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A Comprehensive Review on Polycystic Ovary Syndrome (PCOS)

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ABSTRACT

PCOS is a condition that can affect your periods, fertility, hormones and aspects of your appearance. It can also affect your long-term health. Estimates of how many women it affects vary widely from 2 to 26 in every 100 women [5]. Infertility due to polycystic ovarian syndrome (PCOS) is a worldwide problem that is increasing at alarming rates. It is characterized by polycystic ovaries, chronic anovulation, 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, dietary variations, lack of exercise and stress, etc., are also the contributory factors [9]. Hormonal disturbances, such as hyper-androgenisms, are considered important for developing polycystic ovary syndrome (PCOS) in humans. Accordingly, directly hormone-regulated animal models are widely used for studying PCOS, as they replicate several key PCOS features **[4].** The objective of this study was to review the therapeutic potential of herbal remedies and different animal models used for the PCOS.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) remains one of the leading endocrine disorders encountered by women of reproductive age with the prevalence between 5% and 10%. The polycystic ovary syndrome (PCOS) is a hyperandrogenic disorder associated with chronic oligo-anovulation and polycystic ovarian morphology. It is often associated with psychological impairments, including depression and other mood disorders and metabolic derangements, chiefly insulin resistance and compensatory hyperinsulinemia, which is recognized as a major factor responsible for altered androgen production and metabolism [3].

The reproductive system is essential to keep a species alive and improve breeding and to maintain the fertility and to lessen the adverse effect of medications, herbal plants are excellent substitute to chemical medications, solitary of the main cause for this is little side effect compared to medications, because their scavenging free radicals properties they decrease medications toxicity, furthermore, the herbal plants have capable role in management of numerous diseases which affect on efficacy of reproductive system like Polycystic ovary with least adverse effects, to improve immunity of the body and also standardize menstrual cycle without changeable in hormonal level [11].

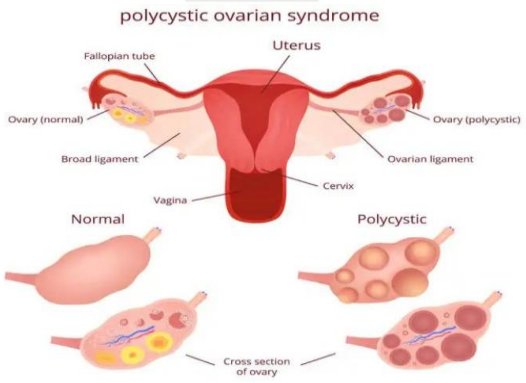

Figure no. 1: Polycystic Ovarian Syndrome [29].

PCOS is also a metabolic syndrome and patients may be predisposed to diabetes type 2, cardiovascular and inflammatory diseases, together with endometrial dysfunction. The evaluation of all this evidence and the relations cannot be done by using clinical trials or working on patient samples. Therefore, several animal models have been designed and developed to evaluate different aspects of the etiology and pathophysiology of PCOS. During recent years, due to the development of knowledge about this syndrome and also the

detection of new predisposing factors for PCOS as well as PCOS itself as risk factors for other metabolic diseases, the need to design new animal models becomes apparent. Therefore, this review focuses on current animal models that have been used to study PCOS and describes and assess methods of establishing PCOS-like animal models in the future [2].

- **Causes of PCOS:**

✓ Testosterone is a hormone that is produced in small amounts by the ovaries in all women. Women with PCOS have slightly higher than normal levels of testosterone and this is associated with many of the symptoms of the condition.

✓ Insulin is a hormone that controls the level of glucose (a type of sugar) in the blood. Women with PCOS, may not respond to insulin (this is known as insulin resistance), so the level of glucose is higher. To try to prevent glucose levels from becoming higher, the body produces even more insulin. High levels of insulin can lead to weight gain, irregular periods, fertility problems and higher levels of testosterone [5].

- **Symptoms of PCOS:**

✓ Irregular periods or no periods at all.

✓ An increase in facial or body hair (hirsutism).

✓ Loss of hair on your head.

✓ Being overweight, experiencing a rapid increase in weight or having difficulty losing weight.

✓ Oily skin, acne.

✓ Difficulty becoming pregnant (reduced fertility) [5].

ANIMAL MODELS OF PCOS:

Various animal models have been developed and studied for human polycystic ovary syndrome (PCOS) for more than 60 years. However, the etiology of PCOS is still unclear because of its complex manifestation as a syndrome and limitations of translational studies using animals [4]. Most commonly used animal models are explained below:

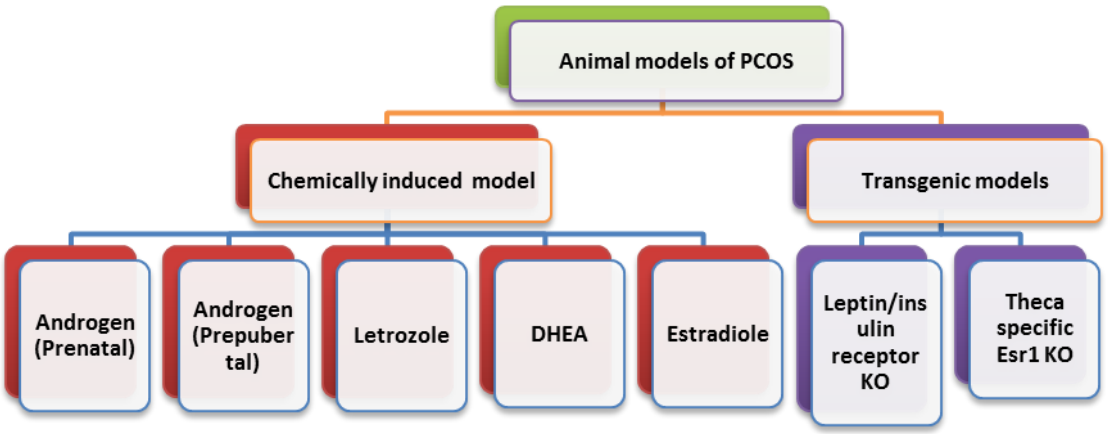

Figure no. 2: Animal models of PCOS.

1. Androgen (Prenatal) Model:

Prenatal androgen (PNA) treatment in sheep and monkeys results in multiple metabolic and reproductive abnormalities. In monkeys, daily subcutaneous injections of 15 mg of testosterone propionate for 40-80 days gestation are needed to induce the syndrome. In ewes, an injection of 100 mg of testosterone propionate twice a week for 60 days between days 30 and 90 of the 147-day pregnancy result in the ovarian abnormalities. In both models, the abnormalities mirror the symptoms found in women with PCOS [14]. These models produce a long-lasting effect in the female offspring mimicking many similar features of PCOS in humans. However, ewes and monkeys incur a large financial commitment for a long gestational period. However, it is noted that although PA monkeys exhibit hyperandrogenemia, the increases are not as extreme as in PCOS women 0.3-0.4 ng/mL (~50-100% elevation above normal); PCOS women, 0.5-0.7 ng/mL (~70-200% elevation above normal) and that although anovulation observed in PNA monkeys, its prevalence is also significantly less than that of PCOS women (PA monkeys: ~40%; PCOS women ~90%) [3].

2. Androgen (Pre-pubertal) Model:

This model exploits the association of elevated androgen levels during puberty and PCOS. Immature rats (approximately 21 days old) are treated for 7-35 days with ~100 µg/day testosterone propionate or dihydrotestosterone. Similar to the PNA animal models, prepubertal androgen (PPA) animal models of PCOS utilize a unique window where administration of exogenous androgens results in permanent damage to the ovarian tissue and

recapitulated the hallmark symptoms of PCOS in an animal model. PPA model shows many similar features to PCOS in women except for the hallmark increase in basal LH levels. This model is reliant on artificial hyperandrogenemia and therefore does not help identify abnormalities upstream of hyperandrogenemia [3].

3. Letrozole induced Model:

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. Decreased aromatase activity in the ovary is one of the pathophysiologic hypotheses of PCOS development [17]. Letrozole is a nonsteroidal aromatase inhibitor that reduces the 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 the letrozole-treated rat. The reduction in estrogen weakens the negative feedback on LH production in the pituitary, resulting in increased LH levels, which further stimulates theca cells te 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[1].

4. Dehydroepiandrosterone (DHEA):

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 [26]. Immature rats or mice (approximately 21-22 days old) are treated with daily s.c. DHEA injections (rats; 6 mg/100 g body weight, mice 6 mg/kg body weight) for 15-20 days. This dose of DHEA is sufficient to induce a hyperandrogenism state similar to that in PCOS women. This model is also reliant on artificial hyperandrogenemia and does not help identify abnormalities upstream of hyperandrogenemia [15].

5. Estradiol:

Estradiol valerate (EV) is a long-acting estrogen and on an administration that causes hypothalamic-pituitary dysregulation of GnRH, resulting in improper release and storage of LH. Luteinizing hormone is considered a key pathogenic factor in the development of PCOS.

A single dose of EV (2 mg) to the young adult cyclic rat induces anovulation and polycystic ovaries within 8 weeks [1].

HERBAL REMEDIES FOR PCOS:

1. Gymnema:

Figure no. 3: Gymnema [30].

Common Name: Gymnema, Gudmar.

Biological Name: *Gymnema sylvestre*

Family: Asclepiadaceae

Biological Source: Gymnema sylvestre is a perennial woody vine native to tropical Asia, China, the Arabian Peninsula, Africa, and Australia [28].

It has various pharmacological effects like antidiabetic, hypoglycemic, and lipid-lowering effects [9]. The individual administration of *Gymnema sylvestre* increases insulin sensitivity, decreases insulin resistance and also decreases the androgen production and the added benefits of reducing the elevated triglycerides associated with PCOS [16].

2. Licorice:

Figure No. 4: Licorice [31].

Common Name: Jethi-made, Kubas- susa, Jethimadh, Mithilakkdi.

Biological Name: *Glycyrrhiza glabra*

Family: Leguminosae

Biological Source: It is an herbaceous perennial legume native to the Middl East, Southern Europe, and parts of Asia, such as India [28].

It has antibacterial, antifungal, antiviral and antihyperglycemic properties [17]. Somjen et al. reported the effects on vascular tissues in vitro and in vivo of two natural compounds derived from liquorice root: glabridin, the major isoflavone, and glabrene, an isoflavone, both demonstrated estrogen-like activities. liquiritigenin a selective estrogen receptor ligand might be one of the bioactive compounds responsible for weight reduction. Other compounds glabridin and glabrene have shown the effect on weight reduction in vivo [9].

3. Shy plant:

Figure No. 5: Shy Plant [32].

Common Name: Shy plant, Lajalu, Sleepy plant, Touch-me-not.

Biological Name: *Mimosa pudica*

Family: Mimosaceae

Biological Source: The species is native to South and Central America but is now a pentropical weed, and can be found in Southern United States, South Asia, East Asia, and South Africa as well [28].

Mimosa pudica significantly reduced histopathological changes in the ovary and endocrinological and biochemical changes induced by hyperandrogenism. Thus Mimosa

pudica was found to have a good potential to be a very good alternative therapy in the treatment of PCOS [9].

4. Flaxseed :

Figure No. 6: Flaxseed [33].

Common Name: Common Flax, Linseed.

Biological Name: *Linum usitatissimum*.

Family: Linaceae.

Biological Source: It is food and fiber crops cultivated in cooler regions of the world [28].

Flaxseed, a food generally renowned for its omega-3 fatty acid content, also is one of the richest sources of dietary lignan, having levels that are 800-fold over that of most other foods, (Thompson, 1995). Prior studies on the use of flaxseed or isolated lignan suggest that it may decrease androgen levels and normalize lipid levels [22].

5. Fenugreek:

Figure No. 7: Fenugreek [34].

Common Name: Methi, Methika, Fenegriek, Menthiyam, etc.

Biological Name: *Trigonella foenum-graecum*

Family: Fabaceae

Biological Source: It is cultivated worldwide as a semiarid crop [28].

The seeds of fenugreek have been reported to have anti-diabetic and hypocholesterolemic effects in both animal models and humans [23]. Fenugreek is enriched in furostanolic saponins (Furocyst), the trial was conducted in female subjects suffering from PCOS over 90 consecutive days. 94% of patients responded positively to the treatment and significant improvement in the menstrual cycle was also observed following Furocyst treatment resulted in a significant reduction in both ovary volume and ovarian cyst. Also, significant increases in LH and FSH were observed following Furocyst treatment. 12% of the study population got pregnant. Approximately 46% of the study population showed a reduction in cyst size, while 36% of subjects showed complete dissolution of the cyst. No significant adverse effects were observed [9].

6. Coconut:

Figure No. 8: Coconut [35].

Common Name: Coconut, coco,coco-da-bahia, coconut of the beach.

Biological Name: *Cocus nucifera*

Family: Arecaceae

Biological Source: The plant is originally from Southeast Asia. Fruit of coconut plant is believed to have been brought to India then to East Africa [28].

Flowers in reducing the major multiple symptoms of letrozole-induced PCOS in female rats. 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 [27].

7. Turmeric:

Figure No. 9: Turmeric [36].

Common Name: Halodhi, Haldu, Haldar, Haldi.

Biological Name: *Curcuma longa*

Family: Zingiberaceae

Biological Source: The plant is perennial, a rhizomatous herbaceous plant native to the Indian subcontinent and Southeast Asia [28].

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 restores 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 conditions and prevent ovarian cell dysfunction, ovulation and thereby improving fertility [9].

8. Maca:

Figure No. 10: Maca [37].

Common Name: Ayak chichira, Ayuk Willku.

Biological Name: *Lepidium meyenii*

Family: Brassicaceae

Biological Source: Native to South America in the high Andes mountains of Peru [28].

Maca resulted in lowering both E2 and PRG, lowering Cortisol and ACTH levels in the ovariectomized rats [25].

9. Cinnamon:

Figure No. 11: Cinnamon [38].

Common Name: Cassia.

Biological Name: *Cinnamomum zeylanicum*

Family: Lauraceae

Biological Source: Cinnamon is the evergreen tree of tropical area, is considered to be native of Sri Lanka and Malabar Coasts of India. It is also found in Jamaica and Brazil [28].

Cinnamon 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 insulin sensitivity in women with PCOS [9].

10. Pomegranate:

Figure No. 12: Pomegranate [39].

Common Name: Anar.

Biological Name: *Punica granatum*

Family: Punicaceae

Biological Source: Pomegranate is native to a region of modern-day Iran to Nothern India [28].

The effect of pomegranate extract in the management of PCOS was performed in adult rats using the control and PCOS group. The concentration of serum estrogen, free testosterone and andrestandoin hormone levels in the experimental group was monitored. The study suggests the beneficial effect of pomegranate extract on hormonal imbalances of the polycystic ovarian syndrome [9].

SUMMARY

Polycystic ovarian syndrome (PCOS) remains one of the leading endocrine disorders encountered by women of reproductive age with the prevalence between 5% and 10%. There has been special attention to medicinal plants since ancient times and today, with numerous studies performed, worthwhile and beneficial medicinal plants are discovered.

In this review, an attempt has been done to summarize some important animal models and medicinal plants for the treatment of PCOS.

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