

# Efficacy of Herbal Medicines in Management of Polycystic Ovarian Syndrome: A Scoping Review

## Review Article

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### Abstract

Polycystic ovarian syndrome (PCOS) is most frequently stated gynaecological and metabolic disorder. Many pharmacological drugs have been used to treat PCOS with numerous side effects, which have resulted in the selection of alternative treatments from natural sources. Hence, this review aims to investigate the efficacy of medicinal herbs in regularising ovulation, hyperandrogenism, and other metabolic condition in PCOS. To conduct this review, extensive literature was searched between 2010 to 2021, from PubMed, Scopus, Google scholar, and ProQuest. Based on the keywords “polycystic ovarian syndrome” or “medicinal herbs” or “ovarian cysts” or “hyperandrogenism” or “insulin resistance”. Irrelevant studies were excluded from the database. Twelve clinical studies and nine animal studies were included in the review paper. Treatment included herbs such as “*Cinnamomum zeylanicum* Meism, 1864”, “*Curcuma longa* L. 1753”, “*Tribulus terrestris* L. (1753)”, “*Cimicifuga racemosa* (L.) Nutt., 1818” and “*Vitex agnus-castus* (1753)”. These bioactive compounds have shown to reduce luteinising hormone, progesterone, oestradiol and fasting insulin levels. The evidence supports *Vitex agnus-castus* and *Cimicifuga racemosa* have a synergistic impact in management of amenorrhea or oligomenorrhea, infertility, and ovulation. cinnamon spp. and *Curcuma longa* improve insulin resistance, dyslipidemia, and type 2 diabetes mellitus. *Tribulus terrestris* alone and in combination with “*Withania somnifera* Dunal, 1852” & “*Nardostachys jatamansi* (D.Don) DC, 1830” has shown promising effects but in the latent stage. Based on the evidence, it may be suggested herbal medicines are effective, alone or in alternative form, in amelioration of the symptoms of PCOS.

**Keywords:** Polycystic ovarian syndrome; Medicinal herbs; *Cinnamomum*; *Curcuma longa*; *Cimicifuga racemosa*, *Vitex agnus-castus*.

### Introduction

Polycystic ovarian syndrome (PCOS) is one the most common heterogeneous, endocrine, and genetic disorders affecting reproductive-aged females. Polycystic means “multiple cysts” and it causes clusters of small, pearl-sized cysts in ovaries, which are filled with fluid sacs and contain immature eggs. Women with PCOS produce higher amounts of male androgen hormones, leading to various clinical symptoms such as irregular menstruation, excess androgen hormone, acne, hirsutism, weight gain, insulin resistance, ovarian cysts, and infertility (1). The exact prevalence rate of PCOS is not known precisely, therefore estimated prevalence in reproductive females is 5-10%. According to Rotterdam criteria-2003, the prevalence will be raised to 10 percent in the general population (2).

The pathogenesis shows mounting evidence that insulin resistance (IR) and hyperinsulinemia are associated with the development of PCOS. Hyperandrogenism and IR in PCOS women are associated with disruption of the hypothalamic-pituitary-ovarian axis, leading to irregular menstruation and anovulation (3).

Various treatment strategies have been applied among PCOS women, such as lifestyle modification, ovulation induction, and supplementation with vitamin D, folic acid and myoinositol, high testosterone therapy, an insulin sensitizer, and surgical therapy (4-5). Insulin sensitizing agents, metformin, clomiphene citrate (CC), and thiazolidinediones, have been reported to be successful in the treatment of PCOS (6). These drugs have been shown to exhibit various side-effects such as nausea, vomiting, and diarrhea. In this situation, medicinal herbs emerge as a promising substitute in the treatment of PCOS. Medicinal herb including *Cinnamomum zeylanicum*, *Curcuma longa*, *Tribulus terrestris*, *Cimicifuga racemosa* and *Vitex agnus-castus* plays an important role as a natural anti-inflammatory and antioxidant in regulating metabolism, hypertension, and hyperlipidemia (7). Additionally, these herbs exhibit steroidogenic responses and estrogen-receptor

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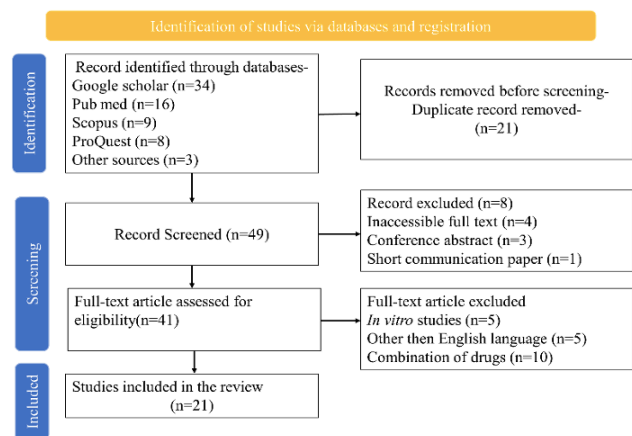
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expression towards PCOS which improve glucose absorption and lower androgen levels (8).

Therefore, the aim of the present review was to compare different approaches of herbal medicine in management of PCOS and their efficacy in regulating ovulation, hyperandrogenism, insulin resistance, and hyperlipidemia in human and animal study.

### Methodology

**Figure 1:** Represent flow diagram of PRISMA 2020 for inclusion of clinical studies



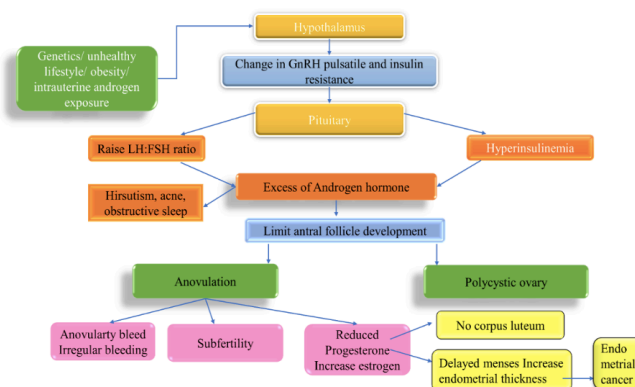
The international databases were searched through Google scholar, PubMed, Scopus, and ProQuest from 2010 to 2021 in order to obtain human and animal studies. Preliminary literature search revealed that five herbal medicines namely Cinnamon, *Curcuma longa*, *Tribulus terrestris*, *Cimicifuga racemosa* and *Vitex agnus-castus* have been found with significant beneficial effects regarding ovulation, hyperandrogenism, oligomenorrhea, insulin resistance, dyslipidemia. These herbal medicines with a demonstrated mechanism of effect have been investigated in the present study. The keywords used while investigation were “polycystic ovarian syndrome” or “PCOS” or “medicinal plants” or “ovarian cysts” or “hyperandrogenism” or “insulin resistance” or “human trial” or “animal trial” or “Cinnamon” or “*Curcuma longa*” or “*Tribulus terrestris*” or “*Cimicifuga racemosa*”, or “*Vitex agnus-castus*”. The inclusion criteria included comprehensible English articles, clinical trials, randomized controlled trials (RCTs), and the effectiveness of commercial medicine on human and animal models. On the other hand, irrelevant, non-English, case reports, reviews, multiple combinations of drugs and short communication papers found during the search were excluded. All articles were searched via electronic process, and only full-text articles which were found appropriate for the study were investigated. Finally, a total of 21 articles were listed as shown in Figure-1.

### Pathogenesis

Stein and Leventhal’s original article stressed a high ratio of luteinizing to follicular-stimulating hormone (FSH) leading to PCOS (normal ratio is 1:1 which increases is to 3:1). However, some studies suggest an increased frequency of GnRH which

stimulates theca cell to produce excessive androgen hormone; lowers the level of FSH (defect in the late luteal phase); insulin resistance through a post-receptor defect in skeletal muscles and fat tissue;  $\beta$ -cell dysfunction in the pancreas; and obesity (9-10). Although, the exact origin and effect of the development of PCOS is incapable to govern. Genetic inheritance was reported in women with monozygotic twins and first-degree relatives of women with PCOS which depicts increase chances of attaining abnormal metabolic syndrome (11-12). However, absence of male PCOS phenotype, variation in research methodology, case-control studies which rather account multifaceted factors of PCOS, infertility, unfamiliar studies all lead to lower the validity of inheritance of genetic factor. Moreover, it is documented that obesity increases menstrual problems and excess androgen levels, whereas decreasing body weight lowers its clinical symptoms. Hyperinsulinemia in association with pancreatic  $\beta$ -cell dysfunction leads to the prevalence of a number of diseases, such as dyslipidemia, hypertension, type 2 diabetes, endothelial dysfunction, atherosclerosis plaques, and heart disease. Insulin further stimulates theca cells of the ovaries to over-regulate testosterone, which led to clinical signs of hyperandrogenism (13).

**Figure 2:** Shows the pathophysiology of the polycystic ovarian syndrome



### Discussion

#### *Cinnamomum zeylanicum*

“*Cinnamomum zeylanicum* Meism, 1864”, is the dried inner bark belonging to the Lauraceae family and is tropically grown in southern India and Sri Lanka. The most common species are *Cinnamomum zeylanicum*, *Cinnamomum cassia*, and *Cinnamomum camphora*. The volatile oil extracted from bark, leaf and root of the cinnamon plant have same array of monoterpene hydrocarbons. However, they differ in their primary constituent: cinnamaldehyde, eugenol and camphor are the basic compound present in bark, leaf and root oil, respectively (14). *Cinnamomum* is one of the most important spices used in traditional medicine for its anti-diabetic properties (15). It has three main components- cinnamaldehyde, cinnamic acid tannin, and methyl-hydroxy chalcone polymer (16). Various studies support cinnamon supplementation reduce insulin resistance, fasting blood sugar (FBS), and serum

lipid profile in type 2 diabetes mellitus (T2DM) patients (17-18), impaired glucose tolerance (19) and nonalcoholic fatty liver (20) in patients with different amount of cinnamon supplementation.

A study conducted by Hajimonfarednejad *et al.* investigate the efficacy of cinnamon powder on IR, anthropometry, glucose and lipid profile, and androgens in women with PCOS. In this study, 1.5g cinnamon per day in combination with progesterone was intervened for 12 weeks, significant reduction was seen in fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in cinnamon supplemented group. One patient reported rash and itchiness after 5 days of treatment. The adverse effect disappears soon after withdrawal from treatment (21). Another study reported 84 obese PCOS women supplemented with cinnamon capsules 500mg of three times a day for 8 weeks, finding report a fall in insulin, glucose, HOMA-IR, serum triglyceride (TG), LDL-C, and total cholesterol (TC) levels and a raise in HDL-C in the cinnamon-treated group (22). Kort *et al.* study randomized 45 PCOS women and intervene with 125mg of cinnamon to the treatment group and the control receive placebo. During 6 months of

intervention, the patient reported a regular menstrual cycle and confirmed progesterone secretion. Testosterone levels were elevated slightly in the both groups (23).

Talaat *et al.* in 2018 mention a study that evaluated added value of cinnamon to metformin in 233 women with PCOS. This study was mainly targeted toward restoring regular cycle meanwhile, they were able to reduce the number of pre-diabetic patients, oligomenorrhea or amenorrhea, BMI, waist-to-hip ratio, and serum luteinizing hormone (LH) level after 6 months of intervention with metformin+ cinnamon (24). A clinical study was performed to understand the effect and mechanism of cinnamon for 45 days in rats with PCOS. As a result, cinnamon can restore oestrous cycle and ovary morphology, reduce serum testosterone level, insulin, and insulin-like growth factor 1 (IGF-1) level, and also increase insulin-like growth factor-binding protein 1 (IGFBP-1) in plasma and ovary in dehydroepiandrosterone (DHEA) -induced PCOS rats (25). At last, the above studies demonstrate that cinnamon has a potential role in improving glucose homeostasis hyperlipidemia, as well as regulating oligomenorrhea.

**Table 1: Role of medicinal herbs in insulin resistance, oligomenorrhea, hyperandrogenism, and polycystic ovarian syndrome**

S.No.	Scientific name	Author/ Country	Sample size	Treatment dose	Duration	Significant outcome	Adverse effect
1	<i>Cinnamomum zeylanicum</i>	Hajimonfarednejad <i>et al.</i> (21) Iran	66 women	1.5g cinnamon powder (3x/d)	12 weeks	Cinnamon in combination with progesterone therapy was well tolerated and shown significant reduction after intervention to fasting insulin, glucose level and increase in HDL-C level.	Rashes and itching were reported in 1 patient (Excluded).
2	<i>Cinnamomum zeylanicum</i>	Borzoei <i>et al.</i> (22) Iran	84 women	500mg cinnamon capsule(3x/d)	8 weeks	Cinnamon improves serum glycaemic index and lipid profile in PCOS women. Significant decline in weight, serum insulin, lipid profile and increased in HDL-C level.	None
3	<i>Cinnamomum zeylanicum</i>	Kort <i>et al.</i> (23) New York	45 women	125mg cinnamon capsule (3x/d)	6 months	Treatment with cinnamon significantly improves menstrual cycle. Sample from luteal phase progesterone confirmed ovulatory cycle.	None
4	<i>Cinnamomum zeylanicum</i>	Talaat <i>et al.</i> (24) Saudi	233 women	Metformin 500mg and cinnamon 112mg(3x/d)	6 months	Cinnamon and metformin shown beneficial effect in weight reduction, redistribute body fat and normalize menstrual cycle. Findings were significant in relation to body weight, lipid profile, number of prediabetic patients.	None
5	<i>Cinnamomum zeylanicum</i>	Dou <i>et al.</i> (25) China	60 Prepuberal C57BL/6 mice	DHEA+ cinnamon extract 10mg/100g b.w.	20-days	Cinnamon was able to restore the oestrous cycle and ovarian morphology, with significant reduction in serum insulin and testosterone, while lower IGF-1 level and increase IGFBP-1 level in plasma.	None

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6	<i>Curcuma longa</i>	Reddy <i>et al.</i> (32) India	30 Wistar rats	Low dose 100mg/kg and high dose 200mg/kg curcumin extract	15-days	Curcumin has shown positive effect similar to CC in letrozole induced PCOS rats. Significant decline in uterine weight, serum insulin, lipid profile, testosterone level, and increase in serum hormone. Low dose increased the antioxidant activity and lipid peroxidation of thiobarbituric acid reacting species (TBARS), while high dose decreased TBARS level. Disappearance of cysts and normal sized healthy follicles were found in intervention group.	None
7	<i>Curcuma longa</i>	Shrivastava <i>et al.</i> (33) India	24 Adult Swiss albino rats	175mg/kg turmeric extract + 150mg/kg Metformin	30-days	Turmeric extract shows promising effect when compared to metformin in treating PCOS. Substantial improvement in body weight, serum glucose, lipid profile, and reduction in plasma interleukin-6, with considerable increase in sex hormones and antioxidant level.	None
8	<i>Curcuma longa</i>	Heshmati <i>et al.</i> (34) Iran	72 women	500mg curcumin (3x/d)	12 weeks	Curcumin supplementation has shown beneficial role in PCOS patients, with significant decrease in DHEA and FPG level and increase in oestradiol level.	None
9	<i>Curcuma longa</i>	Jamalia <i>et al.</i> (35) Iran	60 Women	500mg curcumin/day	12 weeks	Administration of curcumin has beneficial effects on women with PCOS. Significant reduction in body weight, BMI, serum insulin, insulin resistance, lipid indices and increase in PPAR-g and LDLR gene expression.	None
10	<i>Curcuma longa</i>	Sohaie <i>et al.</i> (36) Iran	60 women	500mg curcumin (2x/d)	6 weeks	Curcumin supplementation was able to improve serum insulin and QUICKI in treatment group, while HOMA-IR improve slightly.	Gastrointestinal side effect (n=3) in patients.
11	<i>Tribulus terrestris</i>	Parikha <i>et al.</i> (39) India	12 Swiss mice	500mg/kg ethanolic fruit extract.	25-days	Supplementation with TT restore body mass, serum glucose, insulin sensitivity, and lipid profile with fewer side-effects. Additionally, fewer number of cysts, healthy antral follicles, and newly formed corpus luteum.	None
12	<i>Tribulus terrestris</i> + <i>Withania somnifera</i>	Saiyed <i>et al.</i> (40) India	24 Wistar rats	Treated with combination extract (198mg/kg)	28-days	Combination of TT+ WS shows significant effect on regularising the oestrus cycle in letrozole induced PCOS rats. Reduction in blood glucose, total cholesterol, serum hormonal level, ovarian and uterine weight. Histopathology of ovary returned to normal after treatment.	None



13	<i>Tribulus terrestris</i> + <i>Nardostachys jatamansi</i>	Sandeep <i>et al.</i> (41) India	36 Sprague Dawley rats	NJand TTwith low dose (5mg)+ high dose (10mg).	72-days	Combination of TT+ NJ extract has positive effect on oestradiol valerate induced PCOS-rat. Menstrual cyclicity restored to normal, steroid hormones, and also significant improvement in corpus luteum status. Disappearance of follicular cysts with high dose of NJ.	None
14	<i>Cimicifuga racemosa</i>	Shahin <i>et al.</i> (46) Egypt	206 women	120mgKli madynon®/ day	3 successive cycle & 2 months of rest.	Adding CR to clomiphene significantly improve menstrual cycle, endometrium thickness and pregnancy rates, also maintain serum sex hormones (increasing oestrogen and progesterone and decreasing LH).	None
15	<i>Cimicifuga racemosa</i>	Kamel(47) Egypt	100 women	20mgKlim adynon®/ 2x/d	3 successive cycles	<i>c. racemosa</i> can be used as an alternative to clomiphene for inducing ovulation in PCOS women with lesser side effects. Significant difference was seen in serum hormonal level, ovulation, endometrial thickness and rate of pregnancy.	3 cases of hyperstimulation were reported.
16	<i>Cimicifuga racemosa</i>	Magedet <i>al.</i> (48) Egypt	150 women	20mgKlim adynon®	-	Adding <i>c. racemosa</i> to clomiphene is an alternative to oestrogen in improving number of dominant follicles, endometrial thickness, ovulation and pregnancy rate.	None
17	<i>Cimicifuga racemosa</i>	Mehasenet <i>al.</i> (49) Egypt	100 women	CC 50mg+ C.racemos a 20mg (2x/d)	-	Significant improvement in ovulatory cycle number of dominant follicles, endometrial thickness and pregnancy outcome when administrated with <i>c. racemosa</i> .	None
18.	<i>Vitex agnus-castus</i>	Shahnaziet <i>al.</i> (54) Iran	80 women	Vitex agnus capsule (standardized by Aucubin 2, 1-3, 3mg).	3 months	Vitex agnus plant is as effective as low dose contraceptive in improving the menstrual cyclicity and significantly lowering serum DHEA-S level in PCOS women.	None
19	<i>Vitex agnus-castus</i>	Elshaeret <i>al.</i> (55) Egypt	40 Sprague-Dawley strain rats	Metformin (52.5mg/kg) + DHEA (6mg/100g) +Vitex extract (13mg/kg/day).	30-days	Vitex and metformin combination has shown harmonious effect in treatment of PCOS rats. Met+ VAC+ DHEA treated group showed significant improvement in antioxidant levels, sex hormone and morphological changes in ovaries.	None
20	<i>Vitex agnus-castus</i>	Hamza <i>et al.</i> (56) Arabia	40 Wistar Albino rats	VACextrac t and VPS both receive 8mg/kg dose	15-days	Vitex agnus plant has multiple benefits similar to metformin in treating PCOS. Significant reduction in lipid profile, sex hormones, and raise in HDL-C and antioxidant activity.	None

21	<i>Vitex agnus-castus</i>	Feyzollahi et al. (59) Iran	32 Wistar rat	Vitex agnus (365mg/kg)	30-days	Treatment with vitex agnus not only reverse the sex hormones (LH/FSH ratio and testosterone) to normal, but also maintained the level of KISS-1 gene to normal level. Further, decrease the number and size of cysts while restoring the ovulation cycle.	None
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### Curcuma longa

Turmeric or “*Curcuma longa L. 1753*”, an herbaceous perennial plant of the ginger family widely cultivated in Iran, Malaysia, India, China, Thailand, and Polynesia cuisines (26). Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1-6-heptadiene-3,5-dione), also called diferuloylmethane, is the main polyphenol found in *Curcuma longa* and other curcumin species (27). The traditional properties of turmeric have been known for thousands of years due to its antioxidant, anti-inflammatory (28), antihyperlipidemic, and hypoglycemic properties (29). It has also been shown to protect porcine ovarian granulosa cells (30), and estrogenic effects in breast cancer cell lining (31).

A study was reported by Reddy et al. to evaluate the beneficial effect of curcumin among letrozole-induced PCOS rats, and its effect was compared with CC. Thirty female Wistar rats were administered into doses of 1mg CC for 15 days. Curcumin treatment was able to normalize fasting blood glucose, hemoglobin A1C (HbA1c) serum testosterone, serum TC, TG, and LDL also elevate HDL-C levels and hence, displaying anti-diabetic, insulin resistance, and antihyperlipidemic properties. Antioxidant activities of superoxide dismutase (SOD), catalase was potentially restored after treatment with curcumin. Further absence of cyst, regular-sized healthy follicles, and appearance of corpora lutea with the clearly differentiated oocyte, resulting in a normal ovulation cycle (32). Another similar study was performed inducing PCOS with Letrozole in 24 Swiss albino rats in which the therapeutic potential role of turmeric extract as well as circulating adiponectin was identified in comparison with metformin. Turmeric+ metformin was both given at a dose of 175mg/kg and 150mg/kg orally for 30 days. Turmeric has shown promising effects in glycaemic status, lipid & hormonal profile, antioxidant, and ovarian morphology in letrozole induced PCOS rats, so also resulting into hypoglycemia, and antihyperlipidemic, estrogenic, antioxidant properties, all of which help in normalizing ovarian cell dysfunction, and ovulation (33).

Heshmati et al. reported using 500 mg of curcumin three times a day reduces the amount of DHEA & fasting plasma glucose (FPG), and even increases the level of oestradiol in PCOS women. Curcumin was found to be insignificant in glycaemic response, dietary habits, anthropometric, and hormonal profile (34). In similar study 60 women were randomized in two groups. The intervention group received 500mg/day of curcumin for 12 weeks and the control group received a placebo. Curcumin was

significantly able to lower glycaemic response, body weight, BMI, and the effect of serum lipid profile except for triglycerides and very low-density cholesterol (VLD-C) levels in PCOS patients. Additionally, it was able to improve gene expression of peroxisome proliferator-activated receptor gamma (PPAR-g) and low-density lipoprotein receptor (LDLR) but did not affect glucose transporter type-1 (GLUT-1) expression. PPAR-g has pleiotropic effects in enhancing glucose homeostasis, insulin sensitivity, and controlling gene expression which plays a vital role in glucose and lipid metabolism (35).

In another study, curcumin was administered for a period of 6 weeks among PCOS women. Significant improvement in serum insulin, quantitative insulin sensitivity check index (QUICKI), and marginal difference in HOMA-IR in the curcumin-treated group. Three patients reported gastrointestinal side effects in treatment group, but no patients were drawn from the study. At last, curcumin showed many beneficial effects similar to CC and metformin among human and animal models, also it was found to be safe for consumption by patients suffering from PCOS (36).

### Tribulus Terrestris (TT)

“*Tribulus terrestris L. (1753)*”, commonly known as Gokharu or Gokshur or puncture vine, belongs to the family of *Zygophyllaceae* of which three species, i.e., *Tribulus cistoides*, *Tribulus alatus*, and *Tribulus terrestris* are found in India. It is an annual shrub distributed across subtropical regions of India, China, USA, Mexico, Spain, and Bulgaria. It has been used for a long time in Ayurvedic medicines as tonic, diuretic, antidiabetic, aphrodisiac, anti-urolithic, palliative, astringent, stomachic, hypolipidemic, cardiogenic, anti-inflammatory, hepatoprotective, anticancer, antibacterial, anthelmintic, and larvicidal (37). Tribulus contain three active group of phytochemicals: Dioscin, protodioscin, diosgenin, and other. The hormone balancing effect of Bulgarian TT for women makes this herb suitable for premenstrual syndrome and menopause (38).

In 2019, a study conducted by Parikha et al. investigated the role of TT in regulating insulin resistance in Letrozole-induced PCOS rats. Tribulus extract given at a dose of 500mg/kg body weight for 25 days. It was able to restore serum glucose levels, improve insulin sensitivity, body mass, and hormonal profile and decrease adipose tissue deposition. Additionally, in PCOS mice due to insulin resistant state, inadequate glucose absorption in the ovary is responsible for abnormal follicle growth and

subsequently anovulation. However, which was later restored by TT extract, thus exerting antidiabetic properties (39).

Another study was proclaimed to assess the efficacy of two drugs TT and “*Withania somnifera* Dunal, 1852”(WS) on letrozole-induced PCOS mice. The test group was intervened with a combination of TT and WS (198mg/kg). Results concluded that a combination of drug maintains normalcy in the estrus cycle, ovarian weight, oestradiol, LH, follicle-stimulating hormone (FSH), and testosterone in serum level. The hydroalcoholic extract showed a significant anti-androgenic effect by reducing testosterone levels, and also prevented ovarian dysfunction in rats. Though, this property was due to the presence of phytoestrogens in a combination with test drugs (40). Similar study demonstrated the efficacy of two drugs i.e., TT and “*Nardostachys jatamansi* (D.Don) DC, 1830”(NJ) to estimate anti-androgenic activity in *in vivo* PCOS rat models. Finding concluded that the combination of these two drugs resulted in a normalizing the oestrous cycle, decrease steroid hormone profile, and overall ovarian dysfunction. Histo-morphology and vagismear report that some follicular cysts were present in low-dose NJ and high-dose TT, however, no cysts were observed with high-dose NJ (41). However, further analysis is required to develop a novel therapeutic supplement.

### ***Cimicifuga racemosa***

Black cohosh (rhizomes of *Actaea racemosa* or “*Cimicifuga racemosa* (L.) Nutt., 1818”) is a perennial plant that belongs to the family of buttercup and inherited from North America. It contains pharmacological active compound such as triterpene glycosides (acetin, 23-epi-26- deoxyactein, cimicifugoside), phenolic acids, flavonoids, volatile oils, tannins and other (42). Black cohosh is among the most studied herbal medicine in treatment of menopausal symptoms, such as hot flushes and night sweat, tinnitus, heart palpitations, irregular sleep, irritability, nervousness, and vaginal dryness (43-44). Clinical evidence indicates that it has a potential to reduce pituitary secretion of LH by directly acting upon the hypothalamus altering gonadotropin-releasing hormone (GnRH) (45).

Black cohosh is commercially available in an oral film-coated tablet, prepared from its dry extract (Klimadynon®; Bionorica; Neumarkt i.d.OBF Germany) and, is used in following research. A study reported by Shahnazi *et al.*, investigated the effect of *Cimicifuga racemosa* drug treatment when added to CC induction cycles in PCOS patients. The intervention included oral CC at a dose of 150mg/day from days 3-7 of the cycle. The experimental group received the oral tablet of *cimicifuga* rhizome dry extract preparation (Klimadynon) at a dose of 120mg/day from day 1 till the time of pregnancy test or starting of menstruation. In both groups luteal phase support was given in the form of oral progestin (micronized progesterone), beginning from day 2 after HCG injection till the start of menstruation or end of 12 weeks gestation.

Administration with *c. racemosa* was able to improve the rate of pregnancy, lower mid-cycle LH, and increase serum progesterone and estrogen in the other half, so also thicker endometrium and shorter ovulation cycles (46). In another study, Klimadynon treatment lower LH and LH/FSH ratio, improve ovulation cycle, increase endometrial thickness, and pregnancy rate. Further, allowing better menstruation, and implantation, also alleviating sensitivity toward circulating FSH and improving follicle growth. Overall, three cases of hyperstimulation were reported: one mild of *c. racemosa*, two cases in moderate CC group (47).

In another clinical trial, addition of phytoestrogens (Klimadynon) to CC as an alternative to oestradiol has increased the number of dominant follicles, endometrial thickness, and both menstruation and rate of pregnancy (48). Mehasen *et al.* also reported phytoestrogen plant (Klimadynon) supplementation along with CC improved endometrial thickness, no. of dominant follicles, ovulation, and pregnancy rate (49). However, Klimadynon enhances ovulation in women with PCOS with slight adverse effects compared to clomiphene, although more studies are required to evaluate its optimum dose and duration of this protocol.

### ***Vitex agnus-castus* (VAC)**

“*Vitex agnus-castus*(1753)” or chaste berry is a deciduous shrub belonging to the family of *Verbenaceae*, is a native to the Mediterranean, Europe, and Central Asia. Chemical compounds present in VAC are flavonoids (vitexin, casticin), alkaloids, progestins, iridoid glycosides, and volatile, and essential fatty acids (50). It is used to treat premenstrual syndrome, cyclic mastalgia, premenstrual dysphoric disorder, infertility, lactation difficulties, bacterial, and fungal infection (51-52). Vitex is one of the most important herbs for PCOS treatment since it stimulates and normalize pituitary gland function and assist in regulating LH secretion, improves fertility in case of anovulation and lower estrogen and androgen hormone (53).

A study by Shahnazi *et al.* in 2016 aimed to compare the effect of low-dose contraceptives and VAC in enhancing paraclinical and clinical signs of PCOS. In this study, 80 PCOS were triple-blind randomized and divided into two groups- vitex agnus and low dose contraceptive (LD). Results concluded that both treatments effectively normalize the duration of menstruation cycle, lowered serum DHEA-S levels in PCOS women, and have mild side-effects (54). In another study, Elshaer *et al.* aimed to examine remedial effect of VAC-metformin and establish the therapeutic use of herbal combination on PCOS subjects. Finding conclude that Metformin+ VAC mix have beneficial effect on PCOS as they both augment most of parameters, such as glucose, cholesterol, FSH, prolactin, glutathione, SOD, and malonaldehyde (MDA) level and additionally, improve ovarian tissues with metformin (55). Similarly, Hamza *et al.*, report that VAC either alcohol extract or pharmacological extract reversed the level of insulin, glucose, hormones, lipid profile, and oxidative stress (MDA and Catalase levels) in comparison to PCOS rats (56).



In line with above study, Feyzollahi *et al.* in 2019 reported that animals were orally administered with a dose of 365mg/kg for the VAC group and PCOS + VAC group for 30 days. Treatment with vitex agnus significantly lowered LH/FSH ratio, testosterone level and increase in estrogen level. Moreover, *Vitex agnus-castu* relieve the symptoms related to PCOS and facilitate ovulation cycle. Kisspeptin-1 gene (KISS-1), a neurotransmitter produced by the hypothalamus, function for the binding and activation of G protein-coupled receptor (57). It regulates GnRH and geared numerous aspects of female fertility, including ovulation, menarche, and breastfeeding through positive and negative feedback mechanisms of sex hormones (58). The level of KISS-1 expression was significantly elevated in PCOS rats, although after VAC treatment reversed the level of sex hormone also maintained normalcy in the KISS-1 level in the hypothalamus (59). Vitex acts as a modifier of KISS-1 expression and is prescribed to present various pharmacological benefits, such as hypoglycemic, antihyperlipidemic, and antioxidant effects and is considered as important in management of PCOS.

## Conclusion

Polycystic ovarian syndrome is a frequent medical condition stated among reproductive-age-females, such as hyperandrogenism, oligomenorrhea, infertility, hormonal changes, and metabolic disorder (such as insulinemia, dyslipidemia, & T2DM). The current review evaluated the efficiency of five medicinal herbs in treatment of PCOS. The following evidence supports *Vitex agnus-castus* and *Cimicifuga racemosa* have a synergistic impact in management of amenorrhea or oligomenorrhea, infertility, and ovulation in treatment of PCOS. *Cinnamomum* and *curcuma longa* improve metabolic hormones in PCOS has shown promising effects. However, due to scarcity of studies based on the effect of *Tribulus terrestris* alone and in combination with *Withania somnifera* & *Nardostachys jatamansi*, these results are inconclusive. Further, based on the evidence reflected from different studies it may be suggested that herbal medicine may be used as an alternative or in conjunction with ongoing treatment for PCOS.

## Abbreviations

HOMA-IR- homeostatic model assessment of insulin resistance; FBS- fasting blood sugar; FPG- fasting plasma glucose; T2DM- Type 2 diabetes mellitus; QUICKI- quantitative insulin sensitivity check index; IGF- insulin-like growth factor; IGFBP-1- insulin-like growth factor-binding protein, BMI- body mass index; TC- total cholesterol; TG- triacylglycerol; LDL-C- low density lipoprotein cholesterol; HDL-C- high density lipoprotein cholesterol; VLD-C- very low density cholesterol; DHEA- dehydroepiandrosterone; LH- luteinizing hormone, FSH- follicle-stimulating hormone; SOD- superoxide dismutase; PPAR-g- peroxisome proliferator-activated receptor gamma; LDLR- low-density lipoprotein receptor; KISS-1-

kisspeptin-1 gene; CC-clomiphene citrate; TT- *Tribulus terrestris*; WS- *Withania somnifera*; NJ-*Nardostachys jatamansi*; and VAC- *Vitex agnus-castus*.

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