Review

Could polyphenols be an effective treatment in the management of polycystic ovary syndrome?

A mini-review

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Abstract: Polycystic ovary syndrome (PCOS), is a health problem observed in women of reproductive age. Different diets, physical activity recommendations and lifestyle changes can be effective in dealing with the symptoms of PCOS. Nutrition is indeed an essential part of the treatment of the disease as it directly affects body weight loss, insulin resistance, lipid profile, hormones, and dermatological complaints such as acne. Polyphenols, simply classified as flavonoids and non-flavonoids, are bioactive components found in plant-based foods. The most common polyphenols in the diet are flavanols, flavonols, flavanone, anthocyanins. In particular, polyphenols which are compounds naturally found in foods, have antioxidant, anticancer, anti-inflammatory, antimutagenic benefits along with many other ones. In the treatment of PCOS, polyphenols may help reduce the symptoms, improve insulin resistance and poor lipid profile, and cure hormonal disorders. It has been reported that polyphenols are influential in menstrual cycle disorders and enable a decrease in body weight, hyperandrogenism, estrogen, testosterone, luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratios and LH. For adequate daily intake of polyphenols, which are found in high amounts in fruits and vegetables, at least 5 portions of fruits and vegetables should be consumed in addition to a healthy nutrition pattern. In this review, the effects of various polyphenols on polycystic ovary syndrome are discussed.

Keywords: polyphenols, polycystic ovary syndrome, resveratrol, quercetin, catechin

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age and is claimed to occur in 5–15% of women of reproductive age globally, depending on the diagnostic criteria [1]. The prevalent differences across populations arise from the influence of ethnicity, race, and other environmental factors on the phenotype [2]. The prevalence of polycystic ovary syndrome varies depending on the diagnostic criteria, the group studied and the phenotype [3, 4]. PCOS, characterized by a disorder in sex hormones, often causes infertility, polycystic ovaries, hyperandrogenism symptoms such as hirsutism and menstrual disorders like oligomenorrhea [5]. In addition, PCOS is associated with type 2 diabetes mellitus (T2DM), obesity, cardiovascular diseases (CVD), metabolic syndrome (MetS), and endometrial cancer [6]. In recent years, chronic low-grade inflammation has been shown to play a key role in ovarian follicular dynamics. Therefore, it has been hypothesized that PCOS may be associated with low-grade inflammation and inflammatory markers [7].

Nutritional status and beneficial elements in foods can affect the treatment of patients with PCOS. For example, polyphenols originating from the secondary metabolism of plants have more than 8000 structures. Polyphenols consist of at least one benzene ring and at least one hydroxyl group attached to this ring. It is possible to perform many classifications according to the phenol rings and different structures they have. They are most commonly classified into two groups as flavonoids and non-flavonoids [8]. Systematic reviews and meta-analysis mention the benefits of polyphenols in the prevention and treatment of many diseases [9, 10]. In this review, the beneficial effects of polyphenols on polycystic ovary syndrome are mentioned.

The relationship between polycystic ovary syndrome and disease

The National Health Consensus Conference Panel recommended the use of the 2003 Rotterdam Criteria only if the specific PCOS phenotypes identified are recorded.

The proposed subphenotypes are phenotype A (hyperandrogenism+oligo-anovulation+PCOS morphology), phenotype B (hyperandrogenism+oligo-anovulation), phenotype C (hyperandrogenism+PCOS morphology), and phenotype D (oligo-anovulation+PCOS morphology) [3]. It should be considered that 85–90% of women with oligomenorrhea and 30–40% of women with amenorrhea are likely to have polycystic ovary syndrome [4].

A 70% higher prevalence of dyslipidemia is observed in women with polycystic ovary syndrome [11]. Many pathological changes can be mentioned behind dyslipidemia in women with PCOS, but insulin resistance is an important factor. Whilst insulin resistance supports the increase of very low-density lipoprotein cholesterol (VLDL-C) and apo B-100 synthesis in the liver, it causes a decrease in high density lipoprotein cholesterol (HDL-C) levels [12]. Polycystic ovary syndrome is also a common disease that develops in women due to genetic predisposition and is associated with obesity [13]. It is also positively correlated with visceral adipose tissue total androgen levels and therefore plays an important role in PCOS [14]. Higher levels of free testosterone and androgen indices were observed in overweight PCOS patients compared to PCOS patients in the normal body weight range [15]. Lipogenic enzymes and antilipolytic genes are reported to be higher in omental adipose tissue in women with PCOS, indicating the contribution of androgens to lipid accumulation [16]. Androgens can cause dysfunction in adipose tissue by increasing abdominal fat accumulation [17]. Fat cells regulate androgen levels by producing leptin and adiponectin through paracrine and autocrine glands. It has been reported that adiponectin levels are low in patients with PCOS and that leptin levels boost in some PCOS patients, leading to an increase in serum androgen levels by preventing the conversion of androgens to estrogens [16]. Hyperandrogenism, as one of the most common symptoms of polycystic ovary syndrome, has been reported to be prevalent in 78% in overweight women with polycystic ovary syndrome [18]. Insulin resistance enhances lipolysis in adipose tissue, causing an escalation in the amount of free fatty acids going to the liver. This results in hepatic steatosis [12]. Insulin sensitizers such as metformin positively affect insulin receptor expression, reducing serum insulin levels and increasing insulin sensitivity [19]. It has also been reported that women with PCOS have a raised risk of non-alcoholic fatty liver disease [12].

Polyphenols

Along with vitamins and minerals in fruits and vegetables, one of the different components that have health benefits is polyphenols or polyhydroxyphenols [20]. Amongst the richest sources of polyphenols, foods such as cocoa products, dried herbs, spices, some seeds, dark fruits are given as examples [21].

Polyphenols are chemical compounds that occur naturally in plants. Polyphenols, which contain more than 8000 compounds in total, are divided into 2 main groups as flavonoids and non-flavonoids (ligans, stilbenes, phenolic acids, non-phenolic metabolites and other polyphenols) [22]. Compounds subdivided into flavonoids, flavanols, flavanonols, flavanones, flavones, flavonols, isoflavones, anthocyanins, and anthocyanidins are natural antioxidants with the ability to scavenge free radicals [23]. Flavonoids are widely spread in food such as vegetables, fruits, red wine, tea and cereals [24]. The group of non-flavonoids includes stilbenes, lignans, tannins, phenolic acids, coumarins, curcominoids. They do not show C6-C3-C6 structure that is observed in flavonoids yet contain one or more phenol groups [23]. Table 1 shows polyphenols and some examples.

Polyphenols, which are abundant in many foods, stand out with their antioxidant, antiinflammatory and anticancer effects. It can locally reduce oxidative stress and increase the antioxidant level in the body. It can reduce cytokine formation by causing changes in various gene expressions (nuclear factor erythroid 2 related factor 2 (Nrf-2), nuclear factor kappa B (NF-κB), janus kinases/signal transducer and activator of transcription proteins (JAK/STAT)) [26]. Dysregulation of the nuclear factor erythroid 2 related factor 2 (Nrf2) signaling pathway, which is an important defense system against oxidative stress damage, causes many diseases such as diabetes, cancer and respiratory disorders. Polyphenols, which are known to have many health benefits, regulate the Nrf2 pathway, ensuring its activation and preventing reactive oxygen species (ROS) production [27].

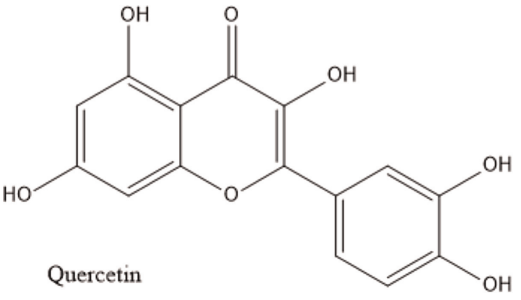
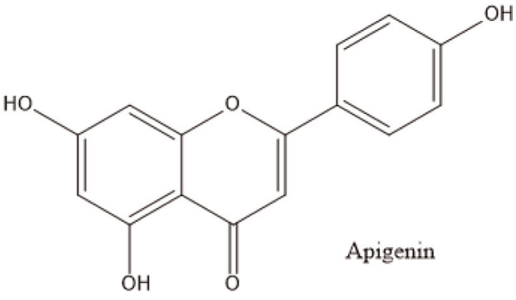
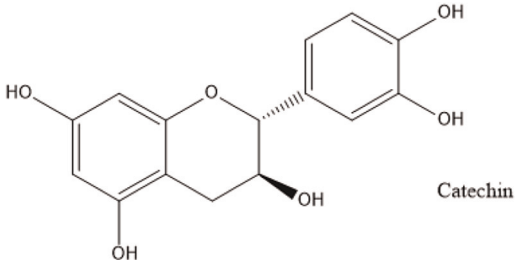
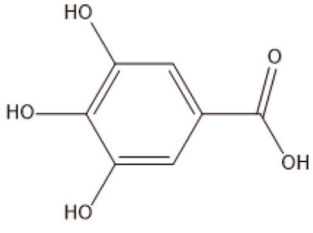
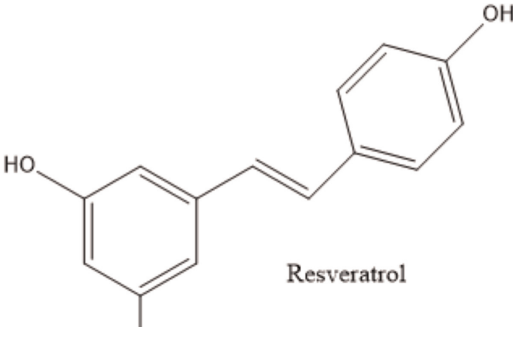
Polycystic ovary syndrome and polyphenols

Cinnamon

Cinnamon, used in almost every country in the world, is obtained from the *Cinnamomun zeylanicum* plant from the *Lauraceae* family. Different polyphenols in the composition of cinnamon exhibit antioxidant properties with their free radical scavenging effect. Further, it has been reported to reduce oxidative stress by inhibiting 5-lipoxygenase [28, 29].

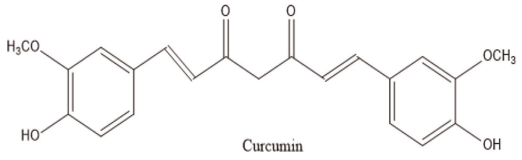
In a study conducted in rats with dehydroepiandrosterone (DHEA)-induced PCOS, cinnamon extract positively affected ovarian morphology, insulin sensitivity and menstrual cycle. PCOS-induced insulin-like growth factor binding protein 1 (IGFBP-1) downregulation and excessive

Table 1. Polyphenols with examples [20, 25]

Flavonoids	Examples	Structure
Flavonols	Quercetin, myricetin, kaempferol	 Quercetin
Flavanones	Hesperidin, naringenin, eriodictol	
Isoflavones	Daidzein, genistein, glystein	 Apigenin
Anthocyanins	Cyanidin, delphinidin, petunidin, malvidin, peonidine	
Flavanols	Catechin, epicatechin, gallocatechin, epicatechin-3-gallate, epigallocatechin-3-gallate	 Catechin
Flavones	Apigenin, luteolin	
Phenolic acids		 Gallic acid
Benzoic acid	Ellagic acid, gallic acid	
Hydroxycinnamic acid	Chlorogenic acid (caffeic), *p*-coumaric acid, ferulik acid, sinapic acid	
Lignans	Pinoresinol, secoisolaricresinol	 Resveratrol
Stilbenes	Resveratrol	
Coumarins	Coumarin	

(Continued on next page)

Table 1. (Continued)

Flavonoids	Examples	Structure
Curcominoids	Curcumin	
Tannins	Tetrafucol A	

insulin-like growth factor 1 (IGF-1) expression in the ovary are decreased [30]. In another study, after 66 women with PCOS were randomly divided into 2 groups, one of the groups was given 500 mg cinnamon powder capsules 3 times a day, and 12 weeks later, fasting insulin and insulin resistance were lower in the cinnamon group compared to the placebo group and low density lipoprotein cholesterol (LDL-C) levels were significantly lower in the cinnamon supplement group [31].

Resveratrol

Resveratrol (3,5,4-trihydroxystilbene), which has a wide range of biological functions, is synthesized by plants against adverse conditions such as mechanical damage, fungi, and bacteria. It consists of two phenol rings linked by a double styrene bond [32]. Resveratrol is abundant in various foods, and the resveratrol content of foods can vary based on environmental and genetic factors. Whereas grapes, peanuts, strawberries, blueberries, cranberries, mulberries, and black mulberries are rich sources, in recent studies, resveratrol has been found in foods such as banana, guava, pineapple, peach, apple, pear, passion fruit, potato, and cucumber [33]. In general, the therapeutic effects of resveratrol have been reported in diseases such as neurological disorders, cardiovascular diseases, diabetes, and inflammation. Additionally, resveratrol can reduce atretic follicles in the ovary, rise the number of oocytes and inhibit apoptosis [34]. It protects the ovaries against ROS and ROS-mediated damage. The protective effects of estradiol on the ovary, such as suppression of metabolic clearance, inhibition of steroidogenesis, response to FSH and IGF-1, indicate that it can be a therapeutic agent in the treatment of PCOS. Resveratrol obstructs androstenedione and androsterone producing theca-interstitial cells by inhibiting CYP17α1 expression [29]. In a study conducted in rats with PCOS, it was reported that resveratrol treatment decreased ROS production, improved insulin sensitivity, and reversed PCOS-related changes in serum LH/FSH, LH, testosterone, tumor necrosis factor-α (TNF-α), antimullerian hormone (AMH) levels [35]. Renchber et al. [36] in their study, showed a decrease in body and ovary weights in rats with PCOS as a result of the combined treatment of 20 mg/kg/day resveratrol, 300 mg/kg/day metformin and the two in rats with dehydroepiandrosterone-induced PCOS. It was revealed that serum testosterone level also decreases with treatment, and treatment with resveratrol or metformin had a positive effect on folliculogenesis by reducing the inflated number of secondary and atrophic follicles [36]. In another study, it was reported that in patients who received 800 mg/day resveratrol therapy for 40 days, C-reactive protein (CRP), TNF-α, interleukin-6 (IL-6), interleukin-1β (IL-1β), interleukin-18 (IL-18) and NF-κB serum levels dropped. Resveratrol was reported to be a potential therapeutic target for endoplasmic reticulum stress patients with PCOS [37]. Considering that approximately 30–40% of women with PCOS have impaired glucose tolerance and 7.5–10% of women with T2DM, it was assumed that resveratrol consumption may have positive effects in this population. That said, since the evidence examining the effect of resveratrol on the PCOS-related condition is limited, more studies are needed to evaluate this effect [38].

Quercetin

Quercetin (3,5,7,3',4'-pentahydroxyflavone), especially found in foods such as tomatoes, onions, broccoli, apples, blueberries, and grapes, is a flavonoid belonging to the phyto-estrogen plant family [29]. It has high antioxidant potential as well as anti-inflammatory, anti-diabetic, anti-cancer, anti-apoptotic functions. It affects ovarian functions by regulating hormonal indices and the steroidogenic activity of the cell [39]. It also influences the antioxidant capacity of the ovaries by regulating the expression of glutathione peroxidase, catalase, superoxide dismutase, glutathione, glutathione reductase in granulosa cells [40].

In a systematic review study, a positive effect of quercetin on folliculogenesis, luteinization and ovarian histomorphology was revealed [41]. In a randomized clinical trial, PCOS patients were treated with quercetin 1 g/day for 12 weeks. At the end of the treatment, blood glucose and insulin levels were lower in the treatment group. At the same

time, quercetin significantly augmented the transcript expression of adiponectin receptors, adiponectin receptor-1 (ADIPOR 1) and adiponectin receptor-2 (ADIPOR 2). Moreover, quercetin supplementation showed a 12.3% elevation in the level of adenosine 5′ monophosphate-activated protein kinase (AMPK), improving the metabolic properties of PCOS patients [42]. In the study performed by Khorchani et al. [43] in rats with dehydroepiandrosterone-induced PCOS, adiponectin, ADIPOR 1, nesfatin-1 expression got higher after quercetin treatment. As a result of the phytoestrogenic effects of quercetin and its function as estrogen, it improved PCOS [43].

Curcumin

Curcumin is a yellow-orange polyphenolic compound obtained from the rhizome of *Curcuma Longa Linn* and extracted from turmeric [44]. It has a strong antioxidant activity due to the methylene or hydroxyl group of the β-diketone (heptadiene-dione) structure it contains [45]. Alongside this, it has an anti-inflammatory effect and improves lipid abnormalities and insulin resistance. Accordingly, it has an important effect on the treatment of various diseases such as obesity, diabetes, cardiovascular diseases, and metabolic syndrome [46].

In a randomized, double-blind, placebo-controlled study on 60 PCOS patients aged 18–40 years, 500 mg/day curcumin was administered for 12 weeks. It was observed that curcumin treatment resulted in significant reductions in body weight and body mass index (BMI) and improved fasting blood glucose as well as serum insulin levels. It was also reported that curcumin treatment reduced insulin resistance, incremented insulin sensitivity and significantly increased serum HDL-C levels while reducing total cholesterol, LDL-C, and total cholesterol/HDL-C ratio [46]. In another study, 1.5 g/day curcumin supplementation was given to patients with PCOS for 3 months, and it was reported that it significantly upsurged glutathione peroxidase enzyme activity and peroxisome proliferator activated receptor γ coactivator 1α (PGC1α) gene expression [47]. In another study, it was found that fasting blood sugar and DHEA levels were significantly reduced and estradiol levels were increased in women with PCOS who consumed 500 mg of curcumin three times a day for 12 weeks [48]. In another meta-analysis study, it was reported that curcumin significantly improved fasting glucose, fasting insulin, insulin resistance parameters, HDL-C, and total cholesterol [49]. It was suggested that curcumin is likely to be a safe and beneficial supplement to ameliorate PCOS-associated hyperandrogenism and hyperglycemia due to its estrogenic, antihyperlipidemic, antioxidant and hypoglycemic activities [48]. It was reported that curcumin has ovarian protective and anti-aging effects, protects the ovaries against ROS by up-regulating antioxidant enzymes, improves ovarian quality and structure, and accumulates the expression of 3βhydroxysteroid dehydrogenase in granulosa lutein cells and thecal cells [29]. It binds to the active sites of cytochrome p450, inhibits CYP17A1 and CYP19A1 enzymes and inhibits steroidogenesis. Therefore, it can be a treatment option for hyperandrogenism in individuals with PCOS [50]. In another study, it was reported that curcumin may be an option for the treatment of PCOS by increasing insulin sensitivity and by upregulating insulin-sensitive glucose transporter 4 (GLUT-4) in rats with PCOS [51].

Catechin

Green tea produced from *Camellia sinensis* leaves is known for its antioxidant activity, especially because it contains polyphenolic compounds such as catechins [52]. There are various catechins in green tea, including epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG). Many effects of green tea such as antiinflammatory, anticancer, antioxidative, antihyperlipidemic, lowering fasting blood sugar are observed in T2DM patients [53]. Treatment of Leydig cells with epigallocatechin-3-gallate and green tea extract can inhibit testosterone secretion. Green tea has positive effects on androgenism as a result of suppressing the conversion of testosterone into dihydrotestosterone and inhibiting the activation of the 5α-reductase enzyme with epigallocatechin-3-gallate [29]. According to the results of a meta-analysis study, it was reported that green tea supplementation positively affects waist/hip ratio, body weight and glycemic control in women with PCOS [54]. A multiplication in antioxidant enzyme levels such as glutathione peroxidase and superoxide dismutase in ovarian tissues of rats treated with green tea, and a decrease in malodialdehyde levels, which are oxidative stress markers, and 8-hydroxy-20-deoxyguanosine, which is a DNA damage marker, were observed. Furthermore, a decrease in serum inflammatory mediator levels has been reported with catechin treatment [55]. According to the results of another meta-analysis, it has been reported that green tea consumption reduces body weight in women with PCOS, as well as a significant decrease in blood glucose and insulin levels [56]. According to the results of the study conducted on women with obesity and PCOS, after 12 weeks of green tea intervention, significant differences were observed in the mean body weights, fasting blood glucose levels and free testosterone levels of the individuals [57]. In another study conducted on mice, catechins obtained from oolong tea effectively decreased estradiol (E2), FSH, LH levels and LH/FSH ratio in the blood. Besides, it has been reported that proinflammatory factors (IL-1b, IL-6 and TNF-α) down-regulate protein

expressions and p-NF-κB p65 expression in the uterus [58]. In an animal model of polycystic ovary syndrome, it has been reported that green tea improves ovulation and follicle progression and prevents cyst formation [59].

Apigenin

Apigenin (4',5,7,-trihydroxyflavone), which belongs to the class of flavonoids and whose molecular formula is $C_{15}H_{10}O_5$, is found in foods such as orange, grapefruit, parsley, onion, chamomile, tea and wheat sprouts [60]. The anti-cancer, antioxidant, anti-inflammatory, antiviral and antimutagenic effects of apigenin have been revealed in many studies [61]. According to a study in rats with PCOS, an upturn in FSH and progesterone levels, and a decrease in testosterone, estrogen, LH and LH/FSH ratios were observed in the apigenin-treated group. Thanks to apigenin, TNF-α and IL-6 levels dropped significantly, while total antioxidant capacity and superoxide dismutase activity advanced. Compared to the control group, theca layer thickness and the number of cysts decreased in the treatment group [60]. In another study, a swelling in ovarian diameter and cysts and deterioration in lipid profile occurred in rats to which DHEA was injected. After apigenin treatment was applied to rats with polycystic ovary syndrome, an accretion in progesterone levels and a decrease in testosterone and estradiol levels were observed [62].

Other polyphenolic compounds

Rutin, antitumor, antibacterial, antiulcer, antioxidant, immunomodulator, vasoprotective and neuroprotective, and alike are obtained from plants such as apple, onion, tea and constitute a flavonol compound with many activities [63]. In a study, it was observed that routine application in rats proliferated antioxidant activity and the number of cystic follicles in the ovaries decreased [64]. Rats with letrozole-induced PCOS were treated with naringenin, a natural flavanone derived from grapefruit, and given 20 mg/kg/day. It was found that naringenin significantly added onto the activity of enzymes such as superoxide dismutase, glutathione peroxidase and catalase, prevented body weight gain, significantly decreased serum glucose and testosterone levels, and normalized steroidogemic enzyme activity [65]. Gymnemic acids are a polyphenol extracted from the leaves of *Gymnema sylvestre* (*Asclepiadaceae*). It was reported that gymnemic acids regulated the menstrual cycle, decreased BMI, total cholesterol and homocysteine levels, serum testosterone level and gained serum sex hormone binding globulin (SHBG) level in rats with PCOS [66]. Isoflavones from soy are naturally occurring plant components classified as phytoestrogens. Thanks to their phenolic ring structure, isoflavones can act as estrogen by binding to estrogen receptors. In rats with letrozole-induced PCOS, a decrease in body weight, serum testosterone levels, oxidative stress, and the activity of the steroidogenic enzymes 3β-HSD (3β-hydroxy steroid dehydrogenase) and 17β-HSD (17β-hydroxy steroid dehydrogenase) were observed as a result of 100 mg/kg soy isoflavones treatment [67]. According to the results of a meta-analysis study, soy isoflavones reduced serum total testosterone levels in women with PCOS [68]. Gallic acid is another natural polyphenol [29]. In general, studies report that gallic acid reduces PCOS-induced oxidative stress by increasing enzymes such as superoxide dismutase and glutathione peroxidase [69]. The studies on some polyphenols are given in Table 2.

Marrubium vulgare, a flowering plant from the mint family, contains polyphenols and flavonoids [84]. Thanks to the apigenin in its structure, it reduces the secretion of LH. While β-testosterone in its essence reduces LH, β-sitosterol can reduce testosterone secretion by lowering cholesterol [53]. Silymarin, a flavonoid extracted from milk thistle (*Silybum marianum L. Gaernt.*), prevents peroxidation of lipids by inhibiting reactive oxygen species and increasing antioxidant enzyme activity in the body. It has been reported that it decreases gluconeogenesis and thus blood glucose level, decreases serum testosterone levels and moves SHBG levels higher by affecting glucose-6-phosphatase [53, 85].

Anthocyanins are found in saffron (*Crocus sativus L*) leaves, giving it a unique color. Saffron leaves contain kaempferol, phenolic compounds, carotenoids, terpenoids and alkaloids together with anthocyanins [86]. It has been reported that saffron petal extracts (SPE) have antioxidant, antitumor, anti-inflammatory and antidepressant effects [87]. According to a study, it was reported that the number of corpus luteum increased after SPE treatment in mice with PCOS, and the number of cystic follicles decreased with SPE treatment. Aside from this, with SPE treatment, while TNFα, IL1ß, IL6, IL18 and CRP levels lower, glutathione (GSH) and glutathione S-transferase (GST) can increase, it has been found to increase antioxidant factors, decrease various inflammatory markers and reduce PCOS symptoms in mice [88].

Another ingredient that has been the subject of studies on polycystic ovary syndrome is berberine. Berberine derived from *Berberis* plants and *Coptis chinensis Franch* is an isoquinoline alkaloid [89]. It was reported that berberine reduces insulin resistance in polycystic ovary syndrome [88], corrects the abnormal lipid profile formed by inhibiting lipid synthesis [90] and reduces the risk of complications that may occur due to polycystic ovary syndrome [91]. According to a meta-analysis, although berberine is a promising component in the treatment of insulin resistance in PCOS, more studies are needed in this area [92].

Table 2. Some studies on polyphenols

Polyphenol	Study design	Treatment dose	Treatment duration	Effects	References
Cinnamon and ginger	Women with PCOS (n=83)	500 mg cinnamon×3 times a day 500 mg ginger×3 times a day 500 mg metformin×3 times a day	8 weeks	• Decrease in body weight and BMI • Significant reduction in insulin resistance and testosterone levels in the Cinnamon and metformin group ($p<0.05$)	Dastgheib et al., 2022 [70]
Cinnamon and *Lagersroemia speciosa* extract	Women with PCOS (n=62)	100 mg/day	6 months	• Decreased free testosterone ($p<0.05$) • Decreased HOMA-IR and triglyceride levels ($p<0.05$) • Improvement in lipid profile and insulin sensitivity	Permadi et al., 2021 [71]
Cinnamon	Wistar female rat (n=64)	200 mg/kg/day	2 weeks	• Decrease in blood glucose, insulin, and lipid profile in plasma ($p<0.05$) • Enhance in the serum level of HDL-C ($p<0.05$)	Khodaeifar et al., 2019 [72]
Resveratrol	Women with PCOS (n=115)	1st group: 500 mg metformin+15 mg piaglitazone per day; 2nd group: 1000 mg of resveratrol+1000 mg of myoinositol per day	12 weeks	• Decreased in serum testosterone level and BMI ($p<0.001$) • Decreased ovarian volume ($p<0.05$) • Improvement in Ferriman Galwey score and the menstrual cycle ($p<0.05$)	Hassan et al., 2023 [73]
Resveratrol	Women with PCOS (n=41)	1000 mg/day	12 weeks	• Decreased ovarian volume and polycystic ovary morphology ($p<0.05$)	Hashemi et al., 2021 [74]
Resveratrol	Women with PCOS (n=61)	800 mg/day	40 days	• Increase in the ratio of quality oocytes and embryos ($p<0.05$) • Decreased VEGF and HIF1 gene expression ($p<0.001$)	Bahramrezaie et al., 2019 [75]
Resveratrol	Women with PCOS (n=30)	1500 mg/day	12 weeks	• Reduction in dehydroepiandrosterone sulfate ($p<0.05$) • Decreased fasting insulin level ($p<0.05$) Increase in insulin sensitivity index ($p<0.05$)	Banaszewska et al., 2016 [76]
Quercetin	Women with PCOS (n=72)	500 mg/day	40 days	• Decrease in LH, TNF-α and IL-6 levels ($p<0.05$)	Vaez et al., 2023 [77]
Quercetin	Female rat (n=42)	25 mg/kg/day	28 days	• Decreased body weight, free testosterone levels, LH and LH/FSH ratios of rats in the quercetin group ($p<0.05$) • Increased estradiol level, E2/free T ratio ($p<0.05$) • Decreased number of atretic follicles and cyst formation ($p<0.05$)	Mahmoud et al., 2022 [78]
Quercetin	Wistar female rat (n=132)	2 mL/day	28 days	• Decrease in body weight ($p<0.01$) • Decreased insulin and HOMA-IR levels ($p<0.01$) • Inhibition of the Toll-like receptor/NF-κB signaling pathway	Wang et al., 2017 [79]
Curcumin	Women with PCOS (n=100)	80 mg/day	3 months	• Increase in HDL-C levels ($p<0.05$) • Reduction in total cholesterol, triglyceride and LDL-C levels ($p<0.05$) • Decreased total testosterone, fasting insulin and HOMA-IR levels ($p<0.05$)	Sohrevardi et al., 2021 [80]
Curcumin	Women with PCOS (n=60)	500 mg/day	6 weeks	• Improvement in serum insulin and Quantitative Insulin Sensitivity Check Index (QUICKI) levels ($p<0.05$)	Sohaei et al., 2019 [81]
Green tea catechins	Women with PCOS (n=45)	500 mg×3 times a day	12 weeks	• Decrease in BMI, body weight, waist and hip circumference ($p<0.05$)	Farhadian et al., 2020 [82]
Green tea catechins	Women with PCOS (n=45)	500 mg/day	45 days	• Decrease in BMI, body fat percentage and waist circumference ($p<0.05$)	Mombaini et al., 2017 [83]

Abbreviations: PCOS: polycystic ovary syndrome; BMI: body mass index; LH: luteinizing hormone; FSH: follicle stimulating hormone; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; E2: estradiol; IL-1β: interleukin-1β; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; NF-kB: nuclear factor kappa B; HOMA-IR: homeostatic model assessment for insulin resistance.

Aloe vera (*Aloe arborescens*) contains various polysaccharides, nutrients, minerals, salicylic acid, tannins and enzymes. Aloe vera gel is composed of water and polysaccharides such as pectin, cellulose, and hemicellulose. It is rich in vitamins A, C and E and shows antioxidant properties by reducing lipid peroxidation. Its leaves and gels contain active ingredients such as aloe, barbaloin, asmodin [93]. In a study on Swiss albino mice, after the mice were divided into test and control groups, the test group was induced with carboxymethyl cellulose control and letrozole for 21 days and treated with Diane and Aloe vera gel for 30 days. As a result of the treatment, it was observed that hormonal imbalances improved in mice and the findings revealed that Aloe vera could have a therapeutic effect on PCOS symptoms [94].

Chamomile (*Chamomile matricaria*) is used for the treatment in many ailments such as diarrhea, nausea and painful menstrual bleeding. Amino acids, fatty acids, polysaccharides, flavonoids, minerals and phenolic compounds such as coumarone and phytoestrogens constitute its main component [95]. Thanks to these components in its content, it is thought to have positive results in the treatment of PCOS. It has been found that testosterone levels are reduced in PCOS patients given 340 mg of oral chamomile capsules daily for three months. Apart from that, a significant change was found in the lipid parameters, dehydroepiandrosterone sulfate level, and LH/FSH ratios of the patients compared to the control group [96].

Ginseng is a fragrant and durable plant whose antioxidant properties are prominent [93]. It can prevent lipid peroxidation by inhibiting hydroxyl radicals and anions in the cell membrane. It shows a curative effect in the regulation of ovulation by lowering plasma LH levels in PCOS patients [96]. In a study conducted in rats with dehydroepiandrosterone (DHEA)-induced PCOS, Korean red ginseng extract was given at 75–150 mg/kg daily. As a result, it has been shown that the increase in the weight of the ovaries, the increase in serum E2 and testosterone levels are inhibited, and that ginseng may be effective in the treatment of PCOS with its antioxidant and anti-inflammatory properties [97].

Since fennel (*Foeniculum vulgare*) is considered a phytoestrogen, it can be used for therapeutic purposes against hormone and metabolic disorders seen in patients with PCOS [49]. It contains 54.9% linoleic acid, 5.4% oleic acid and 5.4% palmitic acid in its structure. Palmitic acid β oxidation reduces testosterone levels by preventing the formation of dihydrotestosterone complex and may have an anti-androgenic effect [98]. Nevertheless, long-term use of fennel may lower androgen levels in women with PCOS who have a natural menstrual cycle, resulting in decreased LH levels [53]. In another study, three different doses of *Foeniculum vulgare* were injected into rats with PCOS for ten days. A decrease in LH and testosterone levels and a significant increase in FSH levels were observed in the 1000 mg/kg Foeniculum vulgare group [99]. In a randomized controlled study, hypochloric high protein diet with fennel did not make a significant difference in the anthropometric measurements of individuals. It has been reported that more comprehensive studies are needed on this subject [100]. In another study, 61 PCOS patients with oligomenorrhea were divided into two groups and treated for 6 months. Group A received fennel infusion and dry cupping, and group B received metformin treatment. In group A, the mean pain intensity, and the number of days between two menstrual cycles were significantly reduced [101].

Conclusions

The symptoms of polycystic ovary syndrome may develop differently in each woman. It is known that polycystic ovary syndrome is a risk factor for many diseases such as obesity, insulin resistance and dyslipidemia. Involuntary increase in body weight, menstrual cycle irregularities, hair growth and alopecia are observed intensely as a result of the deterioration of hormonal balance due to polycystic ovary syndrome in women. In addition to these effects, it may have similar benefits in protecting the ovaries, inhibiting hyperandrogenism, and reducing serum testosterone levels. Polyphenols are thought to be a therapeutic agent for PCOS due to their dozens of beneficial effects on health, and more comprehensive studies are needed on this subject. Nutrition has an important place in both the formation of symptoms and treatment options in polycystic ovary syndrome, but the studies on this subject are insufficient and there is no specific dietary guide for women with PCOS. That being said, since the positive effects of phytochemicals on metabolic and endocrine parameters have been reported, increasing dietary phytochemical intake seems to be a correct strategy. For this reason, fruit and vegetable consumption should be included in the diet, at least 400 g per day [102]. Evidence-based information needs to be clarified so that clinicians can make informed and calculated decisions about whether to use, how to use, and what doses to use polyphenol-containing foods or extracts for their patients during and after PCOS treatment. Large-scale randomized controlled trials are needed to better understand the effects of polyphenols on PCOS.

This study was planned to elucidate the relationship between PCOS and polyphenols. This study demonstrates the importance of adequate and balanced nutrition in the treatment of PCOS. It states the importance of daily consumption of vegetables and fruits for the possible benefits of polyphenols for PCOS. Since there are more animal studies in the literature, less human studies are included in this review, which is the weakness of this study.

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