EMBRACING NATURE'S SOLUTIONS: A COMPREHENSIVE REVIEW OF NATURAL TREATMENTS FOR PCOS MANAGEMENT

Shaffintaj Mohamed Rafik[1,3], Kannan Raman[1,3]*, Kavinkumar MC[2,3], Bharathiraja Anthony Samy [1,3,] Deepen Natarajan[1,3], Suresh Velayutham[1,3], Senthilkumar Natesan[1,3]

[1]Department of Pharmacology, JKKMMRFs Annai JKK Sampoorani Ammal College of Pharmacy, B.Komarapalayam. Tamil Nadu, India - 638183.
[2]Department of Pharmaceutical Chemistry, Vellalar College of Pharmacy, Maruthi Nagar, Thindal, Erode, Tamilnadu – 638012, India.
[3] Affiliated by The Tamil Nadu, Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

***Corresponding Address**
Dr. Kannan Raman*****
Mail - kannanraman320@gmail.com

ABSTRACT:

PCOS refers to a hormonal condition that results in enlarged ovaries and little cysts around the periphery. Polycystic ovarian syndrome is manifested by amenorrhea, hirsutism and obesity associated with cysts. PCOS is a syndrome not a disease characterized by a variable clinical features and has potential multiple etiologies. Causes of PCOS was not clearly known. May be the lifestyle changes plays a major role in PCOS, obesity and mainly linked to elevated insulin resistance, which causes diabetes and may leads to cardiovascular disorders and hypertension. Genetics also plays a role in this syndrome. The nutrients involved in treatment and their mechanism of action was also studied. The currently available drugs in the market and their effectiveness in treatment also discussed. This review focus on the various herbal medicines and natural products utilized as a polycystic ovarian syndrome therapy. Focusing drug targets also the molecule that are closely associated with the disease by using In-silico studies. We analyze about the in-vivo studies and role of letrozole as an inducing agent in study of PCOS.

Key words: PCOS, Medicinal Plant, letrozole,

1. INTRODUCTION

Polycystic ovarian syndrome was initially discovered by Stein and Leventhal in 1935.Stein-Leventhal syndrome is another name for it that is expanded.Polycystic ovarian syndrome was manifested by amenorrhoea , hirsutism and obesity associated with cysts. PCOS is a syndrome not a disease characterized by a variable clinical features and has potential multiple etiologies.[1,2] It is an heterogenous endocrinopathy affects the human of the reproductive age. Infertility is a serious problem which women struggles to get pregnant. Here the management helps to lower the body weight, lower the insulin levels, restore fertility and to regularize menstruation. Generally ovarian follicles consists of egg cells that gets matured and released during the ovulation.[2] But in PCOS due to hormonal imbalance the ovarian follicles prevents the eggs to mature and delays or inhibits the ovulation. The polycystic ovary consists of immature multiple cysts and affects menstrual cycle[3]

1.1 EPIDEMEOLOGY

Hyperandrogenism is the major cause of PCOS. Over 80% of women in reproductive age affected with PCOS, among them 70% of women shows the clinical symptoms of excessive androgens like Hirsutism.10%-15%of women shows Acne on their face which is the specific clinical marker of Hirsutism[4]. Around 30% of women shows unwanted hair growth. Comparing with previous year prevalence is increased about 10-13%.[5]

1.2 ETIOLOGY

Causes of PCOS was not clearly known. May be the lifestyle changes plays a major role in PCOS, obesity and mostly linked to elevated insulin resistance, which causes diabetes and may leads to cardiovascular disorders and hypertension. Impaired pituitary function causes altered in LH/FSH levels leads to hyperandrogenism. Genetic factors like CYP21 gene mutation also plays a role in PCOS. Stress also plays major role in PCOS[6]

1.3 PATHPHYSIOLOGY

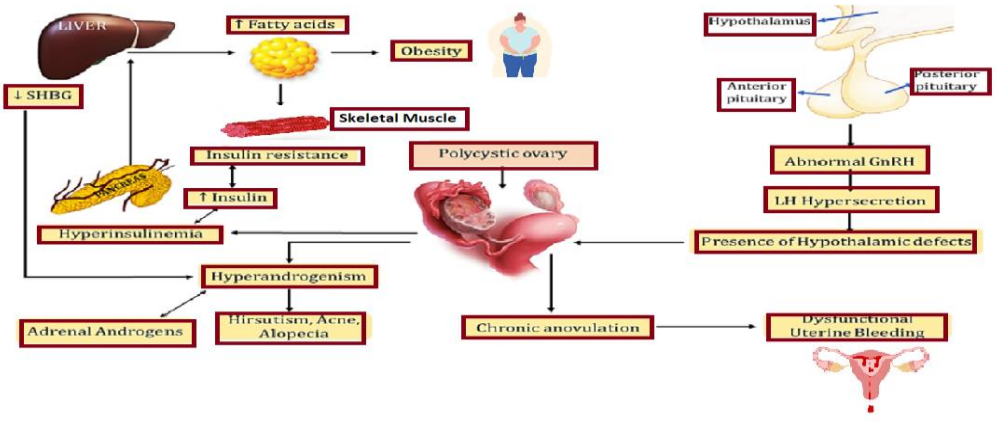

Figure 1: Pathophysiology of PCOS

Increased in frequency of GnRh (gonadotrophin releasing hormone) pulses and LH(leutinizing hormone) increases, with this LH theca cells are stimulated by insulin to produce androgens. The synergistic action of insulin with androgens decreases the hepatic production of hepatic SHBG, which results in rise in testosterone level. The ovaries of PCOS was 2-5 times than the normal size around 2-9mm in size. [7,8]

1.4 NORMAL OVARY Vs POLYCYSTIC OVARY:

Egg cells are normally found in ovarian follicles and are released during ovulation. Anomalies in hormone levels stop follicles in polycystic ovarian syndrome from developing and maturing to release eggs.[9] Rather, the ovaries become overpopulated with these immature follicles. [Twelve or more of these follicles may be present in affected women. With aging, these follicles typically become fewer in number.[10] Certain studies support the theory that the main reproductive symptoms of the illness are typically caused by excess ovarian androgen.In addition to explaining the cutaneous manifestations of PCOS, ovarian hyperandrogenism can also explain all of the histopathologic characteristics of the polycystic ovary: a high intraovarian androgen concentration can explain the polycystic appearance of the ovaries, ovarian enlargement, capsular thickening, thecal/stromal hyperplasia, and luteinization, in addition to enhancing the recruitment of primordial follicles into the pool of growing small pre-antral and antral follicles. Additionally, it can hinder the selection of the dominant follicle. [11]

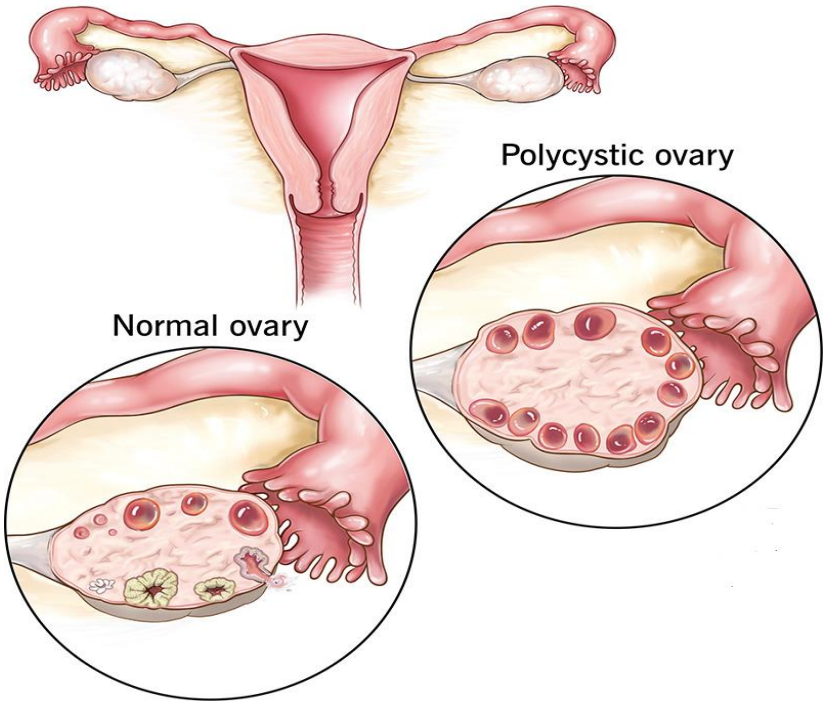

Figure 2 : Normal Ovary Vs Polycystic ovary

1.5 GENETICS AND PCOS:

PCOS is associated with four phenotypes: A, B, C, and D. PCOS phenotypes A and B are traditional. Menstrual disruption, elevated insulin secretion and insulin resistance, and an increased risk of metabolic dysfunction are described characteristics of these phenotypes. [12] This phenotype has a higher risk of hepatic steatosis. Additionally, there is a notable increase in anti-Mullerian hormone levels. [13] Ovulatory PCOS is the term used to describe phenotype C, which is defined by high hirsutism scores. NonhyperandrogenicPCOS, or phenotype D, is typified by normal androgen levels along with marginally raised levels of other endocrine systems and metabolic abnormalities. An increased level of sex hormone binding globulin is one of the endocrine findings. [14] Women who belong to Phenotype D experience periodic aberrations in their usual menstrual cycle. Patients from the same family have varying genetic susceptibilities to different genes.[15,16]

1.6 HERBS AS A TREATMENT OF PCOS

Many approaches, such as laproscopy and allopathic medications, are utilized to treat PCOS. Through a medical technique called laproscopy, ovarian cysts are removed.[18] Presently, PCOS is treated with medications including nafarelin, troglitazone, clomiphene, metformin, and spironolactone.[19] But if these medications are used for an extended period of time, they can have serious side effects as well, such as irregular menstruation, weight gain, nausea, vomiting, and gastrointestinal problems, as well as increased insulin resistance, poor compliance, ineffectiveness, and more contraindications.[20] Due to its adverse effects, patients with cardiovascular problems, women of reproductive age, obese individuals, and nursing moms are more vulnerable when using these medications.[21] Therefore, it is imperative to find and create medications derived from plants that are far more effective than the current allopathic medications. The usage of herbal remedies by medical practitioners to treat PCOS has changed significantly in recent years. Herbal medications consist of whole plant extracts or any portion of a plant that has a significant therapeutic impact and, in comparison to conventional therapy, less adverse effects. [22] They play a big part in recovery, prevention, and treatment. Herbal medications are intricate treatments that have the potential for both antagonistic and synergistic interactions amongst constituents. [23] They are less likely to have side effects than allopathic medications and are crucial for the treatment of PCOS. It is safer and more effective to treat PCOS and decrease the processes that lead to the formation of cysts in PCOS patients by regularly using herbs. [24] Herbal treatments are currently widely used to treat a variety of chronic illnesses, including PCOS. PCOS may be treated more successfully with the use of natural remedies and dietary changes. Various herbs will work against PCOS in different ways, such as by boosting follicle stimulating hormone (FSH), inhibiting prolactin levels, and having anti-androgenic properties. [25,26]

1.7 LETROZOLE INDUCED PCOS

Letrozole is a non-steroidal aromatase inhibitor which decreases the estrogen level. [27] It is specifically used in estrogen sensitive breast cancer. Recent study reveals that the letrozole causes 90% of infertility reporting in an ovulation. [28] This reduces amount of estrogen and increases the FSH level. Increased levels of FSH leads to growth of additional follicles and causes hormonal imbalances in body. [29] FSH stimulates granulosa cell, proliferation and aromatase production. LH stimulates androstenedione production by theca cells that diffuses into granulosa cells, aromatase converts androstenedione to estrogen. Letrozole inhibits the CYP450 aromatase enzyme and decreases the circulating estrogen. [30,31]

2. ROLE OF NUTRIENTS IN PCOS:

2.1. Inositol

The inositol stereoisomers, myo-inositol (MI) and D-chiro-inositol (DCI), which belongs to class of hexahydroxycyclohexanes, which has the same molecular formula as glucose. [32] Inositol acts as a secondary messenger for many hormones like insulin and follicle stimulating hormone FSH. [33] Any defects in this pathway leads to the impaired insulin sensitivity and causes insulin intolerance. By using inositol the insulin resistance can be treated and hence used in treatment of PCOS.[34,35]

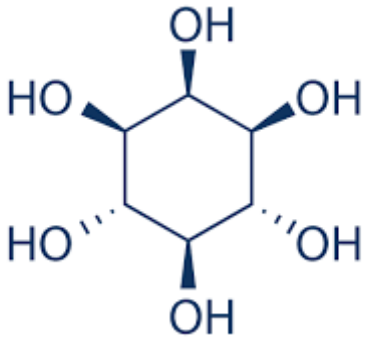

Figure 3: Inositol

2.2. Vitamin A

Oocyte maturation, steroid metabolism, and antioxidant activity are all supported by vitamin A, a dietary supplement that is composed of retinol, retinoids, and retinoic acid.[36] Theca interna cells treated with trans retinol exhibited elevated levels of dehydroepiandestrone and mRNA accumulation of cytochrome P450 17α hydrxylase (CYP17), an enzyme implicated in the generation of androgens and the biosynthesis of retinol.[37] Elevated levels of retinol-binding protein 4 (RBP4) are linked to obesity and impaired glucose metabolism in women with PCOS who are overweight[38] Measurements of RBP4 expression in isolated subcutenous and omental adipose tissue from PCOS-affected women were reported in another RBP4-based study.[39]The authors proposed that increased 17β estrodiol could

upregulate the RBP4 gene, which would then contribute to the changed gonadal and adrenal steroid profile.[40]

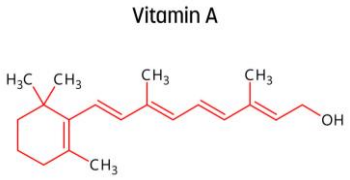

Figure 4: Vitamin A[41]

2.3 Alpha-Lipoic Acid (a-LA)

It works on the mechanism of free radical scavenging. It is the important cofactor of citric acid cycle and regulates the body weight. Recent studies reveals that the alpha lipoic acid increases the ovarian functions like decreased oarian cysts and improved menstrual cycles.[41,42]

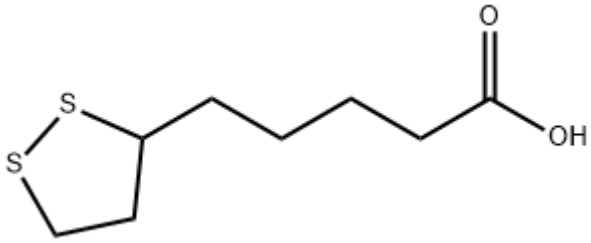

Figure 5: Alpha-Lipoic Acid (a-LA)

2.4 Bioflavanoids

It is made up of plant-found polyphenolic chemicals. Antioxidant, antidiabetic, antiestrogenic, anti-inflammatory, and antiproliferative qualities are demonstrated by flavonoids. [43] They acts be reducing oxidative stress and thereby reduces the cellular damage and decreases the cyst formation.[44]

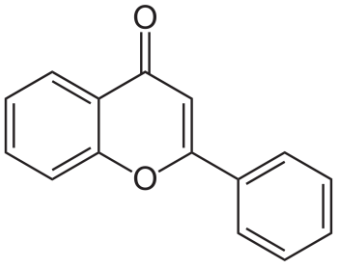

Figure 6: Bioflavanoids

2.5 Carnitine

Carnitine is the quartenary ammonium compound which is found in the gluose metabolism,free radical mechanism and fatty acid metabolism.PCOS were reported with low carnitine levels when compared with non PCOS by increasing the cartinine levels PCOS symptoms is reduced and decrease in oxidative stress.[45]

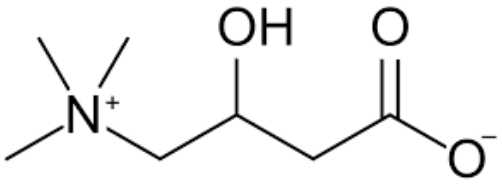

Figure 7: Carnitine

3. DRUGS USED IN TREATMENT OF PCOS

3.1 Oral contraceptives

In approximately two-thirds of hirsute patients, (OCs) inhibit adrenal and ovarian androgen production as well as hair development. [46] There is less ovarian androgen production when the progestin component lowers LH.Lower levels of free testosterone are the consequence of the estrogen component's increased hepatic synthesis of SHBG.Under the skin, estrogens inhibit 5α-reductase, which reduces the conversion of testosterone to DHT.[47]

3.2 Medroxyprogesterone Acetate-

Hirsutism can be effectively treated with oral or intramuscular dose of medroxyprogesterone acetate (MPA).By lowering gonadotropin release and GnRH production, it directly impacts the hypothalamic-pituitary axis by lowering ovarian output of testosterone and estrogen.The levels of free and total androgen are much lower despite a drop in SHBG.[48]

3.3 Gonadotropin

The distinction between androgen derived from ovarian and adrenal sources may be made possible by the use of GnRH agonists. In both idiopathic hirsutism and hirsutism owing to PCOS, treatment with leuprolide acetate administered intramuscularly every 28 days reduces hirsutism and hair diameter.A marked and specific suppression of ovarian androgen levels occurs.[49]

3.4 Glucocorticoids

Dexamethasone, a glucocorticoid, is used to treat PCOS patients with adrenal hyperandrogenism or combined adrenal and ovarian hyperandrogenism.In the beginning, dexamethasone dosages as low as 0.25 mg administered nightly or every other night are utilized to decrease DHEAS concentrations below 400 μg/dL. Ketoconazole: This medication inhibits the main cytochromes that are steroidogenic. When taken at a modest dosage of 200 mg daily, it can considerably lower testosterone, androstenedione, and estimated free testosterone levels.[50]

3.5 Spironolactone

is a particular aldosterone antagonist that binds to aldosterone receptors in the kidney's distal tubular area in a competitive manner. DHT is inhibited competitively at the intracellular receptor level. - An increase in androgen catabolism (with an increase in the peripheral conversion of testosterone to estrone) - Suppression of testosterone production by a decrease in CYP enzymes. The inhibition of 5α-reductase activity in the skin.The usual dosage is 50–100 mg twice a day.[51]

3.6 Cyproterone Acetate

With strong antiandrogenic qualities, cyproterone acetate is a synthetic progestin that is produced from 17-OHP. Competitive suppression of DHT and testosterone at the androgen receptor level is the main mechanism of action of cyproterone acetate. ethinyl estradiol 30 to 50 mg daily on cycle days 5 to 26, and cyproterone acetate 100 mg daily on days 5 to 15. Administered in a reverse sequential regimen.[52]

3.7 Flutamide

Pure nonsteroidal antiandrogen fluftamide is authorized for the treatment of advanced prostate cancer. Its mode of action involves preventing androgens from attaching to their nuclear sites in the targeted tissues. Greater doses (250 mg taken two or three times day) may make up for the decreased potency, even though it has a poorer affinity to the androgen receptor than spironolactone or cyproterone acetate.[53]

3.8 Finasteride:

This particular inhibitor of type 2 5α-reductase enzyme activity is called finasteride.Despite having different effects on androgen levels, finasteride (5 mg daily) and spironolactone (100 mg daily) produced a similar significant improvement in hirsutism in a research.After 7.5 mg of finasteride per day for six months, the majority of the hirsutism improvement was observed with finasteride medication.[54]

3.9 Intense Insulin

Due to the possibility that hyperinsulinemia contributes to anovulation linked to PCOS. If used alone or in conjunction with other forms of treatment, insulin sensitizers can cause an endocrine balance that favors ovulation and pregnancy. For non-insulin-dependent diabetes, metformin (Glucophage) is a commonly used oral biguanide antihyperglycemic medication [55].

4. Plant-based carbon dots (CQDs used for Treatment of PCOS.

Plant-based carbon dots (CQDs) are an intriguing field of research, and their use in medical treatments, including PCOS, is growing. While there are few studies that explicitly link plant-based carbon dots to PCOS therapy, various forms of plant-derived carbon dots have been investigated for their general health benefits and possible therapeutic applications.

S.No	Plant Name	Carbon Dot Name	Mechanism of Action	Reference
1	Moringa oleifera	Moringa-derived Carbon Dots	Antioxidant, anti-inflammatory, and hormonal regulation.	[56]
2	Camellia sinensis	Green Tea Carbon Dots	Antioxidant, anti-inflammatory, and insulin-sensitizing.	[57]
3	Ginkgo biloba	Ginkgo Carbon Dots	Anti-inflammatory and enhances insulin sensitivity.	[58]
4	Curcuma longa	Curcumin Carbon Dots	Anti-inflammatory, antioxidant, and insulin regulation	[59]
5	Coriandrum sativum	Coriander Carbon Dots	Antioxidant, anti-inflammatory, and supports hormonal balance.	[60]
6	Coffea arabica	Coffee Bean Carbon Dots	Antioxidant, anti-inflammatory, and regulates glucose metabolism.	[61]
7	Graptopetalum paraguayense	Graptopetalum Carbon Dots	Antioxidant and helps in metabolic regulation	[62]
8	Hibiscus sabdariffa	Hibiscus Carbon Dots	Antioxidant and supports hormonal balance.	[63]
9	Boswellia serrata	Boswellia Carbon Dots	Anti-inflammatory and enhances insulin sensitivity.	[64]
10	Echinacea purpurea	Echinacea Carbon Dots	Antioxidant and immune-modulating effects.	[65]

11	Aloe vera	Aloe Carbon Dots	Antioxidant, anti-inflammatory, and insulin regulation.	[66]
12	Thymus vulgaris	Thyme Carbon Dots	Antioxidant, anti-inflammatory, and insulin regulation.	[67]
13	Nigella sativa	Nigella Carbon Dots	Anti-inflammatory, antioxidant, and enhances insulin sensitivity.	[68]
14	Rosmarinus officinalis	Rosemary Carbon Dots	Antioxidant and supports metabolic processes.	[69]
15	Allium sativum	Garlic Carbon Dots	Antioxidant, anti-inflammatory, and helps in metabolic regulation.	[70]
16	Bacopa monnieri	Bacopa Carbon Dots	Neuroprotective, anti-inflammatory, and regulates hormonal imbalance.	[71]
17	Cinnamonum verum	Cinnamon Carbon Dots	Antioxidant, anti-inflammatory, and enhances glucose metabolism.	[72]
18	Zingiber officinale	Ginger Carbon Dots	Anti-inflammatory, antioxidant, and supports metabolic health.	[73]
19	Piper nigrum	Black Pepper Carbon Dots	Enhances bioavailability of other compounds and supports metabolic functions.	[74]
20	Silybum marianum	Milk Thistle Carbon Dots	Antioxidant and supports liver health and hormonal balance.	[75]
21	Lippia citriodora	Lemon Verbena Carbon Dots	Antioxidant and anti-inflammatory, supports metabolic health.	[76]
22	Prunella vulgaris	Self-Heal Carbon Dots	Antioxidant and supports metabolic and immune health.	[77]
23	Mentha piperita	Peppermint Carbon Dots	Antioxidant and supports digestive and metabolic functions.	[78]
24	Acer saccharum	Maple Leaf	Antioxidant and supports	[79]

		Carbon Dots	overall metabolic balance.	
25	Malva sylvestris	Mallow Carbon Dots	Anti-inflammatory and supports metabolic health.	[80]

5. Role of natural product in PCOS

Natural products play a significant role in managing Polycystic Ovary Syndrome (PCOS) by providing anti-inflammatory, antioxidant, and insulin-sensitizing effects. Compounds found in herbs, fruits, and vegetables can help regulate hormonal imbalances, improve metabolic profiles, and alleviate symptoms. Their use as complementary therapies offers a holistic approach to PCOS management alongside conventional treatments.

Herb/Plant	**Mechanism of Action**	**References**
Spearmint (Mentha spicata	Anti-androgenic effects, reduces hirsutism.	[81]
Cinnamon (Cinnamomum cassia)	Improves insulin sensitivity, regulates blood glucose levels.	[82]
Vitex (Vitex agnus-castus)	Regulates menstrual cycles, balances hormones.	[83]
Licorice (Glycyrrhiza glabra)	Anti-androgenic effects, may reduce elevated testosterone levels.	[84]
Fenugreek (Trigonella foenum-graecum)	Enhances insulin sensitivity, supports glucose metabolism.	[85]
Rehmannia (Rehmannia glutinosa)	Supports endocrine health, alleviates PCOS symptoms.	[86]
Astragalus (Astragalus membranaceus)	Supports endocrine function, enhances immune health.	[87]
Shatavari (Asparagus racemosus)	Supports female reproductive health, balances hormones.	[88]
Dandelion (Taraxacum officinale)	Anti-inflammatory, supports liver function.	[89]
Green Tea (Camellia sinensis)	Rich in antioxidants, improves insulin sensitivity.	[90]
Ginger (Zingiber officinale)	Reduces inflammation, regulates blood sugar levels.	[91]
Turmeric (Curcuma longa)	Contains curcumin, anti-inflammatory, supports hormonal balance.	[92]
Burdock Root (Arctium lappa)	Supports liver function, balances hormones.	[93]
Dong Quai (Angelica sinensis)	Regulates menstrual cycles, alleviates menstrual discomfort.	[94]
Maca Root (Lepidium	Balances hormones, improves energy levels.	[95]

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Chaste Tree (Vitex agnus-castus)	Normalizes menstrual cycles, reduces PMS symptoms.	[96]
Hawthorn (Crataegus spp.)	Supports cardiovascular health, may help with hypertension.	[97]
Aloe Vera (Aloe barbadensis)	Supports digestive health, has anti-inflammatory effects.	[98]
Gotu Kola (Centella asiatica)	Improves circulation, supports cognitive function.	[99]
Ginkgo Biloba (Ginkgo biloba)	Improves blood circulation, supports cognitive health.	[100]
Black Cohosh (Actaea racemosa)	Regulates hormones, alleviates menstrual symptoms.	[101]
Evening Primrose Oil (Oenothera biennis)	Contains gamma-linolenic acid, supports hormonal balance.	[102]
Red Clover (Trifolium pratense)	Contains phytoestrogens, supports hormonal balance.	[103]
Motherwort (Leonurus cardiaca)	Supports reproductive health, regulates menstrual cycles.	[104]
Hops (Humulus lupulus)	Contains phytoestrogens, helps with hormone balance.	[105]
Psyllium Husk (Plantago ovata)	Supports digestive health, may help with glucose regulation.	[106]
Jasmine (Jasminum sambac)	Offers calming effects, supports reproductive health.	[107]
Sarsaparilla (Smilax officinalis)	Potential hormone-balancing properties.	[108]
Kudzu (Pueraria lobata)	Contains phytoestrogens, helps with hormone balance.	[109]
Holy Basil (Ocimum sanctum)	Reduces stress, supports endocrine health.	[110]
Clover (Trifolium spp.)	Contains isoflavones, supports hormonal balance.	[111]
Licorice Root (Glycyrrhiza glabra)	Balances hormones, supports adrenal health.	[112]

CONCLUSION:

Polycystic Ovarian Syndrome (PCOS) is one of the most common female endocrine disorders which may leads to infertility. Herbal drugs have promising role in treatment of PCOS and shows steady effect with minimal side effects. Herbal drugs enhance immunity of the body also regularize menstrual cycle without fluctuating hormonal level. The mechanisms underlying the beneficial effects of herbal medicines on PCOS were found to be associated with anti-inflammation, anti-oxidative stress, inhibition of autophagy and/or apoptosis, and ovarian nerve growth factor reduction. Herbal medicines and Natural Carbon dots are thought to be promising resources in the development of effective therapeutic agents for PCOS.

Further studies that include methodological quality assessment and quantitative synthesis of outcomes.

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