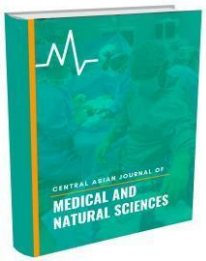

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Article

Medicinal Plants: The Potential of Combining a Group of Medicinal Plants to Avoid the Risks of Polycystic Ovary Syndrome Treatments: A Narrative Review 2010-2024

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Abstract: Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age, characterized by ovarian cysts and hormonal imbalances. While estrogen and combination hormone therapies are commonly used for managing menopausal symptoms, concerns exist about their potential risks. Recently, phytoestrogen-rich plants and medicinal herbs have gained attention as alternative therapies for PCOS. This review examines 18 studies to assess the efficacy of herbal treatments for PCOS, with data sourced from Scopus, PubMed, and Google Scholar. The analysis highlights the chemical properties, mechanisms of action, and therapeutic benefits of several herbs, demonstrating their potential in mitigating PCOS symptoms. The findings underscore the need for further research to validate the effectiveness of these alternative remedies.

Keywords: Curcuma longa, Vitex negundo seed, Carum carvi L, Flaxseeds, Momordica charantia, Inonotus obliquus, Polycystic ovary syndrome, Metformine

1. Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent metabolic illness affecting women who are fertile. There are a number of factors that contribute to PCOS development, but genetic predisposition is likely the main one. Lifestyle and environmental factors also have an impact [1]. Worldwide, 11–13% of women suffer from PCOS. Insulin resistance and hyperandrogenism are two characteristics of PCOS that greatly contribute to the early onset of type 2 diabetes and an elevated risk of cardiovascular disease. Menstrual cycle irregularities, anovulatory infertility, and an elevated risk of endometrial cancer and pregnancy difficulties are among the reproductive repercussions.

Along with its physiological symptoms, PCOS is linked to eating disorders, anxiety, depression, psychosexual dysfunction, and negative body image. Taken together, these conditions lower patients' quality of life when it comes to their health. Even though it was very common up until menopause [2]. Depression risk is raised and mental health is impacted by PCOS. Apart from these anatomical irregularities, a robust correlation exists between PCOS and psychological illnesses. In addition to eating disorders including bulimia, anorexia, or other eating disorders, women with PCOS are more likely to experience depression, substance abuse problems, and bipolar disorder. These mental health conditions can have a major negative effect on PCOS sufferers' quality of life. [3].

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The prevalence of any eating disorder in women with PCOS ranges from 0% to 62%. Compared to controls, women with PCOS had a 3- to 6-fold increased risk of eating disorders, a 30% increased risk of bulimia nervosa, and a 3-fold increased risk of binge eating disorder. There has been little research on anorexia nervosa and other particular eating disorders or feeding disorders (such night eating syndrome), and there hasn't been any indication that these conditions are more common in PCOS. As far as we are aware, no research has been published on pica in PCOS, rumination disorder, or avoidant/restrictive food intake problem. Research has indicated a robust correlation among eating disorders, body dissatisfaction, and weight gain in individuals with PCOS. Although the exact cause of PCOS eating problems is unknown, psychological, metabolic, hypothalamic, and genetic variables are thought to be involved. [4]. Its diverse symptomatology, which includes oligomenorrhea, excess androgens that result in a masculinized appearance, and/or many follicular ovaries, define its heterogeneous nature.

Although the exact cause of this complicated ailment is yet unknown, experts believe that multisystemic linkages play a role in the disease's pathophysiology. There has been discussion of metabolic inflexibility, aberrant gonadal signaling patterns, and environmental, genetic, and developmental variables. Since PCOS is a chronic endocrine condition, there is currently no known cure; instead, treatment for its primary symptoms involves a combination of medication and easy lifestyle changes. [5]. PCOS is a complex, multifactorial disease linked to genes, environment and possibly lifestyle. Due to its heterogeneous clinical manifestations, the etiology of this syndrome is poorly understood. Therefore, the management of this disease remains a challenge due to its multiple consequences [6].

Endocrine-disrupting chemicals (EDCs) are present in everything we use in our daily lives. These are phenols or halogens such as chlorine and bromine [7] . They function similarly to steroid hormones. One of the contributing factors to PCOS is prolonged, continuous exposure to EDCs from infancy through puberty [8] . Bisphenol A (BPA), used in food and beverage packaging and many other purposes, interferes with oogenesis [9] . Bisphenol A interferes with the growth and maturation of oocytes by affecting granulosa cells and reducing the expression of aromatase and estrogen synthesis. Additionally, BPA strongly binds to sex hormone binding globulin (SHBG), dislodging testosterone and raising the level of free testosterone in the process. Increased testosterone lowers the amount of BPA cleared by the liver and deactivates uridine diphosphate-glucuronosyltransferase. As a result, it raises blood levels of free BPA, which has additional detrimental effects on the ovaries. [10].

BPA regulates genes involved in lipogenesis and activates glucocorticoid receptors, thus acting as an obesogen. BPA also triggers the release of interleukin 6 (IL6) and tumor necrosis factor α (TNF-α), leading to obesity and insulin resistance. BPA also affects glucose homeostasis by directly affecting pancreatic cells. Advanced glycosylation end products (AGEs), also called glycotoxins, are pro-inflammatory molecules that affect women's health. They interact with a surface receptor called RAGE (AGE receptor) and stimulate pro-inflammatory pathways and oxidative [11]. In general, polycystic ovaries are formed when they are stimulated to produce large amounts of androgens. Insulin resistance genes and inflammation are associated with excessive production of androgens. Figure (1) shows some inflammatory mediators in patients with polycystic ovary syndrome, where a decrease in the level of interleukin 10 and an increase in the levels of interleukins (6, 8, 18, 33), C-reactive protein (CRP), and tumor necrosis factor were observed [12].

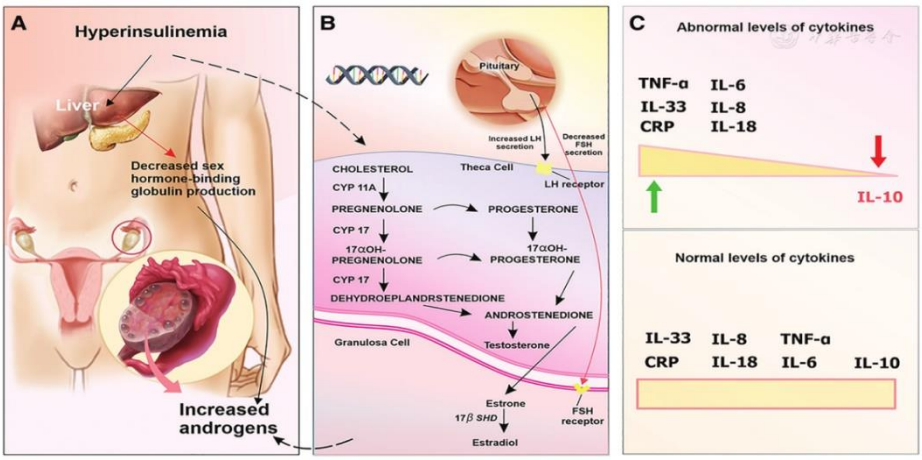

Figure 1. Shows the relationship between polycystic ovary syndrome and some physiological factors and disorders.

On the emotional and physical level, chronic stress causes adipocyte hyperplasia and hyperplasia, which stimulates the secretion of adipokine and the activation of adipose stromal immune cells [13]. Prolonged stress also alters the ratio of oxidation to antioxidants and raises levels of inflammatory cytokines including TNF-α and IL-6. It contributes to the rise in insulin resistance. The hypothalamic-pituitary axis releases cortisol in response to stress. By promoting visceral fat storage, gluconeogenesis, lipolysis, and increased hepatic glucose production, cortisol causes insulin resistance. Stress's impact on PCOS may show changes in sex hormone levels and interference with anti-Müllerian hormone (AMH)[14].

Oxidative stress also leads to the overproduction of oxidative chemicals and causes various damages to biomolecules, including DNA, proteins, and fats. The insulin signaling pathway is inhibited by oxidative stress, which also increases IR. Stress due to oxidation causes fat [15]. Obesity is another factor that may contribute to PCOS because it can result in insulin resistance, hyperinsulinemia, and hyperandrogenism. Blood levels of non-esterified fatty acids (NEFAs) may rise as a result of visceral obesity. As a result, cytokines like TNF and IL6 are released, which are also in charge of adrenal steroidogenesis and hyperandrogenism. In addition to limiting insulin clearance, this inflammatory process brought on by fat also plays a role in hyperinsulinemia. High amounts of leptin are produced by adipocytes, which restrict the expression of aromatase mRNA in granulosa cells, stop androgens from being converted to estrogens, and impede the development of ovarian follicles. [16].

Treatment for PCOS should be customized for each patient in order to satisfy their demands and avoid long-term problems. It is advised that patients who are overweight or obese develop appropriate eating habits, stick to a low-energy diet, and exercise to the extent that their bodies can handle it. Even modest weight loss (2–5% of starting body weight) has measurable health advantages. Menstrual cycle regulation may occur automatically as a result of normalizing testosterone levels, which is positively impacted by reducing insulin resistance. This is the most basic and economical non-pharmacological therapeutic method [17]. Treatment suggestions for symptoms like oligoovulation, hirsutism, and irregular menstrual periods are included in the worldwide guidelines for PCOS.

Adjusting one's lifestyle to include a healthy diet, regular exercise, rest, and stress management is the first step toward restoring normal blood insulin levels. When compared to progestin-only formulations, combined oral contraceptives have demonstrated superior efficacy in treating acne, hirsutism, and irregular menstrual periods. Given that there is no proof that one particular combination of progestin and estrogen is better than another, patients can select combined oral contraceptives depending on their preferences and desire to minimize side effects, One treatment used

for PCOS is metformin, which leads to a slight to moderate improvement in menstrual regularity and is less effective than oral contraceptives. Direct evidence suggests a slight improvement in menstrual regulation with lifestyle with metformin compared to lifestyle [18].

But there has been a greater focus on plants and herbs. The antibacterial, antiviral, antiulcer, anticytotoxic, anticancer, anti-inflammatory, antioxidant, antihypertensive, hepatoprotective, antilipidic, and antiplatelet polyphenolic chemicals found in medicinal plants are among its numerous advantageous qualities. Additionally, a number of studies have demonstrated that, with only minor adverse effects, herbal therapy can help individuals with PCOS by minimizing ovarian cysts, improving hyperandrogenism, and restoring aromatase function [19].

2. Materials and Methods

Inclusion criteria and methods

The review followed the criteria of the Narrative Article Evaluation Scale [20]. It was conducted using a number of databases, including PubMed, Scopus, and Google Scholar. The search terms used were “medicinal plants” or “herbal plants” along with “insulin resistance” or “contraceptives” and “side effects”. "Hyperandrogens" "Obesity" "Oxidative stress" "Emotional stress" "Environmental factors" "Type 2 diabetes" "Vitamin D3" "Heart disease" "Phenols" Through this calculated step, a comprehensive collection of research on the negative and positive effects of medicinal plants on patients with polycystic ovary syndrome will be produced.

Data extraction:

The method used in the entire literature review process, from the first database search to the final round of study selection for review. Description of the amount of papers found, screened and evaluated, ultimately leading to the final selection of relevant research to be included in the review.

Results:

The review of 20 studies [21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38] showed mixed results regarding the effect of medicinal plants on different health aspects. Details of these studies on health, side effects and health are provided For PCOS in Table (1).

Table (1) shows the medicinal plants used in the treatment of PCOS

1-Curcuma longa				
Authors	**Year**	**Effects on**	**Outcomes**	**Reference**
Gupte et al	2023	Sex hormone on PCOS	4 weeks	**[21]**
Alavez	2016	Sex hormone on PCOS	12 weeks	**]22[**
Wahyuni et al	2024	Insulin resistants on PCOS		**]23[**
2-Vitex negundo seed				
Kar et al	2024	Endocrine and metabolic disorder on PCOS	8 weeks	**]24[**
Sharath et al	2022	antiandrogenic agent on PCOS	8 weeks	**]25[**
Shettar et al	2024	Antiovarian cancer on PCOS	8 weeks	**]26[**
3-Carum carvi L				
Sherafatmanesh et al	2020	Insulin resistant and blood glucose on PCOS	8 weeks	**]27[**
Trishna et al	2010	Sex hormone on PCOS	4 Weeks	**]28[**
Akram et al	2019	Antiobsety and antidiabetic on PCOS	4 Weeks	**]29[**
4-Flaxseeds				
Osman et al	2019	Sex hormone on PCOS	8 Weeks	**]30[**
Haidari et al	2020	Level of testosterone and antioxidant effects	4Weeks	**]31[**
Christodoss et al	2018	Level of testosterone on PCOS		**]32[**
5- Momordica charantia				
Hussain et al	2022	Sex hormone on PCOS	4 weeks	**]33[**
Cevik et al	2015	estrogen production and anti-oxidative and anti-apoptotic on PCOS	4 weeks	**]34[**
Bai et al	2018	hypoglycemic effect on PCOS	8 weeks	**]35[**
6-Phyllanthus muellerianus				
Ndeingang et al	2019	Estrus cycle, lipid profile, markers associated with oxidative stress, sex hormones, and ovarian structure on PCOS	2 weeks	**]36[**
7-Hunteria umbellate				
Ineza	2024	Sex hormone on PCOS	8 weeks	**]37[**
8-Inonotus obliquus				
Zhang et al	2024	Sex hormone on PCOS		**]38[**

3. Results and Discussion

Effect of Curcuma longa:

But there has been a greater focus on plants and herbs. The antibacterial, antiviral, antiulcer, anticytotoxic, anticancer, anti-inflammatory, antioxidant, antihypertensive, hepatoprotective, antilipidic, and antiplatelet polyphenolic chemicals found in medicinal plants are among its numerous advantageous qualities. Additionally, a number of studies have demonstrated that, with only minor adverse effects, herbal therapy can help individuals with PCOS by minimizing ovarian cysts, improving hyperandrogenism, and restoring aromatase function. [21].

Additionally, its hypoglycemic, anti-doping, anti-nutritional, and estrogenic properties help to manage PCOS by reducing leukocyte malfunction and promoting fecundity and ovulation. [22]. A factor in the pathophysiology of polycystic ovarian syndrome (PCOS) is insulin resistance. Turmeric enhances insulin sensitivity, however its effects are restricted because of its low bioavailability. Through the measurement of Glut-4 expression, fasting insulin levels, fasting blood glucose levels, and homeostatic model assessment-insulin resistance (HOMA-IR) in PCOS model mice, this study intends to demonstrate the application of self-developed nano-drug delivery system (SNEDDS) on turmeric extract to improve insulin resistance [23].

Effect of Vitex negundo seed

The results of the study conducted by Kar et al [24] demonstrated that administering a Vitex negundo (VNE) hydroethanolic extract corrected the levels of pro-inflammatory cytokines, antioxidant enzymes, and apoptotic indicators, and successfully restored the endocrine and metabolic balance linked to PCOS. The existence of nigondin B, plumbagin, and cinnamic acid as important phytochemicals in VNE was verified by LC-MS analysis. The active ingredients of Vitex negundo extract, which demonstrated hypoglycemia, hypolipidemic, and catabolic effects on body weight, are responsible for the reported positive outcomes, Furthermore, the extract aided in the management of hormonal homeostasis by modifying steroidogenic enzymes, particularly gonadotropin levels and LH:FSH ratio correction, through ERα signaling modulation and downregulation of NR3C4 expression.

The rectification of SOD and catalase activity demonstrated the phytochemicals in Vitex negundo seeds to have antioxidant qualities. Their ability to reduce inflammation and stop cell death was linked to the control of TNF-α, IL-6, BAX, and Bcl2 mRNA expression. The molecular interactions between the aforementioned active phytochemicals of VNE and ERα, NR3C4, and TNFα were also revealed by molecular docking analysis. These interactions are essential for controlling hormone signaling and coordinating the inflammatory cascade. [25]. Furthermore, ethanolic extract outperformed the other extracts under investigation in terms of yield and greatest concentration of total polyphenols, flavonoids, and alkaloids, while having the lowest concentration of tannins, according to phytochemical quantification.

Furthermore, strong biological activities are commensurate with the highest total polyphenol concentration. Indeed, ethanolic extract exhibited greater levels of antioxidant and antisteroidal activity in vitro than other extracts. The antiandrogenic qualities and characterisation of leaf extracts from V. negundo are reported for the first time in this study. One potential application for the ethanolic extract of V. negundo leaves is as an anti-androgenic and antioxidant. Therefore, it may be taken into consideration for the treatment of diseases such polycystic ovarian syndrome that have elevated androgen levels [26].

Effect of Carum carvi L:

In a study conducted by Sherafatmanesh et al. [27]. Oral caraway and thylakoids administration significantly decreased FBS and HOMA-IR parameters in rats with induced PCOS; this finding is in line with other research findings. It seems that inhibition of intestinal or renal glucose absorption as well as hepatic glucose synthesis are the fundamental mechanisms through which caraway produces its hypoglycemic impact. Peripheral tissues' increased use of glucose changed the enzymatic pathways, for example, by making glycolytic enzymes more active and gluconeogenic enzymes less active. Furthermore, it's possible that thylakoids' hypoglycemic process is triggered by an increase in the activity of enzymes that break down glucose, including glucose-6-phosphate dehydrogenase. Moreover, thylakoids are among the highest concentrated sources of beta-carotene, as was previously mentioned .

According to Ford et al., insulin resistance and hyperglycemia were adversely correlated with all serum carotenoids, particularly beta-carotene. Thus, based on the above mentioned mechanisms, it may be concluded that thylakoids and caraway may function as antihyperglycemic drugs in PCOS patients. Furthermore, after treatment with both thylakoid and caraway extracts, there was no discernible change in the baseline plasma insulin levels, indicating that the underlying pathways might not be dependent on insulin secretion. Researchers also looked at how female rats' hormones and reproductive parameters were affected by an aqueous and ethanolic extract of Carum carvi seeds,Significant antifertility activity was recorded. FSH and LH levels were significantly decreased, whereas the amount of estrogen in the ethanolic extract was found to be increased. Treatment with the aqueous and ethanolic extract prevented the oestrus phase.

Additionally, it raised body, ovarian, and uterine weights; nevertheless, the group of immature rats given with extract had higher uterine weights. Consequently, the research demonstrated that Carum carvi has a strong antifertility effect. [28] . It has been used for centuries to treat digestive disorders and obesity in the Unani system of medicine. It is a carminative anti-obesity; anti-flatulent (anti-flatulent); antidote (antidote); haemophiliac (digestive); demulcent (antidote); diuretic (diuretic); And diuretic (galactagogue); diuretic (emmenagogue); lithotripsy (stone crusher); carminative (flatulence expeller) etc. according to classical Greek literature [29].

Effect of flax seeds:

The main characteristics of adult females with PCOS, or polycystic ovarian syndrome, are hyperandrogenism, insulin resistance (IR), and hyperinsulinemia, which raise the risk of type 2 diabetes and cardiovascular illnesses. It was found that using a mixture of flax seeds and their anti-androgenic action could treat PCOS in female rats. Furthermore, no change in estradiol was seen despite a notable increase in serum levels of LH, FSH, and testosterone and a decrease in progesterone. Additionally, it was noted that in ovarian homogenates, there was a large rise in lipid peroxidation, a non-significant increase in nitric oxide, and a significant drop in the activities of glutathione reductase, catalase, and superoxide dismutase. [30].

Large amounts of plant lignans (secoisolariciresinol diglycoside, or SDG), dietary fiber, and alpha-linolenic acid (ALA) can be found in flaxseed (Linum usitatissiumum). According to earlier research, meals rich in lignans may enhance testosterone potential by binding it to the circulation in the enterohepatic region. By raising SHBG levels, lignins can also decrease the bioavailability of free testosterone. The effects of supplementing with flaxseed powder on lipid profiles, insulin sensitivity, inflammatory markers, leptin, adiponectin, and menstrual problems in PCOS patients are, as far as we are aware, poorly studied. [31]. One of the newest superfoods to be found recently is flax seeds, which have been shown to contain health-promoting phytochemicals and fiber components like lignin and omega-3 fatty acids.

These components can be used to reduce cholesterol, cardiovascular disease, obesity, diabetes, and hypertension, as well as manage the symptoms of PCOS. This project aims to increase serum levels of sex hormone binding globulin (SHBG) to lower free testosterone levels and normalize clinical symptoms associated with PCOS conditions. To achieve this, flax seeds rich in lignin and the essential fatty acid alpha-linolenic acid (ALA) in a suitable food matrix are desired for effective absorption into the bloodstream [32].

Effect of Momordica charantia:

The interdisciplinary, endocrine, metabolic, and diverse illness known as polycystic ovarian syndrome (PCOS) affects women who are fertile and aggravates insulin resistance, hyperandrogenism, obesity, irregular menstruation, and infertility. Some regions of the world eat bitter gourd as a vegetable. The purpose of this study was to explain the traditional usage of bitter gourd (Momordica charantia L.) for disorders related to reproduction. The presence of many phytochemicals, including quercetin, gallic acid, benzoic acid, chlorogenic acid, syringic acid, paracoumaric acid, ferulic acid, and cinnamic acid, was discovered through HPLC analysis of the standardized aqueous methanolic extract of bitter gourd. In the PCOS group, histological examination of the ovaries revealed the existence of cystic follicles (9–10), While we observed maturing and developing follicles in every treatment group.

Similarly, a hormone investigation revealed a large increase in FSH levels and a significant decrease in LH, insulin, and testosterone levels. The state of the antioxidant enzyme and the lipid profile were also greatly enhanced. [33]. In this work, using an ovariectomy rat model, we examined the effects of Momordica charantia (MC) on the synthesis of estrogen and E2, as well as its role as an antioxidant and anti-apoptotic. After

ovariectomies, rats were gavagely given a 2 g/kg MC fruit overload for 30 days. Uterine horn tissue was used to evaluate serum levels of 17-β estradiol (E2) and 8-OHdG, as well as oxidative damage markers of ROS, ESRα, and ESRβ, and NF-kB gene levels.

Western blotting was used to assess the expression of the proteins Caspase-3, Caspase-9, TNF-α, IL-6, IL-10, Bcl-2, and Nf-kB. H&E staining was used to look at the structural alterations in the tissues. Administering MC boosted the production of estrogen, increased the levels of the ESRα/ESRβ gene, and prevented oxidative damage. Moreover, anti-apoptosis, anti-inflammatory, and tissue regeneration were enhanced by MC treatment, The information provided here is consistent with the theory that MC acts as a new herb for the treatment of postmenopausal symptoms by directly regulating the uterine response to estrogen [34]. Momordica charantia polysaccharides have been demonstrated to have hypoglycemic effects, which enhance glucose metabolism [35].

Effect: Phyllanthus muellerianus:

This herb is used to treat a number of illnesses, such as anovulation and recurring menstruation. We looked into how Phyllanthus muellerianus extracts affected the ovarian structure, sex hormones, oxidative stress-related indicators, lipid profile, and estrous cycle in rats with letrozole-induced PCOS. Furthermore, Phyllanthus muellerianus raised the concentration of estradiol while dramatically lowering the levels of testosterone and luteinizing hormone. Following the plant's treatment, there was a decrease in cystic follicles as well. In PCOS rats, P. muellerianus reduced the alterations in hormones, reproduction, and structure. This herb may help with the management or therapy of metabolic and reproductive issues linked to PCOS [36].

Effect of Hunteria umbellate:

Prior research examined the potential benefits of this herb, a traditional antidiabetic, in a rat model of PCOS caused by testosterone propionate and a high-fat diet. The effects of HUE were shown to be dose- and time-dependent in evaluations performed 14, 28, and 56 days following PCOS induction. rodents with PCOS were successfully produced, and the rodents had characteristic symptoms such hyperandrogenism, ovulatory issues, and ovarian cysts. [37].

Effect of Inonotus obliquus:

The extract rich in plant antioxidants (gallic acid, chlorogenic acid, rutin, para-coumaric acid, benzoic acid, quercetin, salicylic acid, and kaempferol) alleviates the symptoms of PCOS by modulating oxidative stress markers and eliminating low-grade ovarian inflammation by reducing the expression of TNF-α and IL-6 associated with NF-κB [38].

4. Conclusion

The findings of this review underscore the potential risks associated with long-term use of conventional treatments for Polycystic Ovary Syndrome (PCOS) and highlight the promise of medicinal plants as alternative therapeutic options. The review identified several medicinal plants with notable effects on ovarian physiology, suggesting that these natural remedies may offer viable alternatives or adjuncts to conventional treatments. However, while the evidence for the efficacy of these plants is promising, it is crucial to conduct further in-depth studies to validate their safety and effectiveness. Future research should focus on well-designed clinical trials to establish the optimal formulations, dosages, and long-term effects of these medicinal plants. This approach will help mitigate the risks associated with standard treatments and potentially improve patient outcomes by integrating safer, plant-based options into PCOS management strategies.

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