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Review Article

A Review on Herbal Medicinal Plant for Treatment of Polycystic Ovarian Syndrome (PCOS)

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ABSTRACT

Infertility due to polycystic ovarian syndrome (PCOS) is a worldwide problem that is increasing at alarming rates. It is characterized by chronic anovulation, polycystic ovaries, and hyperandrogenism leading to symptoms of irregular menstrual cycles, hirsutism, acne and infertility. Insulin resistance and elevated levels of male hormones (androgens) are associated with PCOS. The sedentary lifestyle, lack of exercise and dietary variations and stress etc., are also the contributory factors. Various plants like Panax ginseng, Punica granatum, Curcuma longa, Cinnamomum zeylanicum Tribulus terrestris, Symplocos racemosa, Trigonella foenum-graecum, Cocus nucifera etc., proved active in the treatment of PCOS. In this review, attempts have been made to summarize the important medicinal plants which are used in treatment or prevention of PCOS. Special attention is given to the role of insulin resistance and the potential utility of insulin sensitizers in management of PCOS.

Keywords: Polycystic ovarian syndrome (PCOS), Pathophysiology of pcos, Screening methods of pcos,

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. It is recognized by the presence of enlarged ovaries with multiple small cysts and a hypervascularized androgen secreting stroma. The clinical symptoms include menstrual abnormalities, polycystic ovary, obesity, infertility, hairy, acne, and hyperandrogenism[1]. The polycystic ovary syndrome is a clinical diagnosis characterized by the presence of two or more of the following features: chronic oligo-ovulation or an-ovulation, androgen excess and polycystic ovaries[2].

World Health Organization (WHO) estimates that PCOS has affected 116 million women (3.4%) worldwide in 2012[3]. Polycystic ovary syndrome (PCOS) is a heterogeneous disorder of unknown etiology affecting 5%-10% of women of reproductive age[4]. Globally, prevalence estimates of PCOS are highly variable, ranging from 2.2% to as high as 26%. In India, experts claim 10% of the women to be affected by PCOS[5]. PCOS are strongly interlinked by the pathogenesis of various individual disorders; they may be broadly classified into endocrine dysfunction, reproductive dysfunction, metabolic dysfunction and biochemical dysfunction[6]. It is also associated with psychological impairments including depression and other mood disorders. Most women with PCOS are also overweight or obese, further enhancing androgen secretion while impairing metabolism and reproductive functions and possibly favoring the development of the PCOS[7]. Metabolic abnormalities such as dyslipidemia, insulin resistance, therefore, diseases including diabetes, obesity, cancer and infertility as well as coronary heart diseases could be seen along with PCOS[8]. Reactive oxygen species and antioxidants remain in balance in normal individual but when this balance is disturbed, oxidative stress develops[9]. Which may lead to different disorders. Increased oxidative stress contributes to the risk of cardiovascular disease in women with PCOS[10].

Risk factor[11]

- Family history of PCOS
- Family history of diabetes
- Family history of infertility
- Obesity
- Fast food diet habits
- Lack of physical exercise
- Stress

PATHOPHYSIOLOGY OF PCOS

The Gonadotropic releasing hormone is secreted or synthesized Luiteinsing hormone (LH) and Follicle stimulating hormone (FSH). A less amount of intraovarian androgen is use for normal follicular growth. The follicular development provides by FSH and stimulating aromatase enzyme it promotes granulose cell conversion of androgen to oestrogen. LH is initiate of oocyte maturation by inducing theca cell production.

PCOS condition increases LH level and decreasing level of FSH causes to produce more androgen and reduced level of aromatase enzyme with immature follicle development. Excessive androgen in PCOS is related of abdominal fat that leading to Hyperinsulinemia and Dyslipidemia. Increase theca cell androgen production, Hyperinsulinemia reduces sex hormone binding globulin (SHBG) to increases circulating testosterone levels[12].

Screening Methods of Pcos

Androgen-Induced Rodent Models of PCOS[13]***:***

Hyperandrogenism is the primary manifestation of PCOS. One etiologic hypothesis of PCOS is that exposure to excessive androgens early in life leads to PCOS in adult hood. It was reported more than 3 decades ago that elevated concentrations of circulating androgens in the rodent affected ovarian follicular maturation and cyst formation. Several androgens have been used to induce an acute PCOS condition in rats through daily injection or subcutaneous implants, including dehydroepiandrosterone (DHEA), testosterone propionate (TP), and 5a-dihydrotestoterone (DHT). It is important to note that there is some inconsistency between studies in the reporting of endocrine hormones and ovarian histology in different models. In addition, several studies have not assessed Cardiometabolic parameters, and effects of daily androgen injection and/or treatment on physiologic indices such as body weight, stress indicators, or food intake are not usually reported. In these rodent models the pathological induction of PCOS is transient and dependent on androgen treatment. Hence the re-establishment of normal reproductive/ovarian cycling occurs after cessation of andro- gen administration.

DHEA-induced PCOS[13]***:*** Dehydroepiandrosterone is the first androgen to rise in the female peripubertal period. It has been demonstrated that nearly 50% of follicular-synthesized T can be derived from circulating DHEA, and 25% of patients with PCOS demonstrate supranormal circulating DHEA concentrations. Dehydroepiandroster-one was first used by Roy et al. to induce PCOS in rats. Typically, prepubertal rats, aged approximately 22 days, are injected daily with DHEA (6 mg/100 g body weight, dissolved in 0.2 mL of sesame oil) for up to 20–27 days. After treatment, rats become acyclic and anovulatory.

Ovarian Morphology: Dehydroepiandrosterone-induced rats develop varied severity of cystic ovaries, with multiple follicular cysts ranging in size from 0.45 to 2.2 mm in diameter, and these have degeneration of granulose cell layers. The ovarian tunica capsule is not thickened, and the ovarian weight of DHEA-treated rats is increased significantly.

Endocrine hormone profile: Serum DHEA, T, E_2, FSH, LH, and PRL concentrations are significantly increased in DHEA-induced rats compared with control animals, whereas no changes in plasma FSH and LH concentrations have been reported by other groups.

Cardiometabolic abnormalities: Wang et al. showed that fasting serum glucose and insulin concentrations were in- creased in DHEA-induced rats. The resistin messenger RNA level of white adipose tissue was elevated, which may induce obesity-mediated insulin resistance (IR) in this model.

Summary: The DHEA-induced model can be used to reflect early DHEA-related hyperandrogenemia, anovulation and cystic ovaries, and development of aberrations in insulin/ glucose metabolism.

TP-induced PCOS[14]***:*** Testosterone is used to induce polycystic ovaries in immature female rats. In this protocol, 21-day-old animals are injected daily with TP (1 mg/100 g body weight dissolved in propylene glycol) for up to 35 days.

Ovarian morphology: The TP-induced rats have large multiple cystic follicles, hyperthecosis, and a thickened tunica capsule. Corpora lutea fail to develop at 56 days of age, in contrast to control animals. The proportion of preantral follicles increases after TP treatmen, which may be associated with increased early follicular development, as observed in human PCOS.

Endocrine hormone profile: Serum T, LH, and PRL levels are increased, whereas FSH, P, and E_2 levels are decreased in TP- treated rats.

Cardiometabolic abnormalities: TP-treated rats have normal to decreased fasting glucose concentrations, and insulin was increased, leading to a signif- icantly reduced glucose/insulin ratio. The results of these studies suggest that it is possible that excess T may lead to hyperinsulinemia.

Summary: The TP model is a direct model of hyperandrogenemia, T-induced anovulation and cystic ovaries, and development of impaired insulin/glucose metabolism.

DHT-induced PCOS*(15):* DHT, a nonaromatizable androgen, can induce both ovarian and metabolic aberrations in rodents. Three-week-old rats (juvenile) are implanted subcutaneously with 90-day continuous-release pellets containing 7.5 mg DHT (daily dose, 83 mg). Plasma DHT concentrations are elevated 1.7-fold in treated compared with control animals. Irregular ovarian cyclicity and polycystic ovaries are evident after 11–13 weeks of the DHT treatment.

Ovarian Morphology: Ovaries of DHT-treated rats display an increased incidence of atretic and cystic follicles, with reduced granulsa cell layers and hyperthecosis of internal cell layers. Interestingly, the ovarian weight of the DHT- treated animals is decreased, which is unlike other androgen-induced models and human PCOS (depending on the phenotype, for example not all cases present with enlarged ovaries).

Endocrine hormone profile: The plasma concentrations of T and E_2 are within the normal range, which is not representative of hyperandrogenemic phenotypes of PCOS, and P levels are diminished, indicating anovulation.

Cardiometabolic abnormalities: In addition to ovarian dysfunction, DHT-treated rats present with metabolic disturbances, including increased body weight associated with intra-abdominal adipose tissue, decreased insulin sensitivity (assessed by euglycemic– hyperinsulinemic clamp), and elevated plasma leptin concentrations. Despite these meta- bolic changes, which are consistent with PCOS and the metabolic syndrome in women, the DTH-induced model does not develop dyslipidemia. Approximately 70%of women with PCOS are dyslipidemia; therefore, the DHT-treated rodent model, which is resistant to blood lipid changes, may not be representative of this common phenotype of PCOS.

Summary: The DHT model mimics the actions of T and indicates androgen receptor–mediated effects. Although it does not demonstrate hyperandrogenemia, it does have irregular cyclicity and cystic ovaries, which may be used to represent the normoandrogenic phenotype of PCOS in women. The DHT-induced model also provides a model to explore the development of aberrations in insulin, glucose, leptin metabolism, and adiposity in PCOS.

Letrozole-Induced (Aromatase Inhibitor) Rodent Model of PCOS(15)

Aromatase is the key enzyme that converts T and androstenedione into E_2 and estrone, respectively. It is widely expressed in human tissues, such as placenta, ovary, and testis. Reduced aromatase activity in the ovary is one of the pathophysiologic hypotheses of PCOS development. Letrozole is a nonsteroidal aromatase inhibitor that reduces conversion of androgens to estrogens in the ovary, resulting in increased T and decreased E_2 production. Excess T in the ovaries is likely to cause polycystic ovaries directly in Letrozole-treated rats. The reduction in estrogen weakens the negative feedback on LH production in the pituitary, resulting in increased LH levels, which further stimulates theca cells to secrete T. Typically, 6-week-old female rats (puberty) are administered Letrozole orally at doses of 0.1, 0.5, and 1.0 mg/kg daily for 21 days, after which they become acyclic, with histological and biochemical features of human PCOS.

Ovarian morphology: The ovarian morphologic changes of Letrozole-induced rats include the development of cysts with hyperplasia of internal theca cells and a thickened ovarian capsule. The number of corpora lutea is decreased, indicating oligo/anovulation. However, unlike human PCOS, the ovarian weight of Letrozole-induced rats remains un- changed.

Endocrine hormone profile: The serum T and LH levels of Letrozole-induced rats are significantly elevated, and the P and E_2 levels are decreased in a dose-dependent manner. However, in this model, the FSH level is markedly increased in the higher-dose groups (0.5 and 1.0 mg/kg), which are not the typical characteristics of human PCOS.

Cardiometabolic abnormalitie: The metabolic characteristics of the Letrozole- induced rodent model of PCOS. After continuous administration of Letrozole (via a subcutaneous implant) before puberty (at 3 weeks of age) through to adulthood (12–16 weeks of age), no metabolic aberrations were observed, inclusive of adiposity, insulin sensitivity, and dyslipidemia.

Summary: The Letrozole model targets the study of aromatase deficiency–induced classic PCOS and may be an effective co treatment with other treatments that induce Cardiometabolic aberrations to study these factors in the PCOS condition.

HERBAL REMEDIES FOR PCOS

Panax ginseng (Ginseng): The roots of Panax ginseng (Araliaceae) is an herbal medicine. It is used as a tonic and it slow down the ageing properties. Ginseng saponins is active constituent of ginseng. They are composed of ginsenosides namely Rb1, Rb2, Rc, Rd, Re, Ro, Ra and minor ginsenosides. It is a suitable dietary supplement. Induced the polycystic ovary in rats by estradiol valerate. The study analyzed the ovarian morphology. Kampo preparations, is the one the ginseng containing formulation. It is formulation significantly decreases the plasma LH levels and thereby it is effective in improving endocrine condition in the treatment of disturbances of ovulation in patients with PCOS[16].

Tribulus terrestris (Puncture vine): Tribulus terrestris, (Zygophyllaceae) commonly known as Puncture vine or Devil's eyelashes plays an important role in traditional medicine. Tribulus terrestris was found to be effective in polycystic ovarian syndrome. In an investigation done in rats with polycystic ovaries induced with estradiol valerate, found that Tribulus terrestris extract is effective in improvement of ovulation in rats. The extract treatment normalized estrous cyclicity and steroidal hormonal levels and regularized ovarian follicular growth. Many herbalists find tribulus is an effective, overall ovarian stimulant and female fertility tonic, making it an excellent choice for women with polycystic ovary[17].

Gymnema sylvestre (Gymnema): Gymnema sylvestre (Asclepiadaceae) is a herb which is used in traditionally in Ayurvedic system of medicine. It has various pharmacological effects like antidiabetic, hypoglycemic, and lipid lowering effects. The active constituent of gymnema is saponins, especially gymnemic acids. gymnema has potential hypoglycemic activity in experimental models of diabetes. It regulates the blood glucose level. Metformin therapy for treatment of PCOS is convential. Therefore gymnema can be used for the underlying factor of insulin resistance. Gymnema is well indicated for PCOS, due to its insulin modulating activity and the added benefits of reducing the elevated triglycerides associated with PCOS.

Punica granatum (Pomegranate): Pomegranate (Punica granatum of the family Punicaceae) is one of the fruit and has various numbers of medicinal properties. The fruit contains folic acid, vitamins (B2, C, B1), sugars, pantothenic acid, and organic acids. The seed is reported to contain unsaturated and saturated fatty acids. The effect of

pomegranate extract in the control or managment of PCOS was performed in adult female rats using control and PCOS group. The concentration of free testosterone, serum estrogen and andrestandoin hormone levels in experimental group was monitored. The study suggests the protective effect of pomegranate extract on hormonal imbalances of polycystic ovarian syndrome. The phenolic compounds and phytosterols found in the extract have positive effect in improving the complications of PCOS. The study recommends that the consumption of the extract reduces complications associated with PCOS[18].

Aloe barbadensis (Aloe): Aloe barbadensis Mill. (Liliaceae) popularly known as Aloe vera is a well-known plant with various medical properties and pharmacological activities. For management and prevention of polycystic ovarian syndrome the Aloe Vera gel has used. The biochemical clinical characters of PCOS were investigated using female rat model. The phytocomponents of aloe vera formulation were analyzed for flavonoids, polyphenols, sterols and other nutrients. The female rats were then treated orally with the Aloe vera gel formulation. This restored their glucose sensitivity, estrus cyclicity, and the enzyme activity. The histological analysis found, that aloe vera reduce the ovary ateretic cysts. The results were compared with PCOS control. The studies indicate that aloe vera has potential efficacy or beneficial effect in the prevention and maintenance of PCOS[8].

Cinnamomum zeylanicum (Cinnamon): Cinnamon (Cinnamomum zeylanicum of the family Lauraceae) has insulin potentiating properties. Cinnamon is reported to contain polyphenols and procyanidins. This compound regulates the insulin stimulated glucose uptake and glycogen synthesis. A pilot study conducted in fifteen women with PCOS and then fasting and oral glucose tolerance test values were measured. The cinnamon extract improved the insulin sensitivity in women with PCOS. The polyphenols and procyanidins found in cinnamon extract are responsible for the hypoglycemic effect by potentiating the insulin signaling pathway. The study established the role of cinnamon as an adjunctive therapy in the treatment of PCOS. Another study reported the effect of cinnamon on menstrual cyclicity and metabolic dysfunction in women with PCOS. It was a randomized controlled trial with 45 women. Cinnamon supplement were given orally. luteal phase progesterone level and menstrual cyclicity were monitored. The cinnamon supplementation improved the menstrual cyclicity and it is effective for poly cystic ovary syndrome[19].

Glycyrrhiza glabra (liquorice): Liquorice (Glycyrrhiza glabra of the family Leguminosae) has been used in traditional medicine to treat various of diseases. It has antifungal, antiviral, antibacterial, and antihyperglycemic properties. Glycyrrhizic acid is the important bioactive compounds in liquorice. Liquiritigenin, liquiritin, isoliquiritin, isoliquiritigenin, glabidin, glabrene are some of the phytoestrogens present in liquoirice. Reported effects on vascular tissues in vitro and in vivo of two natural compounds derived from liquorice root: glabridin, the major glabrene and isoflavan, an isoflavene, both demonstrated estrogen-like activities. liquiritigenin a selective estrogen receptor ligand might be one of the bioactive compound responsible for weight loss. Other compounds glabrene and glabridin have showed the effect on weight reduction in vivo. It has also been reported that the combined treatment with spironolactone and liquorice in hirsute women is effective in PCOS, in order to reduce the volume depletion induced by spiranolactone and possibly enhance its anti-androgenic activity.[20]

Symplocos racemosa (Lodh Tree): Symplocos racemosa Roxb. From the family Symplocaceae, is a widely used Ayurvedic remedy mainly for female disorders. It is also known as Lodhra and is used in Indian System of Medicine as single drug or in multi-component formulation and preparations. The anti-androgenic properties S. racemosa in the treatment of PCOS was investigated in Letrozole induced female rat model. Syplocus racemosa treatment show significant recovery of estrogen, testosterone, progesterone levels and ovarian tissues. It is prevents ovarian cell dysfunction in PCOS and improved the fertility[4].

Linum usittatissimum (Flaxseed): Flaxseed is obtained from Linum usittatissimum (Linaceae) a food generally renowned for its omega-3 fatty acid content, also one of the richest sources of dietary lignan. Several biologically active compounds like alpha- linolenic acid (ALA), lignans (secoisolariciresinol diglycoside-SDG), soluble flaxseed fibre mucilage (d-Xylose, L-Galactose, LRhamnose, dgalacturonic acid) which have significant health benefits. The studies on the use of flaxseed or isolated lignan suggest that it may decrease androgen levels and normalize lipid levels. Lignans seem to reduce the excess testosterone which plays a key role in the pathogenesis of PCOS. A case study reported that flaxseed supplementation may indeed help regulate androgen levels in women with PCOS. A significant decrease in androgen levels was observed in the study. Decrease in hirsutism also observed. Findings suggest that flaxseed may have a profound impact on testosterone levels, and also may reduces symptoms associated with hyperandrogenism, such as hirsutism. Another study reported the effect of flax seeds on ovarian morphology in PCOS and it has showed that flax seed supplementation significantly reduced the ovarian volume, number of follicles in the ovaries and improved the frequency of menstrual cycles. However the study did not find any change in hirsutism, blood sugar level and body weight[21].

Curcuma longa (Turmeric): Curcumin is a water-insoluble, low molecular weight, polyphenolic curcuminoid derivative found in rhizomes of Indian spice, Curcuma longa of the family Zingiberaceae (turmeric). Turmeric is extensively used as a food additive and coloring agent in Asian cuisine and also in Indian herbal medicine. Curcumin has been reported to possess a wide variety of biological effects like anti-inflammatory, antioxidant hypoglycemic antihyperlipidemic activities and estrogenic effects. A study was conducted in 30 female Albino Wistar rats, using Letrozole-aromatase inhibitor, to induce Polycystic Ovarian Syndrome. Its effect was comparable to that of Clomiphene citrate, most widely used treatment for ovulation induction in PCOS condition. Serum levels of Progesterone and Estradiol were decreased in PCOS induced group. Curcumin restored the hormone and lipid profile, antioxidant and glycemic status as well as ovarian morphology in Letrozole induced PCOS animals. Decreased progesterone levels are also indicative of anovulation and curcumin successfully restore the ovulation. The study suggests that the effects may be attributed to its multiple pharmacological activities like

estrogenic, antihyperlipidemic, antioxidant and hypoglycemic effects which could be useful in managing PCOS condition and prevent ovarian cell dysfunction, ovulation and thereby improving fertility. The studies show that the effect of curcumin is similar to that of Clomiphene citrate[22].

Cocus nucifera (Coconut): The reported the effect of Cocus nucifera (Arecaceae) flowers in reducing the major multiple symptoms of Letrozole-induced PCOD in female rats. Antioxidant status (superoxide dismutase (SOD) and glutathione reductase (GSH)) of the uterus homogenate, lipid profile (total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides (TG)) of the serum was determined. Weights of the uterus and ovaries were separately monitored. The characteristics of changes in the ovary were evaluated by histopathological studies. C. nucifera flower extract-treated groups showed increased uterus weight and estrus cyclicity which indicates the estrogenic effect. The improved ideal lipid profile, good antioxidant status, blood sugar level and histopathology results revealed the recovery from poly cystic ovaries. Histological findings of the treated groups indicated that the extract of C. nucifera may bring down the active levels of hormones, such as FSH and LH, to normal levels, and that may be the reason for the recovery from experimentally induced polycystic ovaries. This is further supported by the presence of methyl (9Z, 12Z)-9, 12-octadecadienoate which possesses anti-androgenic properties], in the GC-MS analysis of the extract. The GC-MS analysis of the aqueous alcoholic extract showed the presence of twenty-five volatile and semi volatile phytoconstituents. The presence of flavanoid (3, 5Dihydroxy-6-methyl-2, 3-dihydro-4Hpyran- 4-one), which is responsible for its hypoglycemic effects[16].

CONCLUSION

Polycystic ovarian syndrome (PCOS) is one of the common endocrine disorder in women of reproductive age. Various risk factors have been investigated in relation to PCOS, which including glucose intolerances, obesity and dyslipidemia. Although so many synthetic drugs are shown effective management, their number of side effects and high cost lead a way to seek plant based remedies for the treatment of PCOS. In this review summarize some important medicinal plants for the treatment of PCOS. It is medicinal plant help for improving and managing PCOD condition. These plants are improving hyperandrogenism, insulin sensitivity, improving fertility and improving menstrual cyclicity.

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