract as a capsule dosage form (1500 *mg*/day) for eight weeks on overweight or obese patients of PCOS was investigated (47). Results showed that serum triglyceride decreased in the cinnamon group compared to baseline values (p=0.001) (47).

Also, 66 patients with PCOS were randomly allocated to be treated with cinnamon powder as 1500 *mg*/day and placebo for 12 weeks. Cinnamon powder administration significantly reduced LDL compared with the placebo group (p=0.049) (48).

Cinnamon extract administrated to adolescent girls (12.6–17 years old) with PCOS caused a reduction in apolipoprotein B: apolipoprotein A1 ratio (46). The results revealed that cinnamon extract makes the balance between atherogenic (LDL, Lp(a), IDL, and VLDL) and antiatherogenic (HDL) lipoproteins.

Modulating the hormones

Regulation of the hypothalamic-pituitary-ovary axis is abnormal in patients with PCOS. Both follicular theca cells and follicular granular cells are required to produce steroid hormones such as estrogen and progesterone. In addition, previous studies indicated that cinnamon extract could increase estrogen and progesterone hormones at a dose of 50 and 200 *mg* (50). It may be related to increasing LH secretion, leading to increased synthesis of estrogen and progesterone (51). According to the previous research, cinnamon as different forms (extract, powder, and supplement) influenced the hormonal status as well as menstrual cycles (20,30,44).

Anti-Mullerian hormone (AMH) is a transforming

growth factor-β, and recently, it was found that AMH has contributed to PCOS. Serum AMH levels may increase up to 3× higher in the patients with PCOS compared to the control group that may be related to follicular arrest (52,53). The cinnamon extract causes the reduction of AMH. It showed fewer side effects in comparison with metformin (53).

Oxidative stress

In patients with PCOS, one of the possible therapeutic mechanisms of herbs is reducing oxidative stress. Numerous studies have described the antioxidant impacts of cinnamon as one of the therapeutic mechanisms.

In one study, cinnamon supplement treatment with a dose of 1500 *mg*/day for eight weeks considerably reduced malondialdehyde (MDA) level (p=0.014) and increased the total serum antioxidant capacity (p=0.005) at the patients with PCOS (49). The MDA molecule is a lipid peroxidation marker that is a secondary lipid peroxidation product (54). MDA reduction indicates the antioxidant effects of cinnamon.

Moreover, several studies represented the antioxidant effects of cinnamon by increasing total antioxidant capacity, increasing glutathione synthesis, improving the activity of antioxidative enzymes such as superoxide dismutase and glutathione peroxidase, and decreasing MDA and lactate dehydrogenase (55-57).

Improving menstrual cyclicity

Herbal medicines can improve reproductive dysfunctions and balance menstrual cycles. The menstrual cycle varies from 21 to 35 days (average duration of 28 days) among adult women (58).

Dou *et al* demonstrated that cinnamon extract treatment for 20 days restores the cyclicity and ovary morphology in the PCOS mice model induced by dehydroepiandrosterone (59).

The effect of cinnamon supplementation during the six-month intervention on menstrual cyclicity on 46 women with PCOS was investigated (34). The results indicated that menstrual cycles improved from baseline and were more frequent in the sample treated group compared to the placebo group (p=0.0085) (34).

In the clinical trial study, the effect of consumption of cinnamon powder for 60 days on the menstrual cycle pattern of 20 women with PCOS aged 18-42 years was investigated. Improvement in the menstrual cycle pattern (51.9%, from baseline menstrual cyclicity) was observed in the treated group by 3000 *mg*/day of cinnamon bark powder (60). In addition, a notable change was observed in ovarian size. More, complete amelioration was reported in 7 patients in the test group. These results show the activity of cinnamon upon the ovarian tissue. The authors suggested that cinnamon may be clinically useful as an alternate therapy for PCOS management, especially in patients with menstrual disturbances in PCOS (60).

Body Mass Index (BMI) and body weight

In most patients with PCOS, obesity and abnormal fat distribution are usually present. Polyphenolic compounds of cinnamon species have anti-obesogenic effects. There are several studies that represent the cinnamon effects on BMI and body weight (45,61). Salehpour *et al* showed that two years of treatment of girls with an age range of 12.6-17 years old with cinnamon extract (500 *mg*) significantly decreased BMI compared to placebo (p<0.05) (46). Furthermore, a 16-week double-blind, randomized, controlled trial on 116 patients with PCOS indicated that consumption of 3000 *mg*/day of the cinnamon extract led to significant decreases of waist circumference (p=0.002) and BMI (p=0.001) in comparison to the placebo group (45).

Combination with other herbal extracts

The cinnamon extract can be utilized in combination with other herbal extracts to manage PCOS complications. Administrated cinnamon along with *Paeonia lactiflora* Pall., *Hypericum perforatum* L., and *Glycyrrhiza spp*. for three months to patients with PCOS led to a reduction in oligomenorrhoea of 32.9% compared to controls (p<0.01) (62). Approximately 122 women contributed to this study. Women in the sample group recorded significant improvements in BMI (p<0.01), insulin (p=0.02), blood pressure (p=0.01), Luteinizing Hormone (LH) (p=0.04), pregnancy rates (p=0.01), quality of life (p<0.01), depression, anxiety and stress (p<0.01) (62).

Administration of *C. zeylanicum* Blume and *Nigella sativa* L. can substantially decrease the serum level of FBS, insulin, insulin resistance, cholesterol,

triglyceride, and LDL levels (30,34,49). It should be noted that this reduction occurred by all forms of *Cinnamomum cassia,* including supplements (34,49), powder (30), and extract (44). Cinnamon seems to have greater efficacy when used over 12 weeks (20).

In addition, administration of *C. burmanii* and *Lagerstroemia spesiosa* L. for six months reduced the patients' BMI considerably (53).

A randomized controlled trial was conducted to evaluate combination therapy of cinnamon with metformin for six months in controlling PCOS symptoms in 175 patients (61). In this study, voluntaries were divided into two groups of A with 89 cases (metformin 500 *mg*) and B with 86 cases (metformin 500 *mg* + cinnamon extract 336 *mg*). The results showed that cinnamon supplements with metformin significantly reduced weight, oligomenorrhea/amenorrhea (regular menstrual cycles) (p=0.00), and BMI (p=0.00) as well as Waist/Hip ratio (p=0.00) (61).

Recently, Permadi *et al* introduced an herbal combination of *C. burmanii* and *L. spesiosa* extract (DLBS3233) for improved lipid profile and insulin sensitivity and free testosterone of women with PCOS and high BMI. This study was conducted on sixty-two patients with PCOS. The results revealed that DLBS3233 reduced triglycerides, homeostatic model assessment of insulin resistance (HOMA-IR), and free testosterone (63).

Adverse effects

Previous studies reported minimum side effects with administrated cinnamon ≤1500 *mg*/day. Also, three months of treatment with *C.burmanii* and *C.cassia* showed no complications (30,53). Additionally, the adverse effects attributed to cinnamon resolved after a short withdrawal period (62).

Conclusion

Cinnamon, as a valuable compound for overcoming metabolic syndrome, shows a promising alternative for PCOS treatment. Also, cinnamon's antioxidant and anti-inflammatory effects can improve oxidative stress in patients with PCOS. Previous studies revealed the improvement of menstrual cyclicity in the treated group with cinnamon, which may be related to modulating hormones or reducing oxidative stress. Cinnamon has several beneficial effects on PCOS, but further studies are required to comprehend the mechanistic reasons for the apparent benefits of cinnamon supplementation in PCOS treatment.

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Conflict of Interest

The authors have no conflict of interest.

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