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 (1). PCOS is characterized by irregular menstrual cycles, elevated androgen levels, insulin resistance, and polycystic ovaries. Currently, there is no cure for PCOS, so treatment focuses on symptom management. Prescription medications like Metformin, which improves 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 (1-2). Compared to prescription medications, herbal supplements generally cause fewer and less severe side effects, are more affordable, and are widely available without needing 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 less potent but are easier to access and may be a promising alternative for women in regions where conventional medications are scarce or expensive. Further clinical research on herbal supplements and greater awareness of these alternatives could help address the global challenges of PCOS.

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).

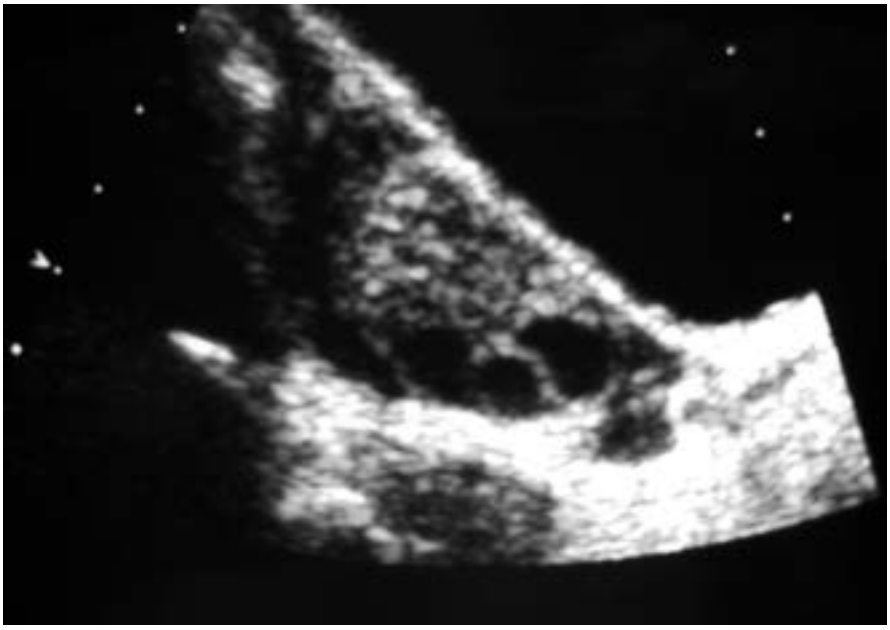

Figure 1: A longitudinal transabdominal ultrasound of an ovary showing multiple peripheral follicles (3).

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 take 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 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, as 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 has 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 issues in 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 what doctors recommend to PCOS patients.This includes reducing sugar and carbohydrates, maintaining weight, and exercising regularly. Weight loss 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 numerous 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 large mental tolls, as women are at higher risk for anxiety and depression. These additional symptoms can necessitate patients to take additional psychiatric drugs. The more 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 even 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 burdens. 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 come from developing countries. For example, prevalence is higher in South Asia —an area where numerous women do not have access to properly handled 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 what is commercially available. Specifically, the cost, effectiveness, and potential for side effects will be compared between widely used prescription medicines and lesser-known natural treatments to provide equitable care alternatives. Additionally, it overviews and evaluates the effectiveness of current practices of PCOS standard of care.

DIABETES

Women with polycystic ovary syndrome (PCOS) are at a higher risk of developing type 2 diabetes compared to those without the condition. 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 leads to insulin resistance 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 number one 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 HbA1c levels (a marker of long-term blood sugar control) by about 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 like GLUT4. GLUT4 transporters are located on the surface of muscle and fat cells, and their activity is crucial for glucose uptake from the bloodstream. Approximately 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 issues 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 might 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.

Ozempic is another medication for diabetes management that has recently emerged. While there is more research going into this medication for PCOS patients, Ozempic (semaglutide) is an injectable prescription medication that is used for managing type 2 diabetes and weight loss. Semaglutide works by mimicking a natural hormone called 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 slows down the rate at which food moves from the stomach to the intestines, helping to prevent rapid spikes in blood sugar and keeping you feeling full longer. 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 issues like nausea and diarrhea, which might be managed with gradual dose adjustments. Fatigue could be severe, affecting the overall well-being of PCOS patients, particularly if combined with other symptoms of PCOS. Less common but more serious side effects include the potential risk of pancreatitis and thyroid issues. As of May 27, 2024, Ozempic is not FDA-approved for Polycystic Ovary Syndrome (PCOS). However, some people with PCOS are prescribed Ozempic 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 is another issue, as Ozempic is more readily stocked in urban pharmacies, leaving rural areas with fewer options and potentially leading to delays in getting the medication. Furthermore, limited access to healthcare providers in rural regions can make it difficult for lesser privileged 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, can have similar effects on 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 for its potential benefits in managing metabolic disorders, including type 2 diabetes and PCOS.

Berberine works through several mechanisms to improve metabolic health (18). Berberine enhances insulin sensitivity by activating the AMP-activated protein kinase (AMPK) pathway –this helps the body use insulin more effectively and stabilize blood sugar levels (18). In addition to this, up to 70% of women with PCOS have 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 like dyslipidemia. It can also be useful in exerting anti-inflammatory effects, therefore reducing inflammation often linked with PCOS (18).

Research on berberine for PCOS is promising but still limited. While some studies report 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) might range from $20-40 (21). Prices can fluctuate based on where you purchase it and whether the product is organic or includes additional ingredients. However, Berberine is widely available as an over-the-counter supplement, thus 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 add to 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 (a marker of long-term blood sugar control) (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. As for side effects, some individuals may experience stomach upset or

nausea. In rare instances, it can cause allergic reactions if introducing cinnamon into one's diet 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). Additionally, 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 praised 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 like 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 for most people, but it can cause some side effects. Common issues 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. You can find it 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 may be on the higher end.

Comparison of 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 result in more optimal results. Utilizing natural supplements can lower glucose levels and improve insulin sensitivity similar to pharmaceuticals, while also helping other health problems such as cholesterol. Research into effective medications for type 2 diabetes has been ongoing for decades, yielding numerous advances. However, 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.

CYCLE AND FERTILITY

Polycystic ovary syndrome also significantly impacts menstrual cycles and fertility in many women. About 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 ultrasounds. 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, commonly referred to as Clomid, is a medication often prescribed for women with polycystic ovary syndrome 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 about 70-80% of women will ovulate after taking Clomid, and about 30-50% will conceive within six cycles of treatment (30). However, its effectiveness can vary based on factors like 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). Furthermore, 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. On the lower side, it often ranges from $10 to $100 for a typical cycle but can increase to up to $1000 depending on the brand (31). Clomid is only available through doctors’ prescriptions as well, and while it is a commonly used first-line treatment for ovulation induction, it's not without risks and may not be the right fit 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 polycystic ovary syndrome (PCOS) who are struggling with infertility.

Regarding its mechanism of action, Letrozole works by inhibiting the aromatase enzyme, which is responsible for converting androgens like testosterone into estrogens. By lowering Estrogen levels, letrozole reduces negative feedback on the hypothalamus and pituitary gland, leading to an increase in follicle-stimulating hormone (FSH) and luteinizing hormone (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 Ovarian hyperstimulation syndrome (OHSS), and bone density reduction with long-term use, though this is more relevant for breast cancer treatment than fertility (32). Letrozole is only available with a doctor's prescription. The retail price of letrozole can vary, typically around $544. However, the final cost may be influenced by factors such as insurance coverage, your specific treatment plan, and the pharmacy you choose. For instance, if purchased without insurance, letrozole may cost approximately $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 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 impact 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. Finally, 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 hails 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 staple 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 luteinizing hormone (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).

Numerous studies have explored chasteberry's role in managing PMS symptoms, irregular menstrual cycles, and conditions like polycystic ovary syndrome. Many women report reductions in breast pain, mood swings, and 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).[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.

Comparison of Cycle Fertility

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 like Clomiphene Citrate and Letrozole have shown significant efficacy in promoting ovulation and enhancing fertility in women with PCOS in the past. However, they come with potential side effects such as Ovarian Hyperstimulation Syndrome (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. 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. Their mild side effect profile, lower cost, and over-the-counter availability make them appealing options for women seeking alternative or complementary treatments.

ANTI-ANDROGENS

Anti-androgens are compounds that block the effects of androgens, which are male hormones like 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 (excess hair growth), 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 blockades inhibit androgen-driven effects, such as hair growth and acne. Androgen production inhibitors are substances that reduce the amount of androgens produced in the body, often by interfering with enzymes involved in androgen synthesis, like 5-alpha reductase, or by inhibiting ovarian androgen production (40). 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 (41). 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 polycystic ovary syndrome (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 (like 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, such as 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 (absence of periods), 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”. 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 issues. In women, it’s often prescribed for hormonal acne, excess body hair, and polycystic ovary syndrome (PCOS) due to its anti-androgen properties (72). Like 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 (excessive hair growth), and alopecia (hair loss). 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 dihydrotestosterone (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 around $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 (male hormones like testosterone) 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 polycystic ovary syndrome (PCOS).

Flutamide works by blocking androgen receptors, preventing androgens (like testosterone) 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 (hirsutism) and severe acne caused by high androgen levels (48). However, its use in women is less common due to potential side effects (see below). 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 with 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.

As for its mechanism of action, the 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 Traditional Chinese Medicine for their immune-boosting, anti-inflammatory, and adaptogenic properties. It's 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 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 issues, 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 around $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 (like turmeric or omega-3 fatty acids) to help reduce symptoms (52).

Comparison of Anti-Androgens

In conclusion, 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. These prices are significantly lower when compared to the price range of pharmaceutical drugs. However, on the downside, the effectiveness of the Chinese Peony and Red Reishi Mushroom has not yet been thoroughly studied or researched through clinical trials, making it a less reliable source than prescription-based drugs.

HORMONAL REGULATION

To manage the symptoms of PCOS, a variety of treatment strategies have emerged, 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 comparison examines the efficacy of both COCs and herbal alternatives, focusing on their mechanisms of hormonal regulation, risks, side effects, and overall accessibility.

Combined Oral Contraceptives (COCs) are a common treatment for women with polycystic ovary syndrome (PCOS), especially those seeking to regulate their menstrual cycles, manage acne, reduce excess hair growth (hirsutism), 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 luteinizing hormone (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 levels of androgens (male hormones), 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 Combined Oral Contraceptive Pills varies depending on insurance coverage and how you choose to pay (out of pocket or through government aid). Some government insurance plans, like Medicaid, cover the cost of COCs, however, 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 for their potential to manage symptoms naturally. These herbs work differently from synthetic hormones like those in combined oral contraceptives (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 like 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 (male hormones). 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 (such as testosterone) lead to symptoms like acne, hirsutism (excess hair growth), 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 traditional Chinese medicine (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. Insulin resistance is a key issue in many women with PCOS, and 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 (excessive hair

growth). For more of a detailed overview of its mechanism of action, Curcumin has been studied for its potential benefits in managing PCOS, particularly for improving insulin sensitivity and glycemic control (62). Research indicates that curcumin enhances insulin-mediated glucose uptake by activating pathways such as 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 profiles (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 (blood thinners) should consult their doctor before using turmeric supplements. Turmeric is widely available throughout the world, through cooking, or additional uses (59).[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, meaning the body absorbs less of it. 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's also employed for medicinal purposes, especially in traditional medicine systems, including treating digestive issues, 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 (excessive hair growth), 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, dihydrotestosterone (DHT). This reduction is crucial because DHT is responsible for many of the symptoms associated with androgen excess. Additionally, Luteinizing hormone (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) published in *Phytotherapy Research* (2007) 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 like 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.

Comparison of Hormonal Regulation

Both Combined Oral Contraceptives (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 come 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. Add somewhere in this paragraph that they are similar in price. This is the only category where prescriptions aren’t significantly more expensive.

CONCLUSION

PCOS affects roughly 10% of childbearing-aged women worldwide, which covers over 116 million 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.

With the information in this research paper, other herbal supplements might prove to be a significant shift in symptom management for PCOS. All these products are generally inexpensive and readily available over-the-counter, with fewer serious side effects. Because of

the absence of studies conducted on the subjects, their effectiveness in clinical settings remains undetermined; their quality also varies considerably among such products.

Prescription drugs such as Metformin, which is known for enhancing insulin resistance, and Clomiphene, which is an ovulation inducer, are well-studied and efficient. 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 have so many 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.

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 extremely 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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