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Integrative approaches for the management of PCOS: A review

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Abstract
Polycystic Ovarian Syndrome (PCOS) is a hyper androgenic condition in a female with persistent oligo-anovulation. Between the age of 18 and 44, almost 5% to 10% of females are impacted by this condition. The most prevalent issue in the world is infertility, which is the inability to conceive after a continuous one-year period of exposure to regular, unprotected, typical coitus. Three-quarters to forty percent of all human infertility are female-originated. Therefore, there is a greater demand for PCOS research and awareness. To decrease current treatments' cost, length, and side effects, integrative approaches must be developed based on the aforementioned variables. These approaches can be used to treat the polycystic ovarian syndrome, its consequences, and symptoms like obesity, irregular menstrual cycles, excessive hair growth, etc. This review consolidates current problems, treatment modalities associated with PCOS, and how integrative approaches can handle this syndrome in females.

Keywords: Polycystic ovary syndrome, hyperandrogenic anovulation, insulin resistance, pathophysiology, hirsutism

1. Introduction
The female reproductive system is in charge of producing gametes (also known as eggs or ova), certain sex hormones, and maintaining fertilized eggs as they develop into a mature foetus and prepare for delivery. A female's reproductive years are defined as the time between menarche (the first menstrual cycle) and menopause (cessation of menses for 12 consecutive months). During this time, ova are cyclically expelled from the ovary, with the potential fertilized by male gametes (sperm). This cyclical egg expulsion is a normal part of the menstrual cycle outer. The outer cortex of each ovary is the site of follicular development, while the inner medulla contains blood vessels and connective tissue [1]. The fallopian tubes are paired tubes that extend from the uterus to the ovaries. They are also known as uterine tubes, oviducts [2], or salpinges (singular salpinx) in females. The fallopian tubes are part of the female reproductive system. In other mammals, they are simply called oviducts [3]. The uterus is divided into two sections: the corpus (body) and the cervix. The fundus is the superior portion of the uterine corpus, while the isthmus/lower uterine segment is the inferior portion near the cervix. The endometrium, myometrium, and serosa are the three layers of the uterine walls. The endometrium is the uterine cavity's lining; it changes in thickness and structure in response to hormonal stimulation. The myometrium is the uterine wall's middle and thickest layer, made up of smooth muscle fibres. The serosa is the outermost lining of the uterus [4]. The vagina is a tubular fibromuscular structure that connects the vulvar vestibule to the uterine cervix. The introitus can be found in the distal vagina. The anterior vagina rubs against the posterior bladder wall, whereas the posterior vagina rubs against the anterior rectum [5]. The labia majora, minora, clitoris, vulvar vestibule, urethral meatus, and vaginal orifice are all part of the vulva [6]. The labia majora are lateral to the labia minora and connect anteriorly to form the mons pubis (a layer overlying the pubic symphysis). The vulvar vestibule is the area medial to the labia minora that contains the urethra and vaginal openings [7]. The Bartholin glands open lateral to the vaginal opening [8]. Stein and Leventhal described Polycystic Ovarian Syndrome for the first time. PCOS is associated with many conditions like chronic oligo-anovulation, polycystic ovarian morphology, psychological issues, metabolic abnormalities, particularly insulin resistance and compensatory hyperinsulinemia. This may lead to altered androgen production and metabolism in the reproductive age. Due to a lack of clearly established diagnostic criteria, many clinicians struggle to recognise this widespread condition [9]. Women with PCOS are more likely to have reproductive problems [10]. This condition, also known as the Stein-Leventhal syndrome, is a major cause of female infertility.

The hormonal imbalance, which has no clear cause, is characterised by a number of ideas. It is distinguished by multiple metabolic abnormalities, polycystic ovaries, and hyperandrogenism (as well as insulin resistance and hyperinsulinaemia) [11]. Pharmaceutical therapies and lifestyle changes are currently part of the standard of care for women with PCOS. Nutrition, calorie restriction, and physical fitness are all linked to lifestyle changes. Metformin, thiazolidinediones, estrogen-progestin combinations, and antiandrogens such as flutamide and spironolactone are among the medications used to treat diabetes (oral contraceptives). While effective, such treatment is costly and may cause weight gain, gastrointestinal discomfort, irregular menstruation, and increased insulin resistance [12]. Medicinal plants have received special attention since antiquity, and today, as a result of countless investigations, valuable and useful medicinal plants are discovered [13]. Numerous studies on herbal treatments have been conducted, including case studies, randomised controlled trials, and animal experiments, because the adverse effects of these medications and their identification are critical [14]. Insulin resistance is common in PCOS patients, who have testosterone levels that are roughly twice those of average females. Later, more recent models of rat PCOS were developed and validated. Understanding the nature of persistent anovulation and polycystic ovary is made possible by the novel concepts provided by these studies [15]. Animal models are required to move from scientific ideas to a real-world understanding of a disease in humans. Validated animal models can be used in preclinical research, fundamental reproductive biology studies, and therapeutic screenings. However, it's possible that chronic anovulation and PCOS animal models don't accurately mimic the human disease's reproductive events [16].

2. Symptoms

PCOS symptoms include hirsutism, acne, alopecia, acanthosis, seborrhea, infertility, insomnia, and irregular menstrual cycles [17].

Hirsutism: Hirsutism is the presence of terminal coarse hairs in females with a male-like distribution. It affects 5-10% of women [18] and is a common aesthetic problem seen in dermatological outpatient clinics (OPD). It is critical not only to identify the root cause of hirsutism, but also to understand how to recommend the best course of action based on the primary contributing factor. The main factor in making the diagnosis is that the form and rate of hair development have changed. A method for assessing hirsutism has been developed using technology and computer software [19]. According to a digital imaging study of hair development, hirsute and non-hirsute women have significantly different hair types and hair growth rates.

Acne: Spots and acne are symptoms of acne, a chronic skin disorder. The main cause is clogging of the hair follicles with oil and dead skin cells, which leads to the formation of whiteheads, blackheads, pimples, cysts, and so on. They are most commonly felt in the upper arms, neck, back, shoulders, and face. It could also be due to the various peripheral sensitivity of androgen receptors [20].

Alopecia: An autoimmune condition called alopecia areata makes your hair fall out, frequently in clumps around the size and shape of a quarter. Everybody experiences hair loss to a different degree. Some folks only occasionally lose it. Many other people lose. Sometimes hair falls off and then comes back. Others experience permanent hair growth [21].

Acanthosis: Acanthosis nigricans (AN) is characterized by dark, coarse and thickened skin with a velvety texture, being symmetrically distributed on the neck, the axillae, antecubital and popliteal fossae, and groin folds, histopathologically characterized by papillomatosis and hyperkeratosis of the skin. The term AN was originally proposed by Unna, but the first case was described by Pollitzer and Janovsky in 1891[22].

Seborrhea: A common inflammatory skin condition known as seborrheic dermatitis (SD), it most commonly affects the scalp, face, and body folds and has a papulosquamous morphology. The condition occurs bimodally, as shown by the infantile (ISD) and adult (ASD) variants. The condition, which frequently manifests as firm, greasy scales on the crown and frontal regions of the scalp, rarely bothers infants but can cause significant parental anxiety. It starts within the first three months of life and typically goes away on its own by the end of the first year. Atopic dermatitis and contact dermatitis are ranked first and second, respectively, for their potential to reduce quality of life, while ASD is distinguished by a relapsing and remitting pattern of disease [23].

Striae: Striae, or stretch marks, are indented streaks that often affect the abdomen, buttocks, thighs, back, breasts, axillae and groin. They are divided into striae atrophicans (thinned skin), striae gravidarum (following pregnancy), striae distensae (stretched skin), striae rubrae (red), striae albae (white), striae nigra (black), and striae caerulea (dark blue). These common complaints are difficult to treat. This activity outlines the role of the interprofessional team in the evaluation and management of stretch marks [24].

Acrochordons: Small, benign growths known as skin tags (acrochordons) usually have the same colour as your skin. They frequently resemble a mass of skin tissue growing from a little stem. They can occasionally be darker and resemble a raised mole. The majority of skin tags range in size from 1 to 5 mm, although some can reach a few centimetres [25].

Infertility: Infertility is the inability of a person, animal or plant to reproduce by natural means. It is usually not the natural state of a healthy adult, except notably among certain eusocial species (mostly haplodiploid insects). It is the normal state of a human child or other young offspring, because they have not undergone puberty, which is the body's start of reproductive capacity [26].

Insomnia: Affective, anxiety, and somatic dysfunctions can all coexist with sleep problems in PCOS. The impairment of the capacity to initiate or sustain sleep, which occurs at least three nights a week and impairs daily functioning, is what defines insomnia. There are three types of insomnia: trnsitory, acute, and chronic. Both primary and secondary insomnia can occur, and both types do in around 80% of instances [27].

Period irregularities: They are a menstrual cycle issue. When there are increased, delayed, or missed bleeding patterns, it is a condition. It further contributes to the reproductive system's issue. With increasing age in women, there is a link between PCOS and low levels of androgen.

Considering above mentioned issues, aromatherapy can be used to relieve stress and to improve overall wellbeing in these cases [28].

3. Pathophysiology

When PCOS is finally diagnosed, it manifests as a phenotype that reflects a vicious cycle that involves ovarian, neuroendocrine, and metabolic abnormalities. Regarding the immediate physiologic causes of PCOS, many theories have been put forth through the years. In PCOS, several proteins and genes interact and are impacted by environmental and epigenetic variable [29]. The causes of PCOS in people and in

preclinical models are broken out in specific sections of this article. Major PCOS symptoms include both clinical and biochemical hyperandrogenism.

A crucial aspect of PCOS is androgen excess, which is seen in 60–80% of people with the condition. The effects of high androgen production include hirsutism and hyperandrogenism. Indeed, hyperandrogenism is the most prevalent aberration seen in the disease and is a major contributor to the aberrant hormones that contribute to the pathogenesis of PCOS. Hyperandrogenism is frequently manifested by elevated levels of free (unbound) testosterone in circulation. The majority of cases have excessive ovarian androgen production, however some patients also have excessive adrenal androgen production. Higher free testosterone concentrations are a result of the increasing androgen levels' suppression of sex hormone-binding globulin (SHBG) concentrations. In this article, we break down this complex illness into its key pathophysiologic elements. Despite the fact that we focus on particular components, PCOS is an illustration of systems biology with various interconnected signaling networks, which in individual instances may not involve all networks [30].

One follicle is often selected for terminal maturity and ovulation in a sequential manner in humans because the factors that affect follicular growth are coordinated in this way. 6-7 million ovarian follicles are diminished to about 2-3 million primordial follicles before birth. As a result, methods to regulate the rate at which primordial follicles enter the expanding pool are crucial for maintaining the ovarian reserve necessary to ensure fertility. Subsequently, primordial follicles are continually recruited from this pool. Since autocrine, paracrine, and local endocrine factors, as well as gonadotropins, govern these poorly understood early stages of follicular development, gonadotropins are not required [31].

Growing follicles and dormant follicles coexist in a dynamic equilibrium. Follicular arrest occurs as a result of PCOS, which is characterised by an imbalance of androgens, anti-Müllerian hormone (AMH), and FSH [32]. Lack of FSH and insufficient androgen to estradiol conversion prevent the theca cells from selecting a dominant follicle, which leads to prolonged anovulation [33]. Abundant LH stimulates the theca cells to generate androgens. Due to its ability to prevent the transformation of primordial follicles into primary follicles, AMH, which is released by granulosa cells, is a key factor in controlling this equilibrium. So, PCOS is characterised by an increase in the size of the tiny follicles, followed by a growth arrest that results in the distinctive polycystic shape. A PCOS ovary's follicles may be fundamentally different from those in a normal ovary, according to some research [34]. Elevated androgen production caused by increased CYP17A1 expression or P450c17 activity is still present in theca cells taken from PCOS-afflicted women [35]. Theca cells taken from PCOS-afflicted women maintain their phenotypic with enhanced androgen secretion due to elevated CYP17A1 expression or P450c17 activity. Proteins implicated in the secondary "backdoor pathway" of steroidogenesis are more abundantly expressed in PCOS theca cells, according to immunohistochemical investigations [36]. Alternative splicing of the DENND1A transcript results in a number of variations, and genome-wide association studies (GWAS) have focused research on this particular locus. In PCOS theca cells, one variation, DENND1A.V2, is expressed more strongly. Intriguingly, overexpression of theca cells from healthy women mimics PCOS phenotype while knockdown of this variation mimics a normal theca cell phenotype in PCOS ovaries [37]. The mechanism controlling the alternative splicing `appears to be independent of the DENND1A gene [38].

Both the zona reticularis and the theca cell, in addition to the adrenal cortex, express a large number of steroidogenic enzymes. Dehydroepiandrosterone (DHEA), DHEA sulphate, and androstenedione are some of the hormones released by the zona reticularis. It is becoming clear that 11-hydroxyandrostenedione, which is eventually transformed into the powerful androgen 11-ketotestosterone, is a component of the adrenal's and maybe the theca cell's steroidogenic repertory [39]. In comparison to control, women with PCOS had greater serum levels of the 11-oxygenated androgens, 11-hydroxyandrostenedione, 11-ketoandrostenedione, 11-hydroxytestosterone, and 11-ketotestosterone [40].

Understanding the pathophysiology of PCOS has been made possible by the correlation between insulin resistance, compensatory hyperinsulinemia, and hyperandrogenism. The cellular and molecular causes of insulin resistance in PCOS have been thoroughly studied, and it is now clear that the main problem is a decline in insulin sensitivity brought on by an abnormality in the post-binding phase of insulin receptor-mediated signal transduction. A smaller but still significant decline in insulin responsiveness also exists [41].

Due to the fact that it is unaffected by obesity, metabolic disorders, anomalies in the distribution of body fat, and levels of sex hormones, it appears that low insulin sensitivity in PCOS may be a genetically predisposed defect in genetically vulnerable women. Increased insulin-independent serine phosphorylation and decreased insulin-dependent tyrosine phosphorylation may be the result of genetic anomalies in the control of insulin receptor phosphorylation [42].

The common link between PCOS and obesity has a synergistic detrimental influence on glucose homeostasis and can exacerbate both hyperandrogenism and anovulation, even though insulin resistance may exist regardless of body mass index (BMI). It is not believed that measuring BMI by itself can accurately predict cardiovascular risk. After accounting for dyslipidaemia, hyperglycaemia, and hypertension, it has been claimed that the link between BMI and coronary heart disease almost vanished. Some women have severe metabolic abnormalities even when they have a normal BMI, whereas others only have a few risk factors when their BMI is elevated. According to some, rather than BMI itself, what matters is how fat is distributed, with android obesity being more dangerous than gynecoid obesity. Because abdominal visceral fat rather than subcutaneous fat is detected by measuring the waist: Hip ratio or waist circumference. Visceral fat is metabolically active and increases in it are associated with higher rates of insulin resistance, type 2 diabetes, dyslipidaemia, hypertension, and enlarged left ventricle. Exercise significantly lowers visceral fat and lowers the risk of cardiovascular disease [43].

Endogenous androgen levels are increased by insulin through a variety of mechanisms of action. A greater blood insulin concentration is the outcome of increased peripheral insulin resistance. In response to LH stimulation, excess insulin increases theca cells androgen synthesis by binding to the IGF-1 receptors [44]. Hyperinsulinaemia also decreases the synthesis of SHBG by the liver. There is therefore an increase in the concentration of free T in the serum and consequent peripheral androgen action. In addition, hyperinsulinaemia inhibits the hepatic secretion of IGF binding protein-1 (IGFBP-1), leading to increased bioavailability of IGF-1 and IGF-2[45], the important regulators of ovarian follicular

maturation and steroidogenesis [46]. Together with more IGF-2 secretion from the theca cells, IGF-1 and IGF-2 further augment ovarian androgen production by acting on IGF-1 receptors[47], [48].

Due to enhanced cytochrome P450c17a enzyme activity, which is crucial for the production of ovarian and adrenal steroid hormones, insulin may also raise endogenous androgen levels. Additionally proven are the overactivity of P450c17a caused by insulin and the heightened responsiveness of serum 17-OHP to GnRHa stimulation [49]. By directly impacting the ovary and accelerating the follicular atresia process, intraovarian androgen excess causes anovulation [50]. Apoptosis of granulosa cells is a hallmark of the later process. As a result, there is an expanding stromal compartment that still responds to LH and continues to release androgens.

4. Diagnosis

Diagnosis of PCOS can be done by looking at morphology of the ovaries, symptoms or by running numerous tests. Enlarged ovaries are a sign of PCOS because of more than 12 follicles. Medical history, such as whether anyone else in the patient's family has the condition previously is also important.

The Rotterdam criteria was developed for the diagnosis of PCOS [51]. They expanded the diagnostic criteria to include ultrasound images of polycystic ovaries as a second diagnostic marker. Various organization and committees, including the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology (ESHRE), slowly and steadily approved these criteria (ASRM). Despite the fact that this standard is debatable and the Androgen Excess Society (AES) [52]. Developed a new set of diagnostic criteria in 2006, this standard is still the one that various guidelines use the most frequently [53], [54]. Numerous obstetricians, gynecologists, and other experts agree with and follow these recommendations [55].

Blood tests can be performed to measure the hormone levels in the body [56]. Determination of testosterone and the free androgen index are the most crucial hormonal tests to check whether women may have hyperandrogenism [57]. In addition to this, LH, FSH, estrogen, dehydroepiandrosterone sulphate, androstenedione, TSH, prolactin, and hormones related to adrenal function tests, such as 17-hydroxyprogesterone, are some of the tests that fall under this category.

This condition is also associated with insulin resistance, cardiovascular disease and diabetes, so it is important to evaluate those risks.

Ultrasound imaging is employed to examine inside organs and tissues. An ultrasound of the uterus, ovaries, and pelvis is advised to detect any cysts and swollen ovaries. Sexually active women can undergo transvaginal ultrasound which is a painless, radiation-free examination. If necessary, an abdominal scan can be performed to determine whether the ovaries can be seen externally through the stomach walls [58].

5. Management of PCOS

The target patient's priorities and the therapeutic strategy that is chosen depend on them. The challenges could include trying to conceive, controlling menstrual irregularities, losing weight, or getting relief from hyperandrogenic symptoms including acne, hirsutism, or androgenic alopecia. To achieve the best outcome, the strategy should in fact be customised for each individual. Physicians are forced to use symptomatic therapy because there is no perfect treatment for all women with PCOS [59].

Loss of weight

Women with PCOS who have elevated androgenic hormone levels acquire weight, primarily in the abdomen. Because of this, a lot of PCOS women have an apple-shaped physique rather than a pear-shaped body [60]. First step is calorie restriction followed by weight loss and would be highly desired [61]. Numerous studies show that even a 5%–10% weight loss can help women resume their regular menstrual cycles [62]. It would be ideal for obese ladies to achieve their normal range of body mass index (BMI). The incidence of metabolic syndrome declines along with weight loss and the level of free testosterone rises [63].

Diet

The optimum diet or nutrient regimen would be the customized one, as was previously said, to reach specific goals for each lady [64]. However, some recommendations might make it easier or harder to decide what to eat. A diet that is high in fibre and low in carbohydrates and saturated fats would be optimal. Low and high glycemic index carbohydrates are categorised according to the blood glucose response they produce within two hours. We prioritise consuming foods and vegetables with low glycemic indexes, such as broccoli, raw carrot, lentils, soy, bran morning cereals, whole-grain bread, etc. Additionally, patients should be informed that some fruits, white rice, cakes, cookies, fries, and items with a high glycemic index should be avoided.

Workout

In order to lose weight, it's important to exercise and be physically active. They might help increase insulin sensitivity [65]. The American Heart Association advises approximately 150 minutes of moderate activity or 75 minutes of strenuous and intensive exercise each week. Other studies have suggested exercising at different times throughout the week. Numerous studies have shown that exercise, whether combined with dieting or not, can help PCOS sufferers regain ovulation. Through modulation of the hypothalamic-pituitary-gonadal (HPG) axis, exercise presumably has an impact on ovulation. Exercise causes decreased insulin and free androgen levels in overweight and obese women, which triggers the restoration of HPA regulation of ovulation.

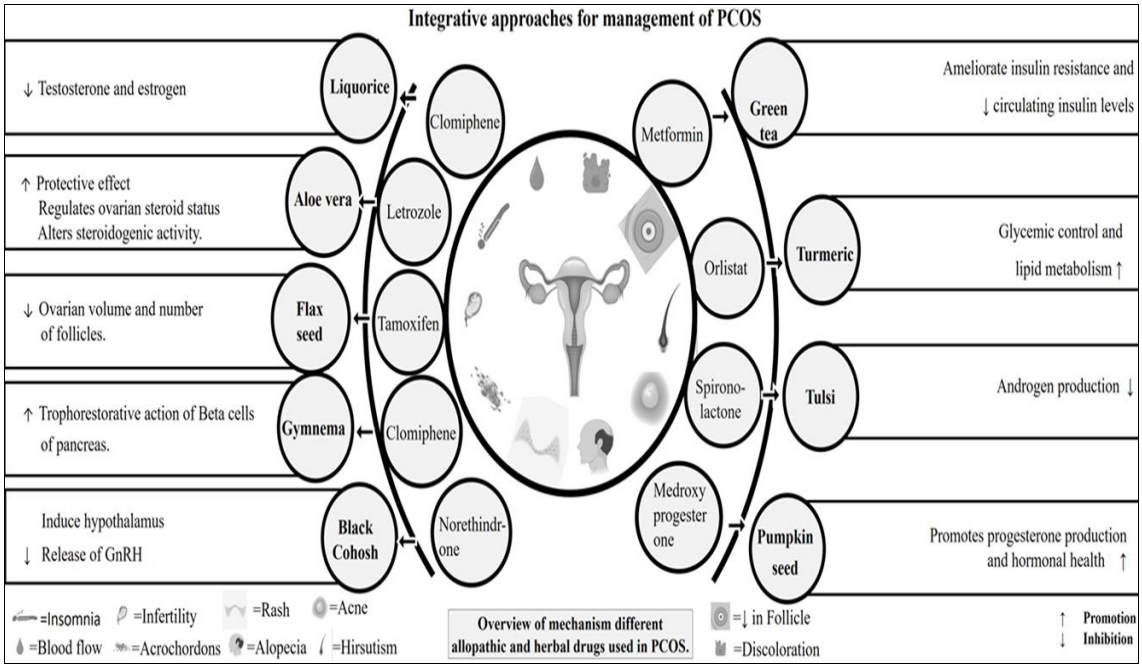

Fig 1: Integrative approaches towards PCOS

6. Herbal remedy for PCOS

Herbal treatment is by applying a multi-pronged approach by correcting the hormonal imbalance, treatment to obesity and avoiding high cholesterol levels and treatment to insulin resistance.

Licorice

Glycyrrhiza glabra is a member of the Leguminosae family of plants. Nine healthy women between the ages of 22 and 26 were examined during the luteal phase of the cycle to determine the impact of liquorice on androgen metabolism. They received 3.5 g of a commercial liquorice mixture containing 7.6% weight-to-weight glycyrrhizic acid per day for two cycles [66]. They were not receiving any additional care. By radioimmunoassay, plasma renin activity, serum adrenal and gonadal androgens, aldosterone, and cortisol were all assessed. Within two months, there was a progressive decline in total serum testosterone. After treatment was stopped, it reverted to pretreatment levels. Due to the blockade of 17-hydroxysteroid dehydrogenase and 17-20 lyase, licorice can lower serum testosterone levels. Licorice may be used as an adjunctive treatment for polycystic ovarian syndrome and hirsutism. Other than this, it functions as a powerful anti-androgen and aids the body in maintaining biosynthesis and estrogen release. The flavonoids in Glycyrrhiza interact with estrogenic receptors and have estrogenic activity, which gives rise to their anti-androgenic effects. Furthermore, flavonoids may aid in the release of insulin, which lowers blood sugar levels and benefits PCOS therapy [67].

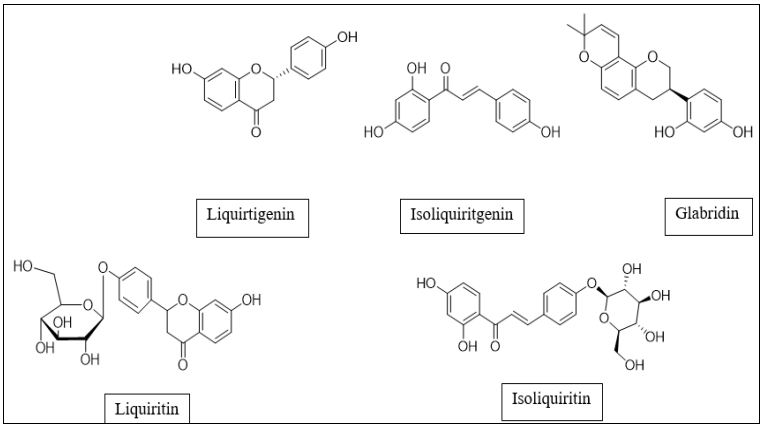

Fig 2: Flavonoids and its analogues

Aloe-vera

Aloe barbadensis is the scientific name; the Liliaceae family. In a study, the effectiveness of an Aloe vera gel formulation was evaluated in a rat model of PCOS. Letrozole, a non-steroidal aromatase inhibitor, was orally administered to five-month-old female Charles Foster rats to elicit PCOS. The Aloe vera gel concoction was then administered orally to the rats (1 ml dose daily for 45 days). Their steroidogenic activity, glucose sensitivity, and oestrus cyclicity were all recovered as a result [68]. The development of the PCOS phenotype was stopped by combining the inductive drug (Letrozole) with the aloe vera gel. By restoring the ovarian steroid status and changing important steroidogenic activity, aloe vera gel formulation has a protective impact against the PCOS phenotype. This is explained by the phyto-components in the extract as aloe-emodin and barbaloin [69].

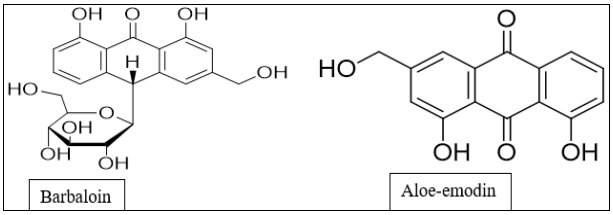

Fig 3: Secondary metabolites of Aloe-vera responsible for altering PCOS

Flax Seed

Linum usitatissimum is the scientific name; the Linaceae family. In a study, the hormonal responses to flaxseed supplementation (30 g/day) in a 31-year-old PCOS patient was noted. The patient consumed 83% of the recommended flaxseed dose over the course of four months. Body Mass Index (BMI), insulin, total serum testosterone, and free serum testosterone levels showed a substantial decrease in both the baseline and 4-month follow-up height-weight measurements and fasting blood samples. At the end of the research period, the patient also noted a reduction in hirsutism. The hirsutism documented in this case study, along with a clinically substantial decline in testosterone levels [70]. The chemical constituents showing anti PCOS activity are lignans namely secoisolariciresinol and secoisolariciresinol diglycoside-SDG along with linolenic acid respectively [71].

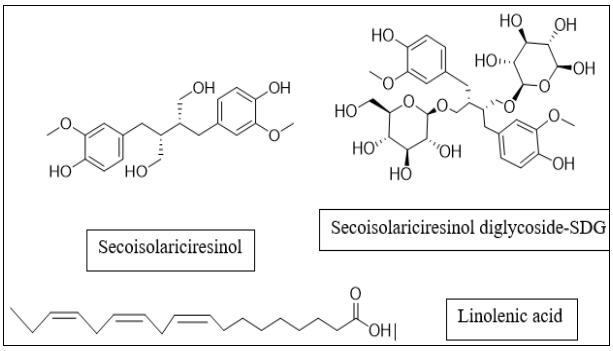

Fig 4: Lignans and polyunsaturated fatty acids present in *Linum usitatissimum* with anti-androgenic activity

***Gymnema sylvestre* (Gymnema)**

Gymnema is a common Ayurvedic herb that supports weight loss and is used as an anti-diabetic, hypoglycemic, lipid-lowering, and anti-lipid agent. Gymnema may have trophorestorative effects on the pancreatic beta cells. The leaf is the plant portion used in medicine. Due to its ability to modulate insulin and the additional advantages of lowering the high triglycerides related to PCOS, gymnema is a good candidate for treating PCOS [72, 73]. Saponins, particularly gymnemic acids, are important Gymnema components. Gymnemic acid conceals the sweet flavour when taken before food since it lowers the sweet taste on the taste buds [74].

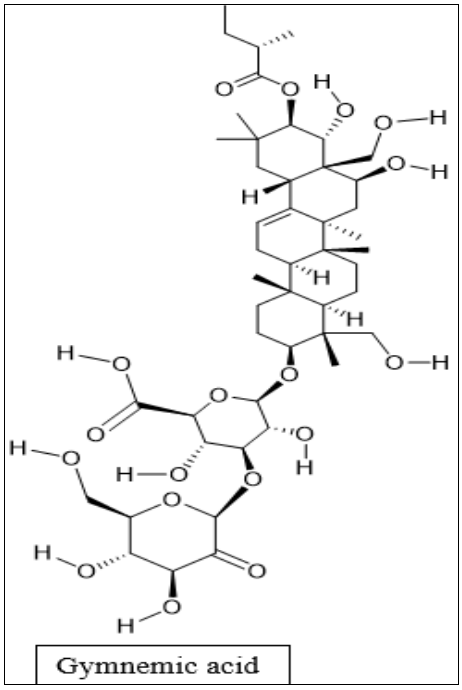

Fig 5: Major chemical constituent of Gymnema, Gymnemic Acid which shows trophorestorative effect on pancreatic beta cells

Black Cohosh Root (*Cimicifuga racemosa*)

Because it contains phytochemicals from class phenylpropanoids that can reduce luteinizing hormone release, *black cohosh* root (*Cimicifuga racemosa*) has a potent impact on the endocrine system. Black cohosh works well for PMS, severe menstrual cramps, and symptoms linked to hormones. Adverse effects: This herb has a number of potential side effects, including headache, dizziness, vaginal spotting, muscle discomfort, gastrointestinal problems, and weight gain. Black cohosh has also been linked to liver problems, so keep a look out for any liver-related symptoms like dark urine, appetite loss, yellowing of the skin or eyes, and nausea [75]. Isoferulic acid, ferulic acid, caffeic acid and cimicifugic acid D are the phytoconstituents belonging to phenylpropanoid class involved in reducing luteinizing hormone release.

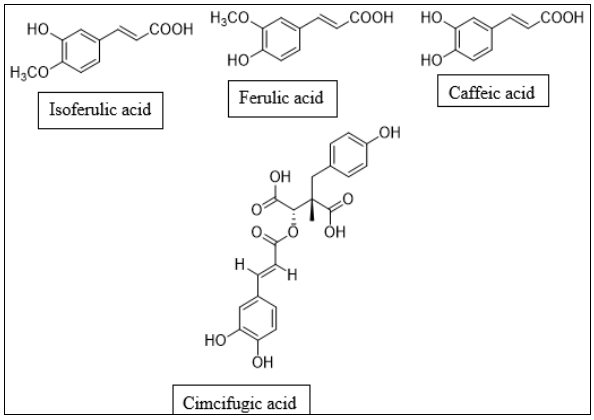

Fig 6: Phenylpropanoids responsible for reduction of luteinizing hormone release

Green Tea

The strong antioxidants found in green tea, specifically catechins like epicatechin, epicatechin-3-gallate, epigallocatechin & epigallocatechin-3-gallate are what reduces the hormone levels that cause ovarian cysts and other associated symptoms. The antioxidants in green tea also help to regulate insulin levels. Daily green tea consumption has an effect on PCOS-related weight gain and aids in your effort to lose this extra weight [76].

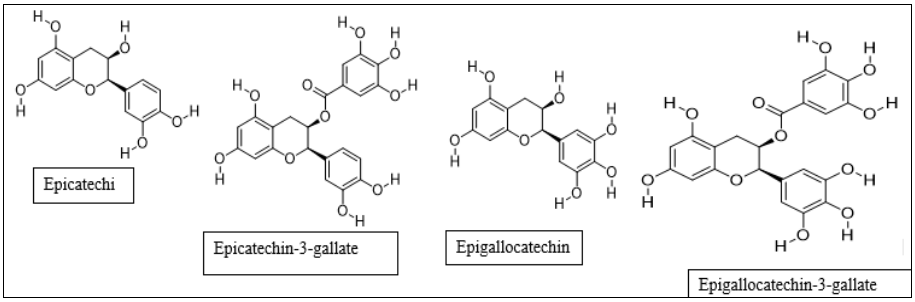

Fig 7: Antioxidants of green tea, catechins, that reduces the hormone levels resulting in ovarian cysts

Curcumin

Curcuminoids of *Curcuma longa* showed beneficial effects in Letrozole induced PCOS in female Wistar rats. Its effect was comparable to that of Clomiphene citrate, most widely used treatment for ovulation induction in PCOS condition [77].

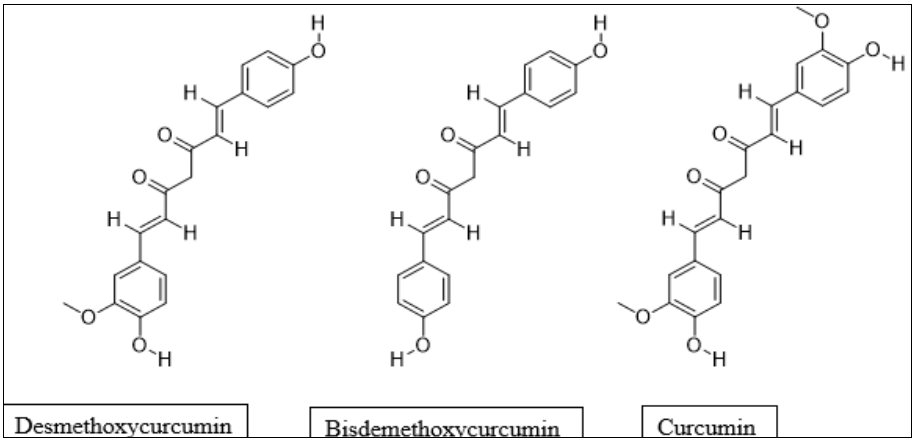

Fig 8: The three major Curcuminoids, Curcumin, Desmethoxycurcumin and Bisdemethoxycurcumin proved to show beneficial effects in letrozole induced PCOS

***Ocimum sanctum* (Tulsi)**

Ocimum sanctum is one of the important plant could be helpful in management of PCOS [78]. It contains various phytochemicals including eugenol, ursolic acid, linalool are studied for various activities [79]. The androgens are not utilized because the ovulation process does not take place. Also, the SHBG protein produced by liver is also pretty low. This is why women struggle to conceive, have excessive facial hair growth, and suffer from acne. Tulsi can reduce insulin levels and regulate androgens. It works wonders as an antioxidant. Leaves should be ingested on an empty stomach in the early morning. Regularly consume boiled Tulsi water.

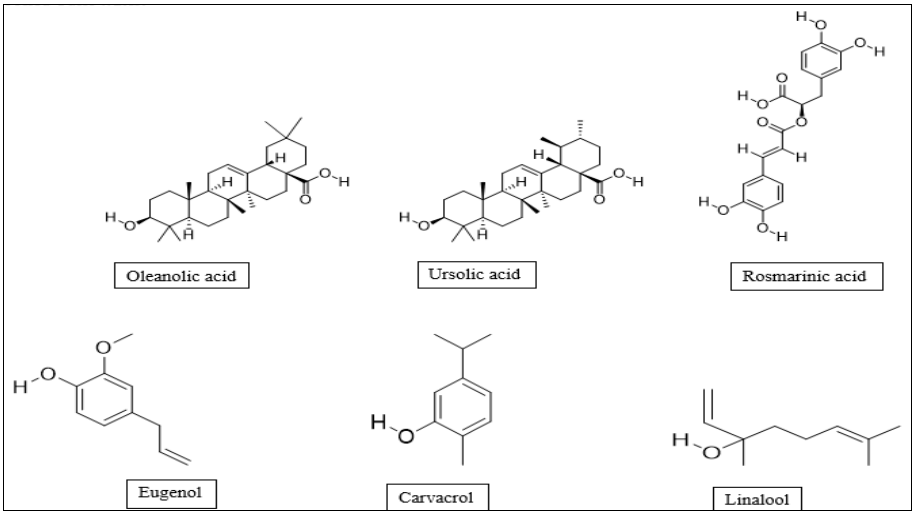

Fig 9: Active constituents of Tulsi, Eugenol being the main chemical constituent that alters the process of PCOS

Pumpkin seeds

Pumpkin seeds also contain omega-3 fatty acids, which can help manage the high cholesterol and insulin levels associated with PCOS. They also contain beta-sitosterol, which can remove excess androgens and treat PCOS symptoms such as hirsutism, acne, and weight gain.

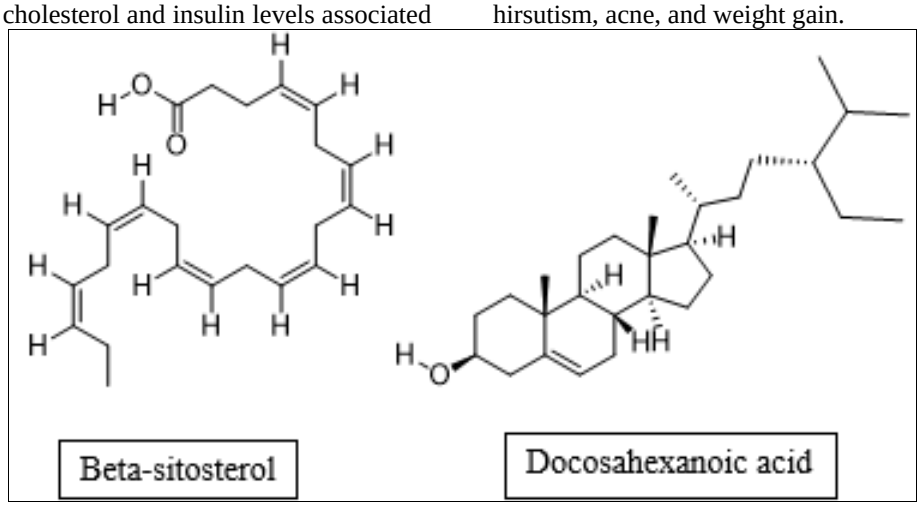

Fig 12: Docosahexanoic acid (DHA) and beta-sitosterol, the two main constituents of Pumpkin seeds which regulates high cholesterol and insulin levels

Table 1: Herbal remedy for PCOS [80]

Sanskrit name	English name	Botanical identity	Part used
Yashtimadhu	Liquorice	*Glycyrrhiza glabra* (Fabaceae)	Root
Ghrit Kumari	Aloe Vera	*Aloe barbadensis* (Asphodelaceae)	Gel
Neempushpi	Flax Seed	*Linum usitatissimum* (Linaceae)	Seed
Madhunashini	Gymnema	*Gymnema sylvestre* (Apocynaceae)	Leaf
Khadira	Black Cohosh	*Cimcifuga racemose* (Ranunculaceae)	Root
Harichaayam	Green Tea	*Camellia sinensis* (Theaceae)	Leaf
Haridra	Turmeric	*Curcuma longa* (Zingiberaceae)	Root
Tulsi	Holy basil	*Ocimum sanctum* (Lamiaceae)	Leaf
Kusmandakah	Pumpkin Seeds	*Cucurbita pepo* (Cucurbitaceae)	Seeds

Table 2: Clinical trials conducted on PCOS: [81]

	Title	Status	Study Results	Interventions	Characteristics	Population Age	Dates	Locations
1	Effects of Combined Resveratrol and Myo-inositol on Altered Metabolic, Endocrine Parameters and Perceived Stress in Patients With Polycystic Ovarian Syndrome	Completed	No Results Available	Drug: Resveratrol (1000mg twice a day), Myoinositol 1000mg (Twice a day) Drug: Metformin (500 mg Twice a day), Pioglitazone (15 mg Twice a day) Study Type: Interventional	Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor) Primary Purpose: Treatment	20 Years to 35 Years (Adult)	Primary Completion: August 3, 2021 Study Completion: August 3, 2021	Gynecology and Obstetric, Hayatabad Medical Complex, Peshawar, Khyber Pukhtunkhwa, Pakistan
2	Effect of Dietary Modification on Microbiota in Overweight and Obese Polycystic Ovary Syndrome Patients	Unknown status	No Results Available	Dietary Supplement: Dietary and life style modification and probiotic Sanprobi Super Formula Other: Placebo	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	18 Years to 40 Years (Adult)	Primary Completion: September 20, 2018 Completion: October 20, 2018	Division of Infertility and Reproductive Endocrinology, Department of Gynecology and Obstetrics, Pozna#, Poland
3	The Effect of	Completed	No	Dietary	Study Type:	18 Years to	Primary	Shariati Hospital, Tehran,

	Astaxanthin on Oxidative Stress Indices in Patients with Polycystic Ovary Syndrome		Results Available	Supplement: Astaxanthin 8 mg Other: placebo	Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Basic Science	40 Years (Adult)	Completion: November 1, 2020 Study Completion: April 7, 2021	Iran, Islamic Republic of
4	Correction of Vitamin D Deficiency and Its Effect on Ovulation Induction in Women With PCOS (VIDEO): A Feasibility RCT	Completed	No Results Available	Drug: Vitamin D Drug: Ovulatory Agent	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	18 Years to 45 Years (Adult)	Primary Completion: November 2018 Study Completion: November 2018	Faculty of Medicine, Ain Shams University, Cairo, Al Qahirah, Egypt
5	Metformin Versus Acarbose Treatment in Infertile Overweight Women with Polycystic Ovary Syndrome (PCOS)	Completed	No Results Available	Drug: Metformin Drug: Acarbose	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Participant) Primary Purpose: Treatment	18 Years to 40 Years (Adult)	Primary Completion: December 2008 Study Completion: December 2008	Royan Institute, Tehran, Iran, Islamic Republic of
6	Effect of Laparoscopic Ovarian Drilling on Outcomes of *in Vitro* Fertilisation in Clomiphene-resistant Women With Polycystic Ovary Syndrome.	Unknown status	No Results Available	Procedure: IVF/ICSI	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Diagnostic	25 Years to 35 Years (Adult)	Primary Completion: August 2018 Study Completion: September 2018	Ain Shams university, Cairo, Egypt
7	Effect of Chromium Supplementation on Intracytoplasmatic Sperm Injection (ICSI) Outcomes in Polycystic Ovary Syndrome Ladies	Completed	No Results Available	Dietary Supplement: Chromium	Study Type: Intervention Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Investigator, Outcomes Assessor) Primary Purpose: Treatment	20 Years to 40 Years (Adult)	Primary Completion: February 21, 2019 Study Completion: February 21, 2019	KasrELAiniH, Cairo, Egypt
8	Transcriptional and	Recruiting	No	Other: DEXA	Study Type:	18 Years to	Primary	AdventHealth Translational

	Epigenetic Program of PCOS Women.		Results Available	Other: Magnetic Resonance (MR) Assessment of the Abdomen Procedure: Adipose tissue biopsy Other: Oral glucose tolerance test	Observational Study Design: Observational Model: Cohort Time Perspective: Prospective	45 Years (Adult)	Completion: December 2022 Study Completion: December 2022	Research Institute, Orlando, Florida, United States
9	N-Acetylcysteine and L-carnitine in PCOS.	Completed	No Results Available	Drug: N-Acetylcysteine Drug: L-carnitine	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor). Primary Purpose: Treatment	18 Years to 40 Years (Adult)	Primary Completion: June 2018 Study Completion: July 2018	Zagazig University, Zagazig, Egypt
10	Vitamin D Supplementation in PCOS Patients.	Completed	No Results Available	Drug: Vitamin D Drug: Placebo Oral Tablet	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Care Provider) Primary Purpose: Treatment	20 Years to 35 Years (Adult)	Primary Completion: March 30, 2022 Study Completion: March 31, 2022	Ayman Shehata Dawood, Tanta, Algharbia, Egypt
11	Insulin Differences Between African-American and Caucasian Female Adolescents With Polycystic Ovary Syndrome (PCOS)	Terminated	No Results Available	Other: Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)	Study Type: Interventional Study Design: Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Diagnostic	12 Years to 18 Years (Child, Adult)	Primary Completion: June 2015 Study Completion: June 2015	Clinical Research Centre at The Ohio University Wexner Medical Center / Nationwide Children's Hospital, Columbus, Ohio, United States
12	Androgen Blockade and Progesterone Augmentation of Gonadotropin Secretion	Recruiting	No Results Available	Drug: Micronized progesterone Drug: Placebo Drug: Flutamide Drug: Estradiol patch	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Crossover Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Basic Science	18 Years to 30 Years (Adult)	Primary Completion: October 1, 2025 Study Completion: October 1, 2025	University of Virginia, Charlottesville, Virginia, United States
13	Probiotic Intervention in PCOS	Recruiting	No Results Available	Dietary Supplement: Probiotic Drug: Metformin Hydrochloride Dietary	Study Type: Interventional Study Design: Allocation: Randomized Intervention	18 Years to 45 Years (Adult)	Primary Completion: December 2023 Study Completion:	Medical University of Graz, Division of Endocrinology and Diabetology, Graz, Styria, Austria

				Supplement: Probiotic Placebo	Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment		December 2023	
14	The Supporting Understanding of PCOS Education and Research (SUPER) Study	Recruiting	No Results Available	Behavioral: DASH diet Behavioral: Very low- carbohydrate diet	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Treatment	21 Years to 40 Years (Adult)	Primary Completion: November 14, 2025 Study Completion: October 14, 2026	University of Michigan, Ann Arbor, Michigan, United States
15	The Mechanism of Modified Utral-long Protocol in Improving Endometrial Receptivity in Patients With PCOS and IR.	Terminated	No Results Available	Procedure: Modified Supper Long Protocol	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	20 Years to 35 Years (Adult)	Primary Completion: September 15, 2018 Study Completion: September 30, 2018	Reproductive & Genetic Hospital of CITIC-XIANGYA, Changsha, Hunan, China
16	n-3 Polyunsaturated Fatty Acids (PUFA) Supplementation in Young Women With Polycystic Ovary Syndrome (PCOS)	Completed	No Results Available	Dietary Supplement: LC n-3 PUFA (fish oil) Supplement Dietary Supplement: Placebo (olive oil) supplement	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Crossover Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	18 Years to 40 Years (Adult)	Primary Completion: July 2008 Study Completion: July 2008	Diabetes Day Centre, The Adelaide and Meath Hospital, Dublin, Ireland Nutrigenomics Research Group, UCD, Dublin, Ireland
17	Research of Intensive Lifestyle Intervention for PCOS Patients With IGT.	Completed	No Results Available	Behavioral: intensive lifestyle intervention Drug: GLP-1 Receptor Agonists Drug: Metformin Drug: Acarbose	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Crossover Assignment Masking: None (Open Label) Primary Purpose: Treatment	14 Years to 50 Years (Child, Adult)	Primary Completion: December 2017 Study Completion: April 2018	Renji Hospital Department of Endocrinology and Metabolism, Shanghai, Shanghai, China
18	Effects of Simvastatin and Micronized Trans-resveratrol Treatment on Polycystic Ovary Syndrome (PCOS) Patients.	Unknown status	No Results Available	Drug: Simvastatin and micronized trans- resveratrol	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Single Group Assignment Masking: Double (Participant, Investigator)	18 Years to 45 Years (Adult)	Primary Completion: June 2017 Study Completion: June 2018	• Division of Infertility and Reproductive Endocrinology, Department of Gynecology and Obstetrics, Poznan, Poland

					Primary Purpose: Treatment			
19	Polycystic Ovary Syndrome (PCOS): Effect of Letrozole and Berberine.	Unknown status	No Results Available	Drug: Letrozole – Berberine Drug: Letrozole Drug: Berberine	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	20 Years to 40 Years (Adult)	Primary Completion: December 2013 Study Completion: December 2013	Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, Anhui, China Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China Guangzhou Medical School First Affiliated Hospital, Guangzhou, Guangdong, China Daqing LongNa Hospital, Daqing, Heilongjiang, China Daqing Longnan hospital, Daqing, Heilongjiang, China Obstetrics and Gynecology,Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, China First Affliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China Mudanjiang maternal and children hospital, Mudanjiang, Heilongjiang, China 2nd Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, Henan, China First Affiliated Hospital of Hunan University of Chinese, Changsha, Hunan, China and 8 more.
20	Phytoestrogens as an Alternative to Estradiol in Ovulation Induction in PCOS.	Completed	No Results Available	Drug: phytoestrogen Drug: estradiol valerate Drug: clomiphene citrate	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment	20 Years to 37 Years (Adult)	Primary Completion: January 2015 Study Completion: January 2015	First Affiliated Hospital of Hunan University of Chinese, Changsha, Hunan, China
21	Myo-inositol, Alpha-Lactalbumin and Folic Acid Treatment in PCOS.	Completed	No Results Available	Dietary Supplement: myo-inositol, alpha-lactalbumin, folic acid	Study Type: Interventional Study Design: Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	18 Years to 40 Years (Adult)	Primary Completion: January 31, 2020 Study Completion: February 28, 2020	AGUNCO Centre, Rome, Italy Hospital Juarez de México, Ciudad de México, Mexico
22	Improved Effects of MI Plus Alpha-LA in PCOS	Completed	No Results Available	Dietary Supplement: myo-inositol plus folic acid Dietary Supplement: myo-inositol plus folic	Study Type: Interventional Study Design: Allocation: Non-Randomized Intervention	20 Years to 35 Years (Adult)	Primary Completion: October 12, 2017 Study Completion:	Department of Woman Health and Reproductive Medicine of Santo Spirito Hospital, Rome, Italy

				acid plus alpha-lactalbumin	Model: Sequential Assignment Masking: None (Open Label) Primary Purpose: Treatment		December 15, 2017	
23	Oral Contraceptive and Cardiovascular Risk in PCOS	Completed	No Results Available	Behavioral: Physical exercise Drug: OC - Drospirenone plus Ethynylestradiol Dietary Supplement: Vitamin, polyvitamins tablets	Study Type: Interventional Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	18 Years to 40 Years (Adult)	Primary Completion: September 2007 Study Completion: December 2007	Department of Molecular and Clinical Endocrinology and Oncology, University "Federico II", Naples, Italy

7. Conclusion

PCOS is a complicated condition, which relates to the mind, the body, and also the reproductive system of women. This chronic illness that manifests throughout life and has a significant impact on both health and the economy. Most PCOS patients, especially those who are overweight, have insulin resistance, which increases their risk of developing metabolic syndrome, prediabetes, and diabetes. Because of this, one needs to understand the role of integrative approaches for management of PCOS including insulin resistance and hyper androgens. For the vast majority of patients, lifestyle is the primary focus of treatment, and an aggressive lifestyle-based multidisciplinary strategy is typically best for managing PCOS symptoms and avoiding long-term consequences. Even if women continue to be clinically in the unhealthy overweight or obese range, small, attainable targets of 5% body weight loss result in significant clinical improvement. Clinically, it is critical to address various parameters like hyperandrogenism, and monitoring and controlling long-term metabolic consequences. Herbal drugs along with integrative approaches could be of significant value in the better management of these symptoms and for the best possible PCOS care.

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