Review

Exploring the Therapeutic Potential of Natural Products on Polycystic Ovarian Syndrome (PCOS): A Mini Review of Lipid Profile, Blood Glucose, and Ovarian Histological Improvements

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Exploring the Therapeutic Potential of Natural Products on Polycystic Ovarian Syndrome (PCOS): A Mini Review of Lipid Profile, Blood Glucose, and Ovarian Histological Improvements

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Abstract: Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women, characterized by fluid-filled sacs in the ovaries and various symptoms, including high androgen levels, endometrial irregularities, and cysts. While the main cause of PCOS remains unknown, it has been linked to genetic, endocrine, and metabolic factors, and there are several treatment options, including lifestyle modifications, medications, and surgery. Natural products, such as medicinal plants and fruits, are being explored as potential treatments for PCOS due to their bioactive compounds with pharmacological effects related to antioxidant, antimicrobial, anticancer, and antidiabetic properties. Some of these compounds improve insulin sensitivity, reduce inflammation, and enhance glucose metabolism, benefiting PCOS patients. This mini review examined the effects of natural products on PCOS, including their effects on ovarian histological changes, blood glucose, sex hormones, and lipid profile, based on animal and human studies. This study suggests that the use of natural products as complementary medicine can be a promising resource for the development of effective therapeutics for PCOS but that further research is needed to understand their benefits fully.

Keywords: natural products; polycystic ovarian syndrome; lipid profile; sex hormone; blood glucose

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in women, also known as Stein-Leventhal syndrome [1]. It is a collection of symptoms that affect the ovaries and ovulation. PCOS is a complex disorder due to high androgen levels, irregularities of the endometrium, and some cysts in the ovaries. The leading causes of PCOS are genetic, lifestyle, and environmental factors [2]. PCOS has been associated with genetic, endocrine, and metabolic factors, but the exact cause remains unknown. In addition, it is associated with multiple symptoms such as ovarian enlargement [3] abdominal obesity [4], impaired metabolism disorder [5], insulin resistance [6] type 2 diabetes [7], and dyslipidemia[8].

According to the World Health Organization (WHO), there were 1.55 million cases of PCOS in women aged 15 to 49 years in 2017, an increase of 4.47% (2.86–6.37%) from 2007 [2]. The prevalence rate of this disease was reported to be 5.6–8% in Europe [9]. According to recent studies, the prevalence of PCOS in Malaysia is 36.23% based on the Rotterdam criteria and 6.8% based on the National Institute of Health (NIH) [10]. It has been shown that the cause of infertility is failure to ovulate in about 75% of cases [9]. PCOS has significant implications for achieving the United Nations' Sustainable Development Goals (SDGs), particularly SDG 3 (good health and well-being) [2].

Various therapies have been used to treat PCOS patients, such as lifestyle modification, surgical treatment for ovulation induction, and other medications [11]. Oral contraceptives, metformin, and

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clomiphene are the most commonly used treatments for PCOS. Metformin is commonly used in PCOS patients to treat and alleviate the metabolic issues of glucose tolerance and insulin resistance, and it is especially suggested for the PCOS metabolic phenotype [12]. However, these drugs can cause side effects such as anorexia, diarrhea, and abdominal pain [13]

In recent years, natural products have shown significant phytochemical isolation in improving the condition of PCOS patients [14]. Plants with medicinal value are a part of human culture and tradition. They have significant nutritional value and are prescribed for various therapeutic purposes [15]. Over 21,000 plant species reported by the WHO have therapeutic values and can be used as medicines [16]. Plant, animal, fungus, and microorganism chemicals form natural goods [17]. In this study, we review the effect of natural products on PCOS, including ovarian histological alterations in both animal and human research, as well as blood glucose, sex hormones, and lipid profiles.

2. Methods

The present study examined the mini review of relevant English-language publications published on PCOS, herbs, medicinal herbs, and plants. International databases such as PubMed, Science Direct, Frontiers, Scopus, and ISI repositories from 2010 to 2023 were searched to find animal studies and clinical trials on herbal treatments for PCOS. The current search was conducted using medical terminology terms and combinations of keywords using the following search strategy: "polycystic ovary syndrome" or "PCOS" and "natural plant" or "herb" or "ovarian cysts" or "fruits" or "medicinal herbs." The references cited in each article found by the automated search were also examined. Non-English-language or irrelevant articles were not included in the review. Reviews, case reports, short communications, and letters to the editor, on the other hand, were not included in the study.

3. Literature Review

3.1. Natural Product

Natural products have recently gained popularity due to their potential therapeutic benefits and minimal adverse effects. Natural products have recently gained popularity due to their potential therapeutic benefits and minimal adverse effects. The phytochemicals extracted from medicinal herbs and plants represent a crucial avenue for exploring and identifying innovative pharmaceutical agents [18]. They have been used for centuries for various medicinal purposes [17]. Many medicinal plants have been reported to exhibit several pharmacological effects related to vital functions, namely antioxidant, antimicrobial, anticancer, and antidiabetic properties [15]. Since plants serve as repositories for various phytochemicals, they can treat various diseases. These chemicals include alkaloids, flavonoids, terpenoids, phenolic acids, and other compounds [15]. Each of these compounds has a unique chemical composition and mode of action, which may be the reason for their various medicinal benefits [17].

Alkaloids are a class of nitrogen-containing plant chemicals with many biological functions [19]. Nevertheless, based on the existing body of literature, it is evident that alkaloids exhibit limited promise in the treatment of PCOS. *Berberis darwinii Hook* [20], *Berberis aquifolium Pursh*. [21] and *Berberis aristata DC*. [22], has improved anti-inflammatory, anti-cancer, and antidiabetic in PCOS patients [23].

Another compound found in natural herbs is quercetin (3,5,7,3′,4′-pentahydroxyflavone), a dietary flavonoid found in numerous fruits and vegetables. It has garnered significant attention due to its antioxidative, anti-inflammatory, antitumor, hypoglycemic, cardiovascular protective, and other properties in regulating ovarian function and preserving ovarian morphology [24–26]. The research revealed that quercetin, which serves as the primary constituent of the Kuntai capsule, a proprietary Chinese medicine, exhibits a significant overlap with potential therapeutic targets for treating polycystic ovary syndrome (PCOS) [27]

Terpenoids are broad and varied bioactive compounds present in numerous plants, fungi, and mammals [28]. Terpenoids, including ginsenosides in ginseng, have anti-inflammatory, antioxidant, anti-obesity, and anti-diabetic properties [28]. Limonene, found in citrus fruits, has high potential antioxidant properties and has been shown to improve lipid metabolism and reduce inflammation [29,30]. Besides that, many seeds, skins of fruits, leaves of vegetables, and cereals contain a group of

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substances known as phenolic acids. They are known for their anti-inflammatory and antioxidant effects [31,32]. Some of them have been shown to help women with PCOS improve their insulin sensitivity and reduce insulin resistance [32]. For example, studies in women with PCOS have shown that chlorogenic acid in coffee and many fruits reduces insulin resistance and enhances glucose metabolism [33]. Several other bioactive chemicals discovered in natural products have also shown beneficial effects on PCOS symptoms. These include omega-3 fatty acids in fish and nuts and resveratrol in red grapes and peanuts [34].

Flavonoids represent a significant class of biologically active compounds commonly present in nature. They exhibit a diverse range of physiological effects, including anti-inflammatory properties [35], antioxidative activity [36], hypoglycemic effects [37], antiviral properties [38], and antitumor activity [37]

Overall, natural products offer a variety of bioactive substances that could be therapeutically useful for PCOS-affected women. Natural products represent a viable avenue for alternative or complementary therapy for PCOS treatment, although further studies are needed to understand their benefits fully. Table 1 summarizes studies of characteristics and lipid profiles, sex hormones, blood glucose, and histological changes.

Table 1. Summary of study characteristics and lipid profile, sex hormones, blood glucose, and histological changes.

References	Intervention	Time of experiment and sample size	Study design	Lipid profile	Sex hormone	Blood glucose	Histological changes
Ibrahim et al., 2022	Pomegranate juice extract (PJE) 400mg/kg/day	3 weeks + 40 rats	Animal	Not measured	FSH: increase LH: increase Testosterone: increase Progesterone: Not measured	Not measured	Increase in endometrial collagen content.
Aliakbari et al., 2022	*B. Persicum* capsule 60 mg + *F. Vulgare* capsule 25 mg.	4 months + 70 women with PCOS	Human	Not measured	FSH: Increase LH: decrease Testosterone: Increase Progesterone: Increase	Not measured	Corpus luteum: not measure. Number follicles: decrease.
Younas et al., 2022	Ethanolic extract of *Fagonia indica* 500 mg/kg	Seven weeks + 25 female rats	Animal	TG: decrease TC: decrease LDL: decrease HDL: Increase	FSH: Increase LH: decrease Testosterone: decrease Progesterone: Increase	Not measured	Corpus luteum: not measure. Number follicles: decrease.
Younas et al., 2022	Kelulut honey (0.5 g/kg/days, 1g/kg/day, 2g/kg/day)	35 days + 24 female rats	Animal	Not measured	Not measured	Not significant	Corpus luteum: decrease Number follicles: decrease.
Gharanjik et al., 2022	Hydroalcoholic extract of *Calendula officinalis* (200, 500, and 1000 mg/kg).	35 days + 60 female adult rats	Animal	Not measured	FSH: Increase LH: decrease Testosterone: increase Progesterone: increase	Decrease	Corpus luteum: decrease Number follicles: decrease.
Peng et al., 2021	*Eucommia ulmoides Oliv.* Leaves (TFEL)	21 days + 60 rats	Animal	Not measured	Not measured	Decrease	Corpus luteum: decrease Number follicles: decrease.
Khani et al., 2021	Hydroalcoholic extract of N. Sativa seeds (50, 100 and 200 mg/kg).	30 days + 36 rats.	Animal	Not measured	FSH: decrease LH: increase Testosterone: Decrease Progesterone: Not measured	Decrease	Corpus luteum: increase Number follicles: decrease.
Permadi et al., 2021	100 mg of *C. Burmanii* + *L. Spesiosa* extract	+ 62 volunteers with PCOS	Human	TG: decrease TC: decrease LDL: unchanged HDL: decrease	FSH: Not measured LH: Not measured Testosterone: Decrease Progesterone: Not measured	Not measured	Not measured

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Yahay et al., 2021	25g of Canola and olive oil	10 weeks + 72 women	Human	TG: decrease TC: decrease LDL: decrease HDL: decrease	Not measured	Not measured	Not measured
Mehraban et al., 2020	Combination of spearmint extract (SE) and flaxseed extract (FE).	30 days + 24 rats	Animal	Not measured	FSH: Not measured LH: Not measured Testosterone: increase Progesterone: increase	Not measured	Corpus luteum: decrease Number follicles: decrease
Mvondo et al., 2020	Aqueous *M. Arboreus* extract (20, 110 and 200 mg/kg)	30 days + 60 adult rats	Animal	Not measured	FSH: Not measured. LH: increase Testosterone: increase Progesterone: Not measured	Not measured	Corpus luteum: increase Number follicles: decrease
Rababa'h et al., 2020)	Majoram extract (20mg/kg)	3 weeks + 75 adult rats	Animal	Not measured	FSH: Not measured LH: Not measured Testosterone: increase Progesterone: increase	Not measured	Not measured
Ashkar et al., 2020	Hydroalcoholic extract of *Berberis integerrima* and resveratrol (3g/kg of barberry and 20g/kg resveratrol)	42 days + 70 adult rats	Animal	TG: Increase TC: Increase LDL: Increase HDL: Decrease	Not measured	Unchanged	Corpus luteum: Increase Number follicles: Decrease
Kakadia et al., 2019	Thylakoid-rich spinach extract and aqueous extract of caraway (*Carum carvi L.*)	8 weeks + 60 rats	Animal	TG: Decrease TC: Decrease LDL: Decrease HDL: Increase	FSH: Unchanged LH: Decrease Testosterone: Not measured Progesterone: Not measured	Decrease	Corpus luteum: Increase Number follicles: Decrease
Kakadia et al., 2019	*Vitex negundo L.* Extract, 200 and 400 mg/kg	40 days + 30 rats	Animal	TG: Increase TC: Unchanged LDL: Not measured. HDL: Unchanged	FSH: Decrease LH: Decrease Testosterone: Increase Progesterone: Decrease	Decrease	Corpus luteum: Increase Number follicles: Decrease
Ndeingang et al., 2019	Methanolic extract of *P. Muellerianus* (30,60, 120 mg/kg)	14 days + 114 rats	Animal	TG: Unchanged TC: Decrease LDL: Decrease HDL: Increase	FSH: Unchanged LH: decrease Testosterone: Decrease Progesterone: Decrease	Decrease	Corpus luteum: Increase Number follicles: Decrease

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Dou et al., 2018	Cinnamon powder (10mg/100g)	20 days + 50 mice	Animal	Not measured	FSH: Increase LH: Decrease Testosterone: Decrease Progesterone: not measure	Decrease	Corpus luteum: Increase Number follicles: Decrease
Mannerås et al., 2010	Malaysian herb *Labisia pumila var. Alata* (LPva) extract (50 mg/kg)	5 weeks + 20 rats	Animal	TG: unchanged TC: unchanged LDL: unchanged HDL: unchanged	Not measured	Not measured	Not measured

* TC, Total cholesterol; TG, triglyceride: HDL, high-density lipoprotein: LDL, low-density lipoprotein: LH, luteinizing hormone: FSH, Follicle-stimulating hormone

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3.2. Lipid Profile Improvement

All aspects of the lipid profile could be affected if the patient has PCOS. Several studies showed the potential of natural products to help improve the lipid profiles associated with PCOS [39]. Dyslipidemia is a condition characterized by abnormal levels of lipids in the blood. It is often characterized by high levels of triglycerides (TG) and low levels of high-density lipoprotein (HDL). These abnormal lipid levels can increase the risk of cardiovascular disease, stroke, and other health problems [40]. Dyslipidemia is not a main diagnostic criterion but a significant metabolic abnormality [46]. It has been discovered that low-density lipoprotein (LDL), TG, and HDL have a 70% prevalence in PCOS patients [39]. Dyslipidemia in PCOS is related to hyperandrogenism, in which androgens decrease the catabolic clearance of LDL through their interaction with the androgen receptor (AR) [41]. Dyslipidemia was also found to impact PCOS patients' long-term outcomes.

3.2.1. Low-Density Lipoprotein (LDL)

Previous studies show that LDL is elevated in women with PCOS, which is unusual for insulin-resistant conditions. Although the cause of the elevated LDL levels in women with PCOS is unknown, they may be linked to hyperandrogenism or a genetic component [39]. According to the review, several studies show significant reductions in LDL levels [42–45]. The reduction in LDL levels is due to the presence of polyphenols. According to some research, resveratrol is an example of a polyphenol that may benefit lipid metabolism and LDL cholesterol levels. Their antioxidant and anti-inflammatory properties may be responsible for these effects [17,46]. The studies showed that natural products have flavonoids, among the phytochemicals found in natural plants, that have demonstrated the ability to lower LDL cholesterol levels [39] Quercetin, catechins, and anthocyanins are some flavonoids linked to potential cardiovascular advantages, such as lowering LDL cholesterol levels [47,48]. By lowering LDL oxidation, enhancing endothelial function, and modifying lipid metabolism, flavonoids may have an effect. These phytochemicals can lower LDL cholesterol levels by several mechanisms, including lowering LDL oxidation, increasing LDL receptor activity, inhibiting cholesterol synthesis, and altering lipid metabolism [49].

Three studies show unchanged LDL levels [50–52]. PCOS is characterized by hormonal imbalances, including elevated levels of androgens such as testosterone. While these hormonal imbalances can affect lipid metabolism and contribute to changes in HDL (high-density lipoprotein) cholesterol levels, they may have a lesser impact on LDL cholesterol [53]. Insulin resistance is a common feature of PCOS, where the body has difficulty effectively utilizing insulin. Insulin resistance can lead to dyslipidemia, an abnormal lipid profile characterized by elevated triglycerides and decreased HDL cholesterol levels. However, the impact on LDL cholesterol may be less pronounced [8].

3.2.2. High-Density Lipoprotein (HDL)

Studies show PCOS increases HDL levels in blood serum [26,29], and several studies show versa result [43,44,50,54]. This condition happens due to hormonal imbalances and insulin resistance. PCOS is characterized by hormonal imbalances, including elevated levels of androgens such as testosterone. It has been suggested that increased androgen levels can stimulate the liver to produce more HDL cholesterol [55]. Insulin resistance is a common feature of PCOS, where the body has difficulty effectively utilizing insulin. Insulin resistance can lead to dyslipidemia, an abnormal lipid profile characterized by elevated triglycerides and decreased HDL cholesterol [56]. However, HDL levels can be increased in some PCOS patients, potentially due to compensatory mechanisms or other factors associated with the condition. Olive oil, which includes extra virgin olive oil in the diet, has been shown to positively impact lipid profiles, including increasing HDL cholesterol levels. Olive oil is a monounsaturated fat that can be used as a healthier alternative to saturated and trans fats [43]. Obesity and a sedentary lifestyle are common in PCOS and can further contribute to dyslipidemia, including decreased HDL cholesterol levels [57]. Lack of physical activity and excess body weight can negatively affect lipid levels[58].

Based on this review, the studies show that the level of HDL remains unchanged. Genetic factors could be the causes of influence HDL cholesterol levels [59,60]**.** Some individuals may have a genetic predisposition to higher or lower HDL cholesterol levels, which may remain relatively stable despite

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lifestyle changes or treatments. Flavonoids and resveratrol have the potential to improve HDL cholesterol levels.

3.2.2. Triglycerides (TG)

Several studies showed a significant decrease in TG levels in PCOS patients [42–44,50]. Catechins and flavonoids have been linked to a potential reduction in triglyceride levels, which has high antioxidant and anti-inflammatory effects [28,48,61,62]. Moreover, resveratrol is also associated with improved lipid profiles and may help lower TG levels [54]. Studies show an increase in TG levels after receiving natural products that are used as treatment [51,54] Insulin resistance in PCOS often results in hyperinsulinemia. Insulin plays a role in lipid metabolism and can stimulate the liver to produce more triglycerides [56]. High insulin levels also decrease the breakdown of TG in fat tissue, further contributing to elevated triglyceride levels. PCOS is characterized by imbalances in female sex hormones, including elevated levels of androgens such as testosterone. These hormonal imbalances can impact lipid metabolism and increase TG levels [8,53].

In summary, natural products can potentially improve the lipid profiles of women with PCOS through their anti-hyperlipidemic effects, glucose metabolism enhancement, enhancement of absorption, and alteration of serum biochemical variables related to lipolysis [11]. Further research is needed to fully understand natural products' mechanisms of action and determine their optimal dosage and treatment duration for PCOS patients.

3.3. Blood Glucose Improvement

Blood glucose levels are a significant symptom commonly observed in PCOS patients [39]. Consequently, pharmacological agents that enhance insulin sensitivity are incorporated into the therapeutic regimen for polycystic ovary syndrome [[63]. PCOS has been proposed as a condition characterized by oxidative stress [64]**.** The human body's antioxidant function is insufficient to effectively manage an excessive presence of reactive oxygen species (ROS**)** [65]**.** This inadequacy contributes to the worsening of clinicopathologic characteristics associated with PCOS in patients, including chronic oligo-anovulation or anovulation, clinical or biochemical indications of hyperandrogenism, and the presence of polycystic ovarian morphology. In the interim, elevated levels of oxidative stress exacerbate the physiological response and frequently coincide with the presence of insulin resistance.

Several studies showed significant improvement in blood glucose levels after receiving the natural product used as their treatment [44,45,47,51,66–68]. The improvement in blood glucose levels shows a decreased tolerance to glucose. Most natural products may increase this glucose tolerance, which has phytochemical properties such as thylakoid, flavonoid, and phenolic compounds in that extract that can affect the secretion and metabolism of insulin and its action [32,48].

Based on previous studies, phenolic compounds can be found in cinnamon and berberine. Cinnamon is a spice from the Cinnamomum genus and contains phenolic compounds that may improve insulin sensitivity and glucose uptake and reduce fasting blood glucose levels in individuals with PCOS [50,68]. Berberine, found in plants like barberry, has potential antidiabetic effects. Flavonoids can be found in berries and olive oil, which act as anti-diabetics, improve glucose metabolism and insulin sensitivity and reduce inflammation. These anti-diabetic effects in natural product help manage diabetes in PCOS patients [69].

In addition, natural products in plants can decrease glucose resistance by increasing insulin levels and regulating glucose production. Therefore, the natural products that are found help to reduce glucose resistance by controlling glucose homeostasis, improving insulin secretion, and enhancing insulin-mediated glucose uptake [47]. Impaired glucose metabolism is highly prevalent in women suffering from PCOS, which can lead to diabetes mellitus type 2 [70]. Meanwhile, several studies reported no significant difference after the treatment [20,21]. Abnormal production of blood glucose levels in PCOS patients has been associated with deficient insulin secretion. Rosklint et al. reported that high androgen production could cause insulin resistance [71]. According to earlier research, androgen may contribute to insulin resistance and alter how insulin functions in the target tissue in PCOS [71].

Although investigations into the therapeutic efficacy of natural products for managing polycystic ovary syndrome (PCOS) and enhancing blood glucose levels are still underway,

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preliminary results indicate their potential to ameliorate the metabolic irregularities linked to the disorder. Nevertheless, additional meticulously planned clinical trials are necessary to establish these organic substances' effectiveness, ideal dosage, and enduring impacts.

3.4. Sex Hormones Improvement

Measurement of sex hormone levels, especially testosterone and luteinizing hormone (LH), is recommended for PCOS diagnosis [18]. Low levels of progesterone and follicle-stimulating hormone (FSH) and increased serum levels of LH and testosterone are the most reliable indicators of PCOS in women [23]. The induction of PCOS and treatment with various extracts have been shown to decrease testosterone and LH levels and increase progesterone and FSH levels [24].

3.4.1 Testosterone

Several studies have shown elevated serum testosterone levels [42,45,50,67,68]. PCOS is characterized by elevated serum testosterone levels, known as hyperandrogenism. The multifactorial cause involves hormonal imbalances, insulin resistance, hyperinsulinemia, and elevated LH levels [53]. Ovarian dysfunction disrupts normal ovulation, leading to excessive androgen production. Insulin resistance causes cells to become less responsive to insulin, resulting in higher blood levels [53,70]. Hyperinsulinemia stimulates the ovaries to produce more androgens, including testosterone[72]. Elevated LH levels contribute to increased androgen production in the ovaries [42,43]. Some examples include spearmint tea and flaxseed. Spearmint tea has been investigated for its potential anti-androgenic effects, while flaxseed contains lignans, which have been studied for their potential hormonal effects [73].

Several studies reported that the testosterone level increased after receiving the treatment [66,74–77]. the presents of tumors have the potential to overproduce androgens, which would result in increased testosterone levels. Supplements and drugs can also directly raise serum testosterone levels. Hormone imbalances can cause symptoms like hirsutism, acne, and irregular menstrual cycles [53,55,63].

3.4.2 Progesterone

Progesterone is primarily produced by the ovaries in females and, to a lesser extent, by the adrenal glands in both males and females. Progesterone, whose synthesis depends on the corpus luteum, regulates reproductive cycles and assists the uterus in implantation in the event of conception [78]. Progesterone levels significantly increased after treatment in several studies [42,66,73,75] and significantly decreased in another study [45,51]. phytoestrogen properties contain compounds that mimic or interact with estrogen in the body. Plants that contain isoflavones have estrogenic effects, which can help increase the level of progesterone in PCOS patients [17,32].

3.4.3 Luteinizing Hormone (LH)

Polycystic ovary syndrome (PCOS) is an endocrine disorder that is distinguished by the presence of heightened levels of luteinizing hormone (LH). The cause is unclear, but it is believed to be related to hormonal imbalances and disrupted feedback mechanisms in the reproductive system [70]. Factors contributing to increased LH levels include excessive androgen production, insulin resistance, dysregulated gonadotropin-releasing hormone (GnRH), and disrupted feedback mechanisms. These factors can lead to anovulation, menstrual irregularities, and increased androgen production [79]. Not all women with PCOS will experience the same degree of LH elevation, and individual symptoms and hormonal profiles can vary [53,70,79]. Studies reported that LH decreased significantly after natural treatment [33,42,44,45,51,66,75]. Phytoestrogens are plant compounds that have estrogenic effects. Some phytoestrogens, such as genistein and daidzein found in soy and other legumes, may have mild estrogenic activity and interact with estrogen receptors in the body. While their effects on LH specifically are not well established, phytoestrogens can influence hormonal balance and feedback mechanisms [17,32].

3.4.3 Follicle-Stimulating Hormone (FSH)

FSH showed an increase in several studies involving in vivo and clinical studies of patients with PCOS [33,74,75]. Polycystic ovary syndrome (PCOS) affects follicle-stimulating hormone (FSH)

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levels, a hormone crucial for ovarian follicle growth and development. Disrupted feedback mechanisms, insulin resistance, and dysregulated GnRH can lead to increased FSH levels [53,70,79]. Hormonal imbalances in PCOS vary among individuals, and the exact mechanisms underlying these increases are still under investigation. These imbalances contribute to characteristic features of PCOS, such as irregular menstrual cycles, anovulation, and ovarian cyst formation. while several studies reported that there are still changes [44,45]. A complex interplay of hormones influences FSH levels, and elevated FSH levels can be a result of hormonal imbalances in the body [70]. If the treatment primarily focuses on addressing other hormonal imbalances, such as reducing luteinizing hormone (LH) levels or insulin resistance, it may not directly impact FSH levels. In polycystic ovarian syndrome, abnormal steroidogenesis is manifested by an increase in the production of androgen and estradiol, and the malfunctioning hypothalamic-pituitary-ovarian axis is manifested by an increase in the secretion of LH and GnRH and a reduction in FSH concentration [63].

3.5. Histological Changes Improvement

Plant-based or herbal natural products have demonstrated potential for mitigating the histological alterations linked to PCOS. As the review demonstrates, several studies have concentrated on hormonal interventions and developmental stages that resulted in changes in ovarian morphology, most commonly an increase in the number of antral and cystic follicles and a decrease in the corpus luteum. An increase in progesterone levels is associated with reduced corpus luteum production [74,80]. Ndeingang et al. (2019) reported that the number of cystic and antral follicles decreased and increased in the corpus luteum after receiving the treatment [45]. Studies reported that the number of cysts decreased and antral follicles increased in the corpus luteum after the treatment [42,44,45,47,51,54,67,68,73,75,76]. Natural product treatments can impact the number of ovarian cysts, antral follicles, and the corpus luteum. Enhanced corpus luteum formation, a temporary structure that develops from the ruptured follicle after ovulation, is crucial for maintaining the uterine lining for a potential pregnancy [48,55,56]. These treatments can help regulate hormone levels, improve insulin sensitivity, reduce inflammation, and support ovarian function.

Kakadia et al. (2019) reported that ovarian histology in the treatment group showed normal follicular development and decreased cyst formation. Gharanjik et al. (2022) and Sherafatmanesh et al. (2020) reported that the corpus luteum increased and the antral follicle did not change significantly. The number of cystic follicles may decrease due to decreased serum testosterone levels [81]. This occurs because most natural compounds contain flavonoids, which have antioxidant properties and can reduce free radical formation in the ovary [12,49,82]. In general, the conclusions of studies on hormonal interventions and developmental stages at the time of the studies varied widely. Most resulted in ovarian morphological changes, mainly an increase in the number of antral and cystic follicles and a decrease in the size of the corpus luteum. Using androgens and natural products acting as stimulants could produce a hyperandrogenic state.

3.6. The Efficacy of Natural Products and Drugs Therapy

Along with being more affordable and having fewer side effects, natural medicines like plants and herbs have long been utilized to treat several gynecological conditions [17]**.** A variety of disorders, including PCOS, have been helped by the use of numerous herbal treatments. PCOS patients' metabolic problems had been the focus of the positive effects on PCOS symptoms. Due to high financial expenditures and many adverse consequences connected with the use of allopathic drugs, the demand for herbal remedies has surged [16]**.**

Plant sources' antioxidant and anti-inflammation potential have been widely studied for a long time. Most natural products can improve the PCOS hormones because they contain various phytochemicals [12,49,83]. Based on the review show that most natural products have anti-inflammatory and antioxidants which can help with PCOS symptoms [62]. The review by Ashkar et al. and Rababa'h et al., 2020) stated that the combination of resveratrol, barberry, and marjoram has a high level of antioxidant and anti-inflammation to regenerate ovarian morphology and improves PCOS symptoms[23,69]. Sherafatmanesh et al., in the year 2020, also stated that the combination of spinach and caraway has a high level of antioxidants such as flavonoids, antiobesity, and anti-hyperlipidemia [44]. Kakadia et al. and Gharanjik et al., (2022), stated that *Vitex negundo L* and *Calendula officinalis* has anti-inflammatory antioxidant that has been used in gynecological disorder

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due to the phenolic compound in the extract. *N. Sativa* seeds have hypoglycemic properties and anti-inflammation, which help to improve the hormonal level [51,66]. Strong antioxidant properties protect the body from the damaging effects of free radicals and improve ovarian morphology, hence can improve PCOS symptoms.

Elevated levels of androgens are also one of the major etiologies behind PCOS. Some natural products have anti-androgenic and antiestrogenic, which can help improve the hormonal level in PCOS patients [53,55]**.** Based on previous studies, natural products contain a high level of anti-androgenic and antiestrogenic which can improve endocrine secretion, including estradiol, progesterone, and testosterone levels [66,84]. Besides, Aliakbari et al., in the year 2022, stated that the combination of *B. Persicum capsule and F. Vulgare* has a phytoestrogen which can help in hirsutism, BMI, and menstrual duration improvement. Antiandrogenic may help it helps the body to maintain biosynthesis and the release of estrogen [84]. The phenolic compound in natural products shows effectiveness against PCOS [31,32]**.** Most plants have anti-inflammation and antioxidant properties, showing anti-PCOS efficacy [36,40,41].

Drug therapy helps to treat hyperandrogenism, infertility, or other conditions depending on the identification and management of symptoms. Patients with PCOS who wanted to regain fertility had been treated with metformin and clomiphene [11]. However, metformin is one of the medicines used in insulin sensitizers in treating PCOS and has long been used to treat type 2 diabetes [11,70]. While others medicine such as clomiphene, have been used to treat infertility, women with PCOS have been advised to take metformin if they have low lipid profiles, glucose intolerance, or both [48]. Diarrhea, nausea, and gastrointestinal disorders have also been linked to the complex long-term use of both medicines [53]. Patients with PCOS whom Infertility are frequently advised to use oral contraceptives, whose main purpose is to regulate menstruation [70]. These medications also lower testosterone levels, which reduces hirsutism, acne, and hirsutism. These drugs are more effective at treating androgenic symptoms than earlier versions. Long-term oral contraceptive use can result in body weight gain, nausea, vomiting, and arterial hypertension. Spironolactone and gonadotropins are other treatment options [53,70]. In PCOS patients, both medications were utilized to inhibit androgen. Long-term gonadotropin therapy for women with anovulatory PCOS can result in vaginal dryness, depression, and bone mass loss. Spironolactone is the most widely used antiandrogen, which is safe, readily available, and inexpensive [11]. The negative effects of prolonged use may result in irregular menstrual cycles, hyperkalemia, and hypotension [53,70]

Although drug therapy is more specifically targeted in PCOS symptoms and leads to more satisfactory clinical results. Based on the review, drug therapy also can lead to other complications for PCOS patients. Natural products are safe and effective therapy over metformin for treating polycystic ovarian syndrome, preferably combined with improved hormone levels, hirsutism, and insulin resistance.

Table 2. Summaries of Summary of different treatment options in the management of PCOS.

Drugs	Effects	Adverse Effects
drugs therapy		
Metformin	Reduce insulin sensitivity, improve lipid profile, help in reducing body weight, Infertility treatment	Diarrhea, nausea, gastrointestinal disorder
Clomiphene	Infertility treatment	Headache, nausea, abdominal pain
Oral contraceptive	Restore regular periods, reduce symptoms of hyperandrogenism	Nausea, vomiting, body weight gain, arterial hypertension

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Gonadotropins	Inhibit androgen	Vaginal dryness, depression, loss of bone mass
Spironolactone	Inhibit androgen	Irregular Menstrual cycles, Hyperkalemia, Hypotension
anti-inflammatory		
insulin-sensitizing effects	Inhibit androgen	Irregular Menstrual cycles, Hyperkalemia, Hypotension
Natural product		
Pomegranate juice extract	Improve endometrial receptivity and normalize the hormonal level.	No side effects
Combination of B. Persicum and F. Vulgare	Decrease hirsutism, and BMI and increase menstrual duration.	No side effects
Fagonia indica	Restore ovarian morphology and down-regulate serum levels of testosterone.	No side effects
Calendula officinalis	Restore blood glucose and promote folliculogenesis in the ovarian tissue.	No side effects
Olive leaves	Inhibit ovarian hyperplasia and restore blood glucose.	No side effects
N. Sativa seeds	Improve the hormone level in PCOS	No side effects
Combination of C. Burmanii and L. Spesiosa extract	Improve testosterone level in PCOS.	No side effects
Combination of Canola and olive oil	Improve endometrial receptivity and normalize the hormonal level.	No side effects
Combination of spearmint and flaxseed	Improves LH levels and promote folliculogenesis	No side effects
M. Arboreus	Restore ovarian morphology and improve level of testosterone.	No side effects
Majoram extract	Improve the PCOS symptoms	No side effects

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Combination *Berberis integerrima* and resveratrol	Improve biochemical factor and regenerate the ovarian morphology.	No side effects.
Combination of spinach and caraway	Improve biochemical factor and regenerate the ovarian morphology.	No side effects
Vitex negundo L.	Improve the sex hormones levels, restore the blood glucose and ovarian histology.	No side effects
P. Muellerianus	Improve blood glucose, lipid profile, oxidative stress and prevent ovarian damage.	No side effects
Cinnamon powder	Improve ovary morphology, improve level of testosterone and insulin sensitivity	No side effects
Labisia pumila var. Alata (LPva)	Improve lipid profile and insulin resistance	No side effect

4. Conclusion

PCOS is a prevalent endocrine disorder among women from adolescence to pre-menopause. The condition is associated with various complications, such as infertility, metabolic and cardiovascular disorders, and chronic health issues that may persist throughout an individual's lifetime. Pharmaceutical interventions have demonstrated effective management of Polycystic Ovary Syndrome (PCOS); however, significant incidences of adverse drug reactions raise concerns regarding their potential for long-term curative benefits. Patients are turning to herbal therapy as a substitute for synthetic medications in managing and treating PCOS to improve recovery rates and increase acceptance. The present review offers a comprehensive analysis of herbal remedies that confer benefits for PCOS and its associated complications. This review shows that natural products can help people with PCOS because of the phytochemicals contained in the plant itself. These natural products can alleviate the changes in ovarian histology, blood glucose and serum hormone levels, and lipid profile. Therefore, natural products as alternative medicine can be considered promising resources for developing effective therapeutics for PCOS.

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References

1. Kurzrock, R.; Cohen, P.R. Polycystic Ovary Syndrome in Men: Stein–Leventhal Syndrome Revisited. *Med Hypotheses* **2007**, *68*, 480–483, doi:10.1016/j.mehy.2006.03.057.
2. Sikiru, A.B.; Adeniran, M.A.; Akinola, K.; Behera, H.; Kalaignazhal, G.; Egena, S.S.A. Unraveling the Complexity of the Molecular Pathways Associated with Polycystic Ovary Syndrome (PCOS) and Identifying Molecular Targets for Therapeutic Development: A Review of Literature. *Middle East Fertil Soc J* **2023**, *28*, 16, doi:10.1186/s43043-023-00142-w.
3. Azziz, R.; Carmina, E.; Chen, Z.; Dunaif, A.; Laven, J.S.E.; Legro, R.S.; Lizneva, D.; Natterson-Horowtiz, B.; Teede, H.J.; Yildiz, B.O. Polycystic Ovary Syndrome. *Nat Rev Dis Primers* **2016**, *2*, 16057, doi:10.1038/nrdp.2016.57.
4. Zhu, T.; Cui, J.; Goodarzi, M.O. Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease, and Stroke. *Diabetes* **2021**, *70*, 627–637, doi:10.2337/db20-0800.
5. Escobar-Morreale, H.F. Polycystic Ovary Syndrome: Definition, Aetiology, Diagnosis and Treatment. *Nat Rev Endocrinol* **2018**, *14*, 270–284, doi:10.1038/nrendo.2018.24.
6. Escobar-Morreale, H.F. Polycystic Ovary Syndrome: Definition, Aetiology, Diagnosis and Treatment. *Nat Rev Endocrinol* **2018**, *14*, 270–284, doi:10.1038/nrendo.2018.24.
7. Sermondade, N.; Huberlant, S.; Bourhis-Lefebvre, V.; Arbo, E.; Gallot, V.; Colombani, M.; Fréour, T. Female Obesity Is Negatively Associated with Live Birth Rate Following IVF: A Systematic Review and Meta-Analysis. *Hum Reprod Update* **2019**, *25*, 439–451, doi:10.1093/humupd/dmz011.
8. Chen, W.; Pang, Y. Metabolic Syndrome and PCOS: Pathogenesis and the Role of Metabolites. *Metabolites* **2021**, *11*, 869, doi:10.3390/metabo11120869.
9. Liu, J.; Wu, Q.; Hao, Y.; Jiao, M.; Wang, X.; Jiang, S.; Han, L. Measuring the Global Disease Burden of Polycystic Ovary Syndrome in 194 Countries: Global Burden of Disease Study 2017. *Human Reproduction* **2021**, *36*, 1108–1119, doi:10.1093/humrep/deaa371.
10. Gao, Y.; Liu, H.; Qiao, L.; Liang, J.; Yao, H.; Lin, X.; Gao, Y. Study of Burden in Polycystic Ovary Syndrome at Global, Regional, and National Levels from 1990 to 2019. *Healthcare (Switzerland)* **2023**, *11*, doi:10.3390/healthcare11040562.
11. Jin, P.; Xie, Y. Treatment Strategies for Women with Polycystic Ovary Syndrome. *Gynecological Endocrinology* 2018, *34*, 272–277.
12. Alahmadi, A.A.; Alzahrani, A.A.; Ali, S.S.; Alahmadi, B.A.; Arab, R.A.; El-Shitany, N.A.E.A. Both Matricaria Chamomilla and Metformin Extract Improved the Function and Histological Structure of Thyroid Gland in Polycystic Ovary Syndrome Rats through Antioxidant Mechanism. *Biomolecules* **2020**, *10*, doi:10.3390/biom10010088.
13. Bednarska, S.; Siejka, A. The Pathogenesis and Treatment of Polycystic Ovary Syndrome: What's New? *Advances in Clinical and Experimental Medicine* 2017, *26*, 359–367.
14. Ma, Q. wen; Tan, Y. Effectiveness of Co-Treatment with Traditional Chinese Medicine and Letrozole for Polycystic Ovary Syndrome: A Meta-Analysis. *J Integr Med* 2017, *15*, 95–101.
15. Palanisamy, C.P.; Cui, B.; Zhang, H.; Panagal, M.; Paramasivam, S.; Chinnaiyan, U.; Jeyaraman, S.; Murugesan, K.; Rostagno, M.; Sekar, V.; et al. *Anti-Ovarian Cancer Potential of Phytocompound and Extract from South African Medicinal Plants and Their Role in the Development of Chemotherapeutic Agents*; 2021; Vol. 11;.
16. Chakraborty, P. Herbal Genomics as Tools for Dissecting New Metabolic Pathways of Unexplored Medicinal Plants and Drug Discovery. *Biochim Open* 2018, *6*, 9–16.
17. Atanasov, A.G.; Zotchev, S.B.; Dirsch, V.M.; Orhan, I.E.; Banach, M.; Rollinger, J.M.; Barreca, D.; Weckwerth, W.; Bauer, R.; Bayer, E.A.; et al. Natural Products in Drug Discovery: Advances and Opportunities. *Nat Rev Drug Discov* 2021, *20*, 200–216.
18. Khatoon, E.; Banik, K.; Harsha, C.; Sailo, B.L.; Thakur, K.K.; Khwairakpam, A.D.; Vikkurthi, R.; Devi, T.B.; Gupta, S.C.; Kunnumakkara, A.B. Phytochemicals in Cancer Cell Chemosensitization: Current Knowledge and Future Perspectives. *Semin Cancer Biol* **2022**, *80*, 306–339, doi:10.1016/j.semcancer.2020.06.014.
19. Kukula-Koch, W.A.; Widelski, J. Alkaloids. In *Pharmacognosy*; Elsevier, 2017; pp. 163–198.
20. Fajardo Morales, V.; Araya, M.; Manosalva, L. Berberis Darwinii Hook. In; 2021; pp. 127–133.
21. Riley, D.S. Mahonia Aquifolium. In *Materia Medica of New and Old Homeopathic Medicines*; Springer International Publishing: Cham, 2022; pp. 167–169.

22. Tamane, P.; Mahadik, K.; Pokharkar, V. Buccal Spray of Standardized Berberis Aristata Extract Causes Tumour Regression, Chemoprotection and Downregulation of Inflammatory Mediators in Oral Cancer Hamster Model. *J Ethnopharmacol* **2023**, *317*, 116732, doi:10.1016/j.jep.2023.116732.
23. Ionescu, O.-M.; Frincu, F.; Mehedintu, A.; Plotogea, M.; Cirstoiu, M.; Petca, A.; Varlas, V.; Mehedintu, C. Berberine-A Promising Therapeutic Approach to Polycystic Ovary Syndrome in Infertile/Pregnant Women. *Life (Basel)* **2023**, *13*, doi:10.3390/life13010125.
24. Li, X.; Ma, J.; Guo, L.; Dong, C.; Zhu, G.; Hong, W.; Chen, C.; Wang, H.; Wu, X. Identification of Bioactive Compounds and Potential Mechanisms of Kuntai Capsule in the Treatment of Polycystic Ovary Syndrome by Integrating Network Pharmacology and Bioinformatics. *Oxid Med Cell Longev* **2022**, *2022*, 1–11, doi:10.1155/2022/3145938.
25. Chen, T.; Jia, F.; Yu, Y.; Zhang, W.; Wang, C.; Zhu, S.; Zhang, N.; Liu, X. Potential Role of Quercetin in Polycystic Ovary Syndrome and Its Complications: A Review. *Molecules* **2022**, *27*, 4476, doi:10.3390/molecules27144476.
26. Pourteymour Fard Tabrizi, F.; Hajizadeh-Sharafabad, F.; Vaezi, M.; Jafari-Vayghan, H.; Alizadeh, M.; Maleki, V. Quercetin and Polycystic Ovary Syndrome, Current Evidence and Future Directions: A Systematic Review. *J Ovarian Res* **2020**, *13*, 11, doi:10.1186/s13048-020-0616-z.
27. Li, W.; Li, D.; Kuang, H.; Feng, X.; Ai, W.; Wang, Y.; Shi, S.; Chen, J.; Fan, R. Berberine Increases Glucose Uptake and Intracellular ROS Levels by Promoting Sirtuin 3 Ubiquitination. *Biomedicine & Pharmacotherapy* **2020**, *121*, 109563, doi:10.1016/j.biopha.2019.109563.
28. Sülsen, V.P.; Lizarraga, E.; Mamadalieva, N.Z.; Lago, J.H.G. Potential of Terpenoids and Flavonoids from Asteraceae as Anti-Inflammatory, Antitumor, and Antiparasitic Agents. *Evidence-Based Complementary and Alternative Medicine* **2017**, *2017*, 1–2, doi:10.1155/2017/6196198.
29. Frabasile, S.; Koishi, A.C.; Kuczera, D.; Silveira, G.F.; Verri, W.A.; Duarte dos Santos, C.N.; Bordignon, J. The Citrus Flavanone Naringenin Impairs Dengue Virus Replication in Human Cells. *Sci Rep* **2017**, *7*, 41864, doi:10.1038/srep41864.
30. Kicinska, A.; Kampa, R.P.; Daniluk, J.; Sek, A.; Jarmuszkiewicz, W.; Szewczyk, A.; Bednarczyk, P. Regulation of the Mitochondrial BKCa Channel by the Citrus Flavonoid Naringenin as a Potential Means of Preventing Cell Damage. *Molecules* **2020**, *25*, 3010, doi:10.3390/molecules25133010.
31. Ozcan, T.; Akpinar-Bayizit, A.; Yilmaz-Ersan, L.; Delikanli, B. Phenolics in Human Health. *International Journal of Chemical Engineering and Applications* **2014**, *5*, 393–396, doi:10.7763/IJCEA.2014.V5.416.
32. Kumar, N.; Goel, N. Phenolic Acids: Natural Versatile Molecules with Promising Therapeutic Applications. *Biotechnology Reports* **2019**, *24*, e00370, doi:10.1016/j.btre.2019.e00370.
33. Yanagimoto, A.; Matsui, Y.; Yamaguchi, T.; Hibi, M.; Kobayashi, S.; Osaki, N. Effects of Ingesting Both Catechins and Chlorogenic Acids on Glucose, Incretin, and Insulin Sensitivity in Healthy Men: A Randomized, Double-Blinded, Placebo-Controlled Crossover Trial. *Nutrients* **2022**, *14*, 5063, doi:10.3390/nu14235063.
34. Amini, M.; Bahmani, F.; Foroozanfard, F.; Vahedpoor, Z.; Ghaderi, A.; Taghizadeh, M.; Karbassizadeh, H.; Asemi, Z. The Effects of Fish Oil Omega-3 Fatty Acid Supplementation on Mental Health Parameters and Metabolic Status of Patients with Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of Psychosomatic Obstetrics & Gynecology* **2018**, 1–9, doi:10.1080/0167482X.2018.1508282.
35. Maleki, S.J.; Crespo, J.F.; Cabanillas, B. Anti-Inflammatory Effects of Flavonoids. *Food Chem* **2019**, *299*, 125124, doi:10.1016/j.foodchem.2019.125124.
36. Shen, N.; Wang, T.; Gan, Q.; Liu, S.; Wang, L.; Jin, B. Plant Flavonoids: Classification, Distribution, Biosynthesis, and Antioxidant Activity. *Food Chem* **2022**, *383*, 132531, doi:10.1016/j.foodchem.2022.132531.
37. Sun, Q.; Liu, Q.; Zhou, X.; Wang, X.; Li, H.; Zhang, W.; Yuan, H.; Sun, C. Flavonoids Regulate Tumor-Associated Macrophages – From Structure-Activity Relationship to Clinical Potential (Review). *Pharmacol Res* **2022**, *184*, 106419, doi:10.1016/j.phrs.2022.106419.
38. Badshah, S.L.; Faisal, S.; Muhammad, A.; Poulson, B.G.; Emwas, A.H.; Jaremko, M. Antiviral Activities of Flavonoids. *Biomedicine & Pharmacotherapy* **2021**, *140*, 111596, doi:10.1016/j.biopha.2021.111596.
39. Desai, B.N.; Maharjan, R.H.; Nampoothiri, L.P. Aloe Barbadensis Mill. Formulation Restores Lipid Profile to Normal in a Letrozole-Induced Polycystic Ovarian Syndrome Rat Model. *Pharmacognosy Res* **2012**, *4*, 109–115, doi:10.4103/0974-8490.94736.

40. Karimi, E.; Heshmati, J.; Shirzad, N.; Vesali, S.; Hosseinzadeh-Attar, M.J.; Moini, A.; Sepidarkish, M. The Effect of Synbiotics Supplementation on Anthropometric Indicators and Lipid Profiles in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. *Lipids Health Dis* **2020**, *19*, doi:10.1186/s12944-020-01244-4.
41. Meshkani, M.; Saedisomeolia, A.; Yekaninejad, M.; Mousavi, S.A.; Ildarabadi, A.; Vahid-Dastjerdi, M. The Effect of Green Coffee Supplementation on Lipid Profile, Glycemic Indices, Inflammatory Biomarkers and Anthropometric Indices in Iranian Women With Polycystic Ovary Syndrome: A Randomized Clinical Trial. *Clin Nutr Res* **2022**, *11*, 241, doi:10.7762/cnr.2022.11.4.241.
42. Younas, A.; Hussain, L.; Shabbir, A.; Asif, M.; Hussain, M.; Manzoor, F. Effects of Fagonia Indica on Letrozole-Induced Polycystic Ovarian Syndrome (PCOS) in Young Adult Female Rats. *Evidence-based Complementary and Alternative Medicine* **2022**, *2022*, doi:10.1155/2022/1397060.
43. Yahay, M.; Heidari, Z.; Allameh, Z.; Amani, R. The Effects of Canola and Olive Oils Consumption Compared to Sunflower Oil, on Lipid Profile and Hepatic Steatosis in Women with Polycystic Ovarian Syndrome: A Randomized Controlled Trial. *Lipids Health Dis* **2021**, *20*, doi:10.1186/s12944-021-01433-9.
44. Sherafatmanesh, S.; Ekramzadeh, M.; Tanideh, N.; Golmakani, M.T.; Koohpeyma, F. The Effects of Thylakoid-Rich Spinach Extract and Aqueous Extract of Caraway (Carum Carvi L.) in Letrozole-Induced Polycystic Ovarian Syndrome Rats. *BMC Complement Med Ther* **2020**, *20*, doi:10.1186/s12906-020-03044-w.
45. Ndeingang, E.C.; Defo Deeh, P.B.; Watcho, P.; Kamanyi, A. Phyllanthus Muellerianus (Euphorbiaceae) Restores Ovarian Functions in Letrozole-Induced Polycystic Ovarian Syndrome in Rats. *Evidence-based Complementary and Alternative Medicine* **2019**, *2019*, doi:10.1155/2019/2965821.
46. Mcdougall, G.J.; Stewart, D. *The Inhibitory Effects of Berry Polyphenols on Digestive Enzymes*; IOS Press, 2005; Vol. 23;.
47. Peng, M. fan; Tian, S.; Song, Y. gang; Li, C. xia; Miao, M. san; Ren, Z.; Li, M. Effects of Total Flavonoids from Eucommia Ulmoides Oliv. Leaves on Polycystic Ovary Syndrome with Insulin Resistance Model Rats Induced by Letrozole Combined with a High-Fat Diet. *J Ethnopharmacol* **2021**, *273*, doi:10.1016/j.jep.2021.113947.
48. Darabi, P.; Khazali, H.; Mehrabani Natanzi, M. Therapeutic Potentials of the Natural Plant Flavonoid Apigenin in Polycystic Ovary Syndrome in Rat Model: Via Modulation of pro-Inflammatory Cytokines and Antioxidant Activity. *Gynecological Endocrinology* **2020**, *36*, 582–587, doi:10.1080/09513590.2019.1706084.
49. Borzoei, A.; Rafraf, M.; Niromanesh, S.; Farzadi, L.; Narimani, F.; Doostan, F. Effects of Cinnamon Supplementation on Antioxidant Status and Serum Lipids in Women with Polycystic Ovary Syndrome. *J Tradit Complement Med* **2018**, *8*, 128–133, doi:10.1016/j.jtcme.2017.04.008.
50. Permadi, W.; Hestiantoro, A.; Ritonga, M.; Ferrina, A.; Iswari, W.; Sumapraia, K.; Muharram, R.; Djuwantono, T.; Wiweko, B.; Tjandrawinata, R. Administration of Cinnamon and Lagersroemia Speciosa Extract on Lipid Profile of Polycystic Ovarian Syndrome Women with High Body Mass Index. *J Hum Reprod Sci* **2021**, *14*, 16–20, doi:10.4103/jhrs.JHRS_141_20.
51. Kakadia, N.; Patel, P.; Deshpande, S.; Shah, G. Effect of Vitex Negundo L. Seeds in Letrozole Induced Polycystic Ovarian Syndrome. *J Tradit Complement Med* **2019**, *9*, 336–345, doi:10.1016/j.jtcme.2018.03.001.
52. Mannerås, L.; Fazliana, M.; Wan Nazaimoon, W.M.; Lönn, M.; Gu, H.F.; Östenson, C.G.; Stener-Victorin, E. Beneficial Metabolic Effects of the Malaysian Herb Labisia Pumila Var. Alata in a Rat Model of Polycystic Ovary Syndrome. *J Ethnopharmacol* **2010**, *127*, 346–351, doi:10.1016/j.jep.2009.10.032.
53. Witchel, S.F.; Oberfield, S.E.; Peña, A.S. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. *J Endocr Soc* **2019**, *3*, 1545–1573, doi:10.1210/js.2019-00078.
54. Ashkar, F.; Eftekhari, M.H.; Tanideh, N.; Koohpeyma, F.; Mokhtari, M.; Irajie, C.; Iraji, A. Effect of Hydroalcoholic Extract of Berberis Integerrima and Resveratrol on Ovarian Morphology and Biochemical Parameters in Letrozole-Induced Polycystic Ovary Syndrome Rat Model: An Experimental Study. *Int J Reprod Biomed* **2020**, *18*, 637–650, doi:10.18502/ijrm.v13i8.7505.
55. Abasian, Z.; Rostamzadeh, A.; Mohammadi, M.; Hosseini, M.; Rafieian-kopaei, M. A Review on Role of Medicinal Plants in Polycystic Ovarian Syndrome: Pathophysiology, Neuroendocrine Signaling, Therapeutic Status and Future Prospects. *Middle East Fertil Soc J* 2018, *23*, 255–262.
56. Fulghesu, A.M.; Piras, C.; Dessì, A.; Succu, C.; Atzori, L.; Pintus, R.; Gentile, C.; Angioni, S.; Fanos, V. Urinary Metabolites Reveal Hyperinsulinemia and Insulin Resistance in Polycystic Ovarian Syndrome (Pcos). *Metabolites* **2021**, *11*, doi:10.3390/metabo11070437.

57. Raja-Khan, N.; Stener-Victorin, E.; Wu, X.; Legro, R.S. The Physiological Basis of Complementary and Alternative Medicines for Polycystic Ovary Syndrome. *Am J Physiol Endocrinol Metab* **2011**, *301*, 1–10, doi:10.1152/ajpendo.00667.2010.-Polycystic.
58. Banting, L.K.; Gibson-Helm, M.; Polman, R.; Teede, H.J.; Stepto, N.K. Physical Activity and Mental Health in Women with Polycystic Ovary Syndrome. *BMC Womens Health* **2014**, *14*, doi:10.1186/1472-6874-14-51.
59. Escobar-Morreale, H.F. Polycystic Ovary Syndrome: Definition, Aetiology, Diagnosis and Treatment. *Nat Rev Endocrinol* **2018**, *14*, 270–284, doi:10.1038/nrendo.2018.24.
60. Palomba, S.; de Wilde, M.A.; Falbo, A.; Koster, M.P.H.; La Sala, G.B.; Fauser, B.C.J.M. Pregnancy Complications in Women with Polycystic Ovary Syndrome. *Hum Reprod Update* **2015**, *21*, 575–592, doi:10.1093/humupd/dmv029.
61. Zhou, Y.; Lv, L.; Liu, Q.; Song, J. Total Flavonoids Extracted from Nervilia Fordii Function in Polycystic Ovary Syndrome through IL-6 Mediated JAK2/STAT3 Signaling Pathway. *Biosci Rep* **2019**, *39*, doi:10.1042/BSR20181380.
62. Zhou, Y.; Lv, L.; Liu, Q.; Song, J. Total Flavonoids Extracted from Nervilia Fordii Function in Polycystic Ovary Syndrome through IL-6 Mediated JAK2/STAT3 Signaling Pathway. *Biosci Rep* **2019**, *39*, doi:10.1042/BSR20181380.
63. Heshmati, J.; Omani-Samani, R.; Vesali, S.; Maroufizadeh, S.; Rezaeinejad, M.; Razavi, M.; Sepidarkish, M. The Effects of Supplementation with Chromium on Insulin Resistance Indices in Women with Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Hormone and Metabolic Research* 2018, *50*, 193–200.
64. Bandariyan, E.; Mogheiseh, A.; Ahmadi, A. The Effect of Lutein and Urtica Dioica Extract on in Vitro Production of Embryo and Oxidative Status in Polycystic Ovary Syndrome in a Model of Mice. *BMC Complement Med Ther* **2021**, *21*, doi:10.1186/s12906-021-03229-x.
65. Sies, H.; Jones, D.P. Reactive Oxygen Species (ROS) as Pleiotropic Physiological Signalling Agents. *Nat Rev Mol Cell Biol* **2020**, *21*, 363–383, doi:10.1038/s41580-020-0230-3.
66. Gharanjik, F.; Shojaeifard, M.B.; Karbalaei, N.; Nemati, M. The Effect of Hydroalcoholic Calendula Officinalis Extract on Androgen-Induced Polycystic Ovary Syndrome Model in Female Rat. *Biomed Res Int* **2022**, *2022*, doi:10.1155/2022/7402598.
67. Khani, S.; Abdollahi, M.; Khalaj, A.; Heidari, H.; Zohali, S. The Effect of Hydroalcoholic Extract of Nigella Sativa Seed on Dehydroepiandrosterone-Induced Polycystic Ovarian Syndrome in Rats: An Experimental Study. *Int J Reprod Biomed* **2021**, *19*, 271–282, doi:10.18502/ijrm.v19i3.8575.
68. Dou, L.; Zheng, Y.; Li, L.; Gui, X.; Chen, Y.; Yu, M.; Guo, Y. The Effect of Cinnamon on Polycystic Ovary Syndrome in a Mouse Model. *Reproductive Biology and Endocrinology* **2018**, *16*, doi:10.1186/s12958-018-0418-y.
69. Wang, Z.; Nie, K.; Su, H.; Tang, Y.; Wang, H.; Xu, X.; Dong, H. Berberine Improves Ovulation and Endometrial Receptivity in Polycystic Ovary Syndrome. *Phytomedicine* **2021**, *91*, 153654, doi:10.1016/j.phymed.2021.153654.
70. Bednarska, S.; Siejka, A. The Pathogenesis and Treatment of Polycystic Ovary Syndrome: What's New? *Advances in Clinical and Experimental Medicine* **2017**, *26*, 359–367, doi:10.17219/acem/59380.
71. Rosklint, T.; Ohlsson, B.G.; Wiklund, O.; Norén, K.; Hultén, L.M. *Oxysterols Induce Interleukin-1 β β β β Production in Human Macrophages*; 2002; Vol. 32;.
72. Nestler, J. Role of Hyperinsulinemia in the Pathogenesis of the Polycystic Ovary Syndrome, and Its Clinical Implications. *Semin Reprod Med* **1997**, *15*, 111–122, doi:10.1055/s-2007-1016294.
73. Mehraban, M.; Jelodar, G.; Rahmanifar, F. A Combination of Spearmint and Flaxseed Extract Improved Endocrine and Histomorphology of Ovary in Experimental PCOS. *J Ovarian Res* **2020**, *13*, doi:10.1186/s13048-020-00633-8.
74. Ibrahim, M.A.A.; Sadek, M.T.; Sharaf Eldin, H.E.M. Role of Pomegranate Extract in Restoring Endometrial Androgen Receptor Expression, Proliferation, and Pinopodes in a Rat Model of Polycystic Ovary Syndrome. *Morphologie* **2022**, *106*, 145–154, doi:10.1016/j.morpho.2021.04.004.
75. Aliakbari, F.; Mirsadeghi, M.N.; Hashemi, E.; Rahimi-Madiseh, M.; Mohammadi, B. Effects of Combination Therapy with Bunium Persicum and Foeniculum Vulgare Extracts on Patients with Polycystic Ovary Syndrome. *Adv Biomed Res* **2022**, *11*, 74, doi:10.4103/abr.abr_163_21.

76. Mvondo, M.A.; Mzemdem Tsoplfack, F.I.; Awounfack, C.F.; Njamen, D. The Leaf Aqueous Extract of Myrianthus Arboreus P. Beauv. (Cecropiaceae) Improved Letrozole-Induced Polycystic Ovarian Syndrome Associated Conditions and Infertility in Female Wistar Rats. *BMC Complement Med Ther* **2020**, *20*, doi:10.1186/s12906-020-03070-8.
77. Rababa'h, A.M.; Matani, B.R.; Ababneh, M.A. The Ameliorative Effects of Marjoram in Dehydroepiandrosterone Induced Polycystic Ovary Syndrome in Rats. *Life Sci* **2020**, *261*, doi:10.1016/j.lfs.2020.118353.
78. Kausar, F.; Rather, M.A.; Bashir, S.M.; Alsaffar, R.M.; Nabi, S. ul; Ali, S.I.; Goswami, P.; Ahmad, A.; Rashid, S.; Wali, A.F. Ameliorative Effects of Cuscuta Reflexa and Peucedanum Grande on Letrozole Induced Polycystic Ovary Syndrome in Wistar Rats. *Redox Report* **2021**, *26*, 94–104, doi:10.1080/13510002.2021.1927396.
79. Huang, D.; Jaswa, E.; Kao, C.N.; Quinn, M.; Cedars, M.; Huddleston, H. Predictors of Adequate Physical Activity within a Multiethnic Polycystic Ovary Syndrome Patient Population: A Cross-Sectional Assessment. *BMC Womens Health* **2021**, *21*, doi:10.1186/s12905-021-01257-w.
80. Kamal, D.A.M.; Ibrahim, S.F.; Ugusman, A.; Mokhtar, M.H. Effects of Kelulut Honey on Oestrus Cycle Regulation and Histomorphological Changes in Letrozole-Induced Polycystic Ovary Syndrome Rats: A Preliminary Study. *Life* **2022**, *12*, doi:10.3390/life12060890.
81. Moshfegh, F.; Balanejad, S.Z.; Shahrokhabady, K.; Attaranzadeh, A. Crocus Sativus (Saffron) Petals Extract and Its Active Ingredient, Anthocyanin Improves Ovarian Dysfunction, Regulation of Inflammatory Genes and Antioxidant Factors in Testosterone-Induced PCOS Mice: Saffron Petal and Its Total Anthocyanin Effects on PCOS. *J Ethnopharmacol* **2022**, *282*, doi:10.1016/j.jep.2021.114594.
82. Wang, J.; Qian, X.; Gao, Q.; Lv, C.; Xu, J.; Jin, H.; Zhu, H. Quercetin Increases the Antioxidant Capacity of the Ovary in Menopausal Rats and in Ovarian Granulosa Cell Culture in Vitro. *J Ovarian Res* **2018**, *11*, 51, doi:10.1186/s13048-018-0421-0.
83. Darabi, P.; Khazali, H.; Mehrabani Natanzi, M. Therapeutic Potentials of the Natural Plant Flavonoid Apigenin in Polycystic Ovary Syndrome in Rat Model: Via Modulation of pro-Inflammatory Cytokines and Antioxidant Activity. *Gynecological Endocrinology* **2020**, *36*, 582–587, doi:10.1080/09513590.2019.1706084.
84. Gulan, T.; Yeernuer, T.; Sui, S.; Mayinuer, N. A Rat Model of Maternal Polycystic Ovary Syndrome Shows That Exposure to Androgens in Utero Results in Dysbiosis of the Intestinal Microbiota and Metabolic Disorders of the Newborn Rat. *Medical Science Monitor* **2019**, *25*, 9377–9391, doi:10.12659/MSM.918600.
85. Aliakbari, F.; Mirsadeghi, M.N.; Hashemi, E.; Rahimi-Madiseh, M.; Mohammadi, B. Effects of Combination Therapy with Bunium Persicum and Foeniculum Vulgare Extracts on Patients with Polycystic Ovary Syndrome. *Adv Biomed Res* **2022**, *11*, 74, doi:10.4103/abr.abr_163_21.
86. Gharanjik, F.; Shojaeifard, M.B.; Karbalaei, N.; Nemati, M. The Effect of Hydroalcoholic Calendula Officinalis Extract on Androgen-Induced Polycystic Ovary Syndrome Model in Female Rat. *Biomed Res Int* **2022**, *2022*, doi:10.1155/2022/7402598.
87. Khani, S.; Abdollahi, M.; Khalaj, A.; Heidari, H.; Zohali, S. The Effect of Hydroalcoholic Extract of Nigella Sativa Seed on Dehydroepiandrosterone-Induced Polycystic Ovarian Syndrome in Rats: An Experimental Study. *Int J Reprod Biomed* **2021**, *19*, 271–282, doi:10.18502/ijrm.v19i3.8575.