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The Effects of Cinnamon on Polycystic Ovary Syndrome

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ABSTRACT

Background & Aim: Polycystic ovary syndrome (PCOS) is a major endocrine disorder in young age women affecting their health-related quality of life (HRQOL) and their mental well-being as well. In this review, the authors discuss the effect of cinnamon as an herbal medicine on PCOS in humans and introduce the advantages and efficacy of these herbs on the control of this problem.
Experimental: In this review, the authors searched the main related keywords e.g. polycystic, and cinnamon in main biological data centers e.g. Science Direct, Pubmed and Google Scholar. Then, the authors classified articles and only discussed the valid full papers in different categories.
Results: The study of papers related to the effect of cinnamon on polycystic ovary syndrome revealed that this herb can control this problem via some route e.g., by control of triglyceride and cholesterol to diminish risk factors of fat deposition and by inhibitory effects on oxidative cascade decreasing the cystic formation process.
Recommended applications/industries: The review proposed the positive effect of cinnamon on the control of PCOS in humans. Therefore, supplementary cinnamon on feed can diminish PCOS via some metabolic cycle.

1. Introduction

Polycystic ovary syndrome (PCOS) is a major endocrine disorder in young age women affecting their health-related quality of life (HRQOL) and their mental well-being as well (Balen, 2017; Escobar-Morreale, 2018). Studies have shown extensive genome association, specific loci, and alleles that play a major role in identifying the PCOS phenotype (Hayes *et al.*, 2015; Shi *et al.*, 2012; Dumesic *et al.*, 2015). Studies show that heredity plays a 70% role in the development of this syndrome. Also, the environment is a fundamental component in the expression of these genes and the development and progression of the disease (Goyal and Ganie, 2018; Albu and Albu, 2019; Spinedi and Cardinali, 2018; Hayes *et al.*, 2015). According to studies, obesity and insulin resistance are the two main causes of this syndrome, but other reasons such as fetal androgen exposure and genetic factors can be added to it (Puttabyatappa and Padmanabhan, 2018). In addition to the above, hyperinsulinemia can also be mentioned because it directly stimulates ovarian and endogenous secretions (Goodarzi *et al.*, 2011). PCOS have an increased risk of presenting with insulin resistance (IR) (Diamanti-Kandarakis and Dunaif, 2012), impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM2) (Moran *et al.*, 2010a), obesity (Diamanti-Kandarakis and Dunaif, 2012), and dyslipidemia (Randeva *et al.*, 2012). Insulin resistance is involved in the development of cardiometabolic disturbances such as dysglycaemia, hyperlipidemia, and obesity (Rehme *et al.*, 2013; Li *et al.*, 2012) and it has been described that between 18 and 24 % of adolescents with PCOS have some degree of abnormal glucose metabolism (Gooding *et al.*, 2014; Flannery *et al.*, 2013). Evidence

shows that first-degree relatives of women with the syndrome are more likely to develop the syndrome, suggesting that the syndrome is inherited (Azziz, 2007). The genes that have been nominated as candidates tend to fall into four different categories; those related to insulin resistance, those related to androgen biosynthesis and actions, those responsible for inflammatory cytokine responses, and others (Deligeoroglou *et al.*, 2009). Although some small studies have suggested an autosomal dominant inheritance pattern, family studies and twin studies have shown confounding patterns of inheritance and these patterns do not fit a Mendelian inheritance pattern (Raperport and Homburg, 2019). Investigations of genetic and epigenetic patterns have led to molecular pathophysiological discoveries. Therefore, applying a multifaceted approach and using advanced experiments and methods has increased researchers' understanding of this syndrome and its treatment. Because of this, researchers have discovered many therapies to treat and restore fertility.

2. Materials and Methods

Several databases (PubMed, PubMed Central, Science Direct, and Google Scholar), were used to identify scientific works and publications related to the application of cinnamon on polycystic ovary syndrome control and treatment. The searches were achieved in two categories. First the prevalence, pathobiology and treatment of polycystic was searched. Second; cinnamon and the biological activity of cinnamon on polycystic syndrome were searched. The poly cystic and cinnamon were used as keywords in the literature search.

3. Results and discussion

3.1. Prevalence of Polycystic Ovary Syndrome

The prevalence of PCOS varies among women in each society. A study in China shows the prevalence of this syndrome was 2.2% among women (Moran *et al.*, 2010b). Another study conducted in Mexico demonstrated a 6% prevalence of PCOS among women of reproductive age according to the National Institute of Health criteria. In addition, a prospective study was conducted on unselected Caucasian women from Spain and demonstrated a 6.3% prevalence of PCOS (Al Khaduri *et al.*, 2014). Ganie *et al.* (2010) published the first Indian case–control study using Rotterdam criteria in 2010, which reported a high prevalence rate of 46.8% as the study was conducted in 176 chronic lymphocytic thyroiditis (CLT) patients. The National Institutes of Health in 1990 suggested that patient PCOS had symptoms including oligoovulation and androgen excess (Azziz *et al.*, 2009). A study of 460 girls aged 15 to 18 in India reported a prevalence of the syndrome of 9.13% (Nidhi *et al.*, 2011). In another study in 2017, the prevalence of PCOS syndrome among 17 to 24 years old girls was 8.2% (Gupta *et al.*, 2018).

3.2. Pathophysiology of Polycystic Ovary Syndrome

PCOS is a hyperandrogenic state with oligo-anovulation that cannot be explained by any other disorder. It is a diagnosis of exclusion. Nevertheless, it accounts for the majority of hyperandrogenic presentations. It can almost be concluded that the major cause of PCOS is functional ovarian hyperandrogenism. Two-thirds of PCOS presentations have typical functional ovarian hyperandrogenism, characterized by dysregulation of androgen secretion with an over-response of 17-hydroxyprogesterone (17-OHP) to gonadotropin stimulation. The remaining PCOS with atypical ovarian hyperandrogenism (FOH) lacks overresponse of 17-OHP, but testosterone elevation can detect it after suppressing adrenal androgen production. About 3% of PCOS patients have a related isolated functional adrenal hyperandrogenism. The remainder of PCOS cases are mild. These lack evidence of steroid secretory abnormalities; most of these patients are obese, which practitioners postulate accounts for their atypical PCOS (Carvalho *et al.*, 2018). Evidence suggests that ovarian hyperandrogenism in PCOS is a result of primary ovarian dysfunction and is secondary to disordered gonadotropin activity. While not included in diagnostic criteria for PCOS, the elevated level of serum luteinizing hormone (LH) in affected patients due to inappropriate secretion has long been recognized. Excess endogenous growth of primary follicles and increase of antral follicles in the early stage of gonadotropin. Impaired folliculogenesis is the result of surplus androgens that disrupt normal androgen synthesis. Studies show that in addition to ovarian hyperandrogenism (Rosenfield and Ehrmann, 2016), insulin resistance is also involved in the development of this syndrome (Diamanti-Kandarakis and Dunaif,

2012). Hyperinsulinemia is the result of insulin resistance, which is associated with increased androgen production capacity (Baldani *et al.*, 2015). Ovarian androgen overproduction contributes in the pathogenesis of PCOS. On the other hand, insulin resistance causes the symptoms of polycystic ovary syndrome, such as increased androgen and menstrual irregularities (Yildiz *et al.*, 2012).

3.3. Treatment of Polycystic Ovary Syndrome

The treatment of this syndrome depends on various factors, such as whether the woman wants to get pregnant again or not. Some treatments include lifestyle changes such as exercise and physical activity to reduce body weight and obesity. Adding grains and fruits to the diet helps lower blood glucose and improves insulin status and hormonal balance in the body. Sugar-free drinks like water, diet soda and flavored water should be given instead of sugary drinks. Around 10% loss in body weight helps in a normal period and makes the menstrual cycle more regular. Birth control pills, which are a combination of estrogen and progesterone, help eliminate acne and control the menstrual cycle. Pills that contain only progesterone do not help remove acne and hair growth, but can only prevent endometrial cancer. This mechanism involves inhibiting the conversion of testosterone to dihydrotestosterone and the binding of dihydrotestosterone to the androgen receptor. Antidiabetic drugs also help treat the symptoms of PCOS syndrome (Ehrmann, 2005; Azziz *et al.*, 2006; Adams *et al.*, 2004; Shan *et al.*, 2015).

3.4. The biological effect of Cinnamon

Cinnamomum zeylanicum is an herbaceous plant of the Lauraceae family. This is one of the important spices used by people all over the world (Ranasinghe *et al.*, 2013). Numerous studies have been performed to identify and quantify the essential chemical components of volatile oils in the bark and leaves of wild cinnamon species (El-Hack *et al.*, 2020). This is one of the most important spices used by people all over the world. The various flavonoids and polyphenols isolated from cinnamon have free radical activity and antioxidant properties (Borzoei *et al.*, 2018a). Cinnamon is composed of various resin compounds including cinnamaldehyde, cinnamate, cinnamic acid and various essential oils (Goel and Mishra, 2020; Vasconcelos *et al.*, 2018). This plant has a numerous therapeutic effect such as anti-diabetic activity (Hajimonfarednejad *et al.*, 2019) anti-oxidative stress (Singletary, 2019) anti-fungal (Pongsumpun *et al.*, 2020) anti-microbial (Elcocks, 2020). Also, studies demonstrated cinnamon can improve renal toxicity, renal function (Abdeen *et al.*, 2019) and cardiovascular disease (Mehrpouri *et al.*, 2020). Studies show that cinnamon and its active ingredients in the form of alcoholic and aqueous extracts have various therapeutic effects on metabolic syndrome such as insulin resistance and dyslipidemia (Ziegenfuss *et al.*, 2006).

3.5. Cinnamon and Glycemic Effect in Polycystic Ovary Syndrome

Insulin resistance has an important role in the pathophysiology of PCOS so using insulin-sensitizing agents in the treatment of PCOS is useful. In vivo and in vitro examinations show that cinnamon can reduce insulin resistance and treat insulin-resistant diabetes (Hajimonfarednejad *et al.*, 2018). Articles demonstrated in a high-fructose diet induce insulin resistance rat model, cinnamon extract not only improves systemic insulin sensitivity and dyslipidemia by enhancing insulin signaling but also effectively ameliorates circulating levels of adipokines partially mediated via regulation of the expression of multiple genes involved in insulin sensitivity and lipogenesis (Qin *et al.*, 2004; Mang *et al.*, 2006). Several studies have investigated the probable effects of cinnamon intake on the glycemic indices of PCOS sufferers. Plasma levels of fast blood sugar and insulin were significantly higher in the PCOS group, as compared to the control. In an animal study, the cinnamon intake (200 mg/kg) for 14 days by the PCOS rats resulted in significant reductions of the plasma levels of and insulin, as compared to the placebo group (Khodaeifar *et al.*, 2019). In one study treatment with an oral cinnamon extract for 56 days showed that cinnamon can reduce fasting glucose and insulin resistance. In addition, oral glucose tolerance tests were 21% reduced and the insulin sensitivity index was elevated. The cinnamon extract improved insulin resistance in women with PCOS to that of age matched control women (Qin *et al.*, 2010). Also, studies on the effect of cinnamon on insulin sensitivity relevant the significant differences in insulin level changes in the cinnamon group ($p = 0.01$) than in the control group ($p = 0.19$) (Hajimonfarednejad *et al.*, 2018; Borzoei *et al.*, 2018a). Several studies have investigated the probable effects

of cinnamon intake on the glycemic indices of PCOS sufferers. Plasma levels of fast blood sugar (FBS) and insulin were significantly higher in the PCOS group, as compared to the control. In an animal study done by Khodaeifar *et al*. (2019), the cinnamon effect intake (200 mg/kg) for 14 days by the PCOS rats resulted in significant reductions of the plasma levels of FBS and insulin, as compared to the placebo group. Several in vitro and in vivo studies have shown cinnamon can reduce insulin resistance by increasing activation of the IRS/PI-3 kinase insulin signaling pathway (Qin *et al.*, 2003). The extracts from cinnamon stimulate autophosphorylation of the insulin receptor and inhibit protein tyrosine phosphatase I (Imparl-Radosevich *et al.*, 1998). Through these two mechanisms cinnamon extract makes adipocytes increase glucose uptake and glycogen synthesis. Oral cinnamon extract reduced fasting glucose, triglycerides, low-density lipoprotein (LDL), and total cholesterol in patients with type 2 diabetes mellitus (Khan *et al.*, 2003) as well as improved insulin sensitivity in women with PCOS (Wang *et al.*, 2007). Based on the above, it can be concluded that cinnamon has an overall effect on improving the condition of women with PCOS (Kort and Lobo, 2014). In a high fructose diet, cinnamon can prevent insulin resistance. Many studies have also shown that cinnamon can improve metabolism by improving insulin resistance (Qin *et al.*, 2004). Another study was carried out on 66 women who diagnosed with PCOS. Participants were randomly allocated to two groups. The intervention group was treated by cinnamon powder capsules 1.5 g/day in 3 divided doses for 3 months and the control group received a placebo. It was concluded that cinnamon significantly decreased insulin resistance and fasting insulin levels in women with PCOS (Hajimonfarednejad *et al.*, 2018). In the experiment of Wang *et al*. (2007) 15 patients with polycystic bursa were randomly divided into oral cinnamon and placebo groups for 8 weeks. After treatment, compared with the baseline insulin sensitivity index of fasting and 2-hour oral glucose tolerance test, IR in the cinnamon group was significantly reduced, while that in placebo group was not. It was found that cinnamomum cassia could enhance the effect of insulin by increasing the activity of phosphatidylinositol 3-kinase in the insulin signaling pathway. Many studies have reported that cinnamon acts as an insulin sensitizer. Many studies have suggested that cinnamon acts as an insulin sensitizer. Cinnamon contains various flavonoids and polyphenols that have antioxidant activity and inhibit free radicals (Kort and Lobo, 2014). Some studies reported that Type-A polymers and procyanidine polyphenols in the cinnamon extract enhance insulin signaling at the post-receptor level, increase the activity of Phosphoinositide 3 (PI3) kinase, increase the glucose uptake via enhancing the GLUT4 glucose transporter, inhibit the glycogen synthesis, and enhance glycogen synthesis and hypoglycemic effects (Wang *et al.*, 2007; Kort and Lobo, 2014). A study by Wang *et al*. (2007) investigated the effect of cinnamon extract on insulin resistance in patients with PCOS. In this study, the control group received 3 meals and 1 capsule of placebo for each meal and the intervention group received capsules containing 333 mg of cinnamon extract per serving 3 times a day. The intervention group had a significant decrease in fasting blood sugar (FBS) and insulin resistance. The cinnamon improved insulin sensitivity and reduced oral glucose tolerance test in this study. Borzoei *et al*. (2018b) reported that using 500 mg of cinnamon 3 days for 8 weeks improved FBS, insulin, and total cholesterol in patients with PCOS. Dou *et al*. (2018) in their study concluded that cinnamon supplementation reduces insulin resistance and improves the health status of people with PCOS. It has also been suggested that cinnamon may reduce testosterone and insulin levels, lower insulin-like growth factor-1 and increase the level of insulin-like growth factor-binding protein in the plasma and ovaries of patients with PCOS. This study therefore identified cinnamon as a therapeutic agent for patients with PCOS. One study indicates that consuming three gram per day of cinnamon for eight weeks leads to significant reduction in some biochemical and anthropometric variables compared with baseline (i.e., FBG decreased by 9.2%, HbA_1c decreased by 6.12%, triglyceride decreased by 15.38%, body weight decreased by 1.19%, BMI decreased by 1.54% and fat body mass decreased by 1.36%). But these reductions were not significant compare to placebo group. Khan *et al*. (2003) studied the effects of one, three, and six grams per day of whole cinnamon powder on FBG and serum lipids in 60 people with poorly controlled type 2 diabetes from Pakistan. Consequently, the authors concluded that small amount of cinnamon represents a safe and effective mean to reduce the risk factors associated with type 2 diabetes. In the cinnamon group, they observed a significant reduction of plasma glucose

(9.2%) after eight weeks of treatment but not in the placebo group. Several articles have shown that taking 1 to 6 grams of cinnamon supplements reduces FBG and H_1C in diabetic patients (Akilen *et al.*, 2012; Medagama, 2015). Another similar study demonstrated that cinnamon supplementation improves blood glucose and lipid profiles in diabetic patients (Allen *et al.*, 2013; Kleefstra *et al.*, 2012). Another study show Cinnamon supplementation elevates glucose uptake by cells, which may be attained by increasing insulin sensitivity via enhanced phosphorylation of signaling proteins (Qin *et al.*, 2010; Solomon and Blannin, 2009). The different studies in this subject were summarized in Table 1.

Table 1. Cinnamon and glycemic effect in POCS.

Study	year	Outcome
Hajimonfarednejad et al.	2018	Cinnamon can reduce insulin resistance and treat insulin-resistant diabetes
Qin et al.	2004	Cinnamon improves systemic insulin sensitivity and dyslipidemia by enhancing insulin signaling
Khodaeifar et al.	2019	Cinnamon intake (200 mg/kg) for 14 days by the PCOS rats resulted in significant reductions of the plasma levels of insulin
Qin et al.	2010	Cinnamon can reduce fasting glucose and insulin resistance. In addition, oral glucose tolerance tests 21% reduced and insulin sensitivity index elevated
Hajimonfarednejad et al.	2018	Cinnamon on insulin sensitivity relevant significant difference in insulin level changes in the cinnamon group ($p = 0.01$) than in the control group ($p = 0.19$)
Borzoei et al.	2018_a	
Khodaeifar et al.	2019	Cinnamon effect intake (200 mg/kg) for 14 days by the PCOS rats resulted in significant reductions of the plasma levels of fasting blood sugar and insulin, as compared to the placebo group
Qin et al.	2003	Cinnamon can reduce insulin resistance by increasing activation of the IRS/PI-3 kinase insulin signaling pathway
Imparl-Radosevich et al.	1998	Cinnamon stimulate autophosphorylation of the insulin receptor and inhibit protein tyrosine phosphatase I and reduce glucose
Khan et al.	2003	Cinnamon extract makes adipocytes to increase the glucose uptake and glycogen synthesis. Oral cinnamon extract reduced fasting glucose, triglycerides, low-density lipoprotein (LDL), and total cholesterol in patients with type 2 diabetes mellitus
Wang et al.	2007	Cinnamon improves insulin sensitivity in women with PCOS
Borzoei et al.	2018_b	Using 500 mg cinnamon 3 days for 8 weeks improved fasting blood sugar, insulin, and total cholesterol in patients with PCOS
Dou et al.	2018	Cinnamon supplementation reduces insulin resistance and improves the health status of people with PCOS. It has also been suggested that cinnamon may reduce testosterone and insulin levels, lower insulin-like growth factor-1 and increase the level of insulin-like growth factor-binding protein in the plasma and ovaries of patients with PCOS.
Akilen et al.	2012	Taking 1 to 6 grams of cinnamon supplements reduces fasting blood glucose and H_1C in diabetic patients
Medagama	2015	
Allen et al.	2013	Cinnamon supplementation improves blood glucose and lipid profiles in diabetic patients
Kleefstra et al.	2012	
Qin et al.	2010	Cinnamon supplementation elevates glucose uptake by cells, which may be attained by increasing insulin sensitivity via enhanced phosphorylation of signaling proteins
Solomon and Blannin,	2009	

3.6. Cinnamon, Anti-Mullerian Hormone and Ovarian Function in Polycystic Ovary Syndrome

Anti-Mullerian hormone (AMH) reduces follicle sensitivity to follicle-stimulating hormone (FSH), so in a situation that AMH level is high, folliculogenesis arrest may occur (Borzoei *et al.*, 2018a). On the contrary, with low AMH level, the inhibitory effect of AMH can be suppressed and follicle sensitivity to FSH can return to normal. Studies have shown that insulin-sensitizing agents can reduce insulin resistance (Wahyuningtyas and Sa'adi, 2021) and can also decrease AMH level (Khan *et al.*, 2003; Radhia *et al.*, 2010). Several investigators have reported that AMH concentrations are correlated with the degree of ovulatory dysfunction. Laven *et al*. (2004) showed that normogonadotrophic anovulatory women with or without PCOS have higher AMH concentrations than their normal ovulatory counterparts, and that serum AMH is correlated with menstrual cycle duration. Moreover, Pellatt *et al*. (2010) have suggested that PCOS can be divided into anovulatory and ovulatory

based on the serum AMH concentrations as women with anovulatory PCOS were found to have 18 times higher AMH concentrations than the women with ovulatory PCOS with no overlapping areas. Pigny *et al*. (2003) investigated the correlation of serum AMH concentrations with FSH in PCOS and found a positive correlation between AMH concentration and small antral follicle number ($P<0.0001$) but a negative correlation with serum FSH concentration ($P<0.04$), suggesting the role of increased AMH in the follicular arrest in PCOS by inhibiting FSH early in folliculogenesis. One study reported that the metformin group had a lower anti-Mullerian hormone level, which is related to PCOS and reduces follicle sensitivity to FSH, compared to the cinnamon group (Ainehchi *et al.*, 2019). However, more side effects were observed in the metformin group compared to the cinnamon group. The ginger and cinnamon supplementation increases catalase, glutathione peroxidase, and superoxide dismutase levels (Wiweko and Susanto, 2017). Studies show that insulin stimulates ovarian thecal and stromal androgen secretion in vitro (Dou *et al.*, 2018). Also, other study shows that cinnamon intake improves menstrual cyclicity and may be an effective treatment option for women with polycystic ovary syndrome (Kort and Lobo, 2014). Extreme ovarian androgen production contributes to the pathogenesis of PCOS. On the other hand, insulin resistance underlies the hallmark symptoms of PCOS, such as androgen excess and menstrual irregularity (Yildiz *et al.*, 2012). Many studies show that cinnamon has an improved role in the insulin sensitivity in the cells, so it is suggested change of ovarian hormones and androgens by mitigating insulin resistance. Reproductive features, such as ovarian hormones, gonadotropins, estrous cycle, androgens, and ovarian morphology and histology, can improve by cinnamon and it has been proved by many previous studies (Hajimonfarednejad *et al.*, 2018; Khodaeifar *et al.*, 2019; Wang *et al.*, 2007; Kort and Lobo, 2014; Dou *et al.*, 2018; Wiweko and Susanto, 2017). Other than animal studies reported that cinnamon intake by the PCOS women has no significant effect on the blood levels of androgens such as dehydroepiandrosterone sulfate and testosterone sex hormone-binding globulin and estradiol (E2) (Hajimonfarednejad *et al.*, 2018; Wang *et al.*, 2007; Kort and Lobo, 2014). Also, one study reported that cinnamon intake (1500 mg/day) for six months improved menstrual cyclicity significantly (from the baseline in the cinnamon group, as also compared to the controls). In these PCOS women, by measuring ovulatory progesterone levels in the luteal phase, ovulatory menses were confirmed (Kort and Lobo, 2014). Previous studies proved dehydroepiandrosterone (DHEA) induced PCOS model represents similar characteristics seen in human patients, such as hyperandrogenism, abnormal maturation of ovarian follicles and anovulation (Dou *et al.*, 2018). Hyperinsulinemia arising from insulin resistance is associated with a higher capacity of ovarian androgen production (Baldani *et al.*, 2015). Overproduction of ovarian androgen contributes to the pathogenesis of PCOS. On the other hand, insulin resistance causes the obvious symptoms of polycystic ovary syndrome, such as increased androgen and menstrual irregularities (Yildiz *et al.*, 2012). Considering the effects of cinnamon on insulin levels, it seems that cinnamon can be useful in modifying endocrine hormones and androgens by reducing insulin resistance. Previous studies have also shown that cinnamon can have healing effects on reproductive characteristics including ovarian hormones, gonadotropins, estrous cycle, androgen, morphology and histology of the ovary (Khodaeifar *et al.*, 2019; Wang *et al.*, 2007; Kort and Lobo, 2014; Dou *et al.*, 2018; Wiweko and Susanto, 2017). Other than an animal study (Dou *et al.*, 2018), others (Hajimonfarednejad *et al.*, 2018; Wang *et al.*, 2007; Kort and Lobo, 2014) have reported that cinnamon intake by PCOS women has no significant effect on blood levels of androgens (testosterone, dehydroepiandrosterone sulfate), sex hormone binding globulin and Estradiol (E2). One study examined the effect of cinnamon on the menstrual cycle in women with PCOS. The study showed that the effect of cinnamon completely improved the menstrual cycle for 6 months (1500 mg/day). In these PCOS women, by measuring ovulatory progesterone levels in the luteal phase, ovulatory menses were confirmed (Kort and Lobo, 2014). Another study showed that cinnamon down-regulates serum levels of testosterone and LH and restores the estrous cyclicity and recovers the ovary morphology induced by the PCOS state (Dou *et al.*, 2018). It was also shown that the ovarian tissue of the PCOS subjects was damaged due to the production of cystic follicles and atretic body in the ovary; also, a decline in the number of the normal follicles was observed. All of these were owing to hyperandrogenism (Maleki *et al.*, 2021). Cinnamon can

regulate the serum levels of LH and testosterone, to restore the estrous cyclicity, and to recover the ovary morphology induced by the PCOS state. In PCOS woman hyperandrogenism leads to damage to the ovarian tissue thus the production of cystic follicles and atretic bodies is damaged in the ovary (Hafizur *et al.*, 2015).

In one study adding of cinnamon induced a significant improvement compared to controls at 15 days for measures of testosterone ng/ml (control 0.747 ± 0.039; metformin 0.647 ± 0.027; Cinnamomum cassia 0.625 ± 0.029); LH ng/ml (control 7.641 ± 0.267; metformin 6.873 ± 0.214; Cinnamomum cassia 6.891 ± 0.221) and insulin resistance (control 10.018 ± 0.217; metformin 7.067 ± 0.184 Cinnamomum cassia 8.772 ± 0.196) ($p < 0.05$) (Heibashy *et al.*, 2013). The different studies in this subject were summarized in Table 2.

Table 2. Cinnamon and ovarian function in POCS.

Kort and Lobo	2014	Cinnamon intake improves menstrual cyclicity and may be an effective treatment option for women with polycystic ovary syndrome
Hajimonfarednejad et al. Khodaeifar et al. Wang et al. Kort and Lobo Dou et al. Wiweko and Susanto	2018 2019 2007 2014 2018 2017	Cinnamon have an improve role on the insulin sensitivity in the cells, so it is suggested change of ovarian hormones and androgens by mitigating insulin resistance. Reproductive features, such as ovarian hormones, gonadotropins, estrous cycle, androgens, and ovarian morphology and histology
Hajimonfarednejad et al. Wang et al. Kort and Lobo Kort and Lobo	2018 2007 2014 2014	Cinnamon intake by the PCOS women have no significant effect on the blood levels of androgens such as dehydroepiandrosterone sulfate and testosterone sex hormone-binding globulin and estradiol (E2) Cinnamon intake (1500 mg/day) for six months improved menstrual cyclicity significantly (from the baseline in the cinnamon group, as also compared to the controls)
Khodaeifar et al. Wang et al. Kort and Lobo Dou et al. Wiweko and Susanto	2019 2007 2014 2018 2017	Cinnamon can have healing effects on reproductive characteristics including ovarian hormones, gonadotropins, estrous cycle, androgen, morphology and histology of the ovary
Kort and Lobo	2014	Cinnamon completely improved the menstrual cycle for 6 months (1500 mg/day). In these PCOS women, by measuring ovulatory progesterone levels in the luteal phase, ovulatory menses were confirmed
Dou et al.	2018	Cinnamon down-regulate serum levels of testosterone and LH and restore the estrous cyclicity and recover the ovary morphology induced by the PCOS state
Hafizur et al.	2015	Cinnamon can regulate the serum levels of LH and testosterone, to restore the estrous cyclicity, and to recover the ovary morphology induced by the PCOS state. In PCOS woman hyperandrogenism lead to damage the ovarian tissue thus production of cystic follicles and atretic body has been damaged in the ovary

3.7. Cinnamon and Oxidative Stress in PCOS

Maintaining the body's physiological functions depends on a balance between oxidants and antioxidants. This ratio changes with increasing levels of reactive oxygen species (ROS) or increasing reactive nitrogen species or decreasing the body's antioxidant defenses (Al-Gubory *et al.*, 2010). ROS include a group of molecules that are derived from oxygen metabolism in aerobic organisms. The major ROS with physiological function is superoxide anion, hydroxyl radical, hydrogen peroxide, organic hydroperoxide, alkoxy and peroxy radicals, hypochlorous acid, and peroxynitrite (Mohammadi, 2019). In contrast, there are molecules in the body that prevent these reactions and their destructive physiological effects. In other words, the body's antioxidant system closely monitors the production of ROS that the most important of which are superoxide dismutase, catalase, glutathione peroxidase and glutathione 6-phosphate dehydrogenase (Yadav *et al.*, 2016). When ROS overcome the body's antioxidant defense system, it creates an unfavorable environment for women's physiological reactions. In other words, reproductive tissues become stable when the state of the body's oxidative and antioxidant systems is in balance. ROS affect various ovarian activities from oocyte maturation to fertilization (Lu *et al.*, 2018). To date, several studies have shown that the accumulation of ROS in the ovaries deteriorates oocyte quality, induces granulosa cell apoptosis, and accelerates degeneration of the corpus luteum (Sohel *et al.*, 2019; Yang *et al.*, 2017). Furthermore, it decreases communication between oocytes and granulosa cell, affecting preovulatory oocyte maturation (Cajas *et al.*, 2020). Oxidative stress generally known to be present

in PCOS women regardless of whether they are lean or have metabolic abnormalities, has been documented in infertile PCOS women (Hyderali and Mala, 2015). Oxidative stress appears to cause PCOS by altering steroidogenesis in the ovaries, which in turn contributes to impaired follicular growth and infertility by increasing androgen levels (Archibong *et al.*, 2018). Also, the decrease in mitochondrial O_2 consumption and glutathione levels along with increased ROS production explains the mitochondrial dysfunction in PCOS patients (Victor *et al.*, 2011). The mononuclear cells of women with PCOS are increased in this inflammatory state, which occurs more so from a heightened response to hyperglycemia and C-reactive protein (CRP). Physiological hyperglycemia generates increased levels of ROS from mononuclear cells, which then activate the release of TNF-alpha and increase inflammatory transcription factor NF-kappa B. As a result, concentrations of TNF-alpha, a known mediator of insulin resistance, are further increased. The resultant oxygen species creates an inflammatory environment that further increases insulin resistance and contributes to hyperandrogenism (González *et al.*, 2006; Costello *et al.*, 2007). Studies have shown that hyperglycemia and insulin resistance are the main factors that increase oxidative stress in women with PCOS however, non-obese PCOS patients without IR were also reported to have elevated oxidant status (Verit and Erel, 2008). One meta-analysis showed that circulating mean malondialdehyde concentrations according to the age and BMI were increased 47% in women with PCOS compared with controls (Murri *et al.*, 2013). A study of malondialdehyde levels in the blood of patients with PCOS and healthy controls showed that people with PCOS had higher levels of malondialdehyde in the blood, which was independent of obesity. It has been suggested that oxidative stress may be involved in the development of this syndrome (Kuşçu and Var, 2009). Another study found that malondialdehyde levels in patients with PCOS were significantly higher than in controls. Age and body mass index were not recorded in this study (Zhang *et al.*, 2008). Herbs and herbs are currently considered as potential sources of antioxidants in various diseases and they can be used to reduce free radicals and reduce the effects of oxidative stress on the physiological and pathological functions of the body (Khalisyaseen and Mohammed, 2021). Cinnamon oil has been reported for potentially exhibiting superoxide dismutase activity as specified by the hang-up of pyrogallol autoxidation. Cinnamon also has different flavonoids and phenolic compounds that have antioxidant character and free radical scavenging capabilities (Rao and Gan, 2014). Taking trans-cinnamaldehyde for example, it upregulates antioxidant and phase II detoxifying enzymes, and eliminates reactive oxygen species via the activation of Nrf2, and thus it could prevent the initiation and progression of cancer, diabetes, chronic nephropathy, and cardiovascular disease (Li *et al.*, 2019). In women with PCOS, a disruption in the activity of both enzymatic and non-enzymatic endogenous antioxidants occurs; this can also be caused by hyperglycemia, which often co-occurs with PCOS and induces mechanisms that produce ROS (Zhao *et al.*, 2015). Results displayed that cinnamon supplementation improved the oxidative stress in the woman with PCOS. So cinnamon is one of the plants with antioxidant capability and it was possible that the elevate in total antioxidant capacity. In this study cinnamon treated group might be due to their decreased consumption for free radical detoxification or utilization which was approved by following reduction in serum malondialdehyde and improvement in total antioxidant capacity levels (Borzoei *et al.*, 2018a). Cinnamic acid has four side chains (R group) in its structure. Depending on the structure of these chains, cinnamic acid has antioxidant, anti-bacterial, anti-viral and anti-fungal properties (Sova, 2012). Also, cinnamaldehyde derivatives, because of having reductive groups like hydroxyl and methyl, have radical scavenging properties. A study shows that cinnamon can have a protective effect on ovarian tissue against oxidative stress (Khodaeifar *et al.*, 2019) Another study shows that cinnamon increases antioxidant capacity in patients with PCOS (Borzoei *et al.*, 2018b).

3.8. Cinnamon, Body Mass Index and Dyslipidemia Effect in Polycystic Ovary Syndrome

Dyslipidemia is the most common metabolic disorder in polycystic ovary syndrome because 70% of these patients have abnormally high serum lipids (Baldani *et al.*, 2015). Exposure to endocrine and metabolic disturbances such as hyperandrogenism, hyperinsulinemia and dyslipidemia might be responsible for PCOS-associated oxidative stress (Sheng *et al.*, 2008). Studies show that reactivity of ROS with lipids leads to increased lipid peroxidation

(Deepika *et al.*, 2014). It was revealed that cinnamon has high levels of different phytochemical compounds with free radical scavenger actions, such as epicatechin, camphene, eugenol, gamma-terpinene, phenol, salicylic acid and tannins (Lee *et al.*, 2013). In patients with PCOS, the high-density lipoprotein (HDL) level decreases significantly. Studies show that consumption of cinnamon significantly increases this factor compared to the control group. Cinnamon also has good effects on lowering cholesterol, low-density lipoprotein (LDL) and triglyceride (TG) (Khodaeifar *et al.*, 2019). However, an Iranian team (Borzoei *et al.*, 2018b) found that cinnamon supplementation (1.5 g /day) improved the serum lipid profile in women with PCOS; despite this, the changes in the serum triglyceride were not significant. In addition, Salehpour *et al*. (2015) reported that the consumption of the cinnamon extract (1000 mg /day) for 12 months resulted in a significant reduction in the apolipoprotein B: apolipoprotein A_1 ratio. In the study done by Hajimonfared Nejad *et al*. (2018) during the 12-week treatment period, supplementation with 1.5 g daily cinnamon resulted in a non-significant reduction of serum triglyceride and cholesterol, while the decrease of LDL was significant. So, they reported that cinnamon supplementation (1.5 g/day) for 12 weeks improved insulin sensitivity and decreased insulin and LDL levels in women with PCOS. One study showed that cinnamon administration (50 mg/kg daily) for 8 weeks decreased TG, total cholesterol, chylomicron-apoB48 and very low-density lipoprotein (VLDL)-apoB100 in Wistar rats fed on a high-fructose diet to induce insulin resistance. In addition, cinnamon extract can regulate lipid metabolism via the up-regulation of PPARα expression (Kim and Choung, 2010). Other study reported that PPARα expression elevated the cellular uptake of fatty acids released from fat tissues. PPARα ligands also increased the expression of the lipoprotein lipase gene, resulting in the anti-hyperlipidemia effect (Sheng *et al.*, 2008). Many examinations performed that cinnamon can reduce levels of low-density lipoprotein cholesterol and total cholesterol. In one of them cinnamon is used to improve anti-diabetic effects. Consume 1, 3, or 6 g of oral cinnamon (cinnamomum cassia) decreases serum glucose, triglycerides, low-density lipoprotein cholesterol, and total cholesterol in type 2 diabetes patients compared with placebo (Khan *et al.*, 2003). Cinnamon has hyperlipidemic activity, which can be attributed to the presence of many polyphenols in cinnamon, which prevent intestinal absorption of cholesterol (Shalaby and Saifan, 2014). In an animal study, cinnamaldehyde altered serum biochemical factors associated with lipolysis, such as glycerol and free fatty acids. Cinnamon also increased adipose tissue lipolysis in mice (Khare *et al.*, 2016). In comparison to their non-PCOS counterparts, PCOS patients were more likely to suffer from obesity; this exacerbates many aspects of the PCOS-related phenotype, especially cardiovascular risk factors such as glucose intolerance and dyslipidemia (Legro, 2012). Several studies have investigated the probable effects of cinnamon intake on anthropometric indices (including weight, body mass index (BMI) and waist circumference of the PCOS sufferers. In an animal study, consuming cinnamon (10 mg/100 g body weight) for 20 days had no significant effect on body weight (Dou *et al.*, 2018). In another study, daily consumption of 1 g of cinnamon for 8 weeks did not have a significant effect on body mass index in women with PCOS (Wang *et al.*, 2007). In contrast, another article showed that consuming cinnamon-containing plant extracts (100 mg/daily) for six months significantly reduced body mass index (Wiweko and Susanto, 2017). Another study also reported that there was no significant difference regarding body mass index between the metformin consumer group and the cinnamon consumer one; however, the treatment with 1000 mg cinnamon extract for 12 months significantly decreased body mass index, as compared to placebo (Salehpour *et al.*, 2015). Another study, which lasted for three months, showed that despite the reduction of anthropometric factors in the daily consumption of cinnamon (1.5 g daily), no significant changes were observed in this reduction of factors (Hajimonfarednejad *et al.*, 2018). In addition, an Iranian team (Borzoei *et al.*, 2018a; Borzoei *et al.*, 2018b) found that body mass index was decreased significantly in the cinnamon group, in comparison with the baseline values; however, decreases in body mass index in the two groups were not significant after the intervention. Despite this, a significant decrease was observed in the body weight of the subjects by cinnamon supplementation. They reported that weight loss in the studied subjects was not sufficient to decrease body mass index, as compared to placebo.

4. Conclusion

The use of herbs for the treatment of female sexual disorders in Iran has a long history and studies have shown that the use of these herbs in the treatment of metabolic diseases such as diabetes and Polycystic ovary syndrome has a positive effect. Cinnamon has the potential to block the activity of free radicals and inhibit lipid peroxidation. Accordingly, this plant has antioxidant and anti-diabetic properties. In addition, previous studies have shown that the extract of this plant is anti-inflammatory and analgesic and can lower cholesterol and triglycerides. According to studies, it can be concluded that cinnamon has good supportive effects in the treatment of polycystic ovary syndrome in women.

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