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HEALTHY APPROACH TO PCOD: REVIEW

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most important gynecological disorders among reproductive-age women. In patients with PCOS, the secretion rate and metabolism of androgens and estrogens are disrupted. With regards to the increasing prevalence of PCOS and associated physical and mental problems as well as the effects of changes in sex hormones in development of this disease, our aim is to investigate the effects of different herbal extracts on changes in the serum levels of sex hormones and ovarian tissue. To conduct this review, an extensive literature search was conducted using, relevant publications published between 1990 and 2017, and indexed in Google Scholar, PubMed, Elsevier, Scientific Information Database, and Science Direct were studied. The search terms used to retrieve the publications were as follows: Herbal medical extract Names of medicinal plants ، polycystic ovary syndrome, PCOS, the mechanism of hormone. According to the evidence, herbal extracts containing phytoestrogens cause decrease in hyperandrogenism, insulin resistance, and ovary weight as well as increase in ovulation. Therefore, these plants can be partly effective in this syndrome via affecting the serum levels of different hormones and ovarian weight and morphology, representing an opportunity to investigate and discovery new bioactive products.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is characterized by endocrine, metabolic, and genetic disorders, chronic absence of ovulation of polycystic ovary, and clinical and biochemical presentations of hyperandrogenism . The symptoms of PCOS include clinical ones (menstrual disorders, hirsutism, acne, baldness, and infertility), changes in endocrine hormones (increased levels of androgen, estrogen, and prolactin and decreased level of progesterone), and metabolic disorders (insulin resistance, diabetes, dyslipidemia, and type 2 diabetes). However, in some cases, estradiol level does not change. In vivo and in vitro studies on theca cells suggested that ovarian theca cells are much more active To convert androgenic precursors into testosterone in women with PCOS than in healthy women. Indeed, Theca cells produce androgen in response to luteinizing hormone (LH); therefore, the blood levels of androgens increase in people with PCOS. The high levels of androgens especially testosterone in PCOS, their role in lack of ovulation, and disrupted synthesis of sex hormones, which causes clinical symptoms and dysfunction of genital tract in the patients, are the main reasons for infertility in reproductive-age women. PCOS is one of the most common gynecological disorders in reproductive-age women with the incidence likelihood of 4–12%. The prevalence rate of this disease was reported 5.6–8% in Europe .

According to the latest studies, the prevalence of PCOS in Iran is 19.5% based on Rotterdam criteria and 6.8% based on the NIH criteria . The cause of infertility is lack of ovulation in approximately 75% of the cases . Currently, clomiphene citrate, metformin, and tamoxifen are the most widely used drugs to treat PCOS. With regards to the side effects of such drugs and relative treatment of PCOS by them, it is essential to identify and develop alternative drugs out of which plant-based drugs especially estrogen-containing ones (phytoestrogens) are considered to be comparatively more effective Phytoestrogens are weak antagonists of estrogen, and exhibit more potent estrogenic effects when estrogen level of the body is low . With regards to the increasing prevalence of PCOS and associated physical and mental problems as well as the effects of changes in sex hormones in development of this disease, our aim is to review evidence on the pathophysiology and etiology of this disease and the effects of different herbal extracts on changes in the serum levels of sex hormones and ovarian tissue. PCOS is the most common reproductive endocrine condition among women who are of childbearing age. As many as 10 percent of teens and young women are living with PCOS. Although conversations about PCOS often focus on the noncancerous growths that it causes, hormonal imbalance is at the heart of the condition. Your body depends on signals from your pituitary gland to produce the right amounts of estrogen, progesterone, and testosterone. PCOS disrupts these signals. Without the right signals from the pituitary gland, your estrogen and progesterone levels drop, and your testosterone levels increase.

This can prevent ovulation and lead to symptoms like:

- Irregular menstruation
- Acne, Hair growth on your face, chest, or back (hirsutism)
- Weight gain or difficulty losing weight
- Patches of dark skin on the back of your neck or other areas (acanthosis nigricans)

PCOS is just one of many risk factors for acne. In general, acne is caused by:

- Excess Oil Production
- Dead Skin Cells trapped deep in your Pores
- Bacteria (Primarily From Propioni bacterium Acnes)
- Excess Hormone activity

Acne may also result from:

- Stress
- Hormonal Changes, Such As During Pregnancy
- Certain Medications, Such As Corticosteroids

Certain behaviours can also increase your risk for acne. This includes:

- Not washing your face regularly
- Not drinking enough water
- Using comedogenic skin care products or makeup

LITERATURE REVIEW

Individual Herbal Extracts:

Aloe vera (L.) Burm.f. reduced plasma levels of total cholesterol (TC), triglyceride (TG), and low density lipoprotein cholesterol (LDL-C); enhanced high density lipoprotein cholesterol (HDL-C) levels (Desai et al., 2012); normalized follicular growth; and recovered the estrous cycle (Maharjan et al., 2010). Atractylodes macrocephala Koidz. induced the recovery of the estrous cycle and the reduction of testosterone levels, androstenedione levels, the free androgen index, LH levels, the LH/FSH ratio, and anti-Müllerian hormone levels (Zhou et al., 2016). Farokhi, 2014).

Quercetin and weight changes in PCOS

In these studies, the presence of PCOS is a contributing factor in the increased incidence of weight gain and overweight. Two of 5 animal studies reported that administration of Quercetin prevented weight gain and caused significant decrease in body weight in PCOS rats . Other animal studies as well as 3 human trials showed insignificant changes in weight, waist circumference and BMI among intervention groups compared to control groups. The education level also impacted what sources of information were chosen to learn about PCOS. Those who were high school graduates were the least likely to get information from their healthcare professional (26.9%) or government website/journal articles (6.0%) compared to the other

education levels. The use of social media to obtain information was popular among those with some college or technical training (27.9%) or an associate's degree or equivalent (27.4%), but was the least popular among those who had a graduate degree (11.4%). Participants with a graduate degree were more likely to obtain information from government (21.3%) than other education levels. Robert L. Rosenfield et al 2007 in this study state that risk factors for PCOS can be recognized in childhood. This study concluded that premature pubarche patients appear to carry about a 15 -20 % risk of developing PCOS. It seems likely that the risk is relatively high in those with exaggerated adrenarche and relatively low in those with ordinary premature adrenarche or idiopathic premature pubarche. PCOS is a complex trait with a large hereditary component. There fore, the presence of PCOS, or central obesity, diabetes, or other insulin resistant features in a parent should heighten the concern about risk for PCOS if the child presents other risk factors. Meher un Nisal (2009) A cross – sectional analytical study was conducted in Qassim University Clinic, in the year of 2007 -2009 . They concluded that obesity plays an important role in the genesis and maintenance of polycystic ovarian disease. PCOD is the leading cause of anovultory infertility in females and affects 1 in 10 women of reproductive age. PCOD is strongly associated with obesity. Angela Kerchner, B.A., el .al (2009) coducted a prospective longitudinal study cocluded that there is a significant risk mood disorders in women with polycystic ovarian syndrome. The persistent high rate of depression and other mood disorders are presents in young women with PCOS. Rosenfield RL. The University of Chicago Pritzker School of Medicine, Department of Pediatrics (2007) conducted a study on polycystic ovary syndrome (PCOS) appears to arise as a complex trait with contributions from both heritable and nonheritable factors. Polygenic influences appear to account for about 70% of the variance in pathogenesis. In view of this evidence for congenital contributions to the syndrome, childhood manifestations may be expected. The objective has been to review the evidence that risk factors for PCOS can be recognized in childhood. Congenital virilizing disorder are average or low birth weight for gestation age; premature adrenarche, particularly exaggerated adrenarche; atypical sexual precocity; or intractable obesity with acanthosis nigricans, metabolic syndrome, and pseudo-cushing syndrome or pseudo-acromegaly in early childhood have been identified as independent prepubertal risk factors for the development of PCOS. During adolescence, PCOS may masquerade as physiological adolescent anovulation. Asymptomatic adolescents with a polycystic ovary occasionally (8%) have subclinical PCOS but often (42%) have a subclinical PCOS type of ovarian dysfunction, the prognosis for which is unclear. Identifying children at risk for PCOS offers the prospect of eventually preventing some of the long-term complications associated with this syndrome once our understanding of the basis of the disorder improves. Fertile steril (2009) conducted a prospective longitudinal study in university they state that there is a significant risk for mood disorders in women with polycystic ovarian syndrome. They found that a high conversion risk for depression over a 1 to 2 year period under scores the importance of routine screening and aggressive treatment of mental health disorders in this population. Duleba AJ, Ahmed IM (2010) observational study to evaluate urinary albumin excretion (UAE) in normotensive and non diabetic women with polycystic ovary syndrome in relation to their clinical, endocrine, and metabolic motiles. They concluded urinary albumin exenetion in women with pcos correlates well with other cordiovcescular events is continuous, evaluation of UAE in the presence of information and may aid in selecting appropriate patients for move aggressive treatment of likely aggravation factors, such as hyperonsulinemia or borderline hypertension. Want Y, et.al says that the family history of diabetes mellitus has the most effect on the clinical phenotype in women with PCOS. The family history of other diseases such as menstrual disorder, premature balding and hypertension play less significant roles.

Table 1. Summarizes evidence on medicinal plants that are effective on PCOS in human (Clinical studies).

Medical plants &scientific name	English name Family	Study design	Study duration	Mechanism of action	Outcomes	References
Mentha spicata	Spearmint	Lamiaceae	42 women with PCOS and hirsutism treated with M. spicata tea twice a day compared with placebo tea.	One month	Not clear	Decreased levels of total and free testosterone in M. spicata-treated group after 1-month treatment, increased FSH and LH, and decreased degree of hirsutism
Cinnamomum zeylancum	Cinnamon	Lauraceae	Fifteen women with PCOS orally treated with C. zeylanicum and placebo.	For eight weeks	Improved insulin sensitivity	Significant decrease in insulin resistance in C. zeylanicum-treated group.
Grifola frondosa	Maitake or Hen-of-the-wood	Meripilaceac	72 patients randomly assigned to the group treated with the extract or clomiphene citrate alone and 18 ones who did not respond were co-treated with the extract and clomiphene citrate.	Treatment with the drug alone for 12 weeks and co-treatment with the drug and extract for 16 weeks.	Improved insulin sensitivity	Observation of ovulation in the patients of all groups
Origanum majorana	Sweet Marjoram	Lamiaceae	25 patients were treated with O. majorana te a (14 patients) and placebo tea (11 patients).	For one month	Improved insulin sensitivity and antiandrog en	Decreasing fasting insulin levels and DHEA-S.
Trigonella foenum-graceum L	Fenugreek	Leguminosa e	58 women with PCOS assigned to two groups: One 30 + individual group treated with T. foenum-graceum seed capsule + metformin and the other group treated with placebo + metformin	8 weeks	Improved insulin sensitivity	According to ultrasound scans, decrease in the polycystic ovaries and improvement of the ultrasound results and menstrual cycle in the women
Phoenix dactylifera	Date palm	Arecaceae	48 female Wistar rats assigned to 6 groups of 8 each: Control group, sham group administered with estradiol	60-day administratio n with estradiol valerate and 21-day	Antiandrog en	Decreased levels of estrogen and LH, increased levels of progesterone andFSH, decreased number of cystic

Medical plants &scientific name	English name Family	Study design	Study duration	Mechanism of action	Outcomes	References
			valerate solvent for 60 days and then treated with water for 21 days, PCOS1 control and PCOS2 control groups.	treatment with the extract.		follicles, increased number of primary and antral follicles and Graafian such as corpus luteum.

Table 2. Summarizes evidence on medicinal plants that are effective on PCOS in animals (Experimental studies).

Medical plants & scientific name	English name	Family	Study design	Study duration	Mechanism of action	Outcomes
Glycyrrhiza glabra L	Licorice	Fabaceae	84 mice assigned to six groups: Control group, hyperandrogenism group, and G. glabra extract (150, 300, and 450 mg/kg) groups	Inducing PCOS using letrozole for 21 days	Antiandrogen and phytoestrogen	Improvement of the adverse effects of hyperandrogenism due to PCOS in female mice's fertility.
Mentha piperita	Peppermint	Lamiaceae	40 Wistar rats with letrozole-induced PCOS.	Daily administration with letrozole for three weeks and treatment with the extract for three weeks	Antioxidant property	M. piperita supplementation caused improvement of ovarian cysts, necrosis of stromal mesenchymal cells, and hyperplasia of luminal epithelial cells.
Vitex agnus-castus	Monk,s pepper tree	Verbenaceae	32 Sprague Dawley rats with letrozole-induced PCOS and the treatment group treated with 365 mg/kg of the extract.	28-day administration with letrozole and 30-day treatment with the extract	Antiandrogen and phytoestrogen	Decreased serum level of testosterone and increased serum level of progesterone
Marrubium Vulgare	White Horehound	Lamiaceae	48 Wistar rats with letrozole-induced PCOS and the treatment group treated with 500 and 1000 mg/kg of the extract.	28-day administration with letrozole and 21-day treatment with the extract	Antiandrogen and phytoestrogen	Significant decrease in LH and testosterone (in 1000 mg/kg) and in estradiol and progesterone (at both doses).

Medical plants & scientific name	English name	Family	Study design	Study duration	Mechanism of action	Outcomes
Camellia sinensis	Green Tea	Theaceae	96 Wistar rats with estradiol valerate-induced PCOS assigned to 4 groups and the treatment groups treated with 50, 100, and 200 mg/kg of the extract.	60-day administration with estradiol valerate and 10-day treatment with the extract	Antioxidant property	Decrease in serum LH levels, decrease in the body's and ovarian weight and insulin resistance; changes in the number of follicles and the thickness of theca layer in histomorphometric studies
Rubus idaeus × strigosus	Raspberry	Rosaceae	120 Wistar rats with estradiol valerate-induced PCOS and the treatment groups treated with 100, 150, and 200 mg/kg of the extract.	60-day administration with estradiol valerate and 10-day treatment with the extract	Antioxidant property	Decrease in testosterone, estradiol, LH, and CRP and increase in progesterone and FSH
Chamaemelum nobile Or Anthemis nobilis L.	Chamomile	Asteraceae	30 rats with estradiol valerate-induced PCOS and treated with 25, 50, and 75 mg/kg of the extract.	60-day administration with estradiol valerate and 10-day treatment with the extract	Antiandrogen and phytoestrogen	Decrease in the symptoms of PCOS and the secretion of LH, FSH, and estradiol.
Pergularia Daemia	Trellis – vine	Apocynaceae	Inducing PCOS using testosterone propionate in Albino Wistar rats and treating them with the extract.	One-week induction and then one-week treatment with the extract	Management of obesity	Normalization of irregular estrous cycle in patients with PCOS after treatment with the extract
Foeniculum vulgare	Fennel	Apiaceae	30 rats with estradiol valerate-induced PCOS and 6 normal rats; the treatment groups were treated with 250, 500, and 1000 mg/kg of the extract.	60-day administration with estradiol valerate and 10-day treatment with the extract	Antiandrogen and phytoestrogen	Increased concentration of FSH after treatment with 500 and 1000 mg/kg of the extract and decreased LH and testosterone after treatment with 1000 mg/kg of the extract.

Medical plants & scientific name	English name	Family	Study design	Study duration	Mechanism of action	Outcomes
Glycine max	Soybean	Fabaceae	Inducing PCOS in Sprague Dawley rats using letrozole and treating them with soybean isoflavones (in 50&100 mg/kg).	21-day administration with letrozole and 14-day treatment with the extract	Antiandrogen and phytoestrogen and antioxidant	100 mg/kg of soybean significantly changed PCOS symptoms through the body's weight loss, and reducing diestrus phase, testosterone, the activities of 3 beta-hydroxysteroid dehydrogenase and 17beta-hydroxysteroid dehydrogenase, and oxidative stress.
Atractylodes macrocephala Koidz (AMK)	Atractylodes	Asteraceae	60 rats assigned to 5 groups of 12 each: Healthy control, PCOS, and three PCOS groups treated with low, moderate, and high concentrations of the extract; inducing PCOS using testosterone propionate.	Inducing PCOS for 12 days and treating with the extract for 8 consecutive weeks.	Antiandrogen	Improving estrous cycle, decreasing the plasma levels of total testosterone, androsetenedione, and FAI, higher levels of FSH and lower LH/FSH and anti-Mullerian hormone in ovary, and decreasing the expression levels of FSH receptor and increasing the expression levels of aquaporin 9.
Corylus avellana	Hazelnut or cobnut	Betulaceae Or Corylaceae	18 Sprague Dawley rats with letrozole-induced PCOS assigned to 3 groups of 6 each: Control, busereline acetate-treated, and treatment	21-day administration with letrozole and 45-day testing of the groups	Antiandrogen	Effective in treating PCOS through regulating serum lipid profile, steroids, and gonadotropins.
Bmbusa Vulgaria	Bamboo	Poaceae	4 groups of 6 each administered with letrozole, group 2 considered negative control, and groups 3 and 4 treated with 0.5 and 1 ml/kg of the extract.	21-day administration with letrozole and 3-week treatment with the extract	Antioxidant and antidiabetic	Improving estrous cycle and exerting hypolipidemic and hypoglycemic effects. Decreasing blood glucose and the levels of cholesterol, LDL, and triglyceride, improving cystic ovarie and ovulation.

Medical plants & scientific name	English name	Family	Study design	Study duration	Mechanism of action	Outcomes
Aloe vera	Aloe, Barbados aloe	Aloaceae	Two groups: Control group daily treated with carboxymethyl cellulose 1% and the other group administered with letrozole to induce PCOS and then treated with nonpolar A. vera extract for 60 days.	21-day administration with letrozole and 60-day treatment with the extract.	Antiandrogen	Decreasing the levels of testosterone and insulin through improving the levels of progesterone and estradiol; decreasing the transcription levels of steroid receptors; increasing aromatase expression.
Labisia pumila var. alata	Labisia	Primulaceae	Mice with PCOS assigned to two groups: The extract-treated and control groups; the extract-treated group orally treated with 50 mg/kg of the extract each day and the control group treated with 1 ml of deionized water.	4–5 weeks	Antiandrogen and phytoestrogen	Increasing uterus weight and insulin resistance; increasing resistin and improving lipid profile; in adipose tissue, decreasing the expression of leptin mRNA but ineffective on the expression of resistin and adiponectin.
Heracleum persicum	Desf	Apiaceae	In 30 rats, PCOS was induced by estradiol valerate and then treated with doses of 200 mg/kg, 400 and 800 Desf extracts.	Induction of PCOS in 60 days and 10 days treatment with extract.	Antiandrogen	Serum levels of estradiol, testosterone and LH increased, and FSH increased.
Cocos nucifera	Coconut palm	Arecaceae	Wistar rats with letrozole-induced PCOS were left untreated for 21 days and then treated with 100 and 200 mg/kg of C. nucifera aqueous extract. A positive control group, a negative control group, and two treatment groups	21-day administration with letrozole and 4-week treatment with the extract.	Antiandrogen and phytoestrogen	Regulating estrous cycle and increasing uterus weight.

Medical plants & scientific name	English name	Family	Study design	Study duration	Mechanism of action	Outcomes
Punica granatum L.	Pomegranate Juice	Lythraceae	56 Wistar rats were assigned to 6 groups of 8 each and PCOS was induced by estradiol valerate. The rats were treated with different doses of P. granatum ex tract.	81 days	Antioxidant property	Improving the levels of testosterone, androsetenedione, and estrogen in the treated groups.

A family history of positive coronary heart disease does not affect the clinical phenotype of such patients. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile.

DISCUSSION

Seven nutritional supplements and four herbal medicines were investigated and meta-analyses were reported for calcium plus vitamin D, Cinnamomum sp., inositol (vitamin B8), omega three fish oils and vitamin D. Menstrual regularity, a defining feature of critical interest to women with PCOS was examined in only four studies and no significant treatment effect compared to controls was found. However secondary outcomes of time to ovulation, ovulation rates, hyperandrogenism, reproductive and metabolic hormones, waist to hip ratio, cholesterol and triglycerides were significantly improved by inositol and total cholesterol was significantly lowered by omega three fish oils compared to controls. Adverse effects were reported in seven studies for four nutritional supplements and one herbal medicine. Mild adverse effects were found for Cinnamomum sp. There were no long term investigations of safety. This review found no single nutritional supplement or herbal medicine significantly improved the primary outcome, menstrual regulation. The oral contraceptive pill (OCP) is first line pharmaceutical treatment for menstrual regularity in women with PCOS however it is contraindicated in women with increased cardiovascular risks and women with PCOS have reported preferences for effective alternatives .Metformin is an effective alternative however women with PCOS have reported high rates of unpleasant side effects. There is low quality evidence from RCTs for menstrual regulation included in this review. Trials were characterized by a high risk of selection, performance and detection biases and an unclear risk of reporting bias. Evidence from methodologically sound RCTs is needed to examine the reliability of findings for calcium plus vitamin D compared with metformin for menstrual regulation.

CONCLUSION:

According to the present study, several medicinal plants, such as Vitex agnus-castus, cinnamon species, Cimicifuga racemosae (L.) Nutt., and Trigonellafoenum-graecumL could be helpful in the management of PCOS, based on current clinical evidence. However, their effectiveness is not certain due to some limitations, such as small sample size and short duration of studies. Therefore, further preclinical and clinical studies are essential with a larger sample size and a more structured methodology in order to evaluate the safety and pharmacological mechanisms of herbal medicines in PCOS.

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