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

Alireza Valizadeh1,2, Shamsali Rezazadeh3, Ali Hanafi2, Zohreh Tarassoli2, Ahmad Shamabadi4 and Ladan Kashani5*

1. Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Research & Development, Samanik Salamat Gostar co., Tehran, Iran
3. Medicinal Plants Research Center, Institute of Medicinal Plants, Academic Center for Education, Culture and Research, Karaj, Iran
4. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
5. Infertility Ward, Arash Women’s Hospital, Tehran University of Medical Sciences, Tehran, Iran

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.

* Corresponding author
Ladan Kashani, MD
Infertility Ward, Arash Women’s Hospital, Tehran University of Medical Sciences, Tehran, Iran
Email: kashani_ladan@tums.ac.ir

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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).

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, *Cinnamomum 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. cassinia, 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 1.** Prevalence rates (%) of clinical symptoms in Iranian women.

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>Prevalence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual disorders</td>
<td>28</td>
</tr>
<tr>
<td>Infertility</td>
<td>8</td>
</tr>
<tr>
<td>Androgenic alopecia</td>
<td>9</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>13</td>
</tr>
<tr>
<td>Obesity</td>
<td>19</td>
</tr>
<tr>
<td>Overweight</td>
<td>21</td>
</tr>
<tr>
<td>Acne</td>
<td>26</td>
</tr>
</tbody>
</table>
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

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Table 2. Nutrient content of cinnamon (22).

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

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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