Research in Pharmacy 2023, 13: 43-56
doi: 10.25081/rip.2023.13.8683
https://updatepublishing.com/journal/index.php/rip

Review Article

ISSN: 2231-539X

A review on polyherbal and supplemental approach to treat Polycystic Ovarian Syndrome

Priya, Shiwank Rana*

Dreamz College of Pharmacy, Sundernagar, Mandi-175036, Himachal Pradesh, India

Received: October 17, 2023
Revised: December 23, 2023
Accepted: December 25, 2023
Published: December 31, 2023

***Corresponding Author:**
Shiwank Rana
Email: shiwankrana@gmail.com

ABSTRACT

Polycystic ovarian syndrome (PCOS) stands as a neuroendocrine metabolic anomaly hallmarked by an erratic menstrual cycle. Our awareness extends to the indications, origins, implicated organs, histological attributes, pathophysiological mechanisms, etiological factors, diagnostic methods, and therapeutic approaches. These insights have been gleaned through a comprehensive exploration of a myriad of resources, including various literary tomes and digital platforms like PubMed and ClinicalTrials.gov. The contemporary analysis centers on the paramount significance of phytotherapeutic compounds and adjuncts in the management of PCOS.

KEYWORDS: PCOS, Herbal medicine, Infertility, Insulin, Obesity, Supplements

INTRODUCTION

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a condition that affects women and is characterized by a combination of symptoms including hyperandrogenism, anovulation, and obesity. Women with PCOS also have enlarged polycystic ovaries as shown in Figure 1 (Copeland *et al.*, 1993). The incidence of PCOS appears to be increasing and affects around 1-5% of women. Changes in lifestyle and increased stress levels are believed to be contributing factors to this rise (Padubidri *et al.*, 2008). PCOS is characterized by hyperinsulinemia, insulin resistance, and hormonal imbalances due to the dysfunction of the hypothalamic-pituitary axis. This leads to increased serum LH/FSH ratio and circulating androgens. Additionally, 70% of PCOS patients have dyslipidemia (Valkenburg *et al.*, 2008). It has been found through research over the past few decades that PCOS is a significant metabolic disorder, which is linked to an increased risk of Type II diabetes mellitus (T2DM) and metabolic syndrome. Increased levels of insulin and luteinizing hormone (LH) are observed in women with PCOS. The excess androgen activity in PCOS may also disrupt the synthesis of estrogen and progesterone in the follicles that are induced by gonadotropins (Maharjan *et al.*, 2010). Diagnosing, treating, and studying PCOS can be quite challenging due to the combination of various factors (Bieber *et al.*, 2006). Women with PCOS typically receive a range of standard care treatments, from lifestyle adjustments to pharmacological interventions. These lifestyle modifications generally involve changes to diet, engaging in exercise, and losing weight (Jang *et al.*, 2014). Since ancient times, medicinal plants have been given special attention for their potential therapeutic benefits. Today, with numerous studies being performed, many worthwhile and beneficial medicinal plants are being discovered and explored (Nowak *et al.*, 2007). "Studies, such as randomized controlled trials, case studies, and animal experiments, are being conducted to investigate the use of herbal drugs as an alternative to traditional pharmacological interventions, given the potential side effects associated with the latter" (Kamel, 2009). Research suggests that a lack of vitamin E may increase the risk of female infertility, miscarriage, premature delivery, eclampsia, and foetal intrauterine growth restriction, among other pregnancy-related conditions. It's important for pregnant women to ensure they are getting enough vitamin E in their diet or through supplements to support a healthy pregnancy (Gagné *et al.*, 2009; Hubalek *et al.*, 2014; Wahid *et al.*, 2014).

Symptoms

Polycystic ovarian syndrome symptoms can vary from woman to woman. I see a list of symptoms that may be related to hormonal imbalances or other health issues. The symptoms include absent periods, acne not associated with puberty, darkening of the skin, excessive hair growth, fatigue, fluid retention, heavy or prolonged periods, infertility, irregular periods, male pattern baldness, menstrual pain, mood swings, ovarian cysts, and weight gain. It's important to seek medical advice if you

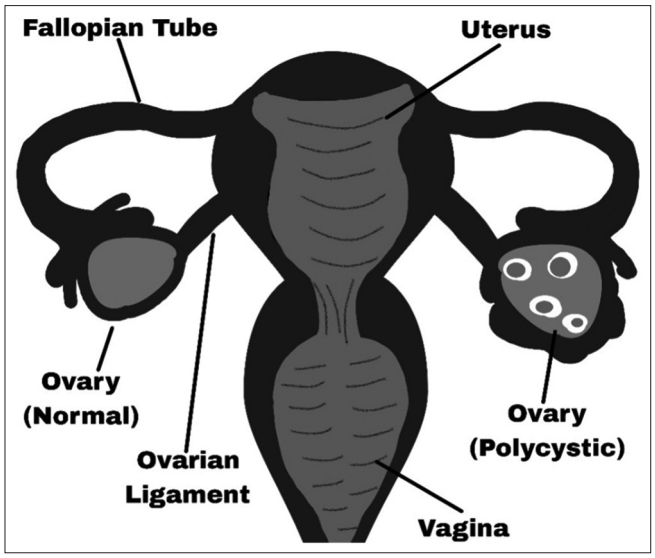

Figure 1: Differentiation between a normal ovary and polycystic ovary

are experiencing any of these symptoms. Female infertility is a significant factor that contributes to 35-40% of overall infertility cases (Carmina *et al.*, 1992).

Causes of PCOS

There are several factors that can contribute to female infertility, including: It seems like the factors that can contribute to certain health issues include genetic predisposition, a history of strong stimulation in the adrenals during childhood, raised insulin levels, contraceptive pills, hormonal imbalance, and stress. It's important to be aware of these potential risk factors and to consult with a healthcare professional if you have concerns about your health (Padubidri & Daftary, 1999).

Organs involved in PCOS

- Ovary - The female gonad organ, also known as the ovary, is located on either side of the uterus.
- Adrenal Gland- Glands above kidneys produce vital hormones.
- Pancreas- The gland responsible for producing insulin in your body.
- Pituitary Gland- Essential gland below the brain produces hormones that regulate the body.

PCOS is caused by increased androgen production by the ovaries, which suppresses the maturation of ovarian follicles. This leads to anovulation and conception problems due to unavailability of ovum. PCOS is also associated with several anatomical abnormalities, including enlarged ovaries with many cysts, increased stroma, and thickened pearly white capsule (Shubhashree, 2012). According to a survey, poor diet is the biggest contributor to PCOS. Women with PCOS, especially those who are young and stressed, tend to consume excessive amounts of fat, sugar, carbonized drinks, and highly refined carbohydrates, causing unhealthy insulin levels. Insulin, in turn, stimulates androgen receptors outside the ovary, leading to typical PCOS symptoms and blocking the release of ovum from the follicle. This type of diet also causes obesity, which aggravates PCOS (Gaware *et al.*, 2009).

Histological Features of PCOS

It seems that there are various changes that can occur in the ovaries, such as enlargement of the entire ovary, thickening of the capsule (more than 100 microns), elevated number of cysts in the subcapsular follicles, insufficient corpora lutea or albicantia, hyperplasia and fibrosis of the ovarian stroma, and early luteinization of the theca cells. It's important to keep an eye on these changes and consult a medical professional if needed (Azziz *et al.*, 2006).

The Pathophysiology of PCOS

Several hypotheses have emerged over time to explain the pathophysiology of PCOS. Initially, it was believed that an excess of intrauterine androgens could cause this disease. Consequently, insulin resistance could contribute to the onset of PCOS and hyperandrogenaemia (de Zegher & Ibáñez, 2009). PCOS is undeniably a multifactorial syndrome, with both genetic and environmental factors contributing to uncontrolled ovarian steroidogenesis, aberrant insulin signaling, and excessive oxidative stress. An intrinsic defect in theca cells can lead to the secretion of high levels of androgens, even in the absence of trophic factors, due to the intrinsic activation of steroidogenesis (Lorenzo *et al.*, 2023). Patients with PCOS may experience intrinsic dysregulation that could potentially impact their granulosa cells. Studies have shown that individuals with PCOS may produce up to four times higher levels of the anti-Mullerian hormone (AMH) than those who do not have the condition (Pellatt *et al.*, 2007; Azziz *et al.*, 2009; Villarroel *et al.*, 2011). Additionally, it has been reported that females with PCOS have multiple follicles, predominantly pre-antral and small antral follicles (Webber *et al.*, 2003; Das *et al.*, 2008). Studies have identified a post-receptor binding defect in individuals with PCOS that leads to reduced insulin resistance. This defect, along with alterations in gene expression of some genes involved in insulin signaling pathways, is an intrinsic component of PCOS, regardless of the presence of obesity (Dunaif, 1997; Cortón *et al.*, 2007, 2008). Furthermore, it has been found that PCOS syndrome is associated with an increase in glycol-oxidative stress (González *et al.*, 2006). Mitochondrial dysfunction has been found to induce insulin resistance (IR) and hyperandrogenism in patients with PCOS (Victor *et al.*, 2009).

Etiology of PCOS

PCOS is caused by disordered gonadotropin secretions, ovarian and adrenal hyperandrogenism, and insulin resistance, leading to hormonal imbalances and metabolic dysfunction. Understanding the underlying causes is crucial for developing effective treatments and improving outcomes for affected women hyperandrogenism and disorder of insulin resistance (Kwon *et al.*, 2020). GnRH regulation can be uncontrolled, leading to increased LH and decreased FSH. This can suppress

ovarian follicle response to FSH, leading to elevated AMH, follicular arrest, and increased secretion of testosterone, estradiol, and dehydroepiandrosterone (Goswami *et al.*, 2012). In these diseases, disrupted ovarian synthesis of steroid hormones can lead to increased circulating androgens which further cause acne, hirsutism, and alopecia. This effect may be more pronounced in women with PCOS (Kwon *et al.*, 2018). It is believed that insulin has the ability to stimulate the production of androgens in the gonads and adrenal glands, a condition known as hyperinsulinism and hypogonadism. Hyperinsulinism is a well-established risk factor for PCOS (Hoberg *et al.*, 1999). In PCOS, the development of immature follicles is often observed as a result of increased levels of LH and decreased levels of FSH. Furthermore, PCOS patients tend to exhibit an elevated production of androgens coupled with decreased blood levels of aromatase. The excess androgens in PCOS are attributed to the accumulation of abdominal fat, which may result in hyperinsulinemia and dyslipidemia which is shown in Figure 2. The rise in cell androgen production and hyperinsulinemia contribute to the reduction of sex hormone binding globulin (SHBG), leading to an increase in circulating testosterone levels. All these factors may exacerbate the progression of the disease (Balen *et al.*, 2004).

Diagnosis

Polycystic ovary syndrome (PCOS) cannot be diagnosed by basic diagnostic tests such as blood tests, culture, and biopsy. Therefore, there is no single definitive test for PCOS. However, differential diagnosis can be used to narrow down the choices by excluding other relevant disorders based on symptoms. To establish a differential diagnosis for PCOS, associated investigations should be conducted to exclude hyperprolactinemia, thyroid disease, Cushing's syndrome, and hyperplasia of the adrenal glands (Witchel *et al.*, 2019). When diagnosing PCOS, medical professionals often recommend investigations such as pelvic examination, transvaginal ultrasound, and hormone level measurement, in addition to considering past medical history, weight changes, and symptoms of insulin resistance. According to the NHS, specific criteria for diagnosing PCOS include irregular or infrequent periods, high levels of androgenic hormones or related symptoms, and ultrasound scans indicating PCOS. The Rotterdam PCOS diagnostic criteria are the most commonly used method for adults. A PCOS diagnosis may be confirmed if at least two clinical or biochemical signs of hyperandrogenism, ovulatory dysfunction, or polycystic ovaries are present during an ultrasound (Sadeghi *et al.*, 2022).

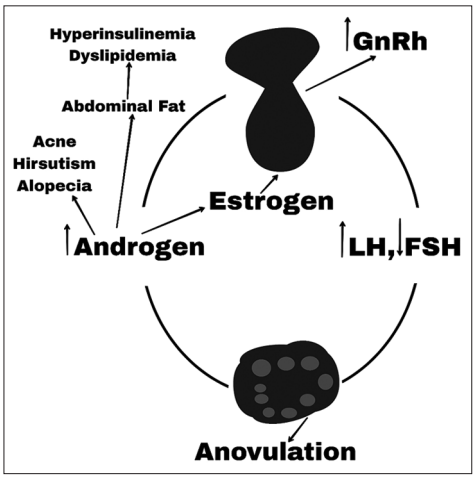

Figure 2: Etiology of PCOS

Management

The management approach and selection of the best therapy option in healthcare depend on various factors, with the target patient's needs and priorities being among the most crucial considerations (Bednarska & Siejka, 2017). The complications may vary from seeking fertility, regulation of menstrual disturbances to weight reduction or relief from hyperandrogenic symptoms, including acne, hirsutism, or androgenic alopecia (Zeind & Carvalho, 2017). Indeed, the approach must be man or woman for anybody to fulfil the best end result (Escobar-Morreale, 2018). In the realm of PCOS, a universal solution remains elusive, thereby rendering healthcare providers with limited options but suggestive treatments (Liu *et al.*, 2015).

ALTERNATIVE REMEDIES AVAILABLE FOR PCOS

Medicinal Herbs

Liquorice

The scientific nomenclature for liquorice is *Glycyrrhiza glabra*, a member of the Leguminosae family. A study delved into the impact of liquorice on androgen metabolism in a cohort of nine healthy women aged 22 to 26, during the luteal phase of their menstrual cycles. Over the course of two cycles, they were administered 3.5 grams of a commercial liquorice preparation, containing 7.6% W/W of glycyrrhizic acid, on a daily basis Consequently, liquorice may be contemplated as an adjunctive therapy for addressing conditions like hirsutism and PCOS (Armanini *et al.*, 2004).

Spearmint tea

Spearmint tea, scientifically known as *Mentha spicata* and belonging to the Labiatae family, was the focus of a study conducted in Turkey. This study, spanning two centers, involved a randomized trial in which participants consumed spearmint tea twice a day for duration of one month. During the 30-day trial with spearmint tea, both free and total testosterone levels experienced a notable decrease, as did the degree of hirsutism in the group. In contrast, levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) showed an increase. This provided clear evidence and confirmation that spearmint possesses antiandrogenic properties (Grant, 2010).

Flaxseed

Flaxseed, known scientifically as *Linum usitatissimum* and belonging to the Linaceae family, was the subject of an

intriguing study. This research focused on the effects of flaxseed supplementation at a dosage of 30 grams per day in a 31-year-old woman with PCOS. Over the course of four months, the patient adhered to the regimen and consumed approximately 83% of the prescribed flaxseed dose. This case study underscores the clinically significant reduction in androgen levels, along with a simultaneous decrease in hirsutism (Nowak *et al.*, 2007).

Ginseng saponin

Ginseng saponin, scientifically known as *Panax ginseng* and categorized within the Araliaceae family, was the subject of investigation in a study involving female Sprague-Dawley rats weighing between 190-210 grams. These rats were induced to develop polycystic ovaries through the intramuscular injection of Estradiol Valerate (EV). The rats were then divided into three groups: an EV control group (n=10), and an EV group receiving Ginseng Total Saponins (n=10). The study aimed to observe ovarian morphology and Nerve Growth Factor (NGF) protein expression. An increased expression of Nerve Growth Factor was observed in the ovaries and the brains of rats afflicted with Polycystic Ovary. Interestingly, the administration of Ginseng Total Saponins demonstrated attenuation in NGF expression in the ovaries, suggesting a potential therapeutic effect in addressing this condition (Pak *et al.*, 2005).

Chaste berry

Chaste berry, scientifically termed *Vitex agnus-castus* and a member of the Lamiaceae family, is a sizable shrub native to Europe. Chaste berry is renowned for its role in addressing estrogen level imbalances, which manifest as menstrual cycle irregularities and various premenstrual symptoms (Merz *et al.*, 1995; Liu *et al.*, 2001; Webster *et al.*, 2006). Vitex fruits are primarily composed of monoterpenoids, with key constituents such as bornyl acetate, limonene, 1,8-cineol, α-pinene, and β-pinene (Sorensen & Katsiotis, 1999; Senatore *et al.*, 2003). A study involving 93 women who had been attempting to conceive for a duration ranging from 6 to 36 months examined the effects of a supplement containing chaste tree, L-arginine, vitamins, and minerals. Furthermore, three women from the supplement group successfully conceived after six months (Westphal *et al.*, 2006).

Turmeric

Turmeric, scientifically known as *Curcuma longa* and categorized within the Zingiberaceae family, is recognized for its rhizome, which is a common spice used in the Asian continent (Wojcik *et al.*, 2018). Turmeric comprises a diverse array of primary and secondary metabolites, with over 250 phytoconstituents documented (Tanvir *et al.*, 2017). Curcuminoids play a pivotal role in the treatment of PCOS, offering significant effects. They contribute to the reduction of the follicular sheath and enhance the formation of the corpus luteum, thereby improving the ovulation process. Consequently, turmeric aids in enhancing the histological characteristics of polycystic ovaries. Additionally, curcuminoids are effective in suppressing serum progesterone levels while elevating estradiol levels in women afflicted with PCOS (Jiménez-Osorio *et al.*, 2016).

Aloe-vera

Aloe vera, known scientifically as *Aloe barbadensis* and a member of the Liliaceae family, was the subject of a study examining its efficacy in a PCOS rat model. The study involved five-month-old female rats of the Charles Foster breed, which were induced to develop PCOS through oral administration of letrozole, a non-steroidal aromatase inhibitor. Subsequently, these rats were treated with an oral dose of the Aloe vera gel formulation, amounting to 1 millilitre daily for a period of 45 days. This treatment successfully restored their oestrus cyclicity, improved glucose sensitivity, and enhanced their steroidogenic activity. The co-administration of the inducer (letrozole) with Aloe vera gel effectively prevented the onset of the PCOS phenotype. Aloe vera gel formulations demonstrated a protective effect against the development of the PCOS phenotype by reinstating normal ovarian steroid levels and modifying crucial steroidogenic processes. This beneficial impact can be attributed to the phyto-components present in the Aloe vera extract (Maharjan *et al.*, 2010).

White peony

The white peony, scientifically termed *Paeonia lactiflora* and a member of the Paeoniaceae family, was a focal point in our study. This investigation delved into the in vivo effects of Unkei-to, a Japanese herbal medicine, and its constituent compounds on steroidogenesis and cytokine secretion in human granulosa cells. Unkei-to was observed to stimulate the secretion of 17-beta-estradiol and progesterone from highly luteinized granulosa cells, which were obtained from patients undergoing in vitro fertilization. This stimulatory effect was primarily attributed to key ingredients found in Unkei-to, such as P. radix, P. lactiflora, Cinnamomi cortex, and Cinnamomum cassia. The diverse beneficial actions of Unkei-to on ovarian function may result from a combination of various stimulating effects on both steroidogenesis and the ovulatory process within the ovary. Furthermore, it may also exert a stimulatory influence on the hypothalamus-pituitary axis (Takahashi & Kitao, 1994; Sun *et al.*, 2004).

Fenugreek

Fenugreek, scientifically identified as *Trigonella foenum-graecum* and belonging to the Fabaceae family, was the subject of a post-marketing surveillance study involving 50 premenopausal women. This study revealed promising results, with the *T. foenum-graecum* seed extract demonstrating its efficacy in reducing cyst sizes in 46% of the study participants. Notably, 36% of the subjects exhibited a complete dissolution of cysts. Additionally, a remarkable 71% of the subjects reported the restoration of regular menstrual cycles following the treatment, and 12% of the participants later achieved pregnancy. Furthermore, the study indicated significant increases in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the patients, underscoring the beneficial impact of fenugreek in addressing related conditions (Swaroop *et al.*, 2015).

Ecklonia cava

Ecklonia cava, scientifically known as *Ecklonia cava* and classified within the Lessoniaceae family, was the subject of a study involving rats in which PCOS was induced using letrozole. The study findings demonstrated that *E. cava* extract played a pivotal role in restoring regular estrous cycles in the rats. Furthermore, it normalized hormone levels, including testosterone, estrogen, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and anti-Mullerian hormone (AMH). These observations indicate the potential of *E. cava* extract in addressing PCOS-related hormonal imbalances (Yang *et al.*, 2018).

Kacip Fatimah

Kacip Fatimah, scientifically known as *Labisia pumila* and belonging to the Myrsinaceae family, was the focus of a study involving 9-week-old PCOS rats. PCOS was induced in these female rats before reaching puberty through continuous treatment with dihydrotestosterone. The PCOS rats were randomly divided into two groups: PCOS herb-treated and PCOS control. Rats in the PCOS herb-treated group received a daily dose of 50 mg/kg body weight, dissolved in 1 mL of deionized water on the same schedule. The results of the study demonstrated a reduction in body weight gain in the ovariectomized rats. Furthermore, the herb treatment led to an increase in uterine weight, indicating estrogenic effects, and improved insulin sensitivity and lipid profile in PCOS rats, all without affecting body composition (Mannerås *et al.*, 2010).

Cinnamon

Cinnamon, scientifically referred to as *Cinnamomum zeylanicum* and a member of the Lauraceae family, has been the subject of studies highlighting its potential to reduce insulin resistance. This effect has been observed in both in vitro and in vivo research, where cinnamon extract enhances the activity of phosphatidylinositol 3-kinase within the insulin signaling pathway, thus amplifying the effectiveness of insulin. In a clinical study involving fifteen women with PCOS, participants were randomly assigned to receive daily oral cinnamon or a placebo for duration of 8 weeks. Comparisons between post-treatment and baseline insulin sensitivity indices, as measured through fasting and 2-hour oral glucose tolerance tests, revealed significant reductions in insulin resistance within the cinnamon group, while the placebo group did not display similar improvements (Wang *et al.*, 2007).

Gymnema

Gymnema, scientifically known as *Gymnema sylvestre* and belonging to the Apocynaceae family, is a traditional Ayurvedic herb with multiple uses. It is employed as an antidiabetic and hypoglycemic agent, as well as for lowering lipid levels and supporting weight reduction. Gymnema is thought to possess a trophorestorative action on the beta cells of the pancreas. In herbal medicine, the leaves of the plant are the primary part used. Gymnema is particularly beneficial for individuals with PCOS due to its insulin-modulating activity. Additionally, it offers advantages by reducing elevated triglyceride levels commonly associated with PCOS (Armanini *et al.*, 2004; Nowak *et al.*, 2007).

Fennel Seeds

Fennel, scientifically named *Foeniculum vulgare* and a member of the Apiaceae family, boasts a volatile content of approximately 4-5%. Fennel's composition is also characterized by its high anethole content, comprising approximately 50-60%. It contains phenolic esters, around 18-22% of fenchone, as well as fixed oils and proteins (Conforti *et al.*, 2006). Additionally, fennel includes various vitamins, such as α-tocopherol, ascorbic acid, β-tocopherol, γ-tocopherol, and δ-tocopherol, making it a rich and versatile botanical resource (Križman *et al.*, 2007). Anethole is a key component of fennel, can promote menstruation, aid in childbirth, and induce estrogenic effects within the ovarian follicle. These properties collectively contribute to its potential in the treatment of PCOS. Furthermore, fennel possesses various pharmacological properties that can be beneficial in addressing helminthic infections, neurological disorders, and hirsutism. It also showcases qualities such as tumor suppression, anti-diabetic effects, and hepatoprotective properties, making it a versatile herb with a wide range of potential health benefits (Pak *et al.*, 2005; Sadrefozalayi & Farokhi, 2014; Shahidi & Hossain, 2018).

Guggal

Guggal, scientifically named *Commiphora wightii* and a member of the Burseraceae family. Guggul contains various essential oils, gum extracts, and resinous substances, all of which possess remarkable healing properties. These components contribute to its significance in traditional and herbal medicine practices (Singh *et al.*, 2015). The study has provided confirmation that Guggul plays a crucial role in reducing morphological abnormalities associated with DHEA-induced PCOS within the ovarian follicles (Kavitha *et al.*, 2016). Gum Guggul has demonstrated its potential benefits in supporting female reproductive organs and maintaining hormonal levels. This underscores the significance of the *C. wightii* plant and its extract in the realm of health and wellness (Rani & Mishra, 2013).

Kanchanar

Kanchanar, scientifically known as *Bauhinia variegata* and a member of the Fabaceae family, is utilized for the treatment of various conditions, including PCOS, typically in the form of Kanchanar Guggul. This herbal remedy has proven effective in addressing conditions such as uterine cysts, joint pains, and hormonal imbalances (Nariyal & Sharma, 2017).

Myrrh

Myrrh, known scientifically as *Commiphora molmol* or *Commiphora myrrha* and classified within the Burseraceae family, contains a variety of essential phytochemical constituents.

These constituents encompass alkaloids, glycosides, volatile oil, saponins, terpenoids, steroids, bitter principles, and more. Myrrh serves a significant role in addressing conditions related to menstruation. In cases of amenorrhea, where menstruation is absent, Myrrh is often combined with iron sources to facilitate the resumption of the menstrual cycle. Moreover, Myrrh plays a crucial role in managing menorrhagia, a condition characterized by heavy and prolonged menstrual bleeding. It helps prevent excessive blood loss during abnormal and extended menstruation. Myrrh is also believed to possess emmenagogue properties, stimulating blood flow in cases of uterine abnormalities. It is used in addressing uterine infections. Additionally, Myrrh aids in addressing issues related to uterine obstructions and contributes to regulating menstrual bleeding (Fahad & Ismath, 2018).

Chamomile

Chamomile, scientifically known as *Matricaria Chamomilla* and belonging to the Asteraceae family, was studied in the context of its impact on PCOS. The study involved thirty virgin adult cycling Wistar rats, each weighing between 200-220 grams. These rats were divided into two groups and housed in cages, with six mice per cage, under standard conditions (21 ± 2 °C, 12-hour light/12-hour dark cycles) for at least one week prior to and throughout the study. Estrous cyclicity of these rats was monitored through vaginal smears obtained between 0800 and 1200 hours. After approximately four days, each rat in the experimental group received an intramuscular injection of Estradiol Valerate, 2 mg in 0.2 mL of corn oil, to induce PCOS. The control group received corn oil injections. After 60 days from the injection, all rats in the experimental group were assessed for the presence of follicular cysts. Rats with PCOS were then subjected to treatment involving multiple doses (25, 50, 75 mg/kg) of intraperitoneal injections of Chamomile alcoholic extract for duration of ten days. The histological and hormonal results indicated that Chamomile can alleviate the signs of PCOS in ovarian tissue and facilitate LH secretion in rats (Farideh *et al.*, 2010).

Milk thistle

Milk thistle, scientifically referred to as *Silybum marianum* and classified within the Asteraceae family, was the subject of a study examining the effects of silymarin, a component known for its insulin-sensitivity properties, on various hormonal levels. These levels included glucose, insulin, testosterone, luteinizing hormone (LH), and progesterone. The study also assessed the ovulation rate and the Homeostasis Model Assessment of insulin Resistance (HOMA) ratio. This research encompassed a 3-month treatment period involving 60 PCOS patients divided into three well-matched groups. The first group, consisting of 20 patients, received silymarin at a dosage of 1500 mg per day. The third group underwent treatment involving a combination of metformin (1500 mg/day) and silymarin (750 mg/day). All groups administered these drugs in divided doses. The results of the study revealed a significant increase in progesterone levels upon the addition of silymarin to the metformin treatment regimen. This combination displayed a positive impact on normalizing disrupted hormone levels and improving the ovulation rate in PCOS patients (Taher *et al.*, 2010).

Tipton weed

Tipton weed, scientifically known as *Hypericum perforatum* and belonging to the Hypericaceae family, is also commonly referred to as St. John's Wort. Historically, Greek Physicians recommended the use of this herb for the treatment of menstrual disorders, underscoring its historical significance in addressing women's health issues (Belwal *et al.*, 2019). In numerous cases, the psychological distress or the psychological well-being of the patient can significantly impact the treatment process and may diminish the overall success rate of the treatment (Mitsi & Efthimiou, 2014). Any triggers that induce negative stress or lead to depression have a detrimental effect on ovarian function and its treatment (O'Reilly *et al.*, 2014).

Black cumin

Black cumin, scientifically known as *Nigella sativa* and part of the Ranunculaceae family. The plant, particularly its oil and seeds, plays a prominent role in these systems and is employed for the treatment of a wide array of medical conditions and diseases (Ahmad *et al.*, 2013). Numerous studies suggest that black cumin is actively employed in the treatment and management of Polycystic Ovarian Syndrome (PCOS) in women. Black cumin is found to play a role in regulating cholesterol and HDL levels while influencing the levels of Low-Density Lipoprotein (LDL) in the body. It is believed that the appetite-suppressing effects of black cumin may lead to a hypolipidemic profile, further contributing to its potential benefits for individuals with PCOS (Sheeraz *et al.*, 2018). In another study, black cumin has demonstrated success in improving the medical condition of women with PCOS, particularly in addressing oxidative stress and dyslipidemia. As a result, black cumin plays a direct role in improving insulin modulation and exerts an anti-androgenic action to mitigate the side effects of PCOS, offering potential benefits for women with this condition (Nafiu *et al.*, 2019).

Ashoka

Ashoka, scientifically known as *Saraca Asoka* and a member of the Leguminosae family. Ashoka bark finds significant utility in addressing a range of women's health concerns, including the treatment of PCOS, irregular menstrual disorders, uncontrolled excessive bleeding, uterine spasms, mild to moderate pain, and dysmenorrhea. It is considered one of the most effective uterine tonics, capable of rectifying irregular menstrual cycles and preventing miscarriages. Women utilize both the flowers and bark of the Ashoka tree to address PCOS and various uterine disorders. The stem portion of Ashoka is also employed to manage uterine bleeding. It is reported to strengthen the innermost lining of the uterus, the endometrium, through its oxytocin action, thereby preventing uterine disorders. Ashoka is believed to mimic the actions of estrogen, facilitating the normal functioning of the uterus and mitigating excessive bleeding. It functions as an astringent to address heavy menstrual bleeding and stimulates uterine muscle contractions. Studies

also indicate its effectiveness in managing uterine fibroids and menorrhagia in cases of PCOS, highlighting its diverse applications in women's health (Aruljothi & Thiruthani, 2019).

Shatavari

Shatavari, scientifically known as *Asparagus Racemosus* and a member of the Asparagaceae family. It is utilized for purposes such as enhancing fertility, regulating the menstrual cycle, supporting ovarian follicle development, and promoting optimal reproductive system function. Shatavari is believed to contain natural plant-based estrogen, known as phytoestrogen, which plays a role in restoring the reproductive system in women (Kalia *et al.*, 2003). Shatavari is considered an herb of choice for addressing menstruation-related problems. One of Shatavari's major constituents is saponin, which aids in maintaining uterine mobility, making it particularly useful in addressing painful bleeding during pre-menopause. (Gaitondé & Jetmalani, 1969). Additionally, Shatavari's roots are used to strengthen uterine muscles, and they can be particularly helpful in cases of abortions (Sharma & Bhatnagar, 2011). Furthermore, Shatavari has the potential to alleviate stress levels in women, contributing to their overall well-being and reproductive health (Pandey *et al.*, 2018).

Guduchi

Guduchi, scientifically known as *Tinospora Cordifolia* and a member of the Menispermaceae family, is a versatile medicinal herb with a wide range of applications, including hypoglycemic, anti-inflammatory, anti-stress, and ovarian balance properties. One of the significant roles of Guduchi is in the treatment of Polycystic Ovarian Syndrome (PCOS). PCOS often leads to insulin disturbance and the development of ovarian cysts, resulting in inflammation in various tissues. Guduchi is believed to have potent anti-inflammatory effects, making it a valuable ally in managing the inflammation associated with PCOS. Moreover, Guduchi serves as a natural immunity booster and aids in overcoming insulin resistance commonly seen in women with PCOS. It also plays a role in modulating menstrual flow, contributing to the overall well-being of women dealing with PCOS (Khandelwal *et al.*, 2016).

Tulsi

Tulsi, known by its botanical name *Ocimum sanctum* and belonging to the Lamiaceae family, is a revered herbal plant with numerous medicinal properties. While it serves various purposes, one of its significant uses is in the treatment of hypoglycemia and obesity (Satapathy *et al.*, 2017). Tulsi is employed in the treatment of Polycystic Ovarian Syndrome (PCOS) due to its anti-androgenic properties. It works by reducing the production of androgens and helping manage obesity, both of which are common issues in PCOS (Pachiappan *et al.*, 2017). In case where proper ovulation processes do not occur, androgens are not effectively utilized by the body. This underutilization of androgens often leads to issues like hirsutism (excessive hair growth) and acne. Tulsi plays a crucial role in the proper management and utilization of androgen levels, helping to alleviate these symptoms. Additionally, it offers antioxidant properties, further contributing to its beneficial effects (Khanage *et al.*, 2019).

Ashwagandha

Ashwagandha, scientifically known as *Withania somnifera* and belonging to the Solanaceae family, contains a wide range of phytochemicals. These include alkaloids and withanolids like withaferin A, withanosides, sitoinosides, beta-sitosterol, and certain amino acids, particularly alanine, have a more prominent impact on fertility status (Azgomi *et al.*, 2018). It is beneficial in various inflammatory conditions, especially oophoritis. It is often prescribed along with other medications in the postpartum period. In cases of infertility, when the powder of this herb is consumed with milk and sugar for 21 days, it can aid in improving the chances of conception (Ghani, 2011). It has been found to possess anti-stress, antioxidant, anticarcinogenic, anti-aging, cardioprotective, hypothyroid, immunomodulatory, hypocholesterolemic, and hypolipidemic activities, making it a valuable herb with a wide range of health benefits (Jain *et al.*, 2012).

Gokharu

The botanical name of gokharu is *Tribulus terrestris*, and it belongs to the family Zygophyllaceae. This herb contains several important chemical constituents, including kaempferol, kaempferol-3-glucoside, kaempferol-3-rutinoside, and tribuloside are found in *T. terrestris*, and some of these compounds have therapeutic properties, including hypoglycemic effects (Saiyed *et al.*, 2016). It shows significant benefits in reducing serum glucose levels, serum triglyceride levels, and serum cholesterol in various studies. Additionally, it has been observed to normalize estrous cyclicity, steroidal hormonal levels, and ovarian follicular growth. Many of the compounds found in *T. terrestris* have stimulating effects on the ovaries and act as fertility tonics for women. This makes it a promising choice for women dealing with conditions like PCOS (Chhatre *et al.*, 2014).

Moringa

The botanical name of moringa is *Moringa oleifera*, and it belongs to the family Moringaceae (Paliwal *et al.*, 2011). *M. oleifera* is a tropical plant with various medicinal uses and significant ethnomedicinal importance. Its leaves, known as *M. oleifera* leaves (MOL), are highly nutritious and offer a wide range of health benefits. These benefits include anti-inflammatory, antimicrobial, antioxidant, anti-obesity, and anti-diabetic properties, making them a potential treatment option for conditions such as PCOS (Afzal *et al.*, 2021). Some other studies reveal that there are some other herbs which are used for the treatment of PCOS are enlisted in Table 1.

Supplementations

Vitamin supplements

Vitamin D is a steroid hormone primarily produced in the body when the skin is exposed to sunlight. In addition to its

skeletal functions, it is believed to have significant metabolic and endocrine roles (Mousa *et al.*, 2017; Mousa, 2020). A meta-analysis that looked at the effects of different doses of vitamin D supplementation over 8-24 weeks in women with PCOS found improvements in HOMA-IR (a measure of insulin resistance) and HOMA-β (a measure of beta-cell function). It also showed improvements in total testosterone levels and LDL cholesterol (Miao *et al.*, 2020).

Vitamin B8 also known as inositol, exists naturally in five stereoisomers, with myo-inositol (MI) and D-chiro-inositol (DI) being the most abundant. In the ovary, MI plays a role in regulating glucose uptake and follicle-stimulating hormone (FSH) signaling, while DI controls glycogen synthesis and insulin-induced androgen synthesis (Nestler *et al.*, 1998; Nestler & Unfer, 2015). A meta-analysis found that myo-inositol (MI) supplementation improved ovulation rates and helped regulate the frequency of menstrual cycles (Pundir *et al.*, 2018). Additionally, restoring the MI to D-chiro-inositol (DI) ratio normalized various hormonal parameters, including progesterone, luteinizing hormone (LH), sex hormone-binding globulin (SHBG), estradiol, and testosterone (Oliva *et al.*, 2018).

Vitamin B9 also known as folic acid is the synthetic form of folate (Greenberg *et al.*, 2011). Folic acid is believed to have antioxidant, anticancer, and cardio- and neuroprotective properties. These properties may be beneficial in the context of PCOS, especially considering the increased systemic oxidative stress and elevated cardiovascular risk often observed in women with this condition (González *et al.*, 2006). A study investigated the effects of 1 or 5 mg per day of folic acid, as well as a placebo, in women with PCOS over an 8-week period. The study found that the higher folic acid dose (5 mg/d) led to a reduction in insulin levels, improved insulin resistance (HOMA-IR), and better lipid profiles compared to the placebo or lower folic acid doses (Asemi *et al.*, 2014).

B group vitamins, including B1, B6, and B12, play a crucial role in breaking down homocysteine (Hcy) in the bloodstream and recycling it within the methionine cycle for future utilization. Consequently, deficiencies in B-group vitamins can result in increased levels of Hcy in the blood, which can potentially harm various bodily systems (Kennedy, 2016). Supplementing with B-group vitamins may be an effective approach to regulate homocysteine (Hcy) levels in women with PCOS, which could potentially lead to improvements in both cardiometabolic and reproductive health (Kilicdag *et al.*, 2005).

Vitamin K, which comes in the form of phylloquinone (K1) from green vegetables or menaquinone (K2) from animal products, is a fat-soluble micronutrient known for its role in coagulation (Bartstra *et al.*, 2021). Emerging research suggests that vitamin K might be a promising supplement for enhancing oxidative stress management and glycemic control in women with PCOS (Razavi *et al.*, 2016).

Vitamin E, also known as tocopherol, is a fat-soluble vitamin stored in the liver. It possesses anticoagulant and antioxidant properties, making it effective at neutralizing free radicals (Palamanda & Kehrer, 1993). Research has indicated that vitamin E supplementation can enhance endometrial thickness in women with unexplained infertility (Cicek *et al.*, 2012). Additionally, when combined with coenzyme Q10 for 8 weeks, it has been shown to increase SHBG (sex hormone-binding globulin) levels and reduce concentrations of free testosterone in women with PCOS (Izadi *et al.*, 2019). There is also evidence that vitamin E can reduce oxidative stress and lower the required dose of exogenous HMG (human menopausal gonadotropin) in certain cases (Chen *et al.*, 2020).

Vitamin A also known as retinol, is a fat-soluble vitamin that is believed to play a role in total antioxidant capacity (TAC), steroid metabolism, and oocyte maturation (Günalan *et al.*, 2018). In women with PCOS, there are differences in the expression of genes related to retinoic acid synthesis. These differences might contribute to inadequate retinol production, leading to an imbalance in metabolic function and androgen production. Additionally, retinol-binding protein 4 (RBP4) has been linked to impaired glucose metabolism and obesity in women with PCOS (Hahn *et al.*, 2007).

Vitamin-like nutrients

Bioflavonoids consist are a group of polyphenolic compounds derived from plants. Bioflavonoids, in general, are well-known for their established properties, including antioxidant, antidiabetic, antiestrogenic, anti-inflammatory, and antiproliferative effects. Furthermore, some metabolites of bioflavonoids have shown promise in addressing PCOS pathogenesis at different levels (Ross & Kasum, 2002; Oh *et al.*, 2016).

Alpha-Lipoic Acid (a-LA) serves as a free radical scavenger, plays a crucial role as a cofactor in the citric acid cycle, and is involved in regulating body weight (Biewenga *et al.*, 1997; Lee *et al.*, 2005). An interesting observation was made when controlled-release α-lipoic acid was administered to six non-diabetic women with PCOS. This administration did not lead to an increase in plasma antioxidant capacity or a reduction in plasma oxidation metabolites (Masharani *et al.*, 2010).

Carnitine is a compound with a quaternary ammonium structure that plays a role in various processes, including fatty acid metabolism, oxidative stress mechanisms, and glucose metabolism (Steiber *et al.*, 2004). According to a clinical study, non-obese women with PCOS exhibit significantly decreased levels of serum total L-carnitine compared to healthy women. This lower L-carnitine level is believed to be associated with hyperandrogenism and insulin resistance (Fenkci *et al.*, 2008). In a randomized clinical trial involving clomiphene-resistant women with PCOS, it was reported that the combination of clomiphene citrate and L-carnitine resulted in a thicker endometrium, higher pregnancy rates, and improved lipid profiles when compared to clomiphene citrate treatment alone (Ismail *et al.*, 2014). Another study showed that supplementation with L-carnitine at a dose of 9250 mg per day for 12 weeks had beneficial effects on mental health and oxidative stress parameters (Jamilian *et al.*, 2017).

Table 1: Medicinal Herbs used in Poly Cystic Ovarian Syndrome (Goswami *et al.,* 2012)

S. No.	Name	Botanical Name	Family	Part Used	Constituent present	Other Uses
1	Sarsaparilla	*Smilax officinalis*	Smilacaceae	Rhizome	Resin	Antibiotic
2	Angelica	*Angelica glauca*	Umbelliferae	Root	Coumarin, Sesquiterpee	Liver and heart disease
3	Cummin	*Cumminum cyminum*	Umbelliferae	Fruit	Volatile oil	Digestant
4	Bitter melon	*Momordica charantia*	Curcubitaceae	Fruit	Glycoside	Antidiabetic
5	Betel nut	*Areca Catechu*	Palmae	Seed	Alkaloid	Antiparasite
6	Colic root	*Dioscoreavillosa*	Dioscoreaceae	Root	Steroidal saponin	Rheumatism
7	Alfalfa	*Medicago sativa*	Fabaceae	Seed	Protein	Antioxidant
8	Indian madder	*Rubica Cordifolia*	Rubiaceae	Root	Resin, Phenolic compounds	Amenorhea, Dysmenorrhea Menopause, Manorrhagia
9	Kelp	*Nereocystisleutkeana*	Laminariaceae	Seaweed	Algin	Hormone balance
10	Myrrh	*Commiphora molmol*	Burseraceae	Oil	Volatile oil	Laxative, Anti-inflammatory
11	Dandelion root	*Taraxacum officinale*	Asteraceae	Whole plant	Germacronalide	Bitter
12	Hops	*Humulus lupulus*	Cannabinaceae	Female cons	Essential oil	Flavouring agent
13	Sesame	*Sesame indicum*	Pedaliaceae	Seeds	Protein	Culinary
14	Bladder wrack	*Fucus vesiculosus*	Fucaceae	Aerial part	Iodine, Bromide	Cosmetics
15	Rose	*Rosa rubiginosa*	Rosaceae	Flower	Carotenoids	Perfumary
16	Squaw vine	*Mitchella repens*	Rubiaceae	Aerial part	Resin	Hypotension
17	Black seed	*Nigella sativa*	Ranunculaceae	Seeds	Fatty acid	Antioxidant
18	Out straw	*Avena sativa*	Poaceae	Seed	Carbohydrate	Food
19	Garlic	*Allium sativum*	Liliaceae	Flower buds	Sulphides	Antiatherosclerotic
20	Mugwort	*Artemisia vulgaris*	Asteraceae	Whole plant	Germacronalide	Bitter
21	Triphala	1. *Emblica Officinalis* 2. *Terminalia beletica* 3. *Terminalia chebula*	Euphorbiaceae Combretaceae	Fruit	Tannin	Astringent
22	Blue cohosh	*Caulophyllumthalictroides*	Berberidaceae	Rot, Rhizome	Saponin	Female problems
23	Black Cohosh	*Actaea racemosa*	Ranunculaceae	Root	Glycoside	Women problems
24	Red Clover	*Trifolium pretense*	Fabaceae	Flower	Glycoside	Skin problem
25	Saraca	*Saraca indica*	Fabaceae	Flower, Leaves	Tannin	Uterine tonic
26	Dong quai	*Angelica sinesis*	Apiaceae	Root	Coumarine	Female, Anticoagulant

Mineral supplements

Calcium is an essential micronutrient that plays a crucial role in egg activity, oocyte maturation, progression of follicular development, and the regulation of cell division in mammalian oocytes (De Felici *et al*., 1991; Homa *et al*., 1993; Ullah *et al*., 2007). It had a positive effect on menstrual cyclicity, follicular maturation, and pregnancy rates, although these changes were not statistically significant (Firouzabadi *et al*., 2012).

Chromium is an essential mineral that plays a crucial role in carbohydrate and lipid metabolism (Lucidi *et al*., 2005). In another study involving 64 women with PCOS, it was observed that daily supplementation of 200 μg of chromium for eight weeks led to significant reductions in several health parameters. These included an improvement in cases of oligo/amenorrhea (irregular or absent menstrual periods), a reduced number of total follicles in the ovaries, lower levels of free testosterone in the blood, and a decrease in ovarian volume as observed through ultrasonographic examinations and biochemical analyses (Amr & Abdel-Rahim, 2015).

Magnesium is one of the most abundant intracellular cations (Touyz, 2004) and plays a crucial role in regulating various cellular processes (Saris *et al*., 2000). Magnesium supplementation is commonly used in the management of neurological disorders, including conditions related to depression such as PCOS. It is also employed in the treatment of hypertension and cardiovascular diseases (Song *et al*., 2005; Eby & Eby, 2006). These studies have noted lower serum magnesium levels and higher calcium-to-magnesium (Ca/Mg) ratios in women with PCOS, which may be associated with insulin resistance (Young *et al*., 1996).

Selenium is an essential element known for its effectiveness in combating oxidative stress. It is also necessary for the embryonic development of gonads and the proper functioning of reproductive tissues (Mirone *et al*., 2013). Biochemical studies have indicated that women with PCOS tend to have lower selenium levels compared to individuals without PCOS (Coskun *et al*., 2013). In this context, selenium supplementation in the form of an immunomodulatory drug (IMOD) was given to female rats with hyperandrogenism-induced PCOS for duration of 21 days. The results showed that IMOD led to a reduction in the production of tumor necrosis factor-α and an increase in antioxidant capacity (Rezvanfar *et al*., 2012).

Zinc is another essential trace element that plays a crucial role in the metabolism of lipids, carbohydrates, and proteins (Tubek, 2007). Studies have indicated that women with PCOS often have lower zinc levels (Guler *et al*., 2014). Zinc levels can play an important role in the development of insulin resistance (IR) in PCOS (Beletate *et al*., 2007). It has been suggested that zinc deficiency in PCOS might be associated with abnormal lipid profiles. Recent clinical research has investigated the effects of zinc supplementation in women with PCOS (Ahmed *et al*., 2010).

Other Supplements

Melatonin (MT) is a neuroendocrine hormone secreted from the pineal gland. High concentrations of MT have been found in follicular fluid, which affects physiological processes in the ovaries, such as folliculogenesis, follicular atresia, ovulation, steroidogenesis in theca cells, and corpus luteum formation due to its powerful free radical scavenger activity (Adriaens *et al.*, 2006; Tamura *et al.*, 2009; Carlomagno *et al.*, 2011). MT may improve oocyte quality and increase pregnancy rates (Tamura *et al.*, 2008). It is suggested that MT administration may be useful in in-vitro fertilization strategies and improve the clinical outcomes of PCOS (Kim *et al.*, 2013).

N-acetyl-L-cysteine (NAC) is the acylated form of the L-cysteine amino acid. Studies have shown that NAC administration supports oocyte quality by exerting an anti-aging effect on mouse oocytes. Additionally, NAC regulates insulin receptor function in erythrocytes and supports insulin secretion from pancreatic β cells (Santini *et al.*, 1994; Dickinson *et al.*, 2003; Liu *et al.*, 2012). The effects of metformin and NAC are compared in terms of their impact on insulin and testosterone levels, as well as ovulation success in women with PCOS (Elnashar *et al.*, 2007).

Omega 3 Fatty Acids are polyunsaturated fatty acids (PUFAs), and the most commonly known members in this group include α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Each fatty acid has distinct metabolic and endocrine properties. PUFAs intake has been associated with reduced triglycerides (TG), while the consumption of monounsaturated fatty acids (MUFAs) has been linked to decreased testosterone levels (Vargas *et al.*, 2011). It is believed that the healing mechanism of omega-3 is associated with the regulation of abnormal gene expression in the pathophysiology of PCOS (Shahnazi *et al.*, 2015).

Probiotics are living microbial dietary supplements found in dairy products, and they have synergism with the gut microbiota (Roberfroid *et al.*, 2000). The effects of probiotic supplementation on pancreatic β cells and C-reactive protein (CRP) in patients with PCOS using multispecies probiotics for 8 weeks were studied (Shoaei *et al.*, 2015). The study involved fecal microbiota transplantation (FMT) and lactobacillus transplantation in rats with PCOS. The results showed that, by the end of the study, all rats in the FMT group had improved estrous cycles, and most of the rats treated with lactobacillus experienced reduced androgen biosynthesis (Guo *et al.*, 2016).

CONCLUSION

Polycystic ovarian syndrome (PCOS) stands as a neuroendocrine metabolic anomaly hallmarked by an erratic menstrual cycle. Our awareness extends to the indications, origins, implicated organs, histological attributes, pathophysiological mechanisms, etiological factors, diagnostic methods, and therapeutic approaches. These insights have been gleaned through a comprehensive exploration of a myriad of resources, including various literary tomes and digital platforms like PubMed and ClinicalTrials.gov. The contemporary analysis centers on the paramount significance of phytotherapeutic compounds and adjuncts in the management of PCOS. Various studies reviewed above validate the usefulness of herbal & supplements combination in PCOS.

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