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Exploring herbal alternatives to pharmaceutical treatments for Polycystic Ovary Syndrome

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Abstract

Polycystic Ovary Syndrome (PCOS) is a hormonal disorder that affects approximately 5-10% of women of reproductive age, making it one of the most common endocrine disorders in this population. PCOS is characterized by irregular menstrual cycles, elevated androgen levels, insulin resistance, and polycystic ovaries. Currently, there is no cure for PCOS, hence treatment focuses on symptom management. Prescription medications like metformin, which improve insulin sensitivity, and clomiphene, an ovulation inducer, are commonly used in clinical practice. However, barriers to accessing these drugs can be significant, especially for women in low-resource settings due to high costs and limited availability. Compared to prescription medications, herbal supplements generally cause fewer and less severe side effects, are more affordable, and are widely available without a prescription. This research paper examines the potential of 10 herbal supplements as alternatives to conventional treatments for PCOS; berberine, cinnamon, fenugreek, shatavari, chasteberry, Chinese peony, red reishi mushrooms, ashwagandha, turmeric, and spearmint. Herbal treatments are generally less potent but are easier to access and may be a promising alternative for women in regions where conventional medications are scarce or expensive, or when fertility is the explicit objective and does not hence necessarily require rapid pharmaceutical efficacy. Further clinical research on herbal supplements and greater awareness of these alternatives could help address the global challenge of PCOS.

Keywords

PCOS, Polycystic Ovary Syndrome, Natural products, Polycystic ovaries, Herbal remedies, Ovulation, Irregular periods, Diabetes, Menstrual cycle, Fertility, Hormonal disorder

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1. Introduction

Polycystic Ovary Syndrome (PCOS) is a complex hormonal disorder that primarily affects people with ovaries during their reproductive years, typically between the ages of 15 and 45 (1). It is one of the most common endocrine disorders among women of reproductive age, affecting approximately 8-21% of this population globally (1). PCOS is characterized by symptoms related to hormonal imbalance and metabolism. The three main features used to diagnose PCOS include irregular periods, excess androgen levels, and polycystic ovaries. Women with PCOS often have irregular menstrual cycles, which means they may have fewer than eight periods a year, periods that occur at irregular intervals, or no periods at all. This irregularity is due to disruptions in the normal hormonal balance necessary for ovulation (3). Androgens, such as testosterone, are typically considered male hormones, though they are present in females in lower amounts. In PCOS, there is often an excess of androgens, which can lead to symptoms such as hirsutism (excessive hair growth on the face, chest, or other areas), acne, and male-pattern baldness or thinning of hair. As seen in Figure 1, on ultrasound examinations, the ovaries of many women with PCOS may appear enlarged and contain numerous small follicles (fluid-filled sacs) that surround the eggs. Despite the name, not all women with PCOS have cysts; the presence of multiple follicles is a more accurate indicator (4).

Figure 1. A longitudinal transabdominal ultrasound of an ovary showing multiple peripheral follicles (73).

In addition to these main features, PCOS is often associated with other metabolic disturbances, including insulin resistance and obesity. Insulin resistance is a condition in which the body's cells do not respond effectively to insulin, leading to higher insulin levels in the blood (5). This can contribute to the development of type 2 diabetes and an increased risk of cardiovascular disease in individuals with PCOS. The exact cause of PCOS is not fully understood, but it is believed to involve a combination of genetic and

environmental factors. Genetically, mutations in several aromatase genes, including CYP11A1, CYP11B2, CYP17A1, CYP19A1, CYP1A1, CYP21A2, CYP3A7, have shown to play roles in PCOS pathogenesis.

PCOS diagnosis is based on a combination of clinical evaluation, symptom assessment, and exclusion of other conditions that may mimic its symptoms (70). Medical history is taken into account first. The healthcare provider will first obtain a detailed medical history, including menstrual patterns, symptoms of androgen excess (like hirsutism, acne, male-pattern hair loss), weight history, and any other relevant symptoms (6). Next, a physical exam is conducted to assess signs of androgen excess, such as excess hair growth (hirsutism), acne, and signs of insulin resistance (e.g., central obesity, *Acanthosis nigricans*). Furthermore, several laboratory tests are conducted to determine whether a patient has PCOS (7). Blood tests are usually performed to measure hormone levels, including those of testosterone, DHEAS (dehydroepiandrosterone sulfate), LH (luteinizing hormone), and FSH (follicle-stimulating hormone). Fasting glucose and insulin levels may be tested to assess for insulin resistance, as well. A lipid panel may be used to evaluate cholesterol levels, since lipid abnormalities are often associated with PCOS. Aside from lab tests, an ultrasound examination of the pelvis may be performed to examine the ovaries. This can reveal the presence of multiple small follicles within the ovaries and assess ovarian size and morphology (7).

While there are many ways that doctors may assess to see if a patient presents with PCOS, there is no cure for this condition. Many doctors and physicians are limited to treating the PCOS symptoms rather than the cause of the disease. Treatments attempt to alleviate symptoms by addressing hormone imbalances. Common diabetes drugs are often prescribed to those who have higher insulin resistance or abnormal glucose control. Anti-androgens with a combination of birth control pills are used for those who exhibit excessive hair, acne, and cycle/fertility problems. A standard anti-inflammatory lifestyle and diet also play a key role in doctors' recommendations to PCOS patients. This includes reducing sugar and carbohydrates, maintaining weight, and exercising regularly. Weight loss - by itself - can improve the regularity of menstrual cycles and acne/hair-related problems. It is important to highlight that every individual reacts to treatment differently. No single treatment will help everyone, but these are the most common practices (7).

While thorough research has been conducted on different PCOS pharmacological interventions, many drugs often have a large number of side effects. Every PCOS patient is prescribed medications based on their symptoms, and this can range from one to several drugs. PCOS has also proven to cause a large mental toll, as women are at higher risk for anxiety and depression. These additional symptoms can necessitate patients to take additional psychiatric drugs. Generally, the more the number of medications —the higher the risk of dangerous drug interactions. However, these drug interactions are often not well-documented, and even doctors may be unaware of how two drugs might interact within a person's body, given the uniqueness of

individual physiology.

Multiple medications combined can cause confusion, lightheadedness, and internal bleeding — all dangerous and damaging conditions (71). Additionally, prescription drugs are costly. While more than 50% of all women in the United States use at least one prescription medication regularly (compared to about 30% of men), nearly 30% of women are still unable to afford a prescribed medication in a given year (compared to less than 20% of men) (8). As a result, women are more likely to not only put off healthcare but also skip medications due to financial burden. Up to 70% of women with PCOS remain undiagnosed worldwide due to various factors such as lack of access to proper healthcare, or ignorance towards their symptoms. The bulk of women who suffer from these symptoms reside in developing countries. For example, prevalence is higher in South Asia —an area where women do not have access to prescription drugs (9).

Natural medications for PCOS could be more accessible alternatives to help alleviate financial burdens and provide safer treatments with lesser side effects. This review paper outlines 10 different herbal supplements for PCOS and compares them to commercially available medicines. Specifically, the cost, effectiveness, and potential for side effects were compared between widely used prescription medicines and lesser-known natural treatments so as to provide equitable care alternatives. Additionally, the paper provides an overview and evaluates the effectiveness of current practices of PCOS standard of care.

2. Discussion

2.1 *Diabetes*

Women with polycystic ovary syndrome (PCOS) are at a higher risk of developing type 2 diabetes compared to those without the condition; although this risk may be bidirectional. Research suggests that up to 30-50% of women with PCOS may develop type 2 diabetes or prediabetes by the age of 40, though this risk can vary depending on individual factors such as weight, insulin sensitivity, and lifestyle (10).

PCOS and insulin resistance occur in tandem in 50-80% of patients (11). This means that the body's cells do not respond effectively to insulin, leading to higher blood sugar levels. Elevated blood sugar levels can damage various organs and systems over time, increasing the risk of cardiovascular diseases, kidney damage, and other health issues. Women with PCOS often have other features of metabolic syndrome, such as obesity, high blood pressure, and high cholesterol (11). These conditions further increase the risk of developing type 2 diabetes. The combination of insulin resistance, obesity, and other metabolic issues creates a higher risk profile for developing type 2 diabetes.

Metformin is the gold standard prescription drug used for treating diabetes in PCOS patients. It is also one of the only drugs found to help PCOS-affected individuals with diabetes, highlighting the limited range of options given to patients (12). Metformin works by decreasing the amount of glucose produced by the liver and increasing insulin sensitivity in muscle and fat tissues. This helps

the body use glucose more effectively and lowers blood sugar levels. It can lower Glycated Hemoglobin (HbA1c) levels (a marker of long-term blood sugar control) by ~ 1-2%, which indicates a significant reduction in average blood glucose levels over time (13). Metformin also enhances insulin sensitivity in peripheral tissues, such as muscle and fat. Increased insulin sensitivity improves the efficiency of glucose uptake by cells, particularly through the promotion of glucose transporters such as Glucose Transporter type 4 (GLUT4). GLUT4 transporters are located on the surface of muscle and fat cells, and their activity is crucial for glucose uptake from the bloodstream. ~ 30-50% of women with PCOS who use metformin may experience improvements in their menstrual cycles and ovulation (13).

Despite the widespread use of metformin, several side effects including gastrointestinal dysfunction such as nausea, diarrhea, and abdominal discomfort are common, especially when starting the medication. Although metformin is generally considered weight-neutral or slightly weight-reducing, some individuals may not experience significant weight loss or may even gain weight due to other factors.

Metformin prices typically range from $5-30 (including insurance coverage) for a one-month supply, depending on the country and specific market conditions (14). However, even though metformin is affordable, out-of-pocket costs can still be a barrier for some individuals, especially in areas with high levels of poverty or limited healthcare coverage. Such barriers to accessing metformin include limited healthcare infrastructure, lack of pharmacies in rural areas, and economic constraints that affect individuals' ability to afford medications.

Semaglutide (Ozempic®) is a recently approved medication for diabetes management. It is an injectable prescription medication that is used for managing type 2 diabetes and weight loss. Semaglutide works by mimicking a natural hormone called Glucagon-Like-Peptide-1 (GLP-1), which helps regulate blood sugar and appetite. It enhances the pancreas's ability to release insulin when blood sugar levels are high, and it reduces the production of glucagon, a hormone that increases blood sugar by prompting the liver to release more glucose (15). Additionally, Ozempic® decreases the rate at which food moves from the stomach to the intestines, helping to prevent rapid spikes in blood sugar and maintaining a longer duration of satiety. It also acts on the brain to decrease appetite, which can aid in weight loss (15).

For women with PCOS, Ozempic® has been promising for managing weight and improving insulin sensitivity. However, common side effects include gastrointestinal dysfunction such as nausea and diarrhea, which may be managed with gradual dose adjustments. Fatigue could be severe, affecting the overall well-being of PCOS patients, particularly if combined with other, non insulin related, symptoms of PCOS. Less common but more serious side effects include the potential risk of pancreatitis and thyroid issues. As of the date of writing of this paper, Ozempic® was not FDA-approved for Polycystic Ovary Syndrome (PCOS). However, it is being prescribed off-label (16).

Ozempic faces significant challenges regarding cost, availability, and accessibility, especially in rural areas. The medication is notably expensive, with monthly costs ranging from $800-1,200 in the United States, which can be a major barrier for those without adequate insurance or financial assistance (17). Availability may be scarce, as Ozempic is more readily stocked in urban pharmacies, leaving rural areas with fewer options and potentially leading to delays in obtaining access to the medication. Furthermore, limited access to healthcare providers in rural regions can make it difficult for patients to get a prescription. Despite patient assistance programs designed to help with costs, navigating these resources can continue to be complex, leaving many patients in developing areas struggling with both the financial and logistical aspects of accessing this essential medication.

Aside from using metformin and Ozempic®, berberine, an herbal medicine, acts similarly to increase insulin sensitivity. Berberine is a natural compound found in several plants, including *Berberis* species, and has been used in traditional medicine for different purposes. It is known traditionally for its potential benefits in managing metabolic disorders, including type 2 diabetes and PCOS.

Berberine acts by several mechanisms to improve metabolic health (18). Berberine enhances insulin sensitivity by activating the Adenosine Mono Phosphate-activated protein kinase (AMPK) pathway –this helps the body use insulin more effectively and stabilize blood sugar levels (18). Up to 70% of women with PCOS exhibit dyslipidemia –a condition where the blood contains abnormal amounts of lipids or fats (19). Berberine can improve lipid profiles by reducing cholesterol and triglyceride levels, which may help manage weight and manage conditions such as dyslipidemia. It can also be useful in exerting anti-inflammatory effects, therefore reducing inflammation often linked with PCOS (18). A recent study investigated the potential of berberine as a therapeutic approach for managing insulin resistance in women with PCOS. Data from various pharmacological clinical trials were analyzed to assess berberine's effects on insulin sensitivity, fertility and pregnancy outcomes. Berberine exhibited hypoglycemic properties that improved insulin resistance (74). By enhancing insulin sensitivity, berberine may also help restore ovulation and regulate menstrual cycles.

Research on berberine for PCOS is promising but still limited. While some studies have reported positive outcomes, more extensive and long-term research is needed to fully establish its effectiveness and optimal dosage for PCOS. Side effects of berberine can include nausea, diarrhea, or constipation. An extreme case would include hypoglycemia since berberine can lower blood glucose levels –especially if taken with other blood sugar-lowering medications (20). The cost of berberine supplements can vary widely depending on the brand, dosage, and formulation. On average, a bottle of 60 to 120 capsules (with each capsule typically containing 500 mg of berberine) costs from $20-40 (21). Prices can fluctuate based on location and whether the product is claimed to be organic or includes additional ingredients. However, berberine is widely available as an over-the-counter supplement, thus being

widely accessible.

Cinnamon is a spice derived from the inner bark of trees from the genus *Cinnamomum*. It is widely used in cooking/baking and has been recognized for its medicinal properties in traditional medicine. Cinnamon contains compounds such as cinnamaldehyde and polyphenols that increase insulin sensitivity. These compounds influence insulin receptor activity and improve glucose uptake by cells. By increasing the body's sensitivity to insulin, cinnamon helps cells use glucose more effectively, reducing insulin resistance—a key feature of Type 2 diabetes. This can lead to better blood sugar control (22).

Several studies have demonstrated that cinnamon can effectively lower fasting blood glucose levels and improve insulin sensitivity. For example, a meta-analysis of clinical trials found that cinnamon supplementation significantly reduced fasting blood glucose levels and improved HbA1c (23). Effective doses used in studies typically range from 1 to 6 grams of cinnamon per day, either as a powder or in supplement form. Cinnamon may cause stomach upset or nausea. In rare instances, it can cause allergic reactions if ingested for the first time. Additionally, high doses of *Cassia cinnamon* may pose a risk of liver toxicity. *Ceylon cinnamon,* on the other hand, has lower coumadin levels and is generally considered safer for long-term use (24). Finally, cinnamon is widely available in grocery stores in numerous different forms such as powder, sticks, and regular supplements online and in stores. While prices vary, cost is normally very affordable, typically ranging from $3-10 depending on the dosage and formulation of the product.

Fenugreek, known as "Trigonella foenum-graecum," is a herb valued for its culinary and medicinal properties. It is a herb native to the Mediterranean region, western Asia, and parts of Europe (25). Fenugreek is associated with enhancing lactation and supporting digestive health. The name "fenugreek" is derived from its historical use as a food and medicine. In traditional practices, this versatile herb is known for its potential to improve metabolic health and balance hormones, making it a popular choice in natural remedies.

Fenugreek exerts its beneficial effects on diabetes regulation through several key mechanisms. Its high soluble fiber content slows carbohydrate digestion and absorption, reducing postprandial blood glucose spikes. Fenugreek contains 4-hydroxy isoleucine, which stimulates insulin secretion and improves insulin sensitivity by enhancing insulin receptor activity. Additionally, it inhibits enzymes such as alpha-amylase and alpha-glucosidase, slowing glucose release into the bloodstream (26). Its antioxidant properties reduce oxidative stress, which is linked to diabetes complications, while its hypolipidemic effects lower cholesterol and triglycerides, supporting overall metabolic health, improved fertility, and more regular menstrual cycles.

Fenugreek is generally safe, but it can cause some side effects. These include gastrointestinal discomfort, such as nausea, diarrhea, and bloating. However, the occurrence of these symptoms is rare. Fenugreek is also widely available in various

forms, including seeds, capsules, powders, and teas. It is widely available in health food stores, grocery stores, and online retailers. Prices typically range from $5-20 for a month's supply, depending on the form and brand. Seed packets are often the most affordable option, while capsules or specialized extracts are more expensive.

2.1.1 *Comparison of pharmaceutical and herbal diabetes treatments*

While metformin and Ozempic® are effective medications for managing diabetes and weight, berberine, cinnamon, and fenugreek offer more natural, gentle alternatives with fewer side effects. The herbal medications can be used as a more complementary approach since they are less invasive treatments. However, while their effects may be slower, combining them with other lifestyle changes can yield results comparable to those obtained with pharmaceuticals. Utilizing natural supplements can lower glucose levels and improve insulin sensitivity similar to pharmaceuticals, while also decreasing cholesterol levels.

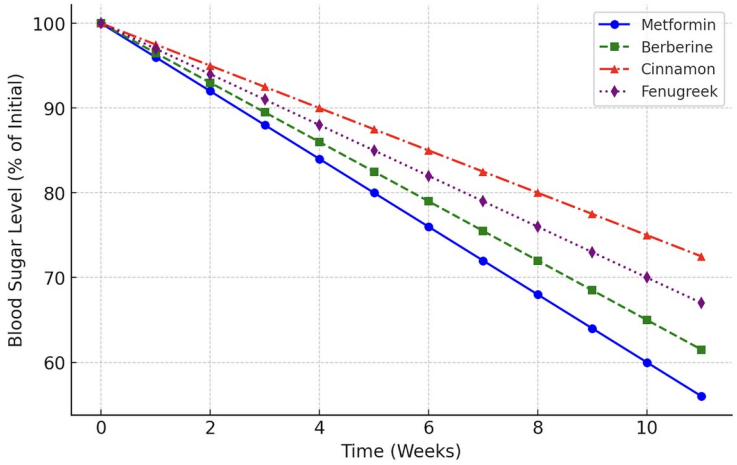

Figure 2. The effects of metformin, berberine, cinnamon and fenugreek on blood sugar levels over 12 weeks demonstrate varying degrees of insulin-sensitizing properties

Figure 2 shows that metformin achieves the most rapid reduction, consistent with its role as a first-line pharmacological treatment for insulin resistance. Berberine follows a similar trend, since it activates the AMPK pathway to enhance glucose metabolism. Fenugreek exhibits a moderate reduction by improving insulin receptor sensitivity and slowing carbohydrate digestion, while cinnamon demonstrates the slowest decline, reflecting its more gradual effect on glucose uptake. Each treatment's trend is represented mathematically using a linear decrease in blood sugar levels over time, with the rate of decline adjusted based on comparative studies. The model assumes that all treatments start at the same baseline blood sugar level (100%) and decline at different rates. The unique relationship between diabetes and PCOS in women has often been overlooked, resulting in limited progress in developing treatments that address both conditions simultaneously.

Increasing awareness of this overlap and conducting further clinical trials on natural medications may mark a significant turning point in the treatment of both diabetes symptoms and the traditional symptoms associated with PCOS.

2.2 *Menstrual cycle and fertility*

Polycystic ovary syndrome also significantly affects menstrual cycles and fertility in many women. ~70% of women with PCOS report irregular menstrual cycles, which can include missed periods, heavy bleeding, or very light periods (27). Some may have fewer than eight menstrual cycles a year, while others experience a complete absence of menstruation (amenorrhea). These irregular periods often coincide with a lack of ovulation, making PCOS a leading cause of infertility in women. PCOS can prevent the ovaries from developing or releasing eggs properly. The follicles that contain the eggs may not mature or be released each month, leading to a buildup of fluid-filled sacs that appear as cysts on ultrasound scans. This is why PCOS is referred to as 'polycystic' ovary syndrome, meaning "many cysts". Additionally, irregular periods can lead to an increased risk of endometrial hyperplasia – thickening of the uterine lining–which can raise the risk of endometrial cancer if not monitored (28). To address these side effects and aid with ovulation, many PCOS patients have been using various medications over the past decades.

Clomiphene citrate, (Clomid®), is a medication often prescribed for women with PCOS to help regulate menstrual cycles and improve fertility. Clomiphene works primarily as a selective estrogen receptor modulator (SERM). It competes with estrogen for binding sites in the hypothalamus, increasing the release of the gonadotropin-releasing hormone (GnRH) (29). This stimulates the pituitary gland to produce more follicle-stimulating hormone (FSH) and luteinizing hormone (LH), promoting ovarian follicle development and ovulation. Clomiphene is generally effective in inducing ovulation in women with PCOS. Studies suggest that ~ 70-80% of women will ovulate after taking Clomid®, and ~ 30-50% will conceive within six cycles of treatment (30). However, its effectiveness can vary based on factors such as age, body mass index (BMI), and the severity of PCOS. Common side effects may include hot flashes, abdominal discomfort/bloating, nausea, mood swings, and tenderness in the breast (30). Less common but more serious side effects can include Ovarian HyperStimulation Syndrome (OHSS) –which can cause swollen ovaries— the risk of multiple pregnancies with twins or more, blurred vision, and seeing spots. Additionally, the cost can vary depending on location and insurance coverage. It can range from $10 to $100 for a typical cycle but can increase to up to $1000 depending on the brand (31). Clomid® is only available by prescription as well, and while it is a commonly used first-line treatment for ovulation induction, it is not without risks and may not work for everyone.

Letrozole, also known by its brand name Femara®, is an aromatase inhibitor primarily used in the treatment of hormone receptor-positive breast cancer in postmenopausal women. However, it has been prescribed off-label for inducing ovulation in women with PCOS who are struggling with infertility.

Letrozole inhibits the aromatase enzyme,

which is responsible for converting androgens such as testosterone into estrogens. By lowering Estrogen levels, letrozole reduces negative feedback on the hypothalamus and pituitary gland, leading to an increase in FSH and LH secretion (32). This promotes ovarian follicle development and ovulation. It has been reported that letrozole can inhibit estrogen levels by at least 97% to 99% (33). However, current data are still insufficient to support the idea that letrozole can be utilized effectively to treat PCOS.

Common side effects of letrozole may include hot flashes, fatigue, dizziness, joint pain or stiffness, nausea, and vomiting. Serious but less common side effects can include OHSS, and bone density reduction with long-term use, though this is more relevant for breast cancer treatment than for fertility (32). Letrozole is only available with a doctor's prescription. The retail price of letrozole can vary, typically costing ~ $544. However, the final cost may be influenced by factors such as insurance coverage, the specific treatment plan, and the pharmacy. For instance, if purchased without insurance, letrozole may cost ~ $134.64 for a pack of 10 tablets at 2.5 mg each (34).

Shatavari, scientifically known as *Asparagus racemosus*, is a perennial herb native to India and other parts of South Asia. It has been used in traditional Ayurvedic medicine for centuries, primarily for women's health. Shatavari, which means “one who has a hundred husbands” or “welcoming to many,” is recognized as both a general tonic and a reproductive tonic for women. This name reflects its potential to enhance fertility and vitality. In Ayurveda, this remarkable herb is often referred to as the “Queen of herbs” due to its ability to cultivate love and devotion (35).

Shatavari contains various bioactive compounds, including saponins, flavonoids, and alkaloids, which contribute to its health benefits. Its adaptogenic properties help modulate the body’s response to stress, while its phytoestrogens may mimic estrogen in the body, aiding in hormonal balance. While anecdotal evidence supports the use of shatavari in managing PCOS symptoms, clinical research is limited. Some women report improvements in menstrual regularity and in symptoms like acne and hirsutism when incorporating it into their regimen (36).

Shatavari is generally considered safe for most people when used appropriately. However, possible side effects can include mild gastrointestinal discomfort (nausea, diarrhea), allergic reactions in some individuals, and hormonal effects that could affect those with hormone-sensitive conditions (37). Additionally, shatavari is available in various forms, including powders, capsules, and teas. The appropriate dosage can vary based on individual needs and health conditions. Shatavari can be found in health food stores, Ayurvedic shops, and online retailers. Prices typically range from $10 to $30 for a month’s supply, depending on the formulation. Shatavari is a versatile herb with a long history of use in traditional medicine, especially for women's health. Its potential benefits for hormonal balance, fertility, and overall well-being make it a popular choice in herbal remedies.

Chasteberry, or *Vitex agnus-castus*, is a flowering plant that originates from the Mediterranean region and parts of Asia (38). Its historical use dates back to ancient times, when it was revered for its medicinal properties. The Greeks and Romans valued it for its purported ability to promote chastity. Traditionally, chasteberry has been utilized in herbal medicine, particularly for women's reproductive health. Its use spans centuries, often recommended for a variety of conditions, including menstrual irregularities, PreMenstrual Syndrome (PMS), and menopause symptoms. Many cultures have employed this herb to support fertility and regulate menstrual cycles, making it a mainstay in various traditional remedies (38).

Chasteberry's effectiveness is primarily linked to its impact on hormonal balance. It influences the pituitary gland, promoting the secretion of LH while inhibiting prolactin release. This hormonal regulation can help restore the balance between estrogen and progesterone, which is crucial for a regular menstrual cycle and ovulatory function. The herb may also have mild anti-inflammatory properties that contribute to overall reproductive health, helping alleviate discomfort associated with hormonal fluctuations (39).

An abundance of studies have explored chasteberry's role in managing PMS symptoms, irregular menstrual cycles, and conditions like PCOS. Many women report reductions in breast pain, in mood swings, and in other PMS-related issues. While promising, the research varies in quality, and more extensive clinical trials are needed to establish definitive conclusions about its effectiveness (39).

Chasteberry is generally considered safe, but some individuals may experience side effects such as mild gastrointestinal upset, headaches, skin rashes, or changes in menstrual patterns. Furthermore, chasteberry is readily available in various forms, including dried berries, capsules, tinctures, and teas. It can be found in health food stores, herbal shops, and online. Prices typically range from $10 to $30 for a month's supply, depending on the formulation and brand.

2.2.1 *Comparison of pharmaceutical and herbal menstrual cycle fertility treatments*

Overall, the management of PCOS, especially regarding menstrual cycles and fertility, involves a spectrum of approaches, ranging from pharmaceutical drugs to herbal alternatives. Pharmaceutical drugs such as clomiphene and letrozole have shown significant efficacy in promoting ovulation and enhancing fertility in women with PCOS. However, they are associated with potential side effects such as OHSS, risk of multiple pregnancies, and relatively high costs. These medications require careful medical supervision. On the other hand, herbal supplements like shatavari and chasteberry offer a more holistic, traditionally rooted approach.

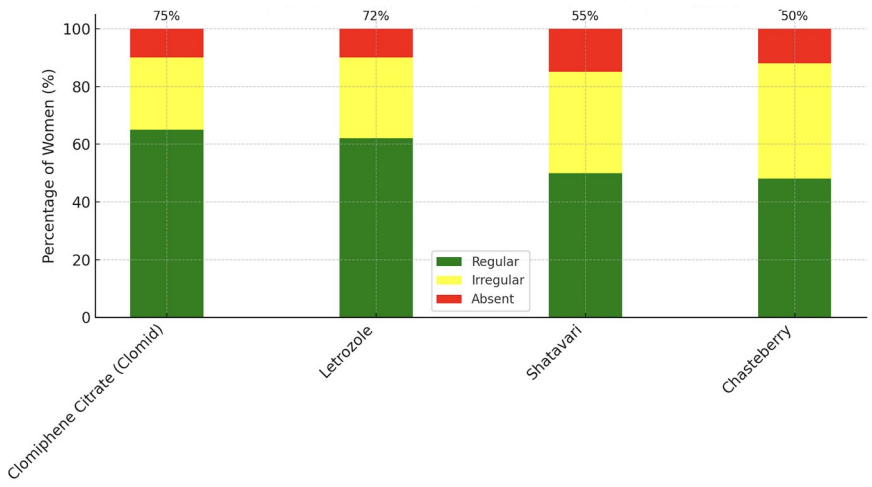

Figure 3. Stacked bar chart comparing ovulation rates and menstrual cycle regularity (regular, irregular, or absent periods) for clomiphene, letrozole, shatavari, and chasteberry in women with PCOS.

As seen in Figure 3, the data for ovulation success and cycle regularity were gathered from existing studies, clinical trials, and anecdotal reports. The X-axis represents the four treatments, while the Y-axis shows the percentage of women who ovulated, with the stacked sections of the bars indicating the proportion of women experiencing regular, irregular, or absent cycles. Clomiphene and letrozole demonstrated the highest ovulation success rates and significantly improved menstrual cycle regularity compared to the herbal treatments, shatavari and chasteberry, which showed more variability in outcomes. The analysis suggests that while pharmaceutical treatments are more reliable in inducing ovulation and regulating menstrual cycles, herbal treatments may offer a complementary approach with some benefits, particularly for hormonal balance, though with less consistent results. While scientific data on their efficacy in treating PCOS remains limited, they have shown promise in regulating menstrual cycles and alleviating some PCOS symptoms, including hormonal imbalances and stress. Additionally, their mild side effect profile, lower cost, and over-the-counter availability make them appealing options for women seeking alternative or complementary treatments.

2.3 *Anti-androgens*

Anti-androgens are compounds that block the effects of androgens, which are male hormones such as testosterone and dihydrotestosterone (DHT) that are present in both males and females (40). These hormones regulate male characteristics, but when present in excess in females, particularly in conditions like PCOS, they can lead to unwanted symptoms like irregular periods, hirsutism, acne, and hair loss. Anti-androgens work by either reducing the production of androgens or blocking androgen receptors, preventing these hormones from binding to their targets. Androgen receptor blockers are compounds that bind to androgen receptors and prevent androgen activation. These blockers inhibit androgen-driven effects, such as hair growth and acne. Androgen production inhibitors; on the other hand; are

substances that reduce the amount of androgens produced in the body, often by interfering with enzymes involved in androgen synthesis, such as 5-alpha reductase, or by inhibiting ovarian androgen production (41). By either blocking androgen receptors or reducing androgen production, anti-androgens can effectively minimize the symptoms of androgen excess, helping to regulate hormonal balance in conditions like PCOS.

Cyproterone acetate (CPA) is a synthetic steroidal anti-androgen used in various medical treatments, particularly for conditions related to hormonal imbalances. It is a medication primarily used to treat conditions related to excessive androgen activity. CPA is used in both men and women for different purposes (42). In men, it is usually used to treat prostate cancer and reduce the effects of testosterone, which can fuel cancer growth. In women, it is often used to manage severe acne, hirsutism (excess body hair), and symptoms of PCOS. It is also used in transgender women (male-to-female) hormone therapy to reduce masculinizing effects. Cyproterone works by blocking androgen receptors, preventing androgens such as testosterone from exerting their downstream effects and reducing the influence of male hormones on the body (42). It also has progestin-like properties, meaning it mimics the female hormone progesterone, which helps regulate hormone levels further.

Regarding effectiveness, maintenance therapy with lower doses of CPA, of 25 mg/day, is effective in preventing relapse of symptoms of hirsutism. Additionally, CPA is very effective in reducing acne and excess hair growth in women, especially when used in combination with estrogen (often in birth control pills) (44). Common side effects include fatigue, weight changes, and mood swings. In women, it can cause irregular menstrual cycles, amenorrhea, breast tenderness, and changes in body weight. More severe side effects include liver toxicity, mood disturbances or depression, and Thromboembolism (blood clots), which is more common when combined with estrogen-containing medications. Prolonged use in high doses may lead to bone density loss (osteoporosis), and there is potential for cardiovascular side effects in some users (45).

Cyproterone is available by prescription under various brand names, including Androcur® and Cyprostat®. In some countries, it may be included in combination with estrogen in oral contraceptive pills like “Diane-35”(43). The cost of cyproterone varies depending on the country, formulation, and whether or not it is covered by insurance. In the U.S., it is less commonly used than in Europe or other parts of the world. For uninsured patients, the cost can range from $30 to $100 per month, depending on the dosage and whether it is used alone or in combination with other medications.

Spironolactone is an anti-androgen that has a range of applications, particularly in treating conditions associated with excess androgen levels, fluid retention, and cardiovascular dysfunction. In women, it’s often prescribed for hormonal acne, excess body hair, and PCOS due to its anti-androgen properties (72). Similar to cyproterone, spironolactone is used in feminizing hormone therapy for transgender women to block testosterone’s effects. Spironolactone is a steroidal antiandrogen

widely used for treating conditions such as acne, hirsutism, and alopecia. It works by directly inhibiting the 17α-hydroxylase enzyme, which is essential for testosterone production, leading to reduced testosterone levels. Additionally, spironolactone blocks the 5-alpha reductase enzyme, preventing the conversion of testosterone into the more potent DHT (46).

Common side effects include increased urination, high potassium levels (hyperkalemia), breast tenderness or enlargement (gynecomastia), and fatigue. Hyperkalemia can lead to dangerous heart and kidney problems, low blood pressure, and menstrual irregularities (47). Typically, without insurance, Spironolactone can range from ~ $10 to $50 per month. The cost of spironolactone varies depending on dosage, insurance coverage, and location. In the U.S., it typically ranges from $10 to $50 per month for uninsured patients. In many places, it is a generic medication, making it relatively inexpensive compared to other treatments.

Flutamide is a non-steroidal anti-androgen (NSAA) medication, meaning it works to block the effects of androgens by preventing them from binding to androgen receptors in the body (48). It is primarily used in combination with other therapies to treat prostate cancer by blocking the stimulating effect of testosterone on cancer cells. In women, it may be used off-label to treat androgen-related conditions like severe acne, hirsutism, and PCOS.

Flutamide works by blocking androgen receptors, preventing androgens from attaching to and activating these receptors. This blockade reduces the influence of androgens in tissues where they typically have an effect, such as the prostate gland and hair follicles. Unlike some other anti-androgens, flutamide does not lower the production of testosterone but rather inhibits its action at the receptor level. It also is effective in reducing excess hair growth and severe acne caused by high androgen levels (48). However, its use in women is less common due to potential side effects. Flutamide can help alleviate some of the symptoms of PCOS, such as acne and excessive body hair, though it is not a first-line treatment. Common side effects include nausea, diarrhea, and liver enzyme changes. One of the most significant risks of flutamide is its potential for liver damage, including hepatitis and, in rare cases, fatal liver failure (48). Regular monitoring of liver function is essential.

Flutamide is available by prescription only and is typically sold under brand names like Eulexin®, though generic versions are widely available. The price of flutamide varies depending on the region and whether it is a generic or brand-name version. Generic flutamide can range from $30 to $150 per month for uninsured patients, depending on dosage and pharmacy.

Chinese Peony (*Paeonia lactiflora*) is a medical flowering plant native to East Asia, often used in Traditional Chinese Medicine (TCM) to support women's reproductive health, liver function, and immune system regulation. Its roots are the primary part used in herbal remedies. Chinese Peony is thought to help regulate estrogen and testosterone levels in both women and men, making it useful for

conditions like PCOS, menstrual disorders, and fertility issues (49). It has potent anti-inflammatory properties, which can help treat pain and inflammation in conditions like arthritis or skin issues. Additionally, it has been used to reduce stress, support liver health, and improve circulation.

Chinese Peony contains active compounds such as paeoniflorin, which can affect estrogen metabolism and promote hormonal balance. In women with estrogen dominance or androgen excess (as seen in PCOS), it helps modulate these hormone levels. Furthermore, Chinese Peony may lower testosterone levels by inhibiting its production, making it potentially useful for managing symptoms like acne, hirsutism, and menstrual irregularities. It inhibits the release of pro-inflammatory mediators and has antioxidant properties, reducing inflammation and oxidative stress in the body (49).

In combination with other herbs, such as Licorice root, Chinese Peony has shown effectiveness in reducing androgen levels and restoring regular ovulation in women with PCOS. Its ability to lower androgens like testosterone may help improve skin conditions such as acne and reduce excess hair growth. Studies have shown it can effectively reduce inflammation and provide relief from pain, though more research is needed to fully understand its effectiveness in various conditions (49).

While Chinese Peony is generally well-tolerated when taken in recommended doses, mild side effects may include stomach discomfort, nausea, or drowsiness when taken in large doses. There is limited data on the long-term safety of Chinese Peony supplementation, so it should be used with caution for extended periods (48).

Chinese Peony is widely available in health stores, herbal medicine shops, and online. It is sold as capsules or tablets, tinctures, extracts, and dried roots for tea or traditional preparations. Prices vary depending on the form and quality of the product. Capsules typically range from $15 to $30 per bottle, depending on the brand and dosage.

Red Reishi mushrooms (*Ganoderma lucidum*), also known as Lingzhi, are medicinal fungi long used in TCM for their immune-boosting, anti-inflammatory, and adaptogenic properties. It is native to humid, tropical regions of Asia, and has been used for over 2,000 years in traditional medicine for its numerous health benefits (50).

Red Reishi is used to contextually modulate the immune system, making it stronger or calmer, depending on the body’s needs. It helps combat inflammation and oxidative stress, which are involved in many chronic diseases. Additionally, it is known to help balance hormones by reducing stress, supporting the adrenal glands, and lowering androgens, making it useful for conditions like PCOS. Studies have shown it has anti-tumor properties, though more research is needed in humans (51).

Red Reishi is an adaptogen, meaning it helps the body adapt to stress. Balancing the body's stress response can help regulate hormone levels, particularly cortisol (a stress hormone).

In doing so, it can indirectly support the balance of sex hormones like estrogen and testosterone. Its active compounds, such as triterpenes and beta-glucans, also help regulate the immune system. This can reduce inflammation and support the endocrine system, which plays a role in hormone production and regulation (51). There is some evidence that red reishi may have mild anti-androgenic effects, making it potentially helpful for managing conditions related to high androgen levels (e.g., acne, hirsutism) (51).

Red Reishi is generally well-tolerated when used in moderate doses. Some possible side effects include dizziness or nausea. Excessive use of reishi mushrooms may lead to digestive discomfort, such as diarrhea or constipation, and low blood pressure (52). Red Reishi mushrooms are widely available in health stores, herbal medicine shops, and online in various forms such as capsules or tablets, powder for adding to teas or smoothies, extracts, and tinctures. It is usually priced ~ $20 to $40 per bottle, depending on the concentration and brand. The mushrooms can be combined with other adaptogenic herbs, such as ashwagandha or rhodiola, to enhance stress reduction and hormone balancing. For people with autoimmune or chronic inflammatory conditions, Red Reishi is often used alongside other anti-inflammatory supplements (such as turmeric or omega-3 fatty acids) to help reduce symptoms (52).

2.3.1 *Comparison of herbal and pharmaceutical anti-androgen treatments*

While comparing synthetic anti-androgens like cyproterone acetate, spironolactone, and flutamide with herbal supplements like Chinese Peony and red reishi mushrooms, it becomes evident that both drug-based and herbal interventions have unique mechanisms for managing symptoms of conditions like PCOS and androgen excess. Synthetic anti-androgens are highly effective in rapidly blocking androgen receptors or reducing androgen production. However, their use is often accompanied by notable side effects, such as liver toxicity, fatigue, menstrual irregularities, and cardiovascular risks. The costs of these medications, especially in countries like the U.S., can range from $30 to $150 per month depending on dosage and insurance coverage. The majority of these drugs are also only available through prescription, which makes them less available for women in developing countries without insurance or proper healthcare facilities. On the other hand, herbal options like Chinese Peony and red reishi mushrooms offer another approach to balancing hormone levels and reducing inflammation. While they may not provide the immediate, targeted effects of synthetic drugs, they tend to have fewer severe side effects and are generally well-tolerated. These herbal supplements are often more affordable, with prices ranging from $15 to $40 per month, depending on the product and brand. However, the effectiveness of the Chinese peony and red reishi mushroom has not yet been thoroughly studied or researched through clinical trials, making them a less reliable source than prescription-based drugs.

2.4 *Hormonal regulation*

A variety of treatment strategies have emerged to manage PCOS symptoms, with Combined Oral Contraceptives (COCs) being one of the most widely used options. COCs work by

regulating the menstrual cycle, reducing androgen production, and alleviating symptoms like acne and hirsutism (53). However, ashwagandha, turmeric, and spearmint offer a different approach to this strategy to manage the hormonal imbalances associated with the condition. This section examines the efficacy of both COCs and herbal alternatives, focusing on their mechanisms of hormonal regulation, risks, side effects, and overall accessibility.

COCs are a common treatment for women with PCOS, especially those seeking to regulate their menstrual cycles, manage acne, reduce excess hair growth, and do not desire to be fertile. These are birth control pills that contain a combination of two synthetic hormones: estrogen and progestin. These mimic the natural female hormones—estradiol (a type of estrogen) and progesterone—produced by the ovaries (54). Estrogen helps regulate the menstrual cycle by stabilizing the endometrium (the uterine lining). It also reduces the release of LH, which is often elevated in PCOS. Progestin helps prevent the thickening of the uterine lining and reduces the risk of endometrial hyperplasia (a concern in women with irregular periods) (54). It decreases androgen levels by suppressing ovarian androgen production. Together, COCs lower the levels of androgens, reducing symptoms like acne and hirsutism.

Common side effects include nausea, breast tenderness, headaches, mood changes, weight gain, and spotting between periods (54). More serious side effects include an increased risk of blood clots, especially in women who smoke or have other risk factors like obesity or a family history of clotting disorders. There is also a slightly increased risk of breast and cervical cancer, though COCs reduce the risk of ovarian and endometrial cancer (55).

Each COC pill pack typically contains 21 active pills (with hormones) and 7 inactive (placebo) pills, which cause withdrawal bleeding that mimics a natural menstrual period. The cost of COC Pills varies depending on insurance coverage and choice of payment (out of pocket or through government aid). Some government insurance plans, like Medicaid, cover the cost of COCs, The annual out-of-pocket cost can range from $20-$80. The first over-the-counter OCP, Opill®, is available for a suggested retail price of $19.99 for one month's supply or $49.99 for three months.

Herbal alternatives to hormonal treatments for PCOS, such as ashwagandha, turmeric, and guduchi, are gaining popularity because of their potential to manage symptoms naturally. These herbs work differently from synthetic hormones such as those found in COCs, but they offer benefits for regulating hormones, reducing inflammation, and managing insulin sensitivity.

Ashwagandha (*Withania somnifera*), also known as Indian ginseng or winter cherry, is a popular adaptogenic herb used in traditional Ayurvedic medicine. It has gained widespread recognition for its ability to help the body cope with stress, balance hormones, and improve overall health, particularly in conditions such as PCOS (56). Ashwagandha is primarily known for its adaptogenic properties, which help regulate the body’s response to stress. It supports the function of the adrenal glands,

which produce stress hormones like cortisol. PCOS can be worsened by high cortisol levels, which contribute to insulin resistance and an increase in androgens. By reducing cortisol, ashwagandha may help alleviate some of the hormonal imbalances associated with PCOS. Ashwagandha has also been shown to modulate endocrine function, particularly the balance of cortisol, thyroid hormones, and androgens (57). This is particularly important for PCOS, where elevated androgen levels lead to symptoms like acne, hirsutism, and irregular menstrual cycles. Ashwagandha may help lower androgens by regulating the body's stress response and improving insulin sensitivity. In addition, many women with PCOS experience mood swings, depression, and anxiety. Ashwagandha has been shown to have anti-anxiety and anti-depressant effects, which can help improve mental well-being (58).

Ashwagandha is generally considered safe for most people, especially when taken in recommended doses. However, potential side effects may include mild gastrointestinal discomfort and drowsiness in high doses, and it can stimulate thyroid activity. Individuals with hyperthyroidism or those taking thyroid medications should use it cautiously. Ashwagandha is widely available in various forms, including capsules, powders, and liquid extracts. It is sold in health food stores, online, and in pharmacies (59). The cost typically ranges from $10 to $25 per bottle, depending on the brand, dosage, and form. It is often sold in concentrations ranging from 300 mg to 1,000 mg per serving, with recommended dosages generally around 300–500 mg taken once or twice daily.

Turmeric (*Curcuma longa*), a golden-yellow spice widely used in cooking, especially in Indian cuisine, has long been valued for its medicinal properties in both Ayurvedic and TCM (60). The active compound in turmeric, curcumin, is a powerful antioxidant and anti-inflammatory agent, making it particularly beneficial for managing PCOS.

Chronic, low-grade inflammation is a hallmark of PCOS, contributing to insulin resistance, elevated androgen levels, and ovarian dysfunction. Curcumin, the bioactive component of turmeric, inhibits inflammatory pathways by suppressing pro-inflammatory molecules like cytokines and C-reactive protein (CRP) (60). By reducing inflammation, curcumin can help alleviate some of the systemic issues that exacerbate PCOS symptoms. Curcumin has been shown to improve insulin sensitivity by enhancing glucose metabolism (61). By regulating blood sugar levels and increasing cellular glucose uptake, turmeric helps reduce insulin levels, which, in turn, decreases androgen production from the ovaries. This leads to better hormonal balance, improved menstrual cycles, and reduced symptoms like acne and hirsutism (62). Research indicates that curcumin enhances insulin-mediated glucose uptake by activating pathways such as PhosphatidylInositol-3-Kinase/Protein Kinase B (PI3K/Akt) and AMPK, which help transport glucose into cells. It also inhibits gluconeogenesis, reducing blood sugar production in the liver. In addition to these effects on glucose metabolism, curcumin may improve lipid profile (62) by regulating cholesterol synthesis and promoting its breakdown, as well as reducing inflammation,

which is often elevated in PCOS patients. In a recent study, six hyperandrogenic PCOS women with hirsutism were treated for 12 weeks with a galenical preparation mixture containing curcumin and teupolioside (62). The results of the study showed that after 12 weeks, there was significant improvement in hirsutism. Additionally, turmeric is generally known to have potent antioxidant properties, which help neutralize harmful free radicals in the body. This antioxidant activity is crucial in protecting cells from oxidative stress, which can worsen insulin resistance and hormonal imbalances. Turmeric supports liver function as well by promoting the production of detoxifying enzymes and enhancing bile production, which helps the body eliminate excess hormones (60). This process can be particularly beneficial for women with PCOS, as impaired liver function can lead to hormone imbalances and worsen symptoms.

Turmeric is generally well-tolerated, but some people may experience side effects, especially with high doses or long-term use. High doses of turmeric may cause nausea, diarrhea, or indigestion. Turmeric has natural blood-thinning properties, so people taking anticoagulants should consult their doctor before using turmeric supplements. Turmeric is widely available throughout the world, through cooking, or additional uses (59). The turmeric powder spice can be used in cooking or made into teas. The spice is its most affordable form, typically costing around $5 to $10 for a ‘large’ container. Turmeric tablets are more concentrated forms, often combined with black pepper extract (piperine) to enhance curcumin’s absorption. Without piperine, curcumin’s bioavailability is low. Capsules generally cost $10 to $30 for a month's supply, depending on the brand and potency. Finally, the curcumin extracts are highly concentrated forms of the active compound, curcumin, and are often sold in liquid or capsule form. Prices range from $15 to $50, depending on the concentration.

Spearmint (*Mentha spicata*) is part of the Lamiaceae botanical family. It is native to Europe and Asia but has now grown in many temperate regions globally, including North America (64). Spearmint is widely used as a flavoring agent in food, toothpaste, and cosmetics. It is also employed for medicinal purposes, especially in traditional medicine systems, including treating digestive discomfort, headaches, and respiratory problems.

One of the primary effects of spearmint in women with PCOS is the reduction of free testosterone, the active form of testosterone that circulates in the blood (65). High levels of free testosterone in women are associated with symptoms like hirsutism, acne, and irregular menstrual cycles. By lowering free testosterone, spearmint helps alleviate androgen-related symptoms in PCOS patients. This anti-androgenic effect is believed to stem from spearmint’s ability to inhibit enzymes involved in androgen production, such as 5α-reductase, which converts testosterone into its more potent form, DHT. This reduction is crucial because DHT is responsible for many of the symptoms associated with androgen excess. Additionally, LH and follicle-stimulating hormone (FSH) are two key hormones that regulate ovarian function and the menstrual cycle. In women with PCOS, the ratio of LH to

FSH is often elevated, which contributes to the hormonal imbalance seen in this condition (66).

Studies have shown that spearmint may help increase FSH and decrease LH levels, bringing the ratio closer to normal (67). This helps promote more regular ovulation and improves the overall hormonal balance in women with PCOS. Regulating the levels of these hormones can improve menstrual regularity and ovulatory function, which is often disrupted in PCOS due to abnormal LH and FSH levels. A randomized controlled trial (RCT) evaluated the effect of spearmint tea on androgen levels in women with PCOS. The participants who consumed spearmint tea showed a significant reduction in free testosterone and an improvement in hirsutism over five days (68).

While spearmint is generally considered safe for most individuals, large quantities can cause side effects such as allergic reactions in sensitive individuals and potential toxicity if consumed in very high amounts over extended periods. Spearmint is cost-effective and widely available, making it a viable option for women seeking natural remedies to complement conventional PCOS treatments. Spearmint products are relatively inexpensive. Spearmint tea can range from $5 to $15 for a pack of 20-30 tea bags. Fresh spearmint leaves, oils, and capsules are also widely available. Spearmint products can be found in supermarkets, health food stores, and online retailers. It is available in various forms such as tea bags, dried leaves, essential oils, and dietary supplements.

2.4.1 *Comparison of pharmaceutical and herbal treatments for hormonal regulation*

Both COCs and herbal alternatives like ashwagandha, turmeric, and spearmint present viable options for managing the hormonal imbalances and symptoms associated with PCOS. COCs provide a well-established method of reducing androgens and regulating menstrual cycles by mimicking natural hormones, but they are associated with potential side effects, including an increased risk of blood clots and cancer. Herbal alternatives, on the other hand, offer a more natural means of addressing hormonal regulation by reducing cortisol levels, improving insulin sensitivity, and lowering androgen levels, often with fewer severe side effects. While COCs remain the mainstream choice, herbal treatments may serve as complementary or alternative options for women seeking holistic and less invasive treatments for PCOS. More research is needed, particularly on the long-term efficacy and safety of these herbal alternatives, to better understand their role in PCOS management. This is the only category of PCOS symptom managing substances where pharmaceuticals are not significantly more expensive.

2.5 *Gut Microbiota, PPAR-γ, and Autophagy in PCOS*

Emerging data indicate that gut microbiota, Peroxisome Proliferator Activated Receptor - γ (PPAR-γ) signaling, and autophagy play pivotal roles in the progression and treatment response of PCOS. Women with PCOS frequently exhibit gut dysbiosis, which disrupts insulin signaling and promotes systemic inflammation.

Herbal interventions such as berberine, curcumin, and inulin exhibit prebiotic effects, restoring microbial diversity and gut barrier integrity (75). These changes subsequently

improve insulin sensitivity and hormonal balance. In supporting these observations further, recent murine studies show that sodium butyrate supplementation (200 mg/kg/day) led to a 42.6% reduction in fasting insulin, 38.5% decrease in the HOmeostatic Model Assessment of Insulin Resistance (HOMA-IR), and 57% lower LH levels in letrozole-induced PCOS mice. It also reduced ovarian TNF-α and IL-6 expression by 60.1% and 49.3%, respectively, and restored estrous cycling in 80% of treated mice, with a 70% increase in antral follicles and corpus luteum formation (79). These findings underscore the potential of Small Chain Fatty Acids (SCFA)-based therapies to target multiple PCOS mechanisms such as insulin resistance, inflammation, and ovarian dysfunction through gut microbiota modulation.

The PPAR-γ pathway, a key regulator of lipid metabolism and insulin action, is downregulated in PCOS patients. Herbs such as curcumin and cinnamon function as PPAR-γ agonists, enhancing insulin sensitivity and potentially improving placental fatty acid uptake—a crucial process for embryo development. Recent murine research found that fatty acid transport impairment at the maternal-fetal interface can induce mid-gestational embryonic lethality (76). This suggests that PPAR-γ-activating herbs could reduce pregnancy complications and improve live birth outcomes in women with PCOS.

Autophagy, the cellular degradation of damaged organelles, is suppressed in the ovarian tissue of PCOS patients. Resveratrol and EpiGalloCatechin Gallate (EGCG) (green tea extract) activate autophagy through AMPK signaling, promoting follicular renewal and reducing cyst formation. These findings support the inclusion of autophagy-enhancing herbs in comprehensive PCOS treatment regimens.

2.6 *Fertility outcomes and live birth data - herbal vs pharmaceutical*

While pharmaceuticals like clomiphene and letrozole are effective ovulation inducers, live birth rates remain moderate: ~ 30–50% with clomiphene after 6 cycles, and slightly higher with letrozole (up to 27.5% in one RCT) (77). In a large RCT, letrozole was also shown to result in significantly higher ovulation rates per cycle (61.7% vs. 48.3%) and live birth rates (27.5% vs. 19.1%, $p = 0.007$) compared to clomiphene (77). However, both agents are associated with risks including OHSS, mood changes, vasomotor symptoms, and an increased likelihood of multiple pregnancies—6.9% with clomiphene and 3.9% with letrozole (77) (Figure 4).

Herbal agents, though less studied, have shown comparable outcomes with fewer side effects. A 2020 meta-analysis (75) reviewed 13 clinical trials and found that berberine improved ovulation rates, reduced androgen levels, and enhanced insulin sensitivity, with live birth rates ranging from 18–25% over 3–6 month treatment periods. Additionally, myo-inositol, a widely studied herbal derivative, improved ovulation and pregnancy rates and decreased gestational diabetes incidence.

Notably, some herbal agents not only improve metabolic and hormonal parameters but also exhibit fertility-enhancing effects via multiple pathways. For example, spearmint (*Mentha*

spicata) was shown in a randomized clinical trial to significantly reduce total testosterone levels from 5.23 ± 1.46 nmol/L to 3.64 ± 1.29 nmol/L ($p < 0.05$) after 30 days of consumption, with concurrent improvements in LH and FSH ratios and subjective reduction in hirsutism scores (78). Similarly, *Cinnamomum zeylanicum* (cinnamon) supplementation for 8 weeks improved insulin sensitivity, resulting in a mean reduction of HOMA-IR scores by 2.27 compared to placebo, and led to improved menstrual cyclicity in 20% more participants compared to controls (78).

Other botanicals such as curcumin, licorice, and *Tribulus terrestris* have demonstrated hormone-modulating properties, but high-quality data on their reproductive outcomes remain sparse. Therefore, the proposed use of human placental and trophoblast organoids can fill this evidence gap (section 2.7) by modeling embryonic lethality, nutrient transport, and placental integrity under herbal exposure. For instance, herbs that enhance PPAR-γ, Fatty Acid Binding Protein (FABP), and Retinoid X-Receptor (RxR) in organoids may show predictive value for increasing human fertility outcomes.

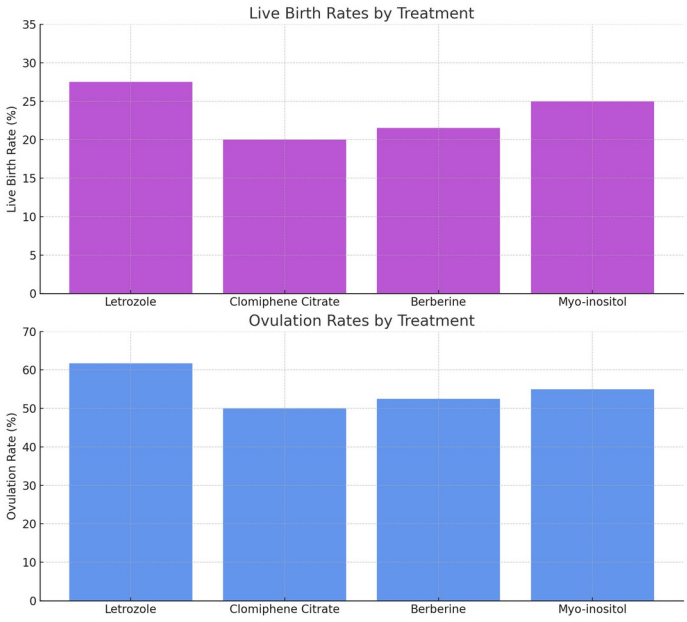

Figure 4. Bar charts comparing live birth and ovulation rates among pharmaceutical (letrozole, clomiphene) and herbal (berberine, myo-inositol, cinnamon, spearmint) PCOS treatments. Herbal data from meta-analyses and controlled trials; pharmaceutical data from RCTs.

2.7 *Overcoming clinical gaps with organoid modeling*

Given the ethical and logistical challenges of conducting long-term fertility studies in humans using herbal compounds, the use of human trophoblast and placental organoids as an intermediate platform for evaluating herbal efficacy fills an important gap. Organoid

models can simulate key aspects of maternal-fetal interface biology, including nutrient transport, trophoblast invasion, and hormonal cross-talk. A recent murine study (76) demonstrated that restricted fatty acid transport in the placenta resulted in mid-gestational embryonic lethality. Replicating such conditions in human organoid systems could allow an assessment of whether herbs that enhance PPAR-γ, FABP, and RxR expression can improve trophoblast lipid uptake and reduce embryonic loss.

Herbs such as curcumin and cinnamon, known PPAR-γ agonists, could be administered to trophoblast organoids *in vitro* to assess their impact on lipid absorption and placental integrity. Key outcome readouts should include FABP4 expression, Human Chorionic Gonadotropin (HCG) secretion, placental Vascular Endothelial Growth Factor (VEGF) signaling, and TUNEL assay-based apoptosis metrics. Organoid-based assays would thus serve as a high-fidelity model to explore mechanistic pathways and screen herbal compounds for safety and efficacy in reproductive outcomes, particularly where clinical data are lacking.

2.8 *Mechanistic overview of herbal compounds*

To optimize therapeutic outcomes and reduce inter-individual variability in herbal responses, a mechanistic profile of key herbs used in PCOS treatment was compiled (Table 1). Each herb's predominant molecular action was identified to inform the formulation of a multi-targeted herbal combination. The objective was to maximize synergy while minimizing pathway redundancy.

Table 1. Comprehensive summary of individual herbs used in PCOS treatment, highlighting their primary molecular targets, dominant signaling pathways, key hormonal and metabolic effects, and proposed roles within a standardized herbal combination. Each herb was selected for its unique mechanism to maximize therapeutic efficacy while minimizing pathway redundancy.

Herbs	Primary Molecular Target	Dominant Pathway Modulated	Key Hormonal/Metabolic Effects	Suggested Role
Berberine	GLUT4 / AMPK	Glucose metabolism, insulin sensitivity	↓ FBG, ↑ insulin sensitivity, ↓ triglycerides	Insulin/glucose modulator
Curcumin	PPAR-γ / NF-κB	Inflammation, lipid uptake	↓ ROS, ↓ cytokines, ↑ placental lipid transport	Inflammation + placental lipid uptake enhancer
Cinnamon	PPAR-γ / GLP-1	Insulin, GLP-1 (weight loss)	↓ blood sugar, ↑ GLP-1, ↓ testosterone	Weight/BMI modulator
Resveratrol	SIRT1 / AMPK	Autophagy, oxidative stress	↑ oocyte quality, ↓ oxidative stress, ↑ SIRT1	Autophagy & oxidative stress balancer
Myo-Insositol	FSH / Insulin receptors	Follicular stimulation, ovulation	↑ FSH sensitivity, ↑ ovulation rate	Ovulation enhancer
Licorice Root	5α-reductase / Androgens	Androgen suppression, lipid metabolism	↓ testosterone, ↓ BMI	Testosterone & BMI regulator
Spearmint	Testosterone modulation	Androgen reduction, anti-hirsutism	↓ hirsutism, ↓ DHEAS	Androgen/hirsutism regulator
Shatavari	Estrogen receptors	Estrogen balance	↑ cycle regularity, ↓ stress	Estrogen modulator
Chasteberry	Dopamine D2 / LH	LH suppression, cycle regulation	↓ prolactin, ↓ LH, ↑ luteal progesterone	Cycle regulator via dopamine pathway
Tribulus Terrestris	FSH / LH	Folliculogenesis, ovulation	↑ ovulation, ↑ FSH	FSH/LH balancer
Aloe Vera	IGF-1 / Estrogen	Estrogen metabolism, ovary support	↑ endometrial thickness, ↑ estrogen metabolism	Endometrial and estrogen supporter
Green Tea	AMPK / mTOR	Autophagy, inflammation	↓ inflammation, ↑ oocyte quality	Inflammation & autophagy enhancer
Fenugreek	Estrogen receptors / GSH	Estrogen regulation, antioxidant	↓ estrogen dominance, ↑ antioxidant activity	Estrogen detoxifier & antioxidant
Ginger	NF-κB / IL-6	Inflammation, insulin sensitivity	↓ inflammation, ↑ insulin sensitivity	Insulin and inflammation modulator

2.9 *Suggested standardized herbal combination for PCOS*

To reduce variability and improve efficacy across patient populations, it is essential to standardize herbal extracts used in clinical or experimental PCOS treatment. This includes the use of High-purity, quantified extracts (e.g., 97% berberine Hcl), Chromatographic methods (HPLC, LC-MS) for active compound quantification, defined bioactive dosing based on molecular weight and absorption metrics and batch-to-batch quality control to ensure reproducibility.

Such measures are critical to establishing herbal therapies that perform with comparable consistency and safety to pharmaceutical interventions. Additionally, based on complementary molecular mechanisms, a standardized combination of herbs could provide a synergistic, multi-targeted treatment strategy for PCOS. A proposed formulation could include the following ingredients.

1. Berberine (500 mg BID) – Meta-analysis and RCTs in PCOS women using ~1 g/day showed significant improvements in insulin resistance, lipid profile, and ovulation rates, comparable to metformin, with no major side effects (80).

2. Curcumin (500 mg/day with 5 mg piperine) – RCTs in metabolic syndrome/T2DM patients using 500 mg/day with piperine (enhancing bioavailability) for 12 weeks demonstrated reductions in fasting glucose, lipids, inflammation, and BMI (81).

3. Myo-inositol (4 g/day) – Systematic reviews and RCTs consistently employ 4 g/day (2 g BID) in PCOS women, reporting restored ovulation and improved oocyte/embryo quality with pregnancy rates up to 15% in large cohorts (82).

4. Cinnamon (1,000 mg/day) – RCTs with 1–1.5 g/day for 8–12 weeks in PCOS patients showed significant reductions in fasting insulin, HOMA-IR, improved menstrual cyclicity, and favorable lipid changes; 1 g/day chosen for efficacy and tolerability (83).

5. Resveratrol (200 mg/day) – Human studies demonstrate that 200 mg/day is sufficient to activate AMPK and autophagy pathways and reduce oxidative stress, with mild tolerability and absence of significant adverse effects (84).

Each herb and myo-inositol was selected to avoid mechanistic overlap and maximize pathway engagement. This blend may reduce the metabolic, endocrine, and reproductive symptoms of PCOS while decreasing variability compared to pharmaceutical mono-therapies. It is obvious that other combinations can be envisaged as well. Future clinical validation and organoid testing are warranted.

3. Conclusion

PCOS affects ~ 10% of childbearing-aged women worldwide. Of these, as many as 70% will go undiagnosed, which leaves millions without proper treatment (69). In many rural and poor regions, access to a wide variety of prescription medications-including metformin and clomiphene - remains severely limited due to various factors related to cost, availability, and deficiencies in healthcare infrastructure. The lack of access to these prescription-only medications further worsens the challenges of

managing PCOS, leaving many women with few options for treatment.

Herbal supplements might prove to be a significant shift in symptom management for PCOS. The herbal products described in this paper are generally inexpensive and readily available over-the-counter, with fewer serious side effects. Because of the relative paucity of well controlled studies conducted on these herbs, their effectiveness in clinical settings remains undetermined. Being non-regulated, their commercial quality also varies considerably.

Prescription drugs such as metformin, which is known for enhancing insulin resistance, and clomiphene, which is an ovulation inducer, are well-studied and efficacious. However, these medications also carry a greater risk of side effects; more precisely, metformin can cause gastrointestinal disturbances and vitamin B12 deficiency, while clomiphene might lead to mood changes, hot flashes, and severe side effects in the form of OHSS.

Herbal supplements are, in general, less potent and hence less likely to exhibit severe side effects. As an example, berberine and cinnamon for blood sugar control, and shatavari and fenugreek for hormone regulation, cause fewer and less serious gastrointestinal side effects and are more suitable for longer-term administration. Their effectiveness, however, is documented to a lesser extent, compared with conventional drugs. As a starting point, what is required is a fixed rational combination of specific herbs, such that some standardization is introduced into treating PCOS with herbal supplements. Such a formulation is described in this paper. Aside from cost and accessibility, the allure of herbal supplements for treating PCOS is that women who explicitly desire to bear children can afford to wait for months for any effects to occur; i.e. the necessity of instantaneous results do not constitute a limitation for this demographic.

The cost of prescription medications is a significant barrier for many women, and access is particularly difficult in rural or developing regions. Medications like Gonadotropins and flutamide are expensive and often only distributed in areas with a high level of medical care. Herbal supplements, however, are often less expensive and widely accessible from various parts of the world; they are often sold through health food stores or online, and most do not require a prescription. This type of wide accessibility is rendered to be a significantly more attractive alternative to women who have less access to prescription drugs. With increased studies and more clinical trials, herbal supplements may offer a paradigm shift in the management of PCOS.

In the future, a balanced approach, potentially combining both conventional and herbal treatments may offer the best outcomes for managing PCOS depending on individual needs and medical guidance. Greater awareness of the various kinds of treatments could offer a better opportunity for more women, especially in under-resourced regions, to take responsibility for their health and determine what works best for them.

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