

Therapeutic efficacy in polycystic ovary syndrome: A comprehensive review comparing pharmaceutical and phytotherapeutic interventions from RCT evidence

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<https://doi.org/10.5281/zenodo.17364676>

Revised: 24-September-2025, Accepted: 14-October-2025, Online First: 16-October-2025

ABSTRACT:

Background: Five to ten percent of women of reproductive age suffer from polycystic ovarian syndrome (PCOS), which necessitates a variety of treatment modalities that address its intricate hormonal, metabolic, and reproductive symptoms. **Objective:** This thorough analysis uses data from randomised controlled trials to compare pharmacological and phototherapeutic approaches for the treatment of PCOS. **Methods:** Systematic analysis of RCTs examining herbal treatments (traditional Chinese medicine, Ayurvedic preparations, botanical supplements) and synthetic drugs (metformin, combined oral contraceptives, clomiphene citrate combinations) for the treatment of PCOS. **Results:** Drug treatments showed strong effectiveness. Ferriman-Gallwey scores and menstrual regularity were considerably enhanced by combined oral contraceptives (EE+DRSP, EE+CA). Metformin continuously improved cardiovascular indicators, lipid profiles, insulin resistance, and glucose tolerance. While combined treatments boosted ovulation in resistant situations, better clomiphene regimens raised pregnancy rates. Ayurvedic Satapushpa Churnam significantly decreased ovarian volume ($p<0.001$), cinnamon enhanced menstrual cyclicity ($p=0.0085$), and traditional Chinese medicine decreased the incidence of Type 2 diabetes (HR: 0.31, $p=0.0014$). Garlic, lavender, and quercetin were among the other herbal therapies that showed benefits in metabolic parameters, inflammation, and hormonal balance. **Conclusions:** In the management of PCOS, pharmacological and phytotherapeutic approaches offer complementing therapeutic potential. Herbal medicines offer special mechanisms and long-term protective effects, whereas synthetic pharmaceuticals have proven efficacy for symptom control and metabolic advantages. Because PCOS is varied, customised, multimodal approaches are supported. To improve inclusion into evidence-based PCOS procedures and bolster the evidence for herbal therapy, larger, more thorough RCTs are required.

Keywords: Polycystic ovary syndrome, Combined Oral Contraceptives, Phytotherapy, Randomized Controlled Trials, Metabolic Syndrome, Insulin Resistance.

1. INTRODUCTION:

Stein and Leventhal established the term PCOS in 1935, and it is generally referred to as Stein-Leventhal syndrome after the researchers (Azziz R 2014). PCOS is a common, complex, and diverse endocrine disorder affecting women caused by a combination of hereditary and environmental factors. PCOS affects

women of reproductive age, especially those in their early to late reproductive years (15–35 years). PCOS now affects one in every ten women worldwide (Zeng et al. 2022). The prevalence of PCOS is about 8-13% worldwide [Hoeger et al. 2021] and 8.1% (according to the Rotterdam criteria) (Mehreen et al. 2021) in India. PCOS is mostly diagnosed based on the Rotterdam

criteria, which include hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. It causes hormonal abnormalities, infertility, insulin resistance, obesity, cardiovascular disease, and psychological problems. Hyperandrogenism increases oxidative stress, inflammation, and insulin resistance, exacerbating symptoms. Advanced glycation end-products (AGEs) worsen ovarian dysfunction. Genetics, triggers from the environment, prenatal exposure to toxins, improper diet, and inactivity all play important roles in PCOS growth (Siddiqui et al. 2022). When we look into the genetic aspects of this disorder, we see that some genes, such as CYP21, CYP19, and CYP18, have altered expression, indicating that the genetic abnormality in PCOD affects signal transduction pathways that control steroidogenesis, steroid hormone action, gonadotropin action and regulation, insulin action and secretion, energy homeostasis, prolonged inflammation, and other processes (Chandak MK 2025). Knowledge gaps remain across medical specialities, resulting in diagnostic delays and unsatisfactory treatment satisfaction (Hoeger et al. 2021). Ongoing research strives to link evidence-based procedures to better patient outcomes.

1.1 Current treatment landscape:

Managing PCOS's multiple manifestations and reducing the long-term health concerns are the main goals of current treatment approaches. Hormonal medications, which include combined oral contraceptives (COCs), are commonly used in conventional medical procedures to control menstrual cycles and reduce androgenic consequences. Oral contraceptives have been the major mode of treatment for PCOS patients. Fourth-generation COC (combined oral contraceptives) comprising ethinylestradiol (EE) and a new progestin, drospirenone (DRSP), are thought to have qualities similar to natural progesterone, such as anti-mineralocorticoid and antiandrogenic activity, and are used to treat PCOS (Li et al. 2020). Furthermore, insulin sensitizers, such as metformin, are frequently used to treat the metabolic dysfunction that is a part of the syndrome. While oral contraceptives are widely used to treat PCOS, the most common side effects that contribute to poor adherence or discontinuation of OCPs include irregular monthly bleeding, nausea, breast tenderness, headache, and mood swings [Yildiz 2008]. At the same time, complementary and alternative medicine including different herbal interventions is gaining popularity. While conventional pharmaceuticals are accessible, there is a great deal of interest in researching natural alternatives to PCOS treatment. Conventional therapies are primarily symptomatic, with limited efficacy in treating underlying hormonal imbalances. As a result, many women resort to herbal therapies as an alternative to traditional treatments. The known adverse effects of traditional pharmaceutical agents,

worries about the possible long-term health implications of hormone therapy, and a need for more comprehensive patient care methods are the main causes of this interest. In order to control PCOS, this paper critically assesses the data pertaining to both conventional herbal medicines and synthetic pharmaceutical interventions.

1.2 Need for systematic comparison of RCTs across diverse therapeutic modalities:

Many randomized controlled trials (RCTs) have been conducted to assess various treatment options, such as pharmacological interventions (e.g., metformin, oral contraceptives, insulin sensitizers, and anti-androgens), lifestyle changes, herbal formulations, and alternative therapies. However, the lack of a systematic comparison of these various interventions makes it difficult to identify the most effective and comprehensive treatment options for PCOS. A structured review of RCTs is essential for determining the efficacy, safety, and long-term effects of these treatments in various groups. By methodically assessing indicators such as hormonal balance, metabolic health, reproductive function, and quality of life, this technique can provide insights into personalised and integrative therapy protocols. Furthermore, evaluating herbal and polyherbal formulations alongside conventional medicines may help to bridge the gap between modern medicine and traditional techniques, allowing for evidence-based adoption of phytotherapy in PCOS care. A complete analysis of existing RCTs would thus assist to modify clinical guidelines, improve patient care, and progress reproductive endocrinology research.

1.3 Purpose of the Report:

Presenting a thorough, evidence-based comparison of synthetic medications and herbal treatments currently used in the treatment of PCOS is the main goal of this paper. The presented research materials serve as the rigorous foundation for this study, which focusses on the stated results, their statistical significance, and the methodological soundness of the supporting studies. The report's goal in synthesising these data is to provide useful information for medical practitioners to aid in clinical decision-making and to pinpoint important areas that require additional study to bolster the body of evidence supporting the best practices for managing PCOS.

2. Pathophysiology:

Inherent ovarian dysfunction that is heavily impacted by extrinsic variables, including hyperinsulinemia and disruptions of the hypothalamic-pituitary-ovarian axis, is part of the pathophysiology of polycystic ovary syndrome (PCOS). Increased luteinizing hormone (LH) secretion due to excessive gonadotrophin releasing hormone (GnRH) pulsatility affects oocyte development as well as ovarian androgen production

(Balen 2004). On the other hand, PCOS impairs the feedback effect that peripheral sex hormones have on GnRH neurone activity, creating a vicious cycle (Liao et al. 2021). The cytochrome P450 (CYP), hydroxysteroid dehydrogenase (HSD), and aldo-keto reductase (AKR) families' steroidogenic enzymes, including AKR type 1C1 (20 α -hydroxysteroid reductase), CYP type 17A1 (17 α -hydroxylase), CYP type 11A (cholesterol side-chain cleavage), and 3 β -HSD type II, are over-expressed genes that are responsible for the molecular characterisation of

PCOS. Fast androgen production is determined by high levels of LH and steroidogenic enzymes (Wawrzekiewicz et al. 2020). Compared to controls, PCOS women have noticeably higher levels of serum luteinizing hormone (LH). A higher risk of miscarriage and a lower chance of conception have been linked to greater serum LH concentrations (Balen 2004). Period irregularities are caused by an imbalance of the hormones AMH, LH, and SHBG (Sex Hormone Binding Globulin) in PCOS (Polycystic Ovary Syndrome) (Mohammed and Qasim 2021).

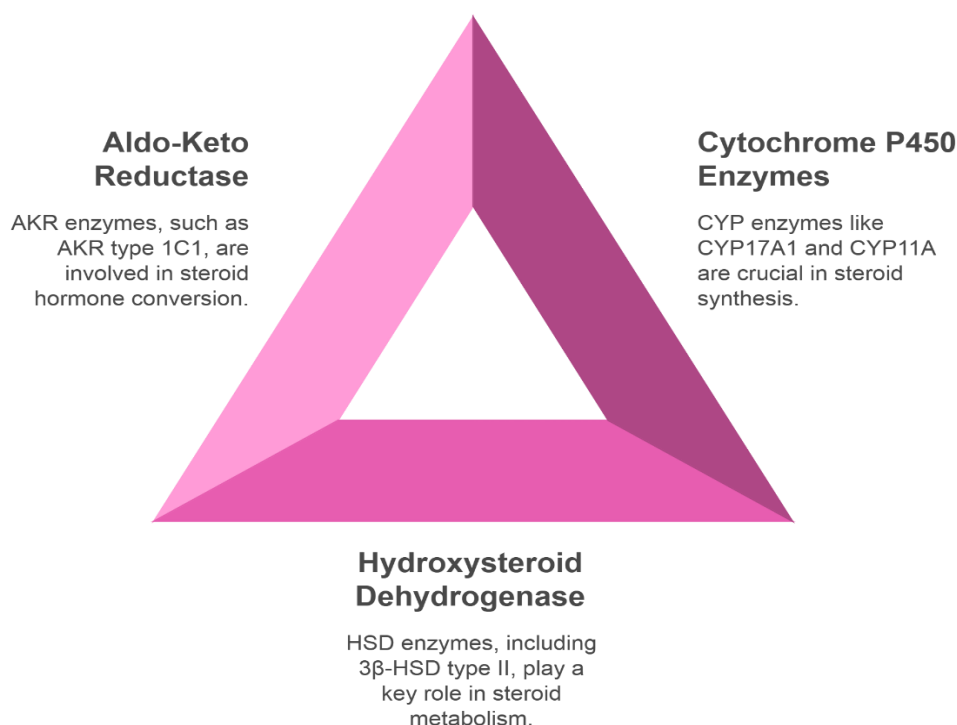


Figure 1. Molecular Foundation of PCOS

3. Complications Associated with PCOS:

Infertility, constant anovulation, irregular menstrual cycles, high testosterone levels, and pregnancy issues have all been connected to PCOS. According to a study, the infertility rate among women with PCOS was 15 times higher than that of women without PCOS, with 72% of PCOS women experiencing infertility compared to 16% of non-PCOS women (Atoum et al. 2022). "Endometrial receptivity" is the ability of the endometrium to permit the implantation of embryos. Two important causes of PCOS-related infertility are decreased endometrial receptivity and ovulation problems/anovulation (Jiang and Li 2022). Women with PCOS are more likely to develop endometrial cancer, especially if they have irregular vaginal bleeding and recurrent amenorrhoea (Witchel et al. 2020). In addition to weight gain, acne, and undesirable male pattern hair development, PCOS patients also have many egg-containing follicles that have not reached full maturation stage visible in the ovaries as cysts (Mohammed and Qasim 2021). Because women with PCOS have more sleep

disturbances and irregular sleep architecture, their melatonin levels also deviate from normal, which also affects melatonin secretion. One hormone that controls the sleep-wake cycle is melatonin (N-acetyl-5-methoxytryptamine), whose production is triggered by darkness and inhibited by light (Shreeve et al. 2013). Menopause symptoms, mood swings, despair, anxiety, and poor thyroid hormone production are all caused by insufficient melatonin output. Studies have shown that obese women with PCOS are more likely to have obstructive sleep apnoea (OSA). Metabolic disorders include insulin resistance, Type 2 Diabetes Mellitus, impaired glucose tolerance, gestational diabetes mellitus, non-alcoholic fatty liver disease, and metabolic syndrome. Excess testosterone frequently results in hirsutism, skin conditions like acne and alopecia brought on by androgenic testosterone, and Acanthosis nigricans, a sign of insulin resistance, is also common. PCOS-related skin symptoms may contribute to women's low self-esteem (Witchel et al. 2020).

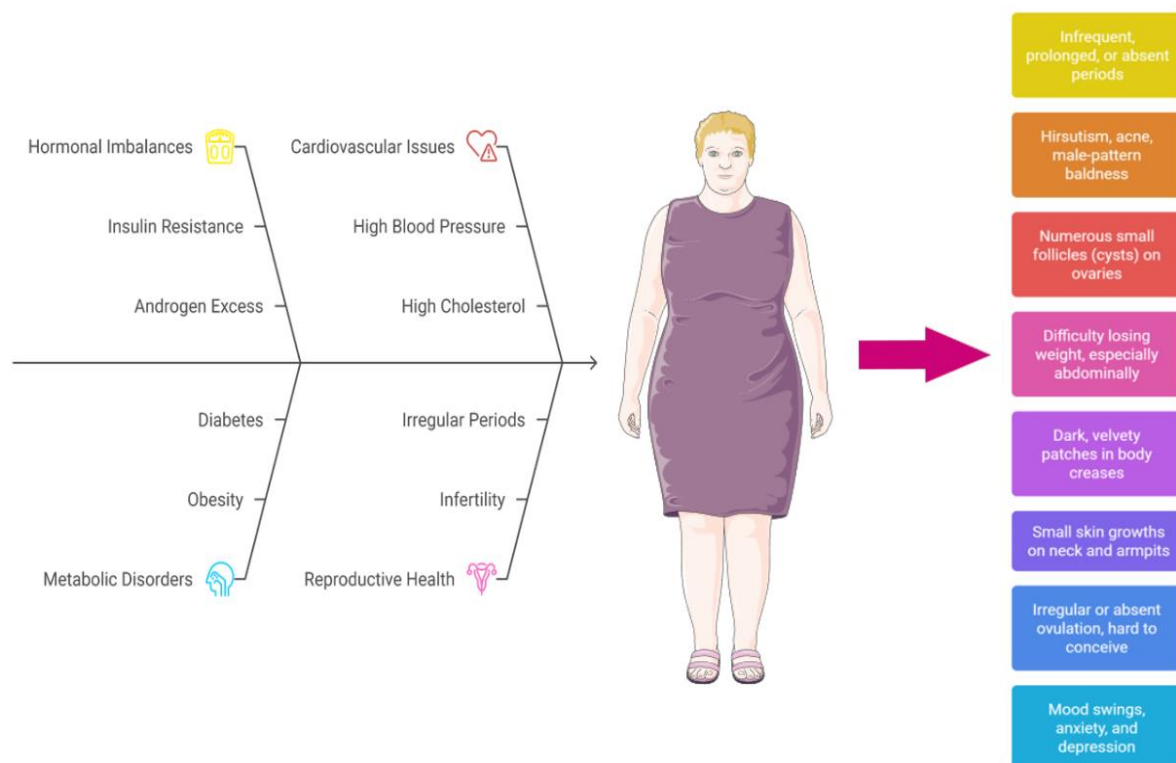


Figure 2. Complications Associated with PCOS

4. Synthetic Drug Interventions for PCOS:

The main way that combined oral contraceptives (COCs) treat PCOS is by inhibiting the release of gonadotropins, especially luteinizing hormone (LH). As a result, this inhibition lowers ovarian testosterone production and LH-mediated ovarian steroidogenesis. Ethinyl oestradiol (EE), an oestrogenic component, is essential because it increases the production of Sex Hormone-Binding Globulin (SHBG) in the liver. The amount of active, free testosterone in the blood is less bioavailable as a result of this increase in SHBG levels. Additionally, some progestins, such cyproterone acetate and drospirenone, have built-in antiandrogenic qualities that directly offset androgenic effects at the level of cellular receptors.

4.1 Hormonal Therapies:

4.1.1 Combined Oral Contraceptives (COCs): Ethinyl Estradiol + Drospirenone (EE+DRSP) and Ethinyl Estradiol + Cyproterone Acetate (EE+CA):

It is commonly known that COCs are effective at controlling menstrual cyclicity and hirsutism. Two distinct EE+DRSP dosage schedules (0.03 mg EE 21/7 vs. 0.02 mg EE 24/4) were carefully evaluated over a 6-month period in a prospective randomised experiment involving 47 women who presented with hirsutism, some of whom also had PCOS. According to the Ferriman-Gallwey (F-G) scoring system, the study unequivocally showed that both regimens were very successful in considerably raising hirsutism

ratings. In particular, F-G scores decreased from a mean of roughly 17.3 to 8.7 in Group 1 ($p < .001$) and from 17.5 to 7.9 in Group 2 ($p < .001$), suggesting that the two groups were equally effective (Oner and Muderris 2011). The regularization of periods in every patient in both treatment cohorts was a noteworthy therapeutic benefit. The antiandrogenic mode of action was confirmed by the considerable increase in SHBG levels and the significant decrease in both total and free testosterone levels ($p < .05$) (Oner and Muderris 2011). The study found no significant changes in mean levels of FSH, LH, oestradiol (E2), androstenedione (A), or dehydroepiandrosterone sulphate (DHEAS). However, EE+DRSP showed strong efficacy in treating hirsutism and monthly regularity. This implies a focused impact on androgen metabolism as opposed to a general suppression of the pituitary-gonadal axis that goes beyond what is required to limit ovulation. Nevertheless, even while EE-CA was helpful in treating clinical symptoms, it was linked to a substantial increase in serum triglycerides ($p = 0.01$) (Moini et al. 2015). This observation suggests a possible metabolic trade-off because it differs from the positive lipid profile frequently seen with metformin. The implications of these findings extend to cardiovascular risk markers. In a crucial clinical randomised study, metformin and Diane 35 Diario (EE+CA) were directly compared in 34 PCOS patients over a 24-week period, with an emphasis on evaluating cardiovascular risk factors (Luqu et al. 2009). According to this study, Diane 35 Diario caused a small rise in the average systolic and diastolic blood

pressure during the day and the 24 hours (Luqu et al. 2009). On the other hand, these blood pressure metrics decreased after using metformin. Notably, carotid intima media thickness (CIMT) readings, an early indicator of atherosclerosis, were reported to improve and return to the normal range with both Diane 35 Diario and metformin therapies.

These findings draw attention to an important clinical consideration: the balance between the impact on metabolic health and the management of explicit PCOS symptoms. In particular, EE-CA demonstrated a rise in serum lipids and a modest increase in blood pressure, despite the fact that COCs, such as EE+DRSP and EE+CA, are quite successful in treating patient-distressing androgenic symptoms like hirsutism and irregular menstruation. This contrasts with metformin, which decreased blood pressure and improved lipids. This creates a glaring clinical conundrum: COCs successfully treat short-term symptoms, yet they may negatively or even detrimentally impact important metabolic and cardiovascular risk variables that are very common in PCOS patients. Therefore, clinicians have to carefully assess the long-term effects on metabolic and

cardiovascular health against the critical need for symptom relief. This frequently calls for a comprehensive conversation with patients regarding the risks and priorities of treatment.

The different and even conflicting effects of metformin and COCs on metabolic markers show that single medication cannot consistently work or suitably for all PCOS patients. This emphasizes how important individualized treatment plans are. Metformin may be a better first-line option or a required COC adjunct for patients with pre-existing cardiovascular risk factors, dyslipidemia, or hypertension. On the other hand, COCs continue to be quite successful for those whose major issue is severe hirsutism or irregular menstruation. This goes beyond straightforward medication selection to a comprehensive evaluation of the patient, incorporating their unique phenotype, metabolic profile, and long-term health concerns into a customized treatment strategy. Additionally, it encourages more investigation into whether particular COC formulations may have a more neutral or even advantageous metabolic profile, which will contribute to clinical guidelines and future medication development.

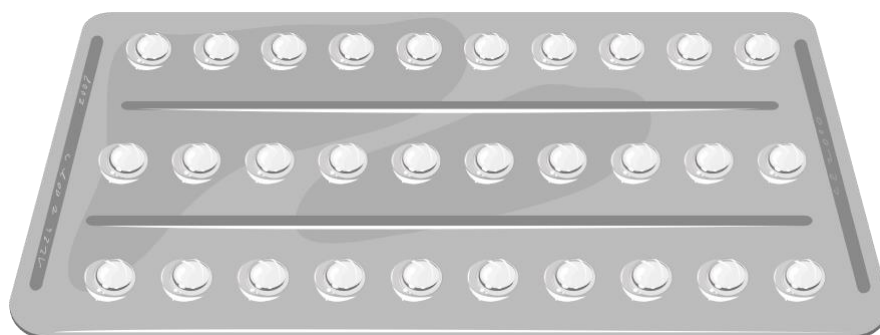


Figure 3. Combined Oral Contraceptives (COCs)

4.1.2 Ovulation Induction Agents: Clomiphene Citrate (CC) with Ethinyl Estradiol (EE) Adjunct:

For women with PCOS-related anovulatory infertility, clomiphene citrate (CC) is commonly acknowledged as the first-choice drug for ovulation induction. Even if 60% to 85% of instances are successful in stimulating ovulation, the actual pregnancy rate is still much lower, usually between 10% and 20%. The anti-estrogenic effects of CC, which can impair the endometrium's capacity to promote implantation, are primarily to blame for this disparity. These consequences can include decreased uterine blood flow, a non-trilaminar pattern, and a thinner endometrial lining, all of which lower the chance of a successful pregnancy. A randomised, double-blind, placebo-controlled study examined the addition of low-dose EE (0.05 mg daily for 5 days) to CC cycles in 95 PCOS women having artificial insemination in order to mitigate these negative effects (Moini et al. 2015). With a p-value of 0.02, the study showed that the clinical pregnancy rate in the CC+EE group was statistically significantly

higher (29%, 13 out of 45 participants) than in the CC + placebo group (10%, 5 out of 50 participants) (Moini et al. 2015). This suggests that fertility results have significantly improved. In terms of endometrial parameters, the CC + EE group had a substantially higher mean endometrial thickness (9.7 ± 2.1 mm) on the day of hCG administration than the CC + placebo group (8.9 ± 1.6 mm), with a p-value of 0.04 (Moini et al. 2015). These findings suggest that EE successfully mitigates CC's anti-estrogenic effects on endometrial proliferation, improving the implantation environment. In order to maximise overall therapy outcomes, this technique demonstrates a complex clinical strategy that entails recognising and managing iatrogenic consequences of a primary treatment. Despite being an excellent ovulation stimulant, clomiphene citrate (CC) has a well-established anti-estrogenic impact that might impair endometrial receptivity and cause a discrepancy between ovulatory and pregnancy rates. Ethinyl Oestradiol (EE) was added as an adjuvant to CC in order to directly target this effect. Endometrial thickness and uterine blood flow, two essential

components of a successful implantation, significantly improved as a result of EE supplementation. Crucially, a statistically significant rise in clinical pregnancy rates was linked to these mechanistic improvements. This method therefore highlights the possibility of a customized intervention to mitigate adverse effects and enhance the overall effectiveness of reproductive medication.

The research's conclusion that CC and EE together provide a "acceptable, cost-effective, and less complex alternative to standard gonadotropin therapy" has significant ramifications for enhancing access to healthcare. Advanced procedures like IVF and treatments like gonadotropins are significantly more costly and resource-intensive. This strategy has the potential to increase access to fertility care by enhancing the efficacy of a straightforward, reasonably priced first-line treatment (CC), especially in regions with limited resources. As a result, these results not only emphasise the clinical advantages but also the socioeconomic effects of increasing access to effective therapies, which lessens the total strain on health systems and encourages greater equity in reproductive care around the world.

4.1.3 Combined Pioglitazone-Metformin and Clomiphene Citrate (CC):

A randomised clinical trial examined the effectiveness of pioglitazone (15 mg) and metformin (850 mg) taken once daily with CC (100 mg daily for 5 days) vs metformin (500 mg three times daily) and CC (100 mg daily for 5 days) for women with clomiphene citrate-resistant PCOS (Fattah et al. 2014). According to the study, the group that received pioglitazone + metformin + CC had a considerably higher cumulative pregnancy rate (58% vs. 34%; $P=0.027$) throughout three cycles, as well as a significantly higher ovulation rate (69.8% vs. 48.8%; $p=0.002$). Furthermore, this combination led to thicker endometrium in the three follow-up cycles, a greater number of follicles ≥ 18 mm, and noticeably higher serum E2 levels on day 12 (Fattah et al. 2014). This implies that pioglitazone, when used with metformin and CC, can overcome CC resistance and greatly enhance reproductive results.

4.1.4 Clomiphene Citrate (CC) vs. Low-Dose Recombinant FSH:

As a first-line treatment for anovulatory PCOS, a single-center randomised controlled trial contrasted low-dose recombinant FSH (75 IU daily step-up protocol) with clomiphene citrate (50-150 mg/day for 5 days) (López et al. 2004). FSH had a substantially greater ovulation rate each cycle (74%) than CC (53%). In first cycles, FSH specifically caused a 66% ovulation rate, compared to 40% for CC ($P=0.02$, RR 1.67, CI 1.08-2.69). There was a trend towards FSH in the pregnancy rate per woman (42% vs. 24%, $P=0.09$), and the pregnancy rate each cycle was 18% for FSH and 9% for CC [32]. In patients who had not become

pregnant with CC, FSH was found to be a determinant that predicted both ovulation and pregnancy (López et al. 2004).

4.1.5 Clomiphene Citrate (CC) + Cabergoline:

In order to induce ovulation in euprolactinemic infertile women with PCOS, a randomised clinical trial examined the adjuvant use of cabergoline (1 mg every three days for nine days) in combination with CC (100 mg/day for five days). Compared to the CC-only group (58.3%), the cumulative ovulation rate in the CC + cabergoline group was considerably higher (76.7%; $p=.032$). Additionally, the combination group's maximum follicle size in each cycle was considerably larger ($p<.05$). Importantly, the CC plus cabergoline group had a significantly higher clinical pregnancy rate (31.7%) than the CC group, which only had 13.3% ($p=.004$) [31]. The rates of ovarian hyperstimulation, multiple pregnancies, miscarriages, and side effects did not differ significantly between the two groups.

4.2 Insulin Sensitizers:

4.2.1 Metformin:

One of the mainstays of treating insulin resistance is the biguanide metformin. Its main mechanisms include increasing peripheral tissue insulin sensitivity, decreasing hepatic glucose synthesis, and boosting cell uptake and utilisation of glucose. Metformin indirectly alleviates the hyperandrogenism associated with PCOS by directly treating insulin resistance and lowering compensatory hyperinsulinemia, which raises ovarian androgen production and lowers SHBG levels.

Metformin's effects on metabolic parameters, insulin resistance, and hyperandrogenism have all been thoroughly investigated. Over the course of three months, 30 PCOS women participated in a prospective, open clinical study that directly compared rosiglitazone (4 mg daily) and metformin (850 mg twice daily). According to the study, metformin produced a "much better decrease" in the free androgen index (FAI) and testosterone levels than rosiglitazone. Although it was observed that rosiglitazone "better influenced" hyperinsulinemia and insulin resistance (HOMA-IR), metformin still had a positive effect on both metrics [26].

A randomised controlled trial (RCT) that compared metformin (500 mg twice daily) with EE-CA in 26 PCOS patients over a 3-month period provides more proof of metformin's metabolic advantages. Triglycerides (TG) and very-low-density lipoprotein cholesterol (VLDL-C) were decreased on metformin treatment, but high-density lipoprotein cholesterol (HDL-C) significantly increased ($P=0.006$). Additionally, it resulted in a substantial decrease in blood testosterone ($P=0.038$) and showed improvements in body mass index (BMI) and glucose tolerance test (GTT) findings (Mhao et al. 2016)

It's crucial to recognise a notable inconsistency in the presented findings, though. According to the results of

a randomised, single-blind controlled study, "Insulin resistance did not change for either of the patients taking cinnamon or metformin ($p=0.899$)" (Khan et al. 2019). The conventional pharmacological concept of metformin as an insulin sensitiser, as well as the consistent evidence in addition are directly contradicted by this conclusion. This disparity, which may be caused by variations in the study's design, duration, dosage, measuring techniques, or patient characteristics, merits thorough examination.

Metformin has positive effects on cardiovascular risk variables in addition to its direct metabolic benefits. Metformin dramatically lowered the average systolic and diastolic blood pressure in PCOS patients during the day and 24 hours in the 24-week research compared to Diane 35 Diario (EE+CA) (Luque et al. 2009). In stark contrast, EE+CA resulted in a minor rise in these parameters. Crucially, carotid intima media thickness (CIMT) readings, an early indicator of atherosclerosis, were seen to improve and return to normal with both metformin and EE+CA therapies (Luque et al. 2009). Although metformin is usually well tolerated, gastrointestinal side symptoms such as nausea, vomiting, and diarrhoea are the most frequent. Patient adherence may occasionally be hampered by these side effects.

Studies consistently demonstrate positive effects on metabolic parameters (lipids, glucose) and important cardiovascular risk markers (blood pressure, CIMT), even though metformin directly treats hyperandrogenism and menstrual regularity (indirectly through IR improvement). Metformin is positioned not just as a symptomatic treatment for PCOS but also as a vital prevention measure against serious long-term health consequences because PCOS patients have an elevated long-term risk for T2DM and cardiovascular disease. Because of its broad vigilant profile, metformin is a cornerstone medication that can be used for more than just urgent gynaecological issues; it is especially useful for PCOS patients who are obese, insulin-resistant, or have an elevated cardiovascular risk.

4.2.2 Thiazolidinediones (e.g., Rosiglitazone):

Thiazolidinediones (TZDs) are a type of insulin-sensitizing medications that operate as agonists for the liver, muscle, and adipose tissue's peroxisome proliferator-activated receptor-gamma (PPAR-gamma). By improving peripheral tissue insulin sensitivity, this activity improves glucose absorption and lowers total insulin resistance. Rosiglitazone (4 mg daily) was found to have a more noticeable effect on insulin resistance (HOMA-IR) and hyperinsulinemia than metformin in a study that compared the two medications (Mitkov et al. 2006). On the other hand, metformin showed a more notable reduction in both the free androgen index and testosterone. With TZDs maybe having a larger direct effect on insulin sensitisation and metformin possibly having a more

direct or indirect effect on androgen levels, this suggests a distinct impact on different parts of PCOS pathogenesis.

Although thiazolidinediones are effective at increasing insulin sensitivity, they have been linked to a number of safety issues. Compared to metformin, these worries have greatly restricted their widespread clinical usage in PCOS. These worries can include cardiovascular hazards like fluid retention and heart failure, as well as possible problems with bone density. This case serves as an example of a basic pharmacotherapy principle: a drug's overall safety profile must always be carefully weighed against its efficacy, regardless of how promising it may seem in particular areas. Even when a medication is highly effective for a specific goal, serious safety issues can make it a less desirable choice for long-term illnesses like PCOS, which can result in its limited use or removal from general clinical practice.

4.3 Combined Metformin and Curcumin:

In a three-month randomised controlled experiment, 100 PCOS-afflicted women were examined to see whether curcumin nanomicelles (80 mg/day) and metformin (500 mg three times day) worked better together than metformin alone (Sohrevardi et al. 2021). According to the study, the combined treatment considerably reduced lipid profiles and insulin resistance. In particular, the curcumin + metformin group had significantly lower levels of total testosterone, HOMA-IR, and fasting insulin than the metformin-only group ($p<0.05$). Furthermore, the combination group had significantly higher HDL-C levels ($p<0.05$) and significantly lower LDL-C levels ($p<0.01$). Triglycerides and total cholesterol also sharply declined. Additionally, curcumin therapy raised FSH levels while lowering amounts of LH, DHEAS, and testosterone (Sohrevardi et al. 2021). This implies that in PCOS patients, curcumin may improve the hormonal and metabolic advantages of metformin.

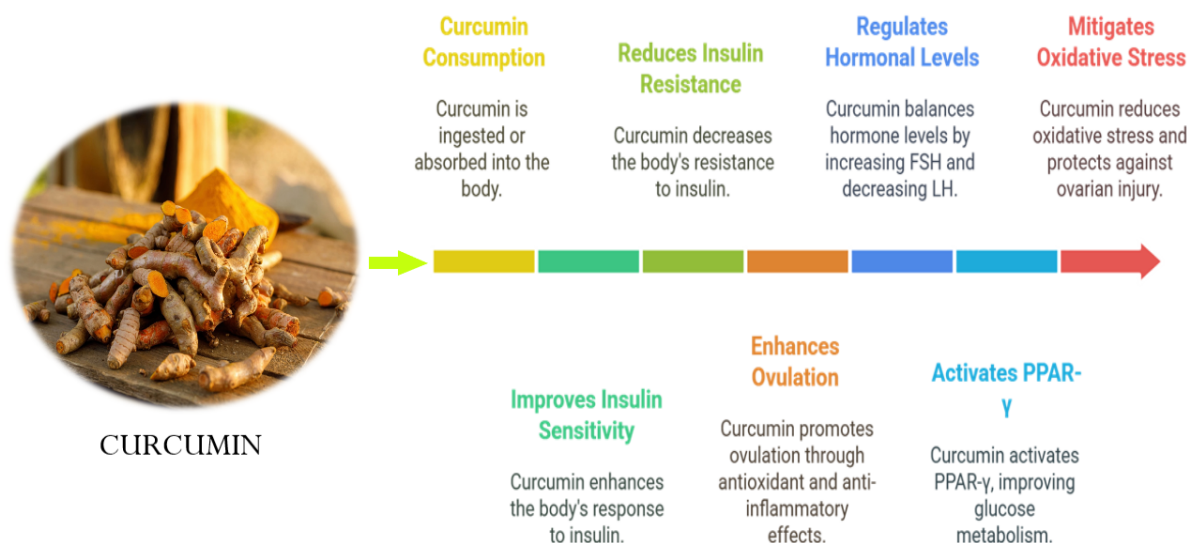


Figure 4. Mode of Action of Curcumin

4.4 Combined Metformin and Liraglutide:

Over the course of 12 weeks, 60 overweight PCOS patients were randomised to receive either metformin monotherapy or metformin plus liraglutide, a GLP-1 analogue [12]. Both treatments resulted in improvements in menstrual periods, glucose metabolism (fasting glucose, fasting insulin, and HOMA-IR), and anthropometric measures (weight, BMI, and abdominal circumference), with no statistically significant difference between the two groups. In contrast, metformin plus liraglutide therapy significantly raised baseline levels of LH, FSH, and progesterone (Prog) and was more successful than metformin monotherapy in reducing hyperandrogenism, including total testosterone (TT), SHBG, and FAI (Xing et al. 2022). It was determined that the combined therapy was more successful in resolving hyperandrogenism and reproductive problems, possibly through adjusting the hypothalamic-pituitary-ovarian axis.

4.5 Combined Metformin and Simvastatin:

Simvastatin (20 mg/day) and metformin (500 mg three times a day) were compared to metformin plus placebo in a prospective, randomised, double-blind, placebo-controlled research that involved 84 women with PCOS during a 12-week period (Kazerooni et al. 2010). Serum testosterone levels dropped substantially more in the combination group (metformin + simvastatin) (25.5% vs. 16.8% in metformin + placebo; $P < .001$), as did LH (45.5% vs. 6.7%) and the LH/FSH ratio (38.3% reduction vs. 4.4% increase). Additionally, there was a higher increase in HDL and a greater drop in triglycerides, LDL (18.5% vs. 1.5%), and total cholesterol (29.5% vs. 4.2%) (Kazerooni et

al. 2010). Significant gains in insulin sensitivity, fasting glucose, and insulin were seen in both groups. This implies that lowering testosterone levels, lipid profiles, and insulin resistance more effectively may result from taking simvastatin and metformin together.

5. Herbal Interventions for PCOS:

5.1 Chinese Herbal Medicine (CHM):

The long-term preventive effects of Traditional Chinese Medicine (CHM) against Type 2 Diabetes Mellitus (T2DM) in women with Polycystic Ovary Syndrome (PCOS) were examined in large, countrywide matched cohort research from Taiwan. Over an average of 5.2 years, the study monitored 342 CHM users and 342 non-CHM controls. The findings showed that the CHM group had a significantly lower chance of developing type 2 diabetes (T2DM) (Hazard Ratio = 0.31; 95% CI: 0.15–0.64; $p = 0.0014$), indicating that CHM plays a major preventive effect in halting the evolution of diabetes in PCOS (Liao et al. 2019). Crucially, research demonstrates how multicomponent herbal therapy may offer long-term health advantages for PCOS patients that go beyond symptom relief to illness prevention. The work highlights the intricacy of CHM, especially its synergy and multicomponent nature, which present methodological difficulties for further investigation. Innovative methods are needed to break down multicomponent formulations, standardise preparations, and thoroughly and reproducibly examine mechanisms of action in order to validate these effects and pinpoint important components.

5.2 Cinnamon (*Cinnamomum cassia*):

Cinnamon's alleged insulin-sensitizing properties have sparked interest in PCOS. Mechanistically, it is thought to improve insulin sensitivity by activating the insulin receptor and modifying glucose transit within cells through intermediary metabolites.

A prospective, double-blind, placebo-controlled Randomised Controlled Trial (RCT) examined the effects of 1.5 gm of cinnamon per day on menstrual cyclicity in 45 PCOS-afflicted women. The results demonstrated that menstrual cycles were significantly more frequent in the cinnamon group (median (IQR) 0.75 (0.5-0.83) cycles/month) compared to the placebo group (0.25 (0-0.54) cycles/month) ($p=0.0085$, Mann Whitney U test), despite the fact that only 17 women finished the full 6-month study period (a known limitation). Additionally, compared to the placebo group, the cinnamon group's menstrual cyclicity improved considerably from baseline (+0.23 cycles/month; $p=0.0076$, Wilcoxon signed rank test). In a subgroup of individuals, luteal phase progesterone levels confirmed ovulatory menses. A different randomised, single-blind controlled study that compared the effects of metformin and cinnamon (1.5g twice day) over a shorter period of time (60 days) in 26 PCOS patients also found that the cinnamon group experienced a "marked improvement in the menstrual cycle pattern" (51.9% improvement) (Khan and Begum 2019). The RCT found no significant differences in blood testosterone levels or insulin resistance measurements (e.g., HOMA-IR, QUICKI) for either the cinnamon or placebo groups, despite the suggested insulin-sensitizing mechanism. This result runs counter to the earlier pilot study (Wang et al. 2007), which found that cinnamon increased insulin sensitivity. This lack of impact was further supported by the RCT, which found that "Insulin resistance did not change for either of the patients taking cinnamon or metformin ($p=0.899$)." Additionally, this particular metformin finding runs counter to other strong evidence. A major obstacle to the RCT was a high dropout rate (more than 50% at six months), which

limited the generalisability of the results and made them preliminary. A noteworthy knowledge gap is the difficulty to pinpoint a precise mechanism (no discernible alteration in androgens or insulin sensitivity) in spite of improved menstrual cyclicity. The two-month trial period may not have been long enough to detect meaningful metabolic changes.

Although the suggested underlying mechanism (insulin sensitisation) was not statistically confirmed in these studies and even contradicted previous pilot data from the same research group, the observation that cinnamon consistently showed a positive and statistically significant effect on menstrual cyclicity, a key clinical outcome for PCOS patients, highlights a common challenge in medical research. The clinical effectiveness of a treatment may be clear, but its exact mode of action is still unknown or necessitates larger, more sensitive, or longer-term investigations to identify minute changes. This indicates to academics that more research is necessary in order to fully comprehend how, as opposed to just verifying that, cinnamon has positive effects on PCOS. Its reference to a prior pilot research, along with its clear designation as "Preliminary Evidence" and the assertion that it "should be considered a pilot study," did not reproduce a particular mechanistic finding in the current, larger (albeit still small) RCT, despite reporting better insulin sensitivity. This exemplifies a prevalent occurrence in scientific literature: encouraging outcomes from smaller pilot studies might not be reliably repeated in later, bigger (yet still constrained) trials. It also calls into question possible publication dynamics; wherein favourable clinical outcomes may be highlighted despite a conflicting or incompletely explained underlying molecular rationale. This makes it necessary to interpret "preliminary" findings with caution and emphasises how crucial it is to conduct larger, meticulously planned, and openly reported investigations in order to establish a strong body of evidence.

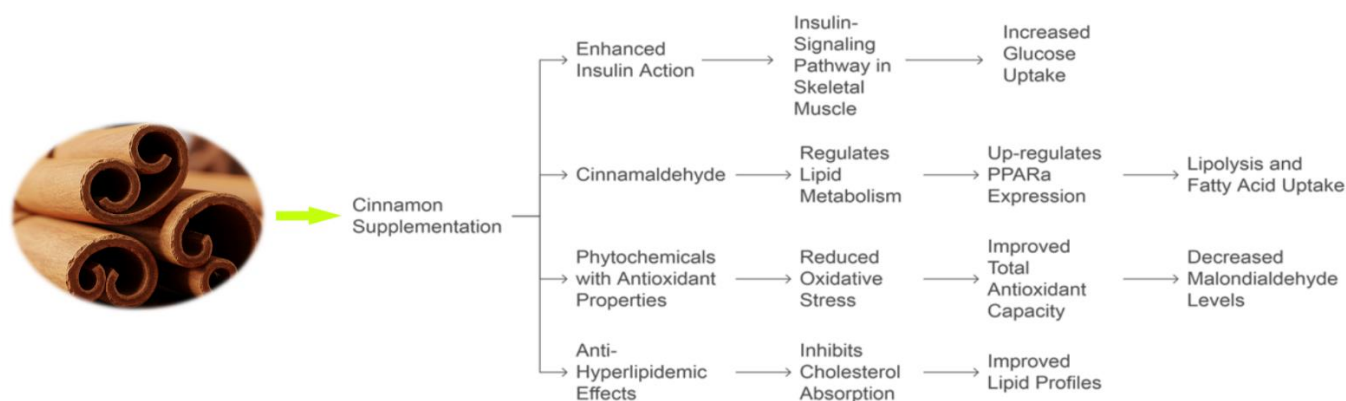


Figure 5. Mode of Action of Cinnamon

5.3 Ayurvedic Formulations: Satapushpa Churnam with Tila Tailam:

In particular, this study examined how an Ayurvedic formulation called Satapushpa Churnam (Anethum sowa Kurz.) with sesame oil (Tilatailam) as an anupanam (vehicle) affected PCOS-related oligomenorrhea. The investigation was carried out in an outpatient and inpatient department setting as a single-group, before-and-after intervention study. Thirty women between the ages of 18 and 35 who satisfied the Rotterdam criteria for PCOS and had been diagnosed with oligomenorrhea for more than three consecutive menstrual cycles were included. Participants were given six grams of for three months, take 12 millilitres of Tilatailam twice a day along with Satapushpa powder. Three and six months after the intervention, the treatment's efficacy was evaluated (Jacob et al. 2021). Following three months of treatment, the results demonstrated a significant decrease in the menstrual interval ($p < 0.001$), suggesting that menstrual cycles had been successfully regularised. A noteworthy discovery was the substantial decrease in ovarian volume. At baseline, the right ovary's median interquartile range (IQR) volume was 10 (7.2-14.8) cm^3 ; at baseline, it was 5.3 (4.7-7.6) cm^3 ($p < 0.001$). Likewise, the left ovary's median (IQR) volume decreased from 9.1 (6.7-11.9) cm^3 to 5.1 (4.6-7.1) cm^3 ($p < 0.001$) (Jacob et al. 2021). The polycystic ovaries have undergone a significant morphological alteration. Neither the volume of bleeding nor the length of the menstrual cycle changed much. The study found that regularising the menstrual cycle and dramatically lowering ovarian volume are two benefits of treating PCOS with Satapushpa powder and Tilatailam for three months.

The Ayurvedic study is the first to report a statistically significant decrease in ovarian volume, which is a direct morphological change in polycystic ovaries, a crucial diagnostic characteristic of PCOS. Numerous other PCOS treatments mainly target biochemical improvements (e.g., insulin resistance, androgen levels) or clinical alleviation (e.g., hirsutism, menstrual regularity). Even while they are significant, a direct decrease in ovarian size points to a deeper effect on the underlying ovarian disease. This conclusion is especially strong since it raises the possibility that the intervention may be addressing the underlying cause of the ovarian malfunction rather than just treating its symptoms. To validate this significant effect, more research with more exacting study designs is necessary. The foundation of this research is the ancient medical system known as Ayurveda. The study offers initial scientific validation for an age-old technique by evaluating a traditional formulation using contemporary scientific methodologies (such as statistical analysis and ultrasonic measurements). There may be a solid scientific foundation for incorporating traditional treatments into modern

medical practice if these important findings especially the decrease in ovarian volume are confirmed in bigger, carefully monitored Randomised Controlled Trials (RCTs). This demonstrates a significant and expanding trend in medical research: the methodical investigation and validation of traditional medical knowledge through the application of exacting contemporary scientific methodologies, which may result in the identification of novel therapeutic agents or the creation of integrated treatment plans for complicated diseases like PCOS.

5.4 Lavender (*Lavandula angustifolia*):

68 PCOS patients participated in a 90-day randomised, double-blind research experiment to examine the effects of metformin (500 mg three times a day) and lavender (250 mg twice a day). According to the study, progesterone levels were significantly raised by both lavender and metformin ($P < 0.001$ for both), but there was no discernible difference between the two treatments ($P = 0.9$). Furthermore, the length of the menstrual cycle was significantly reduced by both treatments (from 60 to 50.0 days for metformin and from 56.0 to 42.0 days for lavender; $P < 0.001$ for both). Although metformin had a smaller effect on menstrual cycle length than lavender, the difference was not statistically significant ($P = 0.06$). This implies that lavender might be a viable herbal option for treating PCOS, providing advantages comparable to those of metformin in terms of regulating menstrual cycles and progesterone levels.

5.5 Quercetin:

For 40 days, 72 women with PCOS participated in a randomised clinical trial that examined the effects of quercetin (500 mg daily) or a placebo. In addition to dramatically lowering inflammatory indicators like TNF-alpha ($p = 0.008$) and IL-6 ($p = 0.001$), the study found that quercetin significantly decreased LH levels (from 5.35 ± 1.62 to 3.16 ± 1.43 ; $p = 0.029$). Additionally, a higher proportion of oocytes in meiosis II (79%) and AB-grade embryos (67%) were the results of quercetin ingestion, which also improved oocyte and embryo grade. It is noteworthy that the quercetin group had a much greater pregnancy rate (26 out of 31 individuals) than the control group (4 out of 33 patients). These results imply that quercetin may improve PCOS patients' reproductive outcomes by modifying hormonal and inflammatory markers.

5.6 Sumac (*Rhus coriaria*):

Over the course of 12 weeks, 88 women with PCOS participated in a double-blind, randomised controlled clinical experiment to examine the effects of 3g of sumac powder daily. Sumac was shown to considerably lower blood glucose ($p < 0.05$) and hs-CRP levels ($p = 0.008$). It also improved lipid profiles by dramatically lowering total cholesterol and

triglycerides ($p<0.05$) and raising HDL levels ($p<0.05$). In the sumac group, insulin sensitivity also rose significantly ($p<0.05$). Anthropometric measurements and sex hormones (LH, FSH, testosterone, progesterone, and DHEA-S) were unaffected by sumac, though. Although this suggests

that sumac can successfully lower inflammation, enhance lipid profiles, and improve glycaemic status in PCOS patients, more research is needed to determine how it affects hormonal and clinical symptoms such as hirsutism and acne.



SUMAC



Characteristic	Sumac
 Insulin Resistance	Reduces
 Hyperandrogenism	Improves
 Anti-inflammatory	Exhibits
 Antioxidant	Exhibits
 Insulin Secretion	Enhances
 Glucose Uptake	Enhances
 Blood Glucose	Lowers
 Lipid Profiles	Lowers

Figure 6. Mode of Action of Sumac

5.7 Common Sage (*Salvia officinalis*):

Over the course of eight weeks, 60 euglycemic PCOS patients participated in a randomised, triple-blind, placebo-controlled study to evaluate the effectiveness of *Salvia officinalis* extract (330 mg daily). According to the findings, the *S. officinalis* group experienced a statistically significant drop in BMI ($P=0.001$), waist circumference ($P=0.036$), and diastolic blood pressure ($P=0.025$). Additionally, it resulted in a significant

increase in QUICKI ($P<0.001$) and a significant decrease in insulin levels ($P<0.001$) and HOMA-IR ($P<0.001$), suggesting improved glycaemic management and insulin sensitivity. The waist-to-hip ratio and systolic blood pressure did not show any discernible changes. According to this study, PCOS patients' anthropometric indices and insulin resistance markers may be improved with *Salvia officinalis*.

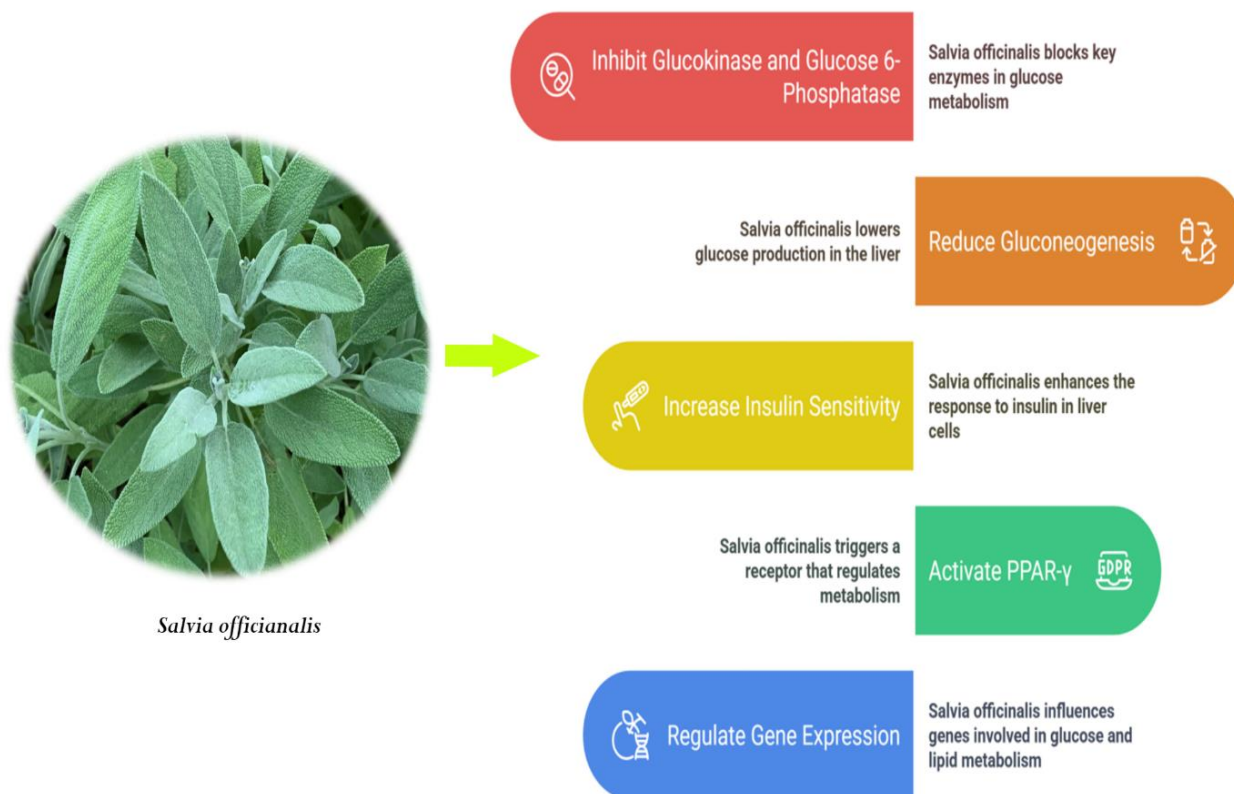


Figure 7. Mode of Action of *Salvia officinalis*

5.8 Garlic (*Allium sativum*):

Eight weeks of a randomised, double-blind controlled trial examined the effects of 800 mg of garlic per day on 80 PCOS patients. Garlic significantly decreased blood LDL-C levels (change mean difference: -7.67; $p=0.042$) and total cholesterol (change mean difference: -8.05; $p=0.036$) when compared to a placebo, according to the study. Serum triglyceride

levels ($p=0.084$) and systolic blood pressure ($p=0.071$) also showed a trend towards a noticeable decline. The levels of diastolic blood pressure and HDL-C, however, did not differ significantly. In women with PCOS, these results imply that taking supplements of garlic may help improve lipid indicators and possibly systolic blood pressure.

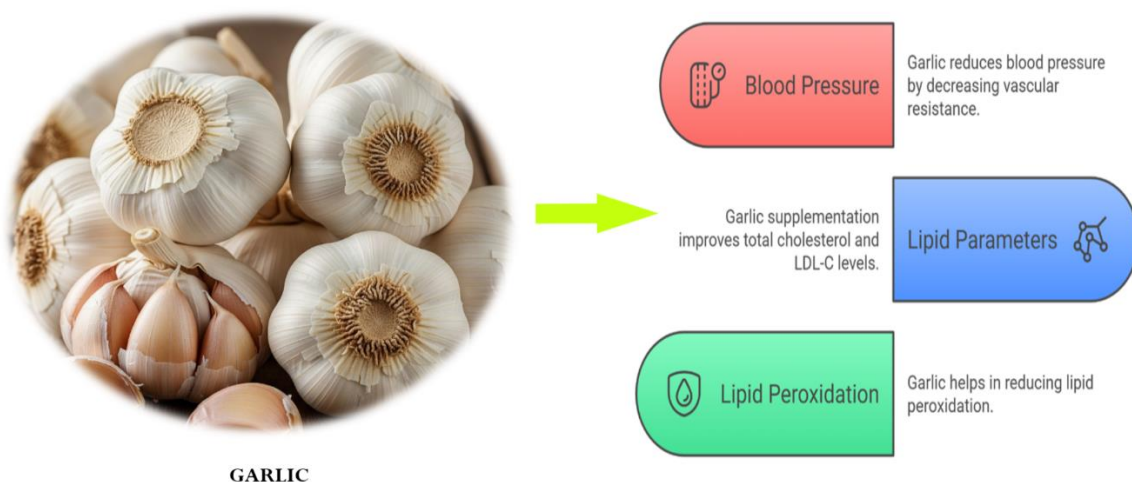


Figure 8. Mode of Action of Garlic

5.9 Spinach-derived Thylakoid:

A 12-week randomised, double-blind, placebo-controlled clinical study examined the effects of a calorie-restricted diet and a 5 g/day supplement of spinach-derived thylakoids in 48 obese women with PCOS. The thylakoid group experienced considerably larger reductions in weight (-6.97 ± 0.52 kg vs. -3.19 ± 0.72 kg; $P < 0.001$), waist circumference (-7.78 ± 2.50 cm vs. -3.73 ± 1.40 cm; $P < 0.001$), and fat mass (-5.19 ± 0.53 kg vs. -1.36 ± 0.39 kg; $P < 0.001$) than

the calorie restriction alone group. Serum testosterone ($P < 0.05$), insulin resistance measures (HOMA-IR, QUICKI; $P < 0.05$), and insulin levels (-5.40 ± 1.86 $\mu\text{U/mL}$ vs. -1.19 ± 0.85 $\mu\text{U/mL}$; $P < 0.001$) were also considerably reduced as a result. In obese PCOS women, this suggests that thylakoids produced from spinach can dramatically improve anthropometric changes and insulin sensitivity while lowering hyperandrogenism when paired with a calorie-restricted diet.

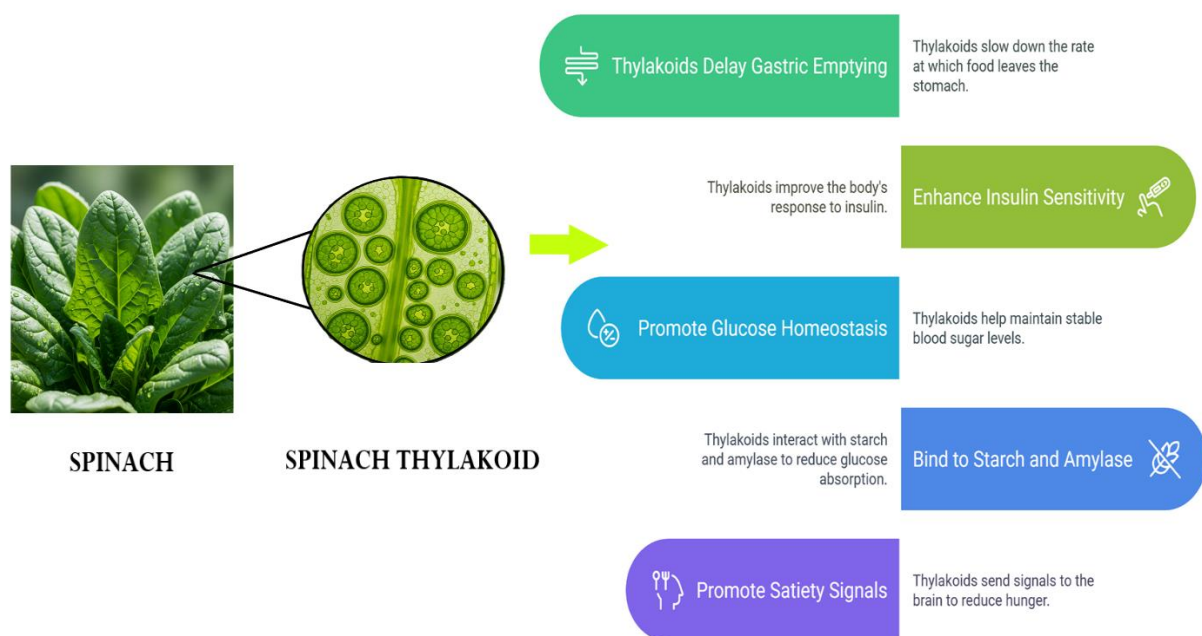


Figure 9. Mode of Action of Spinach Thylakoid

5.10 Femitex-SP4 (Herbal Formula):

The effectiveness of a herbal mixture called Femitex-SP4 (500 mg twice day, comprising *Saraca indica* L., *Vitex agnus castus* L., *Embelica officinalis* L., and *Symplocos racemosa* Roxb.) in 48 PCOS patients was evaluated in a randomised clinical trial. The menstrual cycle duration decreased significantly from 60.6 ± 17.80 days to 30.8 ± 9.22 days ($p < 0.00001$), according to the study. Significant decreases in follicle count (from 12.8 ± 1.0 to 7.6 ± 1.5 ; $p < 0.00001$), stromal thickness (from 8.48 ± 0.57 to 6.04 ± 0.60 ; $p < 0.00001$), and

ovarian volume (from 17.39 ± 1.8 to 10.37 ± 1.0 ; $p < 0.00001$) were also observed in ovarian size and morphology. Although the numerical figures given (1.49 ± 0.87 to 2.55 ± 0.80 ng/ml) show an increase, the reported significant decrease in free testosterone levels ($p < 0.00001$) raises the possibility of a reporting error. Progesterone and fasting blood sugar levels did not alter substantially. This herbal remedy seems to be clinically beneficial, especially for ovarian morphology and irregular menstruation.

6. Comparative Analysis: Synthetic Drugs vs. Herbal Interventions for PCOS:

Table 1. The various interventions discussed are directly compared side by side in the following table. The table discusses the specific agents, their primary targeted PCOS aspects, the magnitude of reported outcomes, and, crucially, the statistical strength of the supporting evidence.

Intervention Type	Specific Agent/Formula	Primary PCOS Aspect Targeted	Key Outcome Measure	Reported Result	Statistical Significance	Study Design & Sample Size	Duration	Notes/Key Findings
Synthetic Drug	Ethinyl Estradiol + Drospirenone (EE+DRSP)	Hirsutism, Menstrual Cyclicity, Metabolic Health, Body Composition, Ovarian Morphology	F-G Score, Menstrual Regularity, BMI, BP, Lipid Profile, Ovarian Follicle Number, Ovarian Volume	F-G score reduced from 17.3 to 8.7 (Group 1); 17.5 to 7.9 (Group 2). All patients had regular cycles. BMI fell by 0.52 kg/m ² (1.9% fall). Systolic and diastolic BP fell. LDL decreased by 7.2% (p<.01), HDL increased. Ovarian follicle number and volume significantly decreased.	p<.001 ; p=.01 (BMI fall) ; p<.01 (LDL decrease)	RCT n=47 (24 Group 1, 23 Group 2) ; Prospective RCT n=60 (30 EE+DRSP, 30 EE+Desogestrel)	6 months	Comparable efficacy between 21/7 and 24/4 regimens. Significant decrease in total/free T, increase in SHBG. Better outcomes than EE+Desogestrel in cycle regularity, antiandrogenic effect, BMI, BP, lipid profile, glycemic and hormonal profile.
Synthetic Drug	Ethinyl Estradiol + Cyproterone Acetate (EE+CA)	Menstrual Cyclicity, Hirsutism, Acne, Metabolic Health, Cardiovascular Markers	Menstrual Cycle Control, Hirsutism, Acne, Serum TG, LDL-C, Blood Pressure, CIMT, Fasting/After-load Insulin, GIR	Significant improvement in menstrual cycle control, hirsutism, acne. Significant increase in serum TG (P=0.01). Slight increase in daytime and 24-hour average systolic and diastolic blood pressure. Improved CIMT to normal range. Significant rise in fasting and after-load	p=0.01 for TG increase ; BP increase stated as "slight increase" ; CIMT improved to normal range ; Significant changes in insulin/GIR	RCT n=26 ; Clinical randomized trial n=34 ; RCT n=117 (40 COC, 39 control) ; Prospective RCT n=101 (44 OCP, 42 metformin completed)	3 months ; 24 weeks ; 24 months ; 6 months	Superior in clinical manifestation improvement vs. metformin, but increased serum TG. Increased blood pressure, but improved CIMT. Associated with deterioration of

				insulin, GIR dropped significantly (deteriorating insulin sensitivity). Non-significant weight gain.				metabolic syndrome. Higher reduction in LH and androgens, more prominent increase in ovarian stromal RI and PI.
Synthetic Drug	Ethinyl Estradiol + Desogestrel (EE+Desogestrel)	Menstrual Cyclicity, Hirsutism, Metabolic Health, Body Composition	Menstrual Regularity, Hirsutism Score, BMI, BP, Lipid Profile	Effect of regular cycles persisted in 17.24% at 6 months post-treatment. No change in hirsutism score. BMI increased by 5.3%. Systolic and diastolic BP rose. LDL levels significantly increased by 6.5% (p<.05). Total cholesterol and triglycerides rose.	p<.05 (LDL increase)	Prospective RCT n=60 (30 EE+DRSP, 30 EE+Desogestrel)	6 months	Less favorable outcomes compared to EE+Drospirenone.
Synthetic Drug	Clomiphene Citrate (CC)	Ovulation Induction, Pregnancy, Live Birth	Ovulation Rate, Pregnancy Rate (PR), Live Birth Rate	Ovulation rate: 59%. PR: 15.4%. Live birth rate: 15.4%. Ovulation rate per cycle: 53%. Pregnancy rate per woman: 24%. Pregnancy rate per cycle: 9%.	Not significant for PR/Live Birth ; P=0.02 (ovulation rate in first cycles vs FSH)	RCT n=115 (39 CC) ; Single-center RCT n=76 (38 CC)	Max 6 months ; Up to 3 cycles	Should be first-line treatment for ovulation induction. Lower ovulation and pregnancy rates compared to FSH.
Synthetic Drug	Clomiphene Citrate (CC) + Ethinyl Estradiol (EE)	Fertility (Ovulation Induction), Endometrial Receptivity	Clinical Pregnancy Rate, Endometrial Thickness, Uterine PI	29% clinical pregnancy rate (CC+EE) vs 10% (CC+placebo). Endometrial thickness 9.7mm vs 8.9mm. Uterine PI (Right) 2.4 vs 2.8; (Left) 2.3 vs 2.9.	p=0.02 (pregnancy); p=0.04 (endometrial thickness) ; p=0.03 (Right PI); p=0.001 (Left PI)	RCT n=95 (45 CC+EE, 50 CC+placebo)	1 IUI cycle	Addresses CC anti-estrogenic effects; improves endometrial receptivity and uterine perfusion. No adverse effects reported.
Synthetic Drug	Clomiphene	Ovulation	Cumulative	Cumulative	p=.032	RCT n=130 (65	Not	Higher

etic Drug	ene Citrate (CC) + Cabergoline	Induction, Fertility	ve Ovulation Rate, Largest Follicle Size, Clinical Pregnancy Rate	ovulation rate: 76.7% vs 58.3% (CC group). Largest follicle size significantly more. Clinical pregnancy rate: 31.7% vs 13.3% (CC group).	(ovulation rate); p<.05 (follicle size); p=.004 (pregnancy rate)	CC+Cabergoline, 65 CC)	specified, but multiple cycles implied	ovulation and pregnancy rates compared to CC alone. No difference in miscarriage, multiple pregnancy, OHSS, or adverse effects.
Synthetic Drug	Low-dose Recombinant FSH	Ovulation Induction, Fertility	Ovulation Rate per Cycle, Pregnancy Rate per Woman, Pregnancy Rate per Cycle	Ovulation rate per cycle: 74% vs 53% (CC). Ovulation rate in first cycles: 66% vs 40% (CC). Pregnancy rate per woman: 42% vs 24% (CC). Pregnancy rate per cycle: 18% vs 9% (CC).	P=0.02 (ovulation rate in first cycles); P=0.09 (pregnancy rate per woman, trend)	Single-center RCT n=76 (38 FSH, 38 CC)	Up to 3 cycles	More effective than CC for ovulation and pregnancy. Low multiple pregnancy rates and mild OHSS.
Synthetic Drug	Pioglitazone + Metformin + Clomiphene Citrate (CC)	Fertility (Ovulation Induction), Ovulation Rate	Ovulation Rate, Pregnancy Rate, Serum E2, Endometrial Thickness, Follicle Number	Ovulation rate: 69.8% vs 48.8% (Metformin+CC). Cumulative pregnancy rate: 58% vs 34% (Metformin+CC). Higher serum E2, thicker endometrium, higher number of follicles ≥ 18 mm.	p=0.002 (ovulation rate); P=0.027 (pregnancy rate)	RCT n=100 (50 Pioglitazone+Metformin+CC, 50 Metformin+CC)	3 cycles	More effective for ovulation and pregnancy rates in CC-resistant PCOS.
Synthetic Drug	Rosiglitazone + Clomiphene Citrate (CC)	Fertility (Ovulation Induction)	Ovulation Rate, Number of Follicles ≥ 14 mm, E2 on Day 12, Pregnancy Rate	Ovulation rate: 64.3% vs 36.4% (Metformin+CC) (P=.035). Follicles ≥ 14 mm: 2.2 ± 1 vs 1.1 ± 0.9 (P=.02). E2 on Day 12: 1991 ± 1389 pmol/L vs 548 ± 327 (P<.001). Pregnancy rate: 50% vs 38.5% (P=.58, not significant).	P=.035 (ovulation rate); P=.02 (follicles); P<.001 (E2)	RCT n=25 (12 Rosiglitazone+CC, 13 Metformin+CC)	3 cycles	Higher ovulation rates, follicle number, and E2 compared to Metformin+CC. Pregnancy rate higher but not significant. May be preferred due to

								better therapy outcomes.
Synthetic Drug	Metformin	Insulin Resistance, Hyperandrogenism, Metabolic Health, Cardiovascular Markers, Body Weight, Ovarian Vascularity	Testosterone, FAI, HOMA-IR, HDL-C, TG, VLDL-C, GTT, BMI, Blood Pressure, CIMT, Fasting/After-load Insulin, GIR, Weight, Ovarian Stromal PI/RI	Decreased testosterone, FAI. Increased HDL-C (p=0.006), decreased TG (p=0.006), VLDL-C (p=0.006). Improved GTT, BMI. Reduced BP. Improved CIMT. Significant decline in fasting/after-load insulin, rise in GIR. Significant weight loss. Significant reduction in BMI, WC, IR. Increased ovarian stromal PI/RI. Ovarian blood flows similar to healthy women in ovulating cycles. One study reported no change in IR (p=0.899).	p=0.038 (testosterone); p=0.006 (lipids); BP reduction significant (p<.05); Significant changes in insulin/GIR; Significant reduction in BMI, WC, IR	Open Clinical Study n=30; RCT n=26; RCT n=34; RCT n=26; RCT n=117 (40 metformin); Prospective RCT n=101 (42 metformin completed); Prospective cohort study n=40	3 months; 24 weeks; 60 days; 24 months; 6 months	Better for hyperandrogenemia than rosiglitazone. Favorable lipid profile and blood pressure. Gastrointestinal side effects common. Improves ovarian vascularization.
Synthetic Drug	Rosiglitazone	Insulin Resistance, Hyperinsulinemia, Hyperandrogenism	HOMA-IR, Hyperinsulinemia, Testosterone, FAI	Better influenced IR and hyperinsulinemia compared to metformin.	Not specified for HOMA-IR, but stated "better influence d"	Open Clinical Study n=30	3 months	Associated with multiple safety concerns, limiting widespread use.
Synthetic Drug	Metformin + Curcumin Nanomicelles	Insulin Resistance, Lipid Profile, Hormonal Parameters	Fasting Insulin, HOMA-IR, Total Testosterone, LDL-C, HDL-C, Total Cholesterol, Triglycerides	Fasting insulin, HOMA-IR, total testosterone significantly lower in combination group (p<0.05). LDL-C: 91.12 vs 117.9 mg/dL (p<0.01). HDL-C: 44.12 vs 38.1 mg/dL (p<0.05).	p<0.05 (insulin, HOMA-IR, testosterone, HDL-C, total cholesterol, triglycerides); p<0.01	RCT n=100 (50 Metformin, 48 Metformin+Curcumin completed)	3 months	Synergistic effect with metformin. Promising alternative.

			des, FSH, LH, DHEAS	Total Cholesterol decreased (p<0.05). Triglycerides decreased. Increased FSH, decreased LH, DHEAS, testosterone.	(LDL-C)			
Synthetic Drug	Metformin + Liraglutide	Hyperandrogenemia, Reproductive Abnormalities, Menstrual Cycles, Anthropometric Parameters, Glucose Metabolism	TT, SHBG, FAI, LH, FSH, Prog, Menstrual Cycles, Weight, BMI, AG, FG, FINS, HOMA-IR	Improved menstrual cycles, anthropometric parameters, and glucose metabolism (no statistical difference vs MET monotherapy). Improved TT, SHBG, FAI, LH, FSH, Prog more effectively than baseline. May improve TT, SHBG, FAI, LH, Prog more effectively than MET monotherapy.	P<0.01 (menstrual cycle recovery vs baseline); P<0.01 (weight, BMI, AG vs baseline); P<0.05 (FG, FINS, HOMA-IR vs baseline); P<0.01 (LH, FSH, Prog, TT vs baseline in COM group)	RCT n=60 (25 MET, 27 COM completed)	12 weeks	More effective than MET monotherapy in improving reproductive abnormalities and hyperandrogenemia.
Synthetic Drug	Metformin + Simvastatin	Androgen Levels, Lipid Profile, Insulin Resistance	Serum T, LH, LH/FSH ratio, Total Cholesterol, LDL, TG, HDL, Fasting Glucose, Fasting Insulin, Insulin Sensitivity	Greater decrease in serum T (25.5% vs 16.8%, P<.001), LH (45.5% vs 6.7%), LH/FSH ratio (38.3% decrease vs 4.4% increase). Greater decrease in total cholesterol (29.5% vs 4.2%), LDL (18.5% vs 1.5%), TG. Greater increase in HDL. Significant decrease in fasting glucose and insulin, improved insulin	P<.001 (serum T difference); P<.001 (lipid profile differences)	Prospective, randomized, double-blind, placebo-controlled study n=84 (42 Metformin+Simvastatin, 42 Metformin+Placebo)	12 weeks	Combination therapy results in better reduction of androgen levels, lipid profile, and insulin resistance.

				sensitivity in both groups.				
Synthetic Drug	DRP/20EE (Ethinyl Estradiol 20µg + Drospirenone 3mg)	Metabolic Profile, Insulin Sensitivity, Androgen Levels	Basal Insulin, Insulin Response to OGTT, SHBG, FAI, Androstenedione	Improved insulin sensitivity (decrease in basal insulin, insulin response to oral glucose load). SHBG significantly increased (P<.001). FAI significantly reduced (P<.001). Androstenedione significantly reduced (P<.05).	P<.05 (AUC for insulin decreased); P<.001 (SHBG, FAI); P<.05 (androstenedione)	Randomized, open-label clinical trial n=48 (16 DRP/20EE)	6 months	Lack of negative impact on carbohydrate metabolism. Overall beneficial effects on metabolic profile.
Synthetic Drug	DRP/20EE + Metformin	Metabolic Profile, Insulin Sensitivity, Lipid Profile, Androgen Levels	HDL-C, Basal Insulin, Insulin Response to OGTT, SHBG, FAI, Androstenedione	HDL-C significantly increased. Improved insulin sensitivity (decrease in basal insulin, insulin response to oral glucose load). SHBG significantly increased (P<.001). FAI significantly reduced (P<.001). Androstenedione significantly reduced (P<.05).	P<.05 (HDL-C increase); P<.05 (AUC for insulin decreased); P<.001 (SHBG, FAI); P<.05 (androstenedione)	Randomized, open-label clinical trial n=48 (16 DRP/20EE + metformin)	6 months	Further improvement in HDL-C compared to DRP/20EE alone.
Synthetic Drug	DRP/20EE + Cyproterone Acetate (CPA)	Metabolic Profile, Insulin Sensitivity, Lipid Profile, Androgen Levels	Fasting Insulin, AUC for Insulin, HOMA-IR, TG, Total Cholesterol, SHBG, FAI, Androstenedione	Fasting insulin significantly increased (P<.001). AUC for insulin significantly increased (P<.01). HOMA-IR significantly increased (P<.005). TG and Total Cholesterol significantly increased. SHBG significantly	P<.001 (fasting insulin); P<.01 (AUC for insulin); P<.005 (HOMA-IR); P<.001 (SHBG, FAI); P<.01 (androstenedione)	Randomized, open-label clinical trial n=48 (16 DRP/20EE + CPA)	6 months	Worsened insulin and glucose metabolism. High doses of CPA may reduce insulin sensitivity.

				increased (P<.001). FAI significantly reduced (P<.001). Androstenedione significantly reduced (P<.01).				
Synthetic Drug	Letrozole + Metformin + Pioglitazone	Ovulation Induction, Pregnancy, Endometrial Thickness	Cumulative Ovulation Rate, Cumulative Pregnancy Rate, Endometrial Thickness	Cumulative ovulation rate: 86.9% vs 92.3% (CC+Metformin +Pioglitazone) (P=0.184, no significant difference). Cumulative pregnancy rate: 26.2% vs 20.5% (CC+Metformin +Pioglitazone) (P=0.423, no significant difference). Endometrial thickness significantly higher in Letrozole group (P=0.023 for cycle 2, P=0.004 for cycle 3).	P=0.184 (ovulation rate); P=0.423 (pregnancy rate); P=0.023 (endometrial thickness cycle 2); P=0.004 (endometrial thickness cycle 3)	Prospective double-blind RCT n=100 (50 Letrozole group, 50 CC group)	3 cycles	Efficacious for CC-resistant PCOS. Higher endometrial thickness compared to CC combination.
Herbal Intervention	Traditional Chinese Medicine (CHM)	T2DM Risk Reduction	Incidence of T2DM	Incidence of T2DM significantly lower (HR=0.31).	HR=0.31; 95% CI, 0.15-0.64; p=0.0014	Nationwide Matched Cohort Study n=342 (per group)	Mean 5.2 years	Long-term preventive effect against T2DM. Five formulas and two single herbs showed protective effects.
Herbal Intervention	Cinnamon (Cinnamomum cassia / Darchini)	Menstrual Cyclicity, Insulin Resistance, Antioxidant Status, Serum Lipids	Menstrual Cyclicity, HOMA-IR, Androgen Levels, TAC, MDA, TC, LDL-C, HDL-C,	Menstrual cycles more frequent (median 0.75 vs 0.25, p=0.0085). Cyclicity improved from baseline (p=0.0076). Marked improvement in menstrual	p=0.0085; p=0.0076; Not specified for 51.9%; p=0.899 for IR in one study; P=0.005 (TAC); P=0.014 (MDA);	RCT n=45 (17 completed 6 months); RCT n=26; RCT n=84 (42 Cinnamon, 42 Placebo)	6 months; 60 days; 8 weeks	High dropout rate in. Conflicting results on insulin resistance. Improves antioxidant status and lipid profile.

			TG	pattern (51.9%). No significant change in insulin resistance or serum androgen levels in some studies . TAC significantly increased (P=0.005). MDA significantly decreased (P=0.014). TC, LDL-C, HDL-C significantly improved (all P<0.05). No significant effect on TG.	P<0.05 (TC, LDL-C, HDL-C)			
Herbal Intervention	Satapushpa Churnam with Tila Tailam (Ayurveda)	Oligomenorrhea, Ovarian Morphology	Menstrual Interval, Ovarian Volume	Significant reduction in menstrual interval (p<0.001). Right ovarian volume reduced from 10 to 5.3 cm ³ (p<0.001). Left ovarian volume reduced from 9.1 to 5.1 cm ³ (p<0.001).	p<0.001 (menstrual interval); p<0.001 (ovarian volume)	Single-Group Before-and-After Study n=30	3 months	Direct morphological impact on ovaries. No change in menstrual duration/bleeding amount.
Herbal Intervention	Lavender (Lavandula angustifolia)	Progesterone Levels, Menstrual Cyclicity	Serum Progesterone, Menstrual Cycle Length	Progesterone increased from 0.35 to 2.5 ng/mL (Lavender) and 0.8 to 2.74 ng/mL (Metformin) (P < 0.001 for both). No significant difference between groups (P=0.9). Menstrual cycle length decreased from 56.0 to 42.0 days (Lavender) and 60 to 50.0 days (Metformin) (P < 0.001 for both).	P < 0.001 (progesterone, menstrual cycle length within groups); P=0.9 (progesterone between groups); P=0.06 (menstrual cycle length between groups, not significant)	Randomized, double-blind clinical trial n=68 (31 Lavender, 31 Metformin completed)	90 days	Similar effects to metformin on progesterone and menstrual cycle regulation. Promising candidate.
Herbal	Quercetin	Inflammation,	LH, IL-6, TNF-	LH reduced (5.35 to 3.16;	p=0.029 (LH);	Randomized clinical trial	40 days	Improves oocyte and

Intervention		Hormonal Parameters, Oocyte/Embryo Grade, Pregnancy Outcome	alpha, Oocyte Grade, Embryo Grade, Pregnancy Rate	p=0.029). TNF-alpha decreased (p=0.008). IL-6 decreased (p=0.001). More oocytes in meiosis II (79%). Higher AB-grade embryos (67%). Pregnancy rate: 26/31 (Quercetin) vs 4/33 (Control).	p=0.008 (TNF-alpha); p=0.001 (IL-6)	n=72 (31 Quercetin, 33 Placebo completed)		embryo grade, increases pregnancy rate. Decreases inflammatory and LH parameters.
Herbal Intervention	Sumac (Rhus coriaria)	Inflammation, Blood Glucose, Lipid Profiles, Insulin Sensitivity	hs-CRP, Blood Glucose, TG, Total Cholesterol, HDL-C, LDL-C, Insulin Sensitivity, Sex Hormones, Menstrual Regularity, Acne, Hirsutism	hs-CRP significantly reduced (p=0.008). Blood glucose significantly reduced (p<0.05). TG, Total Cholesterol significantly decreased (p<0.05). HDL-C significantly increased (p<0.05). Insulin sensitivity significantly increased (p<0.05). No significant effect on LDL-C (p=0.090), sex hormones, anthropometric parameters, acne, or hirsutism.	p=0.008 (hs-CRP); p<0.05 (blood glucose, TG, Total Cholesterol, HDL-C, Insulin Sensitivity)	Double-blind randomized controlled clinical trial n=88 (39 Sumac, 36 Placebo completed)	12 weeks	Reduces inflammation, improves glycemic status and lipid profile. No significant effect on sex hormones or anthropometric parameters.
Herbal Intervention	Salvia officinalis (Common Sage)	Anthropometric Indices, Insulin Resistance Markers	BMI, WC, DBP, Insulin Levels, HOMA-IR, QUICKI, SBP, WHR, HC	BMI significantly decreased (P=0.001). WC significantly decreased (P=0.036). DBP significantly decreased (P=0.025). Insulin levels significantly decreased (P<0.001). HOMA-IR significantly	P=0.001 (BMI); P=0.036 (WC); P=0.025 (DBP); P<0.001 (Insulin, HOMA-IR, QUICKI)	Randomized, triple-blinded, controlled trial n=60 (30 Salvia, 30 Placebo completed)	8 weeks	First clinical trial on S. officinalis for PCOS. Favorable effects on anthropometric indices and insulin resistance markers.

				decreased (P<0.001). QUICKI significantly increased (P<0.001). No significant effect on SBP (P=0.283), WHR, HC.				
Herbal Intervention	Garlic (Allium sativum)	Lipid Parameters, Blood Pressure	TC, LDL-C, TG, HDL-C, SBP, DBP	TC significantly reduced (change MD: -8.05; p=0.036). LDL-C significantly reduced (change MD: -7.67; p=0.042). Trend to significant decrease in TG (p=0.084) and SBP (p=0.071). No significant difference in HDL-C or DBP.	p=0.036 (TC); p=0.042 (LDL-C)	Randomized, double-blinded control trial n=80 (40 Garlic, 40 Placebo)	8 weeks	Improves TC and LDL-C. Marginal improvement in TG and SBP.
Herbal Intervention	Spinach-derived Thylakoid + Calorie Restriction	Anthropometric Parameters, Metabolic Profiles, Hormonal Parameters	Weight, WC, FM, Insulin Levels, HOMA-IR, QUICKI, Testosterone, BMI, WHR, FFM, FBG, NEFA, LH, FSH, DHEAS, SHBG, FAI	Significantly greater decreases in weight (-6.97kg vs -3.19kg; P<0.001), WC (-7.78cm vs -3.73cm; P<0.001), FM (-5.19kg vs -1.36kg; P<0.001), Insulin levels (-5.40μU/mL vs -1.19μU/mL; P<0.001). Significantly improved HOMA-IR, QUICKI (P<0.05). Significantly decreased Testosterone (P<0.05).	P<0.001 (Weight, WC, FM, Insulin); P<0.05 (HOMA-IR, QUICKI, Testosterone)	Double-blind placebo-controlled RCT n=48 (21 Thylakoid, 23 Placebo completed)	12 weeks	Enhances anthropometric improvements and insulin sensitivity, reduces hyperandrogenism when combined with calorie restriction.
Herbal Intervention	Femitec-SP4 (Saraca indica L., Vitex agnus castus L., Embelica officinalis)	Menstrual Cycle, Ovarian Morphology, Free Testosterone, FBS, Progesterone	Menstrual Cycle Duration, Number of Follicles, Stromal Thickness,	Menstrual cycle duration: 60.6 to 30.8 days (p<0.00001). Number of follicles: 12.8 to 7.6 (p<0.00001). Stromal	p<0.00001 (Menstrual Cycle, Ovarian parameters, Free Testosterone)	Randomized clinical trial n=48 completed	Not explicitly stated, but "two months afterw	Clinically effective for menstrual irregularities and ovarian morphology.

s L., Symplocos racemosa Roxb.)		Ovarian Volume, Free Testosterone, FBS, Progesterone	thickness: 8.48 to 6.04 ($p < 0.00001$). Ovarian volume: 17.39 to 10.37 ($p < 0.00001$). Free testosterone reported to drop significantly ($p < 0.00001$), but numerical values show increase (1.49 to 2.55 ng/ml). No significant change in FBS or Progesterone.			ord" for some parameters.	Conflictin g data on free testosterone change.
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7. DISCUSSION:

A comprehensive analysis of herbal treatments and synthetic pharmaceuticals for polycystic ovary syndrome demonstrates a complex treatment environment. Herbal treatments exhibit a wider range of effects, including long-term preventative benefits and direct influences on underlying pathophysiology, generally with fewer reported adverse effects than synthetic drugs, which frequently offer targeted and quick symptomatic relief.

7.1 Menstrual Regularity and Ovulation:

In PCOS, both synthetic and natural treatments are highly effective at resolving irregular menstruation and encouraging ovulation. Menstrual periods can be regularly regulated with the help of Combined Oral Contraceptives (COCs), such as EE+DRSP and EE+CA. In a 24-month trial of teenagers, it was discovered that COC was just as successful as metformin at promoting regular cycles, with all users (100%) achieving regular cycles. Clomiphene Citrate (CC) and Ethinyl Oestradiol (EE) together optimise uterine blood flow and endometrial receptivity, which greatly increases clinical pregnancy rates for patients seeking fertility. Additionally, pioglitazone greatly increases ovulation and pregnancy rates in women who are resistant to CC when taken with metformin and CC. In women with CC resistance, rosiglitazone plus CC also demonstrated noticeably greater follicular growth and ovulation rates than metformin plus CC. Low-dose recombinant FSH showed a tendency towards greater pregnancy rates per woman (42% vs. 24%) and significantly higher ovulation rates each cycle (74% vs. 53%) as compared to CC. In patients with euprolactinemic PCOS, cabergoline added to CC dramatically raised cumulative ovulation (76.7% vs. 58.3%) and clinical pregnancy rates (31.7% vs. 13.3%). By reducing insulin resistance, metformin itself indirectly promotes regular menstruation. With

recovery rates of 88% for metformin alone and 92.59% for the combination after 12 weeks, the combination of liraglutide and metformin also improved menstrual periods.

Herbal treatments also present encouraging opportunities. Supplementing with cinnamon has been shown to increase cycle frequency and have a positive, statistically significant impact on menstrual cyclicality. In a similar vein, regularisation resulted from the Ayurvedic formulation Satapushpa Churnam with Tilatailam, which demonstrated a significantly substantial reduction in menstrual interval. Similar to metformin, lavender also demonstrated efficacy in controlling menstrual cycles, particularly in raising progesterone levels and reducing the duration of menstrual periods. The length of the menstrual cycle was also significantly improved by the herbal formula Femitex-SP4, returning it to normal for a sizable portion of patients. Quercetin dramatically decreased LH levels, which can indirectly assist ovulation and cycle regularity, even though it was not explicitly evaluated for menstrual regularity. However, there was no discernible impact of sumac on irregular menstruation.

In comparison, herbal options like cinnamon, Satapushpa Churnam, lavender, and Femitex-SP4 offer effective alternatives to synthetic hormonal therapies like COCs, which offer strong and predictable menstrual regulation, and FSH, which offers superior ovulation and pregnancy rates compared to CC. This is especially true for individuals seeking non-hormonal approaches or who are experiencing side effects from conventional drugs. The patient's tolerance profile and main objective (such as contraception versus fertility versus symptom treatment) frequently influence the decision. Combinations with dopamine agonists (cabergoline) or insulin sensitisers (pioglitazone, metformin, rosiglitazone) greatly improve reproductive outcomes for CC-resistant individuals.

7.2 Insulin Sensitivity and Metabolic Health:

PCOS is primarily caused by insulin resistance and related metabolic dysfunctions, which are the focus of both synthetic and natural treatments. Metformin continues to be a mainstay, often showing notable improvements in glucose tolerance, lipid profiles (raising HDL-C, reducing TG and VLDL-C), and insulin resistance (HOMA-IR, QUICKI). Metformin significantly improved the glucose/insulin ratio and fasting and after-load insulin levels in teenagers, according to 24-months research. When metformin and curcumin nanomicelles are taken together, they have a synergistic impact that increases HDL-C while further lowering triglycerides, total testosterone, HOMA-IR, fasting insulin, and LDL-C. Simvastatin plus metformin both increased insulin sensitivity and led to a higher increase in HDL and a greater drop in total cholesterol, LDL, and triglycerides. Although safety issues limit its use, rosiglitazone also has a considerable impact on insulin resistance; one study suggests that it has a more marked effect on HOMA-IR than metformin. Insulin sensitivity improved when DRP/20EE was taken alone or in combination with metformin, but insulin and glucose metabolism deteriorated when DRP/20EE was taken with high-dose CPA.

There is compelling evidence that herbal remedies can boost metabolism. Sumac powder improved lipid profiles (lowering TG, TC, and raising HDL) and dramatically decreased blood glucose and insulin sensitivity. *Salvia officinalis* extract significantly decreased BMI and waist circumference while also improving insulin sensitivity (raising QUICKI and reducing insulin and HOMA-IR). Despite the suggested mechanism, there is inconsistent data regarding cinnamon's impact on insulin resistance in the studies that have been published. Two RCTs found no discernible difference. When paired with calorie restriction, spinach-derived thylakoid produced noticeably larger improvements in insulin levels, weight, fat mass, and insulin resistance indicators than when calorie reduction was used alone. Supplementing with garlic dramatically lowered LDL-C and total cholesterol while also showing a tendency to lower triglycerides. There are considerable underlying metabolic benefits to Traditional Chinese Medicine (CHM), as evidenced by its significant long-term reduction in the risk of Type 2 Diabetes Mellitus. Although research on cinnamon's impact on insulin resistance has been mixed, it has been proven to significantly enhance lipid profiles (TC, LDL-C, and HDL-C) and antioxidant status.

All things considered, metformin and its combinations (such as with pioglitazone or curcumin) provide strong and proven advantages for insulin sensitivity and metabolic health. Although an increasing amount of data points to a number of herbal remedies (including cinnamon, garlic, CHM, spinach-derived thylakoid,

salvia officinalis, and sumac) as useful adjunctive or alternative methods for enhancing lipid profiles, glucose metabolism, and long-term diabetes risk, frequently with good safety records.

7.3 Androgen Levels and Hirsutism:

A key component of PCOS treatment is controlling hyperandrogenism, which affects symptoms including acne and hirsutism. Combination oral contraceptives (COCs), especially EE+DRSP and EE+CA, are very good at lowering free and total testosterone levels as well as clinically improving acne and hirsutism. By dramatically lowering blood testosterone and the Free Androgen Index (FAI), metformin also helps to reduce hyperandrogenism. This impact is further enhanced when metformin and curcumin are taken together, which results in a considerable decrease in DHEAS and total testosterone levels. Additionally, there was a notable drop in testosterone levels in thylakoids generated from spinach. LH levels were considerably lowered by quercetin, which may have an indirect effect on the pathways involved in androgen synthesis. Although there was a discrepancy in the numerical data, it was stated that Femitex-SP4 dramatically decreased free testosterone levels. However, there was no discernible impact of sumac on testosterone or other sex hormones. COCs continue to be very successful for the direct and strong lowering of testosterone levels and clinical manifestations such as hirsutism. A more thorough approach to hyperandrogenism is made possible by metformin and specific herbal treatments (curcumin, spinach-derived thylakoid, quercetin, Femitex-SP4), which provide extra or different approaches to regulate androgen levels.

7.4 Ovarian Morphology:

Although it is not as frequently reported, some therapies have a direct effect on ovarian morphology. A statistically significant decrease in both the right and left ovarian volumes was revealed in the Ayurvedic study on Satapushpa Churnam with Tilatailam, which suggests a basic effect on the polycystic ovaries themselves. Likewise, the herbal compound Femitex-SP4 showed notable decreases in ovarian volume, stromal thickness, and follicle count. The given synthetic drug studies do not specifically describe changes in ovarian shape, despite the fact that COCs are known to decrease ovarian activity and can eventually lower ovarian volume. This suggests that some traditional herbal formulations have a special ability to directly affect the structural pathology of PCOS ovaries, which calls for further thorough research.

7.5 Pregnancy Outcomes:

Certain therapies are clearly beneficial for PCOS people who want to become pregnant. Clinical pregnancy rates among women undergoing intrauterine insemination were considerably raised by the

combination of clomiphene citrate and ethyl oestradiol. Pioglitazone, when combined with metformin and CC, dramatically increased the rates of ovulation and cumulative pregnancies in patients with CC-resistant PCOS. The intervention group had a significantly greater pregnancy rate as a result of quercetin's exceptional capacity to enhance oocyte and embryo quality. Direct pregnancy outcome statistics are not always available for all herbal therapies, even when other interventions (such as cinnamon, lavender, and Femitex-SP4) that increase menstrual cyclicity and ovulation indirectly support conception. The strongest evidence to date has been found for synthetic ovulation induction drugs and their combinations (CC+EE, Pioglitazone + Metformin + CC) in terms of direct fertility enhancement and pregnancy rates. Even quercetin offers a strong herbal alternative for raising oocyte quality and pregnancy rates, indicating a useful supplementary function in fertility control.

7.6 Cardiovascular Risk Markers:

Interventions that have a good effect on these markers are essential since PCOS patients have an increased risk of cardiovascular disease. Because metformin lowers blood pressure and increases carotid intima media thickness (CIMT), it continuously exhibits a positive cardiovascular profile. On the other hand, despite improving CIMT, Ethinyl Estradiol-Cyproterone Acetate (Diane 35 Diario) was linked to a minor rise in blood pressure. The long-term risk of type 2 diabetes, a significant independent risk factor for cardiovascular disease, was dramatically decreased by traditional Chinese medicine (CHM), suggesting an indirect but considerable cardiovascular effect.

A number of herbal remedies have potential benefits for cardiovascular health as well. Sumac powder dramatically improved lipid profiles, decreased blood glucose, and decreased hs-CRP, an inflammatory marker associated with cardiovascular risk. Supplementing with garlic dramatically lowered LDL-C and total cholesterol while also showing a tendency to lower systolic blood pressure. The extract from *Salvia officinalis* improved anthropometric measurements such as waist circumference and BMI, which are cardiovascular risk factors, and dramatically reduced diastolic blood pressure. Cinnamon increased antioxidant status and improved serum levels of HDL-C, LDL-C, and total cholesterol. Metformin and curcumin together also shown positive benefits on lipid profiles, with HDL-C rising and total cholesterol, LDL-C, and triglycerides falling.

This thorough review shows that both herbal remedies and synthetic medications have unique benefits for treating different aspects of PCOS. Herbal treatments offer distinct advantages in areas like long-term T2DM prevention (CHM), direct ovarian morphological changes (Ayurveda, Femitex-SP4), and improvements in oocyte quality (Quercetin), even though synthetic medications like COCs and metformin have proven

efficacy for symptom control and metabolic regulation. Along with frequently having a good safety record, many herbal treatments also have notable beneficial effects on lipid profiles, insulin sensitivity, and inflammatory markers. This implies that these disparate methods might be really complimentary rather than antagonistic.

For instance, a combination therapy may be the best option for a patient. For instance, a COC for hirsutism combined with metformin for insulin resistance and weight control, or even a herbal adjunct for long-term metabolic advantages or special effects like ovarian volume reduction. This makes it possible to create integrated, multimodal treatment plans that are suited to the long-term health risks, preferences, and phenotypes of each patient. Depending on the particular symptoms, metabolic profile, fertility objectives, and patient preferences, the choice of which intervention is "better" is quite personal and frequently results in a combination strategy for best results.

8. Discussion of Study Designs and Limitations:

For synthetic drugs and other herbal remedies, there are numerous Randomized Controlled Trials (RCTs) included. Because randomization reduces bias and confounding variables, RCTs offer the strongest evidence for observed effects and are hence the gold standard for proving causation.

The presented RCTs frequently have constraints that impact the generalisability and long-term results, despite their inherent strength. These consist of:

- **Small Sample Sizes:** Relatively small cohorts are used in several research (e.g., n=17 completion in, n=26 in, n=30 in, n=26 in, n=34 in, n=30 in, n=68 in, n=72 in, n=88 in, n=60 in, n=80 in, n=48 in, n=48 in). Type II errors may result from small sample sizes that restrict the statistical power to identify subtler but clinically significant effects and limit the findings' generalisability to larger PCOS populations.
- **Short Durations:** The duration of interventions is often limited to a few months, such as two to six months. This period is enough for tracking changes in acute symptoms, but it is insufficient to evaluate persistent benefits, long-term efficacy, or the onset of delayed adverse effects in a chronic illness such as PCOS.
- **High Dropout Rates:** Participant dropout rates were substantial in several studies, especially those with above 50% dropout and 59 out of 154 randomised patients eliminated from final analysis. Due to the possibility of systematic differences between completers and non-completers, this can add selection bias and

further reduce the results' representativeness and generalisability.

The CHM countrywide matched cohort study's remarkably high sample size and long follow-up time (mean 5.2 years) yield strong observational data. For long-term results and real-world data, this kind of research is crucial. However, because unmeasured confounders may potentially affect the observed outcomes, observational studies are by their very nature unable to show direct causality with the same level of assurance as RCTs. The Ayurvedic study is classified as a before-and-after study including only one group. Because there is no concurrent control group, these studies are vulnerable to confounding variables, the placebo effect, and natural disease development, even if they may offer early indications of success (such as a considerable reduction in ovarian volume). Although encouraging, the results of these research need to be replicated in more exacting designs, such as randomised controlled trials, to ensure their effectiveness and reduce bias.

9. CONCLUSIONS:

A thorough examination of synthetic medications and herbal remedies for polycystic ovary syndrome reveals a wide range of treatment alternatives, each with unique advantages and disadvantages backed by differing degrees of data. Synthetic medications, especially metformin and combined oral contraceptives (COCs), show strong success in treating important PCOS symptoms. With statistically substantial increases in F-G scores and monthly regularity, COCs like EE+DRSP and EE+CA are quite helpful at controlling menstrual cycles and reducing hyperandrogenic symptoms like hirsutism. It is necessary to carefully assess a patient's overall metabolic profile because certain COC formulations, such as EE-CA, may be linked to adverse metabolic alterations, such as elevated triglycerides and a minor increase in blood pressure. Insulin resistance, glucose tolerance, lipid profiles, and cardiovascular risk indicators such as blood pressure and CIMT are all reliably improved by metformin. This makes metformin an important preventative measure against long-term problems like type 2 diabetes and cardiovascular disease, rather than just a symptomatic treatment. By increasing uterine perfusion and endometrial receptivity, ethyl oestradiol, when added to clomiphene citrate, improves clinical pregnancy rates and overcomes a major drawback of CC monotherapy. Additionally, in CC-resistant PCOS patients, pioglitazone, metformin, and CC greatly increase ovulation and conception rates. Herbal therapies offer strong early evidence for their function in PCOS management, despite the fact that they are frequently researched with less rigorous designs or smaller sample numbers. A hazard ratio of 0.31 ($p=0.0014$) in a large cohort study indicates that

traditional Chinese medicine (CHM) has a statistically significant long-term protective effect against the development of Type 2 Diabetes Mellitus in PCOS patients. Supplementing with cinnamon has the potential to improve lipid profiles and antioxidant status while also enhancing menstrual cyclicity, as seen by noticeably more frequent cycles in treated groups ($p=0.0085$). The potential of Satapushpa Churnam with Tilatailam to considerably lower ovarian volume ($p<0.001$) in addition to regularising menstrual intervals is a novel and noteworthy discovery from Ayurvedic medicine. Like metformin, lavender efficiently raises progesterone levels and controls menstrual periods. In addition to improving oocyte/embryo quality and conception rates, quercetin dramatically lowers LH and inflammatory markers. Sumac powder improves lipid profiles, insulin sensitivity, blood glucose, and inflammation. Anthropometric measures and insulin resistance indicators are improved by salvia officinalis extract. Supplementing with garlic dramatically lowers LDL-C and total cholesterol. When paired with calorie restriction, spinach-derived thylakoids dramatically increase anthropometric measurements, improve insulin sensitivity, and lower testosterone levels. The Femitex-SP4 herbal compound greatly enhances ovarian morphology and the length of the menstrual cycle.

The observed variations in these therapies' strengths point to the possibility of complementary roles in individualised PCOS treatment. For example, a patient may benefit from a herbal adjunct for long-term metabolic advantages or particular effects like ovarian volume reduction, or a combination of COCs for hirsutism symptomatic relief and metformin for metabolic health. This emphasises the necessity of multimodal, integrated treatment plans that are customised to the long-term health risks and phenotypes of each patient.

Many studies are constrained by small sample sizes, brief durations, or observational methods, which impact the ability to generalise and assurance of the findings despite encouraging results, especially from herbal therapies. Future studies are necessary to confirm the effectiveness and mechanisms of action of herbal treatments and to investigate the best combination therapies, especially large-scale, well planned randomised controlled trials. This will bolster the body of evidence and make it easier to incorporate successful conventional methods into current, evidence-based PCOS treatment guidelines.

10. Acknowledgement:

I would like to express my gratitude the Director, School of Life and Basic Sciences, and Director, School of Pharmaceutical Sciences, Jaipur National University for academic support. I also want to thank everyone who contributed, as their work and knowledge greatly enhanced this study.

11. Conflict of Interest:

Regarding the publication of this review paper, the author discloses that they have no conflicts of interest. For this work, no grants, honoraria, or funding were obtained. No affiliations, financial or non-financial interests, or personal or professional relationships could have influenced the review's interpretation or substance.

12. Funding Source:

No funding was received for the preparation, writing, or publication of this review paper.

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Abbreviations

S.No.	Particular	Abbreviations
1.	PCOS	Polycystic Ovarian Syndrome
2.	RCTs	Randomized Controlled Trials
3.	AGEs	Advanced Glycation End-Products
4.	COCs	Combined Oral Contraceptives
5.	EE	Ethinylestradiol
6.	DRSP	Drospirenone
7.	OCPs	Oral Contraceptives Pills
8.	LH	Luteinizing Hormone
9.	HSD	Hydroxysteroid Dehydrogenase
10.	AKR	Aldo-Keto Reductase
11.	SHBG	Sex Hormone Binding Globulin

12.	OSA	Obstructive Sleep Apnoea
13.	CA	Cyproterone Acetate
14.	F-G	Ferriman-Gallwey
15.	CIMT	Carotid Intima Media Thickness
16.	CC	Clomiphene Citrate
17.	FSH	Follicle Stimulating Hormone
18.	HOMA-IR	Hyperinsulinemia And Insulin Resistance
19.	FAI	Free Androgen Index
20.	TG	Triglycerides
21.	VLDL-C	Very-Low-Density Lipoprotein Cholesterol
22.	HDL-C	High-Density Lipoprotein Cholesterol
23.	BMI	Body Mass Index
24.	GTT	Glucose Tolerance Test
25.	CHM	Traditional Chinese Medicine
26.	T2DM	Type 2 Diabetes Mellitus