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Review Article

A Review on Medicinal Plants of Natural Origin for Treatment of Polycystic Ovarian Syndrome (PCOS)

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ABSTRACT

Polycystic ovarian syndrome (PCOS) related infertility is a global problem that is spreading at an alarming rate. Chronic anovulation, polycystic ovaries, and hyperandrogenism, as well as abnormal menstrual cycles, hirsutism, acne, and infertility, are all symptoms of this condition. PCOS is linked to insulin resistance and elevated levels of male hormones (androgens). Among other things, an inactive lifestyle, a lack of exercise, dietary changes, and stress are all contributing factors. Curcuma longa, Aloe barbadensis, Mentha piperita, Allium fistulosum Cinnamonum zeylanicum, and other plants have been shown to be effective in the treatment of PCOS. The aim of this review is to summarise the most effective medicinal plants that are used in the treatment or prevention of PCOS. Special emphasis is placed on the role of insulin resistance and the possible utility of insulin sensitizers in the treatment of PCOS.

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

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INTRODUCTION

eventhal and Stein in 1935 first defined a disorder, which would ultimately become known as polycystic ovary (or ovarian) syndrome (PCOS)¹. Polycystic ovary syndrome (PCOS), a unitization of symptoms, which affects women of child-bearing age is assumptive in epidemic proportions. A resultant of imbalance in proportion of female sex hormones, results in cysts within antral follicles of ovaries. Once multiple cysts are formed in the ovarian follicles because of the hormonal imbalance, it is characterized as PCOS. Anovulation and absence of menstrual cycle prevents fertilization, and conception in women, thus pregnancy becomes troublesome². PCOS affects 6-10% of women throughout the globe. According to 1990 NIH criteria 7-12 and even more individuals. According to the broader Rotterdam criteria, which makes it one of the most common human disorders and the single most common endocrinopathy in women of reproductive age.³ The oxidative stress (OS), that will increases in inflammation, which also been reported as

possible cause of PCOS⁴. Women with PCOS has several risk factors which are associated with the development of uterine cancer including fatness, hyperinsulinemia, diabetes mellitus and abnormal uterine bleeding.⁵ The frequency of depression and anxiety is higher in women with PCOS than in the general population. Mood disorders are capable of impairing quality of life, which are well-known in young adult women, concerned with fertility, and in women of all ages with respect to obesity, and clinical manifestations of excessive androgen.⁸

RISK FACTORS⁶

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

PATHOPHYSIOLOGY OF PCOS⁷

The pituitary gonadotropin is fundamental to reproductive function-its production and secretion of FSH and LH is directly stimulated by hypothalamic GnRH and it is also influenced by integrated feedback mechanisms. The initial stimulus for follicular development and also granulosa cell conversion of androgens to oestrogens by stimulating the aromatase enzymes is provided by FSH. Luteinizing Hormone(LH) characteristically known for its role in the luteal phase by promoting secretion of progesterone, also it has a vital role in the follicular phase, for inducing thecal androgen production. Women with PCOS often secrete more LH and this might result in higher theca cell androgen secretion. to maintain gonadotropin secretion pulsatile GnRH stimulation is required, but the continuous exposure of the pituitary to GnRH causes desensitisation and a suppression of gonadotropin secretion. Due to Changes in the pulsatility of GnRH alter the ratio of secretion of the two pituitary gonadotropins throughout the menstrual cycle. 'Excessive androgen in PCOS is related with increase in abdominal fat leads to dyslipidemia and hyperinsulinemia. Thus, hyperinsulinemia reduces hepatic sex hormone-binding globulin(SHBG) to increase circulating bioactive testosterone levels.8 urnal of

Screening Methods of PCOS

Androgen Induced PCOS Model⁹:

Hyperandrogenism is the most common symptom of PCOS. One of the etiologic hypotheses for PCOS is that early life exposure to excessive androgens leads to PCOS later in life. Increased levels of circulating androgens in the rodent affected ovarian follicular maturation and cyst development, according to a study published more than 30 years ago. Several androgens, including dehydroepiandrosterone (DHEA), testosterone propionate (TP), and 5a-dihydrotestoterone, have been used to induce an acute PCOS condition in rats through regular injection or subcutaneous implants (DHT). However, there is still some inconsistency in the reporting of endocrine hormones and ovarian histology in different models. Furthermore, some studies did not look at cardiometabolic parameters or the effects of daily androgen injections and/or treatment on physiologic indices like body weight, stress indicators, or food intake. The pathological induction of PCOS in these rodent models is transient and dependent on androgen treatment. As a result, natural reproductive/ovarian cycling happens again after androgen administration is stopped.

DHEA Induced PCOS⁹:

The first androgen to increase in the female peripubertal cycle is dehydroepiandrosterone. Nearly half of follicular synthesised T can be obtained from circulating DHEA, and 25% of PCOS patients have higher-than-normal circulating DHEA levels. Roy et al. were the first to use dehydroepiandrosterone to induce PCOS in rats. DHEA (6 mg/100 g body weight, dissolved in 0.2 mL sesame oil) is injected daily for up to 20-27 days into prepubertal rats, typically aged 22 days. Rats become acyclic and anovulatory after treatment

Ovarian Morphology: Multiple follicular cysts varying in size from 0.45 to 2.2 mm in diameter, as well as degeneration of granulosa cell layers, grow in dehydroepiandrosterone-induced rats. The ovarian tunica capsule is not thickened, and the ovarian weight of DHEAtreated rats is substantially increased.

Endocrine hormone profile: DHEA-induced rats have significantly higher serum DHEA, T, E2, FSH, LH, and PRL concentrations than control rats, while no changes in plasma FSH and LH concentrations have been identified by other groups. Fasting serum glucose and insulin concentrations were higher in DHEA-induced rats, indicating cardiometabolic abnormalities.

Early DHEA-related hyperandrogenemia, anovulation, cystic ovaries, and the production of insulin glucose metabolism abnormalities can all be detected using the DHEA-induced model.

TP- Summary: Induced PCOS Model¹⁰:

Testosterone propionate (TP) can cause hyperandrogenemia in rats when given prenatally or postnatally. Furthermore, prenatal T exposure during the crucial time of foetal development has been linked to reproductive system developmental and morphological abnormalities. Pregnant rats were given a single dose injection of T on gestational day 20 or T propionate (TP) from days 16 to 19 (3 mg T daily) of pregnancy for prenatal administration. Rats were given TP at a dose of 1.25 mg/100 g body weight at 5 days of age, or daily injections of 1 mg/100 g body weight from 21 to 56 days of age.

Estrous cyclicity: T prenatally treated rats had longer and more irregular estrous periods. Estrous cyclicity was disrupted and diestrus phase was persistent in postnatally treated rats.

Ovarian morphology: In the ovaries of rats treated prenatally with T, the number of preantral and antral follicles increased, whereas the number of pre-ovulatory follicles and corpus luteum (CL) cells decreased, as opposed to control rats. In prenatal T-treated rats, cystic follicles were also discovered. Rats given T postnatally, on the other hand, had massive cystic or atretic follicles and luteinization of theca cells in the ovaries. When postnatal T treated rats were fed a high fat diet, their body weight increased while their fasting glucose levels remained unchanged.

Summary: The ovary of rats treated with postnatal T showed morphological changes that mirrored the human PCOS phenotype. Prenatal T therapy, on the other hand, increased the number of preantral and antral follicles in rats, despite the fact that cystic follicles and ovary weight were unchanged in this model, and the reported changes did not match the ovarian morphology of people with PCOS. Both prenatal and postnatal T therapy increased serum T levels. Prenatal T administration had no effect on serum E2 and P4 levels, while continuous postnatal T treatment increased E2 levels, likely due to T conversion. An increased number of kisspeptin-positive cells in the ARC of

prenatal T-treated ewes may be linked to defects in GnRH/LH secretion feedback control 11; however, one drawback of this study is that LH levels and ovarian morphology were not examined..

DHT induced PCOS models¹⁰:

Since DHT is not converted to E2 by aromatase, the PCOS phenotype in DHT-treated animals can be studied without taking into account the effects of oestrogen derived from androgens.

Prenatal DHT treated models:

Mice were injected with 250 g of DHT on days 16, 17, and 18 of gestation 28 to generate prenatal DHT-treated animals, while rats were given 3 mg of DHT daily from gestational day 16 to 19. The offspring were used as PCOS models that had been prenatally treated with DHT.

Estrous cyclicity: Prenatally administered DHT caused irregular cycles in rats and mice. The mice spent more days in diestrus and fewer days in proestrus than controls, resulting in fewer litters being produced every three months.

Ovarian morphology: Prenatal DHT treatment resulted in fewer normal large, antral, preovulatory follicles and CLs, as well as more atretic cyst like follicles. In prenatal DHT treated mice, CL and antral follicle wall areas were reduced, but the number of atretic cyst like follicles and the thickness of the antral follicle theca cell layer increased.

Neuropeptides in the hypothalamus: The number of kisspeptin and NKB positive cells in the ARC of the hypothalamus increased significantly in prenatal DHT treated rats, whereas the number of kisspeptin positive cells in the AVPV did not differ from that of control animals in diestrus. The input of aminobutyric acid (GABA) to GnRH-expressing neurons was increased in mice given DHT prenatally, according to a recent study.

Metabolic features and adiposity: Prenatal DHT-treated rats and mice had body weights that were close to control animals. Prenatal DHT therapy, on the other hand, increased adipocyte region in parametrial fat and the degree compared to the control group.

DHT prenatally treated rats and mice had abnormal estrous cycles and ovarian morphology similar to PCO. In prenatal *Summary:* DHT-treated rodents, increased LH levels were observed, along with an up regulation of kisspeptin in the ARC. There was no discernible difference in body weight, on the other side. This phenotype is similar to PCOS, which is marked by normal body weight and increased LH secretion.

Letrozole-Induced (Aromatase Inhibitor) Rodent Model of PCOS¹¹:

Abnormal follicular development and polycystic ovary may result from intraovarian androgen excess caused by circulating hyperandrogenemia or abnormal steroidogenesis. P450 aromatase, which was expressed in the placenta, ovary, and testis as well as a wide variety of human tissues, converted testosterone and androstenedione into estradiol and estrone, respectively; a decrease in the enzyme's activity could result in increased ovarian androgen production and the development of PCOS. Aromatase is the key enzyme that converts T and androstenedione into E2 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 E2 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.

Estrous cyclicity: Regular vaginal smear examinations were used to monitor estrus cycles. In the analysis, only animals with two consecutive standard 4-day periods were used. The rats and mice treated with letrozole were fully acyclic. This rat model's vaginal smears showed an excess of leukocytes, the diestrus phase's predominant cell type.

Ovarian morphology: Ovaries from control group exhibited follicles in various stages of development including secondary follicles, graffian follicles, and fresh corpora lutea. In study groups, letrozole inhibited growth of follicles in a dose-dependent manner. Small follicles could be observed in early development, in addition to follicles showing evidence of atresia, and many large cysts with virtually no granulosa cell layer or large cystic follicles with scant granulosa cells. Ovaries from the sample groups had a higher rate of subcapsular ovarian cysts and capsular thickening than the control group. together with incomplete luteinization and a dose-dependent decrease in the amount of corpora lutea In some of the research classes, there was also evidence of theca cell hyperplasia..

Summary: Acyclicity, cystic ovarian morphology, elevated serum LH levels, and higher Kiss1 mRNA expression in the posterior hypothalamus are all observed in letrozoleinduced PCOS model rats compared to control rats. This model accurately reproduces the metabolic characteristics of human PCOS, including a PCO-like morphology and elevated serum LH levels, and is thus suitable for studying human PCOS. Increased KNDy neuron activity was linked to a reduction in the negative feedback effect of sex steroid hormones, as evidenced by increased Kiss1 mRNA and serum LH levels.

Medicinal plants of natural origin-

*Curcuma Longa (Turmeric)*¹²:Curcumin is a waterinsoluble polyphenolic curcuminoid derivative found in the rhizomes of Curcuma longa, an Indian spice (turmeric). Turmeric is widely used in Asian cuisine as a food additive

and colouring agent, as well as in Indian herbal medicine. Curcumin makes up around 2-8% of all turmeric preparations. Curcumin has been shown to have a wide range of biological effects like Anti-inflammatory, antioxidant, hypoglycaemic, antihyperlipidemic and properties The study used virgin, cyclic, adult female Wistar Albino rats weighing 160-200 g. Once everyday for 21 days, followed by treatment with curcumin. Letrozole treatment resulted in abnormalities in the serum sex steroid profile, lipid profile, glucose, and glycosylated haemoglobin levels and antioxidant activity has been depleted. Whereas Curcumin was able to exert its calming effect by returning all parameters to normal and causing cysts in the ovaries to vanish. Curcumin, like Clomiphene citrate, has a number of beneficial effects in the treatment of PCOS.

Aloe barbadensis (*Aloe*)¹³:Aloe barbadensis Mill. (Liliaceae) is a well-known plant with such properties. Polyphenols, sterols, flavanoids, and other nutrients were analysed qualitatively and quantitatively for polyphenols, sterols, flavanoids, and other nutrients in the Aloe vera gel formulation. To induce PCOS, five-month-old Charles Foster female rats were orally fed letrozole, a non-steroidal aromatase inhibitor. The rats were then given the Aloe vera gel formulation orally.AVG treatment of PCO rats resulted in a reduction in ovary atretic cysts as compared to PCOS controls, according to histological review. By restoring ovarian steroid status and modifying main steroidogenic behaviour, aloe vera gel formulation protects against the PCOS phenotype.

Glycyrrhiza glabra (liquorice)¹⁴: Traditional medicine has used liquorice (Glycyrrhiza glabra of the Leguminosae family) to treat a variety of ailments. Antifungal, antiviral, antibacterial, and antihyperglycemic properties are all present in it. The most bioactive compound in liquorice is glycyrrhizic acid. Phytoestrogens found in liquorice include liquiritigenin, liquiritin, isoliquiritin, isoliquiritigenin, glabidin, and glabrene. The effects of two natural compounds derived from liquorice root on vascular tissues in vitro and in vivo were reported: glabridin, the main glabrene, and isoflavane, an isoflavene, both demonstrated estrogen-like activities. One of the bioactive compounds responsible for weight loss may be liquiritigenin, a selective oestrogen receptor ligand. Some molecules, such as glabrene and glabridin, have been shown to reduce weight in vivo. It has also been documented that treating hirsute women with a combination of spironolactone and liquorice may help with PCOS by reducing the volume depletion caused by spiranolactone and possibly increasing its antiandrogenic activity.

Mentha piperita(*Peppermint*) ¹⁵:Peppermint (Mentha piperita L.) is a member of the Labiatae family that originated in the Mediterranean region and is now widely cultivated all over the world. Antioxidant, antitumor, antiallergenic, anti-inflammatory, antiviral, antibacterial, and antifungal properties are all present in peppermint. It also has anti-androgenic properties, lowering the level of free testosterone in the blood after three weeks of treatment

with letrozole and peppermint. Females with PCOS had significant changes in serum testosterone, oestrogen, LH, and FSH function. Ovarian cysts with a reduced granulosa layer, atretic follicles, and a small number of corpora lutea were found in the PCOS community. Peppermint was found to have a strong potential as an alternative therapy in the treatment of PCOS, as shown by necrosis in stromal mesenchymal cells, hyperplasia of luminal epithelial cells, and necrosis in stromal mesenchymal cells.

Allium fistulosum (Onion)¹⁶: In Asian countries, the Welsh onion (Allium fistulosum) is well-known for its use in food and traditional medicine. For treatment, administered AF extract to letrozole-treated rats for 2 weeks. In terms of serum hormonal levels, the LH/FSH ratio and serum oestrogen levels were positively affected by AF extract therapy. FSH and LH are necessary for ovulation, and PCOS patients often have a two- to three-fold increased LH/FSH ratio, which is enough to cause ovulation disruption. The findings suggest that AF extract normalises follicular growth and ovarian cysts. In the letrozole-induced PCOS rat model, the steroid hormone-related receptors demonstrated restoration of m-RNA expression after treatment with AF extract A. fistulosum extract treatment relieved hormonal imbalance and altered ovarian function.

*Linum usittassimum (Flaxseed)*¹⁷: Flaxseed is made from Linum usittassimum (Linaceae), an omega-3 fatty acid-rich food that is also one of the best sources of dietary lignin. ALA, lignans (secoisolariciresinol diglycoside-SDG), and soluble flaxseed fibre mucilage (d-Xylose, L-Galactose, L-Rhamnose, d-galacturonic acid) are all biologically active compounds with major health benefits. Flaxseed or isolated lignan has been shown in studies to lower androgen levels while also normalising lipid levels. Lignans seem to minimise excess testosterone, which is a crucial factor in the development of PCOS. Flaxseed supplementation can help women with PCOS control androgen levels, according to a case study. The study found a substantial reduction in androgen levels. There was also a decrease in hirsutism. Flaxseed can have a significant effect on testosterone well levels. as as symptoms associated with hyperandrogenism, such as hirsutism, according to the findings. Another research looked at the impact of flax seeds on ovarian morphology in PCOS patients, finding that flax seed supplementation decreased ovarian volume, increased the amount of follicles in the ovaries, and improved menstrual cycle duration. However, hirsutism, blood sugar levels, or body weight did not improve as a result of the research.

Panax ginseng (Ginseng)¹⁸: Herbal medication is made from the roots of Panax ginseng (Araliaceae). It has antiaging properties and is used as a tonic. Ginseng saponins are ginseng's active ingredient. Rb1, Rb2, Rc, Rd, Re, Ro, Ra, and minor ginsenosides make up these ginsenosides. It can be used as a dietary supplement. Estradiol valerate induced polycystic ovary in rats. The ovarian morphology was examined in this analysis. The ginseng-containing formulation is known as Kampo preparations. 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.

Tribulus terrestris (Puncture vine)¹⁹: Puncture vine or Devil's eyelashes, Tribulus terrestris (Zygophyllaceae), plays an important role in traditional medicine. The herb Tribulus terrestris has been shown to help with polycystic ovarian syndrome. Tribulus terrestris extract was found to be successful in improving ovulation in rats with polycystic ovaries induced with estradiol valerate in a study. The extract treatment improved ovarian follicular development and normalised estrous cyclicity and steroidal hormone levels. Many herbalists believe that tribulus is an excellent overall ovarian stimulant and female fertility tonic for women with polycystic ovary syndrome.

Gymnema sylvestre (Gymnema)²⁰: Gymnema sylvestre (Asclepiadaceae) is an Ayurvedic herb that has been used for thousands of years. It has a wide range of pharmacological effects, including anti-diabetic, hypoglycemic, and lipid-lowering properties. Saponins, especially gymnemic acids, are the active constituents in gymnema. Gymnema has been shown to have hypoglycemic properties in diabetic animal models. It keeps blood glucose levels in check. Metformin therapy is a convenient way to treat PCOS. Gymnema can thus be used to treat the root cause of insulin resistance. Gymnema is a good choice for PCOS because of its insulin-modulating properties and the added advantage of lowering the high triglycerides that come with the condition.

Punica granatum (Pomegranate)²¹: Pomegranate (Punica) granatum of the Punicaceae family) is a fruit with a wide range of medicinal properties. Folic acid, vitamins (B2, C, B1), carbohydrates, pantothenic acid, and organic acids are all contained in the fruit. Unsaturated and saturated fatty acids are said to be present in the crop. In adult female rats, the effect of pomegranate extract in the control or management of PCOS was studied using a control and a PCOS community. The levels of free testosterone, serum oestrogen, and andrestandoin hormone were measured in the experimental community. Pomegranate extract seems to have a protective impact on polycystic ovarian syndrome hormonal imbalances, according to the report. The extract's phenolic compounds and phytosterols have been shown to help alleviate PCOS complications. Consumption of the extract, according to the report, decreases the complications associated with PCOS.

Symplocos racemosa (Lodh Tree)²²: Symplocos racemosa Roxb, a member of the Symplocaceae family, is a common Ayurvedic remedy for female problems. It's also known as Lodhra, and it's used as a single medication or in multicomponent formulations and preparations in Indian medicine. In a Letrozole-induced female rat model, the anti-androgenic properties of S. racemosa were investigated in the treatment of PCOS. Treatment with Symplocos racemosa resulted in substantial improvements in oestrogen, testosterone, progesterone, and ovarian tissue levels. It improves fertility and prevents ovarian cell dysfunction in PCOS patients. *Cinnamomum zeylanicum (Cinnamon)*²³: Cinnamon (Cinnamomum zeylanicum of the Lauraceae family) is an insulin potentiator. Insulin-stimulated glucose uptake and glycogen synthesis are controlled by this compound. Fasting and oral glucose tolerance test values were assessed in fifteen women with PCOS in a pilot study. In women with PCOS, the cinnamon extract increased insulin sensitivity. Cinnamon extract contains polyphenols and procyanidins, which potentiate the insulin signalling pathway, resulting in a hypoglycemic impact. Cinnamon's function as an adjunctive therapy in the treatment of PCOS was identified in this research. Cinnamon's impact on menstrual cyclicity and metabolic dysfunction in women with PCOS was studied in another research. It was a 45woman randomised controlled trial. Oral cinnamon supplements were given. Menstrual cyclicity, luteal phase, and progesterone levels were all tracked. Cinnamon supplementation increased menstrual cyclicity and was shown to be beneficial in the treatment of polycystic ovary syndrome.

Vitex Negundo(Chaste Tree)²⁴:Vitex negundo is a plant belonging to the (Linn) Verbenaceae family, genus Vitex, and species negundo. It's the five-leaved chaste flower, also known as monk's pepper. It has been documented to have anti-inflammatory, analgesic, antioxidant, antifungal, antiviral, and anti-inflammatory properties, as well as being used in gynaecological disorders. It also has antiandrogenic and estrogenic properties (linoleic acid-like estrogenic compounds). For the induction of PCOS, letrozole was given orally (p.o) for a duration of 21 days. The rats were then given extract of vitex negundo, which has positive effects on the ovary as well as effects on glucose tolerance, estrous cycle irregularities, LH: FSH steroidogenic ratio, enzymes, and cardiovascular parameters. It was able to successfully treat the rats with extract, which caused abnormalities in serum sex steroid profile, lipid profile, glucose, and estrous cycle. This may be attributed to the extract's phyto-components.

CONCLUSION:

The most common cause of menstrual irregularities and hyperandrogenism is polycystic ovary syndrome (PCOS). It is the most common cause of female infertility. Several risk factors for PCOS have been studied, including glucose intolerances, obesity, and dyslipidemia. Many treatments are currently available, but they are associated with moderate to serious side effects, and their high cost has led to a search for plant-based remedies to treat PCOS. In this study, summarize some of the most important medicinal plants for treating PCOS and helps with PCOD symptom relief and management. Hyperandrogenism, insulin sensitivity, fertility, and menstrual cyclicity are all aided by these plants.

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