An Integrated Approach to Non-Pharmacological Intervention for Polycystic Ovarian Syndrome

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Abstract:

Background- PCOS, or polycystic ovarian syndrome, is a prevalent condition affecting women these days. Polycystic ovarian syndrome is a complex endocrine and metabolic disorder that affects 9–22% of women. Anovulatory infertility is a possible outcome of this condition in women who are fertile. It is commonly linked to many metabolic problems, including diabetic complications, diabetes-related insulin resistance, adiposity (increased weight), high cholesterol, and hyperandrogenism (which can present as hirsutism, acne, and irregular menstruation).

Objective- To investigate the safety and effectiveness of non-pharmacological therapies for women with polycystic ovarian syndrome.

Methods- The Cochrane library, PubMed, ScienceDirect, SpringerLink, The Journal of Clinical Endocrinology & Metabolism, and other databases were searched for information on gynecology. We searched several clinical trial databases from the previous year and past systematic reviews.

Result- Non-pharmacological therapies for PCOS is incredibly successful for treating PCOS symptoms and is also excellent for maintaining general health, such as regular menstruation. This is supported by several reviews and research studies.

Conclusion- The investigation revealed that lifestyle modification and physical activity are the most popular strategies in today's culture. There are other equally effective treatments for controlling polycystic ovarian syndrome, but women tend not to know about them, thus they are frequently disregarded.

Keywords: *Polycystic ovarian syndrome, hyperandrogenism, non-pharmacological managements, endocrine disorder, lifestyle modification.*

Introduction

The majority of health problems in this developing world are thought to be gender-specific. Changes in lifestyle in emerging nations have an impact on women's health. PCOS is a serious condition associated with abnormalities in the reproductive, psychological, and metabolic systems. Polycystic ovarian syndrome (PCOS) or Polycystic ovarian disorder (PCOD) is one of the most prominent disorders affecting around 19-24% of women at reproductive aged. PCOS or PCOD is defined as "a complex endocrine and metabolic disorder characterized by hyperandrogenism, hirsutism, obesity and acne." It was identified that it is due to the imbalance of gonadotropin stimulating hormone (i.e. Follicle stimulating hormone and Luteinizing Harmone). The imbalance of FSH and LH leads to menstrual problems results in infertility. PCOS is caused multiple range of reasons like imbalance between luteinizing hormone (LH), estrogen, testosterone and follicle stimulating hormone (FSH) (Imbalance of reproductive hormone), the imbalance in these hormone level leads to disturbance in normal menstrual cycle and further cause menstrual irregulatries **[1,2]**. While doing a pelvic examination in 1935, American gynecologists Stein and Leventhal were the first to identify and characterize this condition [3]. During this examination, they found hirsutism, amenorrhea, and an enlarged ovary. The abnormal form of the ovary is shown by histopathology, and an assay indicates a high level of testosterone [4]. Research from the National Institute of Diabetes and Digestive and Kidney Disease (2023) and V. De Leo et al. (2016) indicates that this condition may raise the risk of developing multiple illnesses, including Hypertension, diabetes, various cardiovascular risk as well multiple metabolic issues [6]. Infertility [11,12], hypothyroidism, irregular menstruation [7, 8], dysmenorrhea [9, 10], and chronic anovulation are among the signs and symptoms of PCOS. A combination of internal (hormone and neurological) and external (environmental) variables that lead to androgen and ovulatory dysfunction characterize PCOS. It is also connected to the dysfunctional feedback system of the pituitary gland, which can result in an overabundance of LH [13].

A meta-analysis report on the occurrence of this disease in India is conducted by Bharali MD et al. 2023 [10], yielding a 10-12 percent prevalence, particularly among women of reproductive age. The WHO estimated that the frequency was between 15 and 25 percent globally [14–16]. As per NIHODP, about 7 - 8 percent of Indian women have PCOS [17–19]. A number of factors, such as heredity, insulin resistance, oxidative stress, low-grade inflammation, and lifestyle, can lead to PCOS [20]. Infertility might result from this condition if treatment is not received [21]. Increased levels of luteinizing hormone, including frequency, amplitude, serum concentration, and ratio of LH to FSH, are indicative of PCOS, a neuroendocrine disorder [22].

Today, there are several therapy options for polycystic ovarian syndrome, with metformin and clomiphene citrate serving as the first line of treatment for inducing ovulation. Nowadays, clomiphene citrate, metformin, tamoxifen, and laparoscopy—a surgical technique in which ovaries' cysts are removed—are the most regularly prescribed medications for PCOS [23]. On the other hand, prolonged use of these medications may lead to serious side effects like irregular menstruation, nausea, vomiting, and gastrointestinal problems; distention of the abdomen; blurred vision; weight gain; increased insulin resistance; decreased compliance; poor efficacy; and an increased number of contraindications [24].

New research show that metformin may be an insulin-sensitizing drug, although its mechanism of action remains unclear. In addition, it may lead to multiple pregnancies, ovarian hyperstimulation, the creation of many follicles, and fetal abnormalities such neural tube defects, all of which might negatively affect the course of therapy [25].

Finding and developing alternative treatments is crucial given the negative effects of these medications and how well they treat PCOS. Dietary changes, non-pharmacological intervention, and plant-based therapies—especially those that contain phytoestrogens, or oestrogen—are thought to be far more effective than pharmaceutical interventions [26–29]. This non-pharmacological strategy may be beneficial for women with PCOS, according to some data [30]. These techniques have shown promise in helping PCOS patients and lowering the risk of related problems in other groups.

In this review, we provide a comprehensive overview of all the non-pharmacological approaches that have been shown to be successful in managing poly-ovarian cysts syndrome, along with the underlying molecular mechanisms of these approaches.

Methodology

A thorough analysis of the electronic databases of PubMed, Scopus, Goggle Scholar, Elsevier, Springer, and research gate was undertaken. These databases comprise medical literature, scientific reports, and numerous research papers. This study aims to find articles produced in English between 1990 and 2023 that specifically focus on PCOS in relation to dietary and herbal therapy, physical exercise, yoga, aromatherapy, acupressure, dietary intake, acupuncture and other non-pharmacological intervention. The review’s includes prospective quantitative studies using PCOS woman samples as well as diverse studies on management of PCOS with non-pharmacological intervention. The terms "PCOS," "polycystic ovarian syndrome," "herbal treatment," "nutrition," "diet," "lifestyle modification," "pathophysiology," "diagnostic criteria," and "management of PCOS", “physical exercise,” “yoga,” “aromatherapy,” “acupressure,” “dietary intake,” “acupuncture” was used to search the literature.

The titles of the produced articles were then assessed. Articles whose titles did not align with the goal of the systematic review were disregarded. The remaining papers' abstracts were then evaluated, and those that did not fit the inclusion criteria and the goals of the review were also eliminated. The remaining studies were then looked up in their full text versions, and those that did not fit the criteria for the review were discarded.

Etiology of PCOS

An oligogenic condition brought on by both hereditary and environmental causes is polycystic ovarian syndrome, or PCOS. Reproductive hormone imbalances, including high levels of androgens, luteinizing hormone, and follicle-stimulating hormone, are its defining features. Menstrual cycle irregularities, acne, and hirsutism are the symptoms that result from this. Higher luteinizing hormone and decreased follicle-stimulating hormone levels are common in PCOS-affected women, which can lead to irregular ovulation and ovarian cysts. Common characteristics of PCOS include insulin resistance and hyperinsulinemia, which raise insulin levels and exacerbate symptoms [31].

Insulin resistance and obesity are caused by a combination of environmental and lifestyle variables, including sedentary lifestyles and bad eating habits. Women with PCOS frequently exhibit chronic low-grade inflammation, which adds to insulin resistance and the etiology of the condition. Knowing the etiology is essential for developing effective treatment strategies. Figure 1 shows the factors responsible for the onset of disease in women.

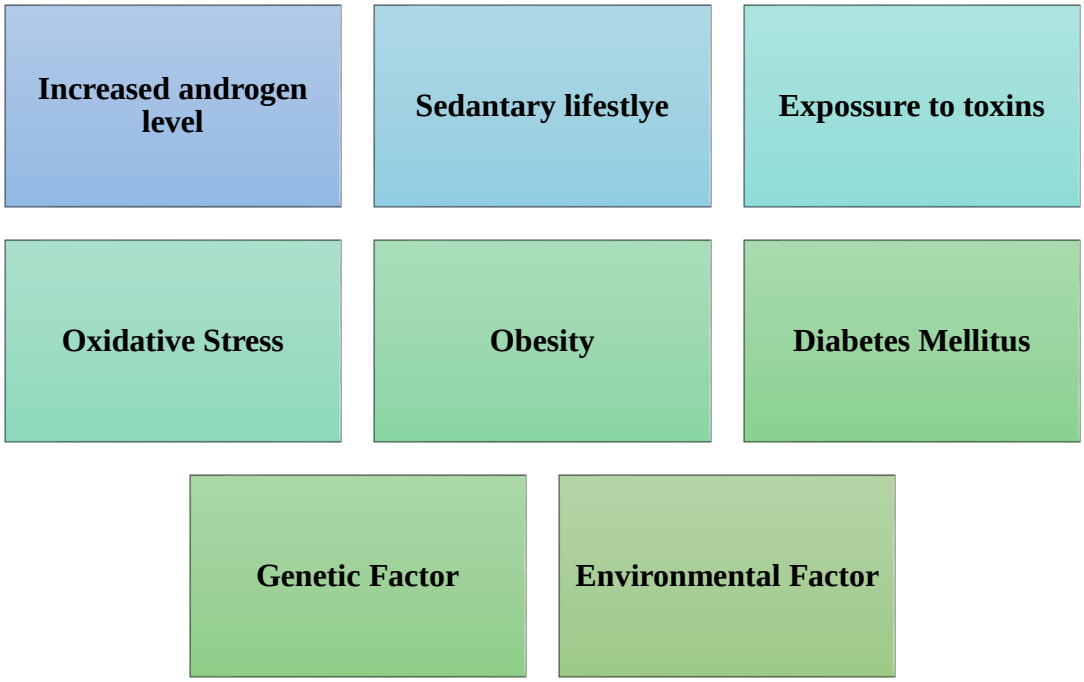

Figure 1: Factor Responsible for the Development of polycystic ovarian syndrome.

As per the findings of the Kabel AM 2016 study [32], the ailment is typified by the formation of an ovarian cyst as a result of elevated androgen levels. This disruption of the menstrual cycle, as well as the secretion of follicle stimulating hormone and testosterone, leads to the development of various skin problems such as hirsutism and acne. These factors also contribute to infertility, hirsutism, and acne-like clinical manifestations, and they are hypothesized to be associated with hyperandrogenism, insulin resistance, and inflammation in PCOS [33]. PCOS is largely impacted by the genetic and environmental variables that cause obesity, according to studies by Lim et al. [34] and Gonzalez F et al. (2006) [35]. The exact association between oxidative stress and inflammatory markers is yet unknown, however obesity, oxidative stress, inflammation, and angiogenesis indicators are all positively correlated with androgen levels in PCOS.

Insulin resistance, hyperinsulinemia, and hyperandrogenism are all promoted by these risk factors. Lastly, the combination of hyperandrogenism, insulin resistance, and inflammation may be the root cause for several of the adverse fertility results in PCOS [36] [125].

Acupuncture

These days, acupuncture is one of the most popular methods. This technique, which has its roots in ancient China, is applied in traditional Chinese medicine. Needles are inserted under certain skin and muscle tissues in particular body parts during this therapy **[37]**.

According to the study by ***Ee C et al. (2020)***, this strategy is vital for regulating and restoring vegetative function **[38]**. Numerous studies have also documented the use of acupuncture in the treatment of a wide range of illnesses and disorders, including polycystic ovarian syndrome, dysmenorrhea, and anti-inflammatory effects. Additionally, acupuncture has been shown to have minimal side effects and to affect several biological systems, including the immune, digestive, respiratory, neurological, locomotory, circulatory, endocrine, and genitourinary systems **[39-41].**

According to study *Julia J and Elisabet SV (2013)* reported the role of acupuncture in the induction of ovulation **[42].** Various study *Lansdown A, Aled Rees D (2012), Sun J et al. (2013), Manneras L et al. (2009) and Li J et al. (2015)* also reported the role of acupuncture in the treatment of polycystic ovarian syndrome by modifying insulin resistance, androgen hypersecretions, lipids metabolism, control obesity and anxiety **[43-46].** It helps in PCOS by managing various factors shown in figure 2.

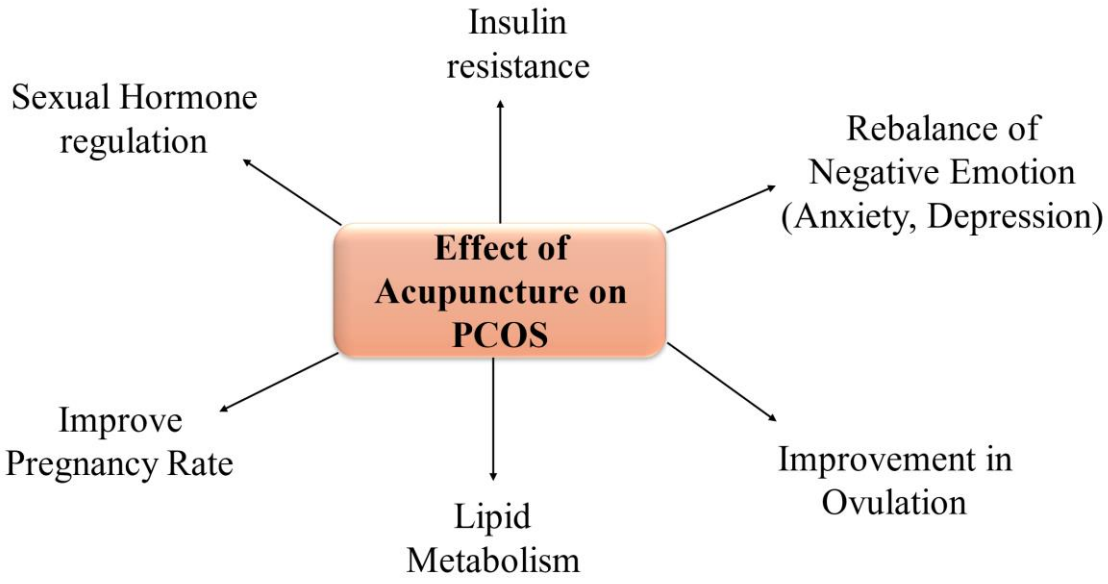

Figure 2: Various benefits of acupuncture on the patients suffering from polycystic ovarian syndrome.

Acupuncture controlled the sympathetic nervous system, which promotes the gonadotropin-releasing hormone and controls the hypersecretion of testosterone from the hypothalamus, according to a study by ***de Oliveira NM et al. (2023)*** **[47].** The therapy enhances metabolic and endocrine processes. Additionally, it has been claimed to enhance reproductive activity by reestablishing the equilibrium between the follicle stimulating hormone and the luteinizing hormone. This therapy lowers the levels of testosterone in PCOS patients' blood and fat tissue. In preclinical research, it was also discovered that it decreased serum testosterone in female rats by binding to central opioid receptors, which helps to control PCOS and preserve symptoms like acne and hirsutism. ***Zhang HL et al. (2020) and (Hickman FE et al. 2018)*** reveals that acupuncture reduces anxiety and depression in PCOS patients by controlling the levels of androgens and β-endorphins in the blood **[48,49].**

In PCOS rats, electroacupuncture treatments have been shown to suppress the sympathetic nervous system's hyperactivity, which stops the expression of the p75 neurotrophins receptor (p75NTR) from rising. Additionally, β-endorphin production and secretion are regulated by acupuncture, which lowers cortisol levels and may enhance fertility and ovulation induction. Infertile PCOS patients have also been observed to benefit from electroacupuncture in terms of oocyte quality and potential for embryonic development **[50-55]**. Figure 3 presents a thorough process of acupuncture proposed in PCOS patients.

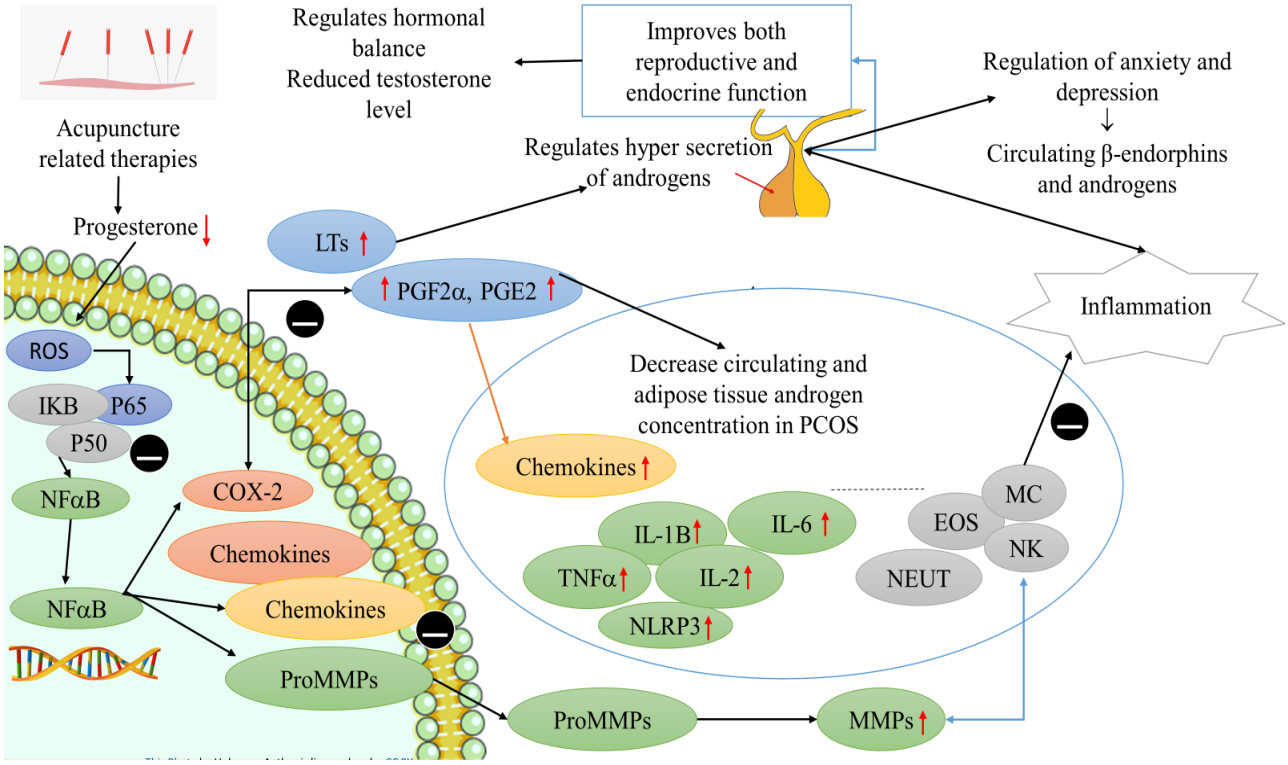

Figure 3: Mechanism of acupuncture in polycystic ovarian syndrome, (1) regulates hormonal balance and reduce testosterone level; (2) decrease circulating adipose androgen concentration in PCOS; (3) regulates endorphins levels.

Physical Exercise

Frequent physical activity is essential for maintaining overall health because it enhances daily functioning, promotes a healthy lifestyle, lowers the incidence of illness, builds bones and muscles, and lowers the risk of disease. Adults who exercise moderately to vigorously and reduce their sitting time have better health. Frequent exercise can enhance function, happiness, and quality of life while also aiding in the management of chronic illnesses and impairments like arthritis. It also lowers the risk of heart disease and helps regulate blood sugar **[56].**

According to study *Cheryce L. Harrison et al. (2011)* physical exercise is a first line approach to treat poly-cystic ovarian disorder **[57].** Additionally Physical activity and scheduled physical activity provide metabolic, cardiovascular, and cognitive benefits at the population level **[58-59].** Exercise regimen, frequency, intensity, and type all have a big impact on women with polycystic ovarian dysfunction **[60].**

International guidelines based on evidence state that exercise has been shown to be more beneficial for women with PCOS than minimal or no intervention **[61].** Numerous studies have also demonstrated that, often without appreciable weight loss, women with PCOS and overweight/obesity have improved cardiometabolic features, cardiorespiratory fitness, body composition, reproductive features, and psychological well-being **[62-65].**

About 50% of women with PCOS have improved ovulation and menstrual periods because of exercise training, which also improves body composition **[66].** Additionally, losing weight can lower the amplitude of luteinizing hormone (LH), which lowers the production of androgen. Exercise help in balancing the hormonal level (i.e., Luteinizing hormone and follicle stimulating hormone) **[67].** Exercise increases intramyocellular triacylglycerol concentration, which improves insulin sensitivity by modulating lipid metabolism and insulin sensitivity in skeletal muscle. Apolipoprotein, adiponectin, and muscle lipid absorption, transport, utilization, and oxidation are all enhanced by exercise training. Along with enhancing muscle fiber hyperplasia, capillary density, mitochondrial density, number, neural sensitization, motor learning, and adaptations, it also improves exercise capacity and lessens exercise intolerance in PCOS patients **[68]**. Figure 4 illustrates the diagrammatic portrayal of the benefits of exercise for PCOS women.

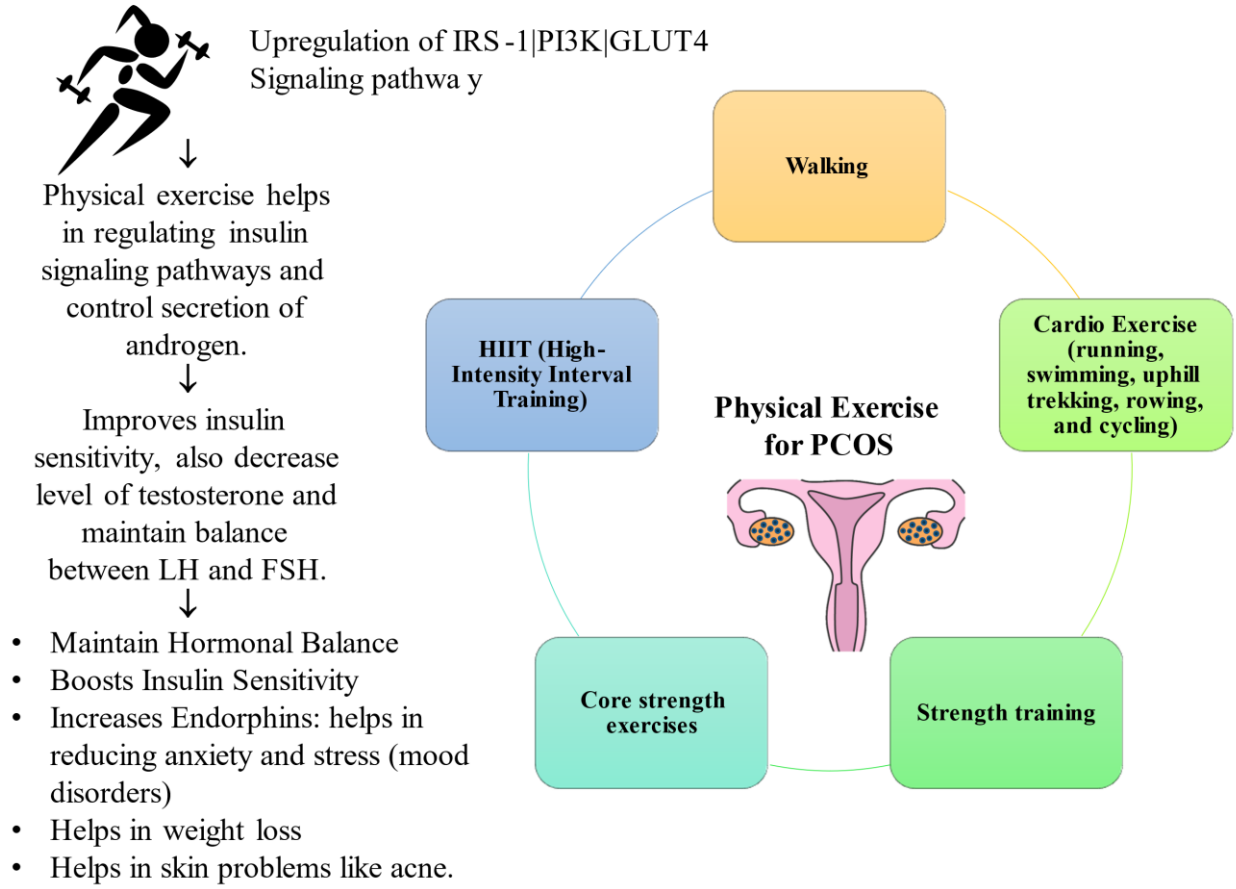

Figure 4 : Role of physical Exercise in PCOS.

Table 1 different physical exercise along with their description for Poly Cystic Ovarian Syndrome (PCOS).

S. No	Physical Exercise	Description	Duration	Ref.
	Aerobic Exercise	Various RCT studies revealed doing treadmill or cycling 3 days per week results in decrease insulin resistance and improvement in insulin sensitivity and glucose infusion rate.	30-60 minutes (3-4 days/week)	**[69,70]**
	High Intensity Interval Training	Prospective and case control studies revealed that HIIT improves glucose tolerance and results in restoring balance between LH and FSH. HIIT also helps in BMI.	3 months	**[71]**
	Zumba	It helps in reducing stress and helps in maintaining hormonal balance.	30-40 minutes (3-4 days/week)	**[72]**
	Stretching	Not only can exercise help with dysmenorrhea, but it also helps in regulating hormonal balance.	20-45 minutes (2-3 days/week)	**[73]**
	Others: Running, Swimming and jogging	These exercise helps in reducing stress and release of endorphins help in the alleviation of mood disorders. It also improves sleep quality. Studies also revealed these exercise helps in maintaining glucose and cholesterol levels.	20-30 minutes (2-3 days/week)	**[74]**

Yoga

Yoga presents a comprehensive approach to fostering a healthy body and mind, capable of addressing the underlying causes of PCOS. It is widely acknowledged that lifestyle modifications, including yoga and exercise, can mitigate PCOS symptoms and their severity. Yoga is a holistic system comprising physical, mental, and spiritual practices, including postures (asanas), breathing exercises (pranayama), meditation, and ethical principles **[75,76].** Yoga aids in releasing deeply stored stress in the system, thereby improving PCOS symptoms. Firstly, weight-bearing poses promote muscle building, which helps combat insulin resistance, a key aspect of managing PCOS. Secondly, an active yoga practice elevates heart rate, providing a cardiovascular workout conducive to weight loss. Thirdly, asanas and pranayama promote hormonal balance and deep relaxation, regulating adrenal and cortisol levels in stressed PCOS individuals. Lastly, according to yoga philosophy and Ayurveda, certain poses stimulate stagnant energy systems within the body, thereby restoring balance **[77].**

According to study ***Kumari et al. 2023*** **[78],** yoga can help control PCOS by lowering hormone levels, restoring menstrual cycles, and enhancing physical attractiveness and psychological well-being. Yoga addresses hormonal imbalances, mitochondrial function, metabolic syndrome, microRNA modulation, cellular lifespan, and mental health.

Aromatherapy

Aromatherapy is a technique to support the health of the body, mind, and soul by using essential oils that are extracted from plants. These unpredictable chemicals have varying fragrances and include oxides, acetates, aldehydes, alcohols, mono-terpenes, esters, ketones, and phenols. They have distinct chemical compositions and may have varying therapeutic effects, and they come in different chemotypes. In addition to being a topical treatment for skin disorders, aromatherapy is used as a stress reliever, anxiolytic, hormone balancing and to treat a variety of illnesses and symptoms **[79]**. Since PCOS is also seen as a disorder of harmonic imbalance, using essential oils in treatment aids in the disease's control **[80].** It offers several advantages, as illustrated in figure 5.

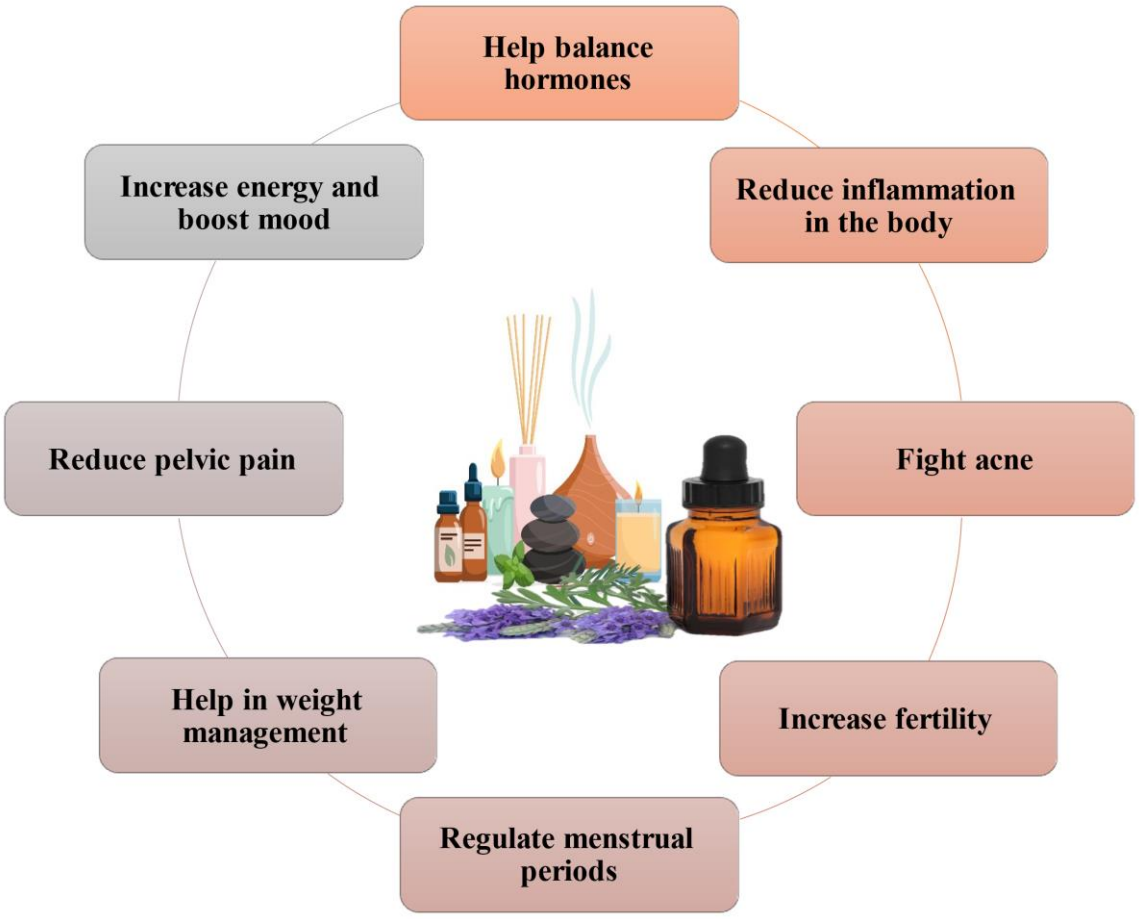

Figure 5: Role of Aromatherapy in PCOS

Aromatherapy is important in the treatment of Polycystic Ovary Syndrome (PCOS). It's an alternative medicine method that uses aromatic plant compounds, like essential oils like clary sage, lavender, and sandalwood, to improve overall health and wellness. While aromatherapy cannot completely cure PCOS, it can assist manage its symptoms.

Aromatherapy can lessen the symptoms of PCOS. It is believed that the aroma of essential oils stimulates the limbic system, which controls emotions and hormones, and the brain's olfactory system **[81].** Considering this, aromatherapy may help to relieve mental stress, restore hormonal balance, and promote a feeling of peace and wellbeing—all of which are factors in the decrease of PCOS symptoms. According to study *Heydari et al. (2019)*, The premenstrual syndrome symptoms were effectively alleviated by essential oils of Rosa damascena and Citrus aurantium, which also had an impact on the mental and physical symptoms as well as the social functions of females **[82].** In a study of *Tiffanny Jones et al. (2021),* Lavender Aromatherapy to Reduce Anxiety and assist in the treatment of pain as well. Aromatherapy with lavender oil has been used for a variety of women's health issues **[83].** Lavender essential oil has been demonstrated to reduce the psychological states of pain, anxiety, and depression in women with premenstrual syndrome, polycystic ovarian disease, and primary dysmenorrhea (pain associated with menstruation). This oil has also been demonstrated to alleviate sleep disruptions and reduce stress, anxiety, and dissatisfaction **[84-86].** Table 1 lists a few traditional oils used as aromatherapy for PCOS.

Table: 1 List of Essential Oil used in the management of PCOS.

S.No.	Essential Oil	Role In PCOS
1	Lavender oil	Body relaxation, reduce risk of PCOS, help in the aid of hormonal imbalance
2	Geranium oil	Control stress, decrease secretion of androgen
3	Clary sage oil	Aid in mood swings, mental disorder like depression and anxiety
4	German chamomile	Helps in reducing inflammation and improving reproductive health
5	Rose atto	Help in maintaining regular menstrual cycle
6	Sweet fennel	Reduces the hormonal fluctuations
7	Cypress oil and Cinnamon Oil	Regulates level of blood sugar, control weight
8	Eucalyptus oil	Regulates hormonal balances, decreases blood sugar level
9	Sandalwood oil	Acts as a reproductive tonic
10	Rose oil	Hormonal balance, maintain regular mensuration

Dietary or Nutritional Supplements

According to research by Alesi S et al. (2022) [87,88], women with PCOS frequently have vitamin and mineral deficiencies, which can result in physical and mental health problems such insulin resistance, diabetes, infertility, and depression. For these women, nutritional supplements and complementary and alternative medicine may be helpful in treating PCOS problems such as hyperandrogenism, oxidative stress, insulin resistance, and immature oocytes. Dehydroepiandrosterone and cytochrome P4-50-17 hydroxylase, which are necessary for androgen production and retinol biosynthesis, are produced in greater amounts in trans retinol-treated cells. According to research conducted in 2018, Elif G et al. [89], vitamins, minerals as well as various nutritional supplements helps in controlling PCOS symptoms.

There is various nutritional supplement have proven to manage and treat factors associated with PCOS are shown in Figure 6 [90-91].

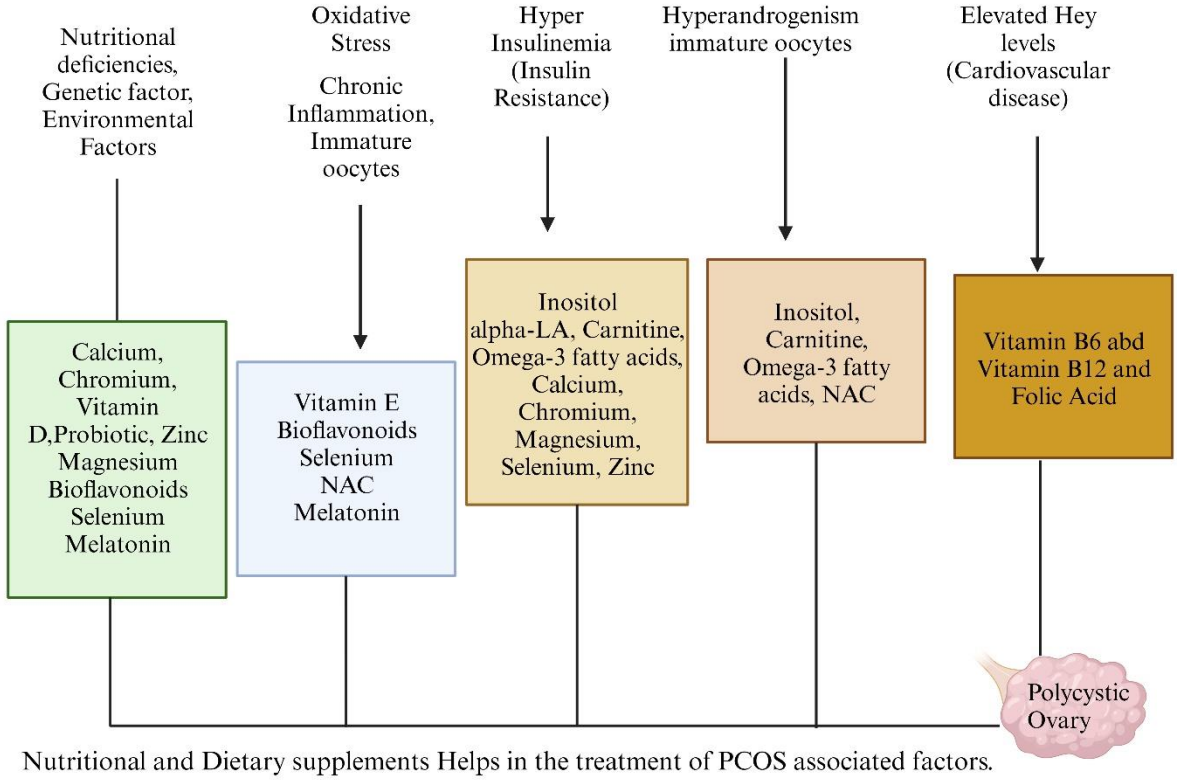

Figure 6: Dietary supplements are used to control and treat PCOS issues.

Vitamin D

One important steroid hormone in the therapy of PCOS is vitamin D. Vitamin D plays a role in insulin resistance in women with PCOS and enhances endocrine and metabolic activity, according to Mousa A et al. (2017). According to the study, 70 percent of PCOS-affected women are vitamin D deficient [92]. Vitamin D insufficiency has been linked to insulin resistance [93], according to to studies conducted by Lathief S. and Pal L. (2013). Vitamin D controls genes involved in glucose and lipid metabolism. Research by Lin MW and Wu MH (2015) suggests that vitamin D deficiency contributes to the endocrine and metabolic features of polycystic ovary syndrome. Studies have connected low levels of vitamin D to dyslipidemia, obesity, insulin resistance, hyperandrogenism inflammation, depression, and an increased risk of diabetes and cardiovascular disease [94]. According to current studies, vitamin D controls glucose homeostasis, luteinization, and the formation of ovarian follicles. Through receptors in skeletal muscle and pancreatic β-cells, as well as the production of the enzyme 1-α-hydroxylase and a vitamin D response element in the human insulin promoter, vitamin D influences glucose homeostasis. Women who have anovulation may develop ovarian dysfunction due to PCOS, or polycystic ovary syndrome. It is identified by polycystic ovarian morphology, hyperandrogenism, and chronic anovulation. Women with PCOS are between 67 to 85% deficient in vitamin D, with blood 25(OH)D levels less than 20 ng/ml [95]. The image below illustrates the suggested mechanism for vitamin D's involvement in PCOS.

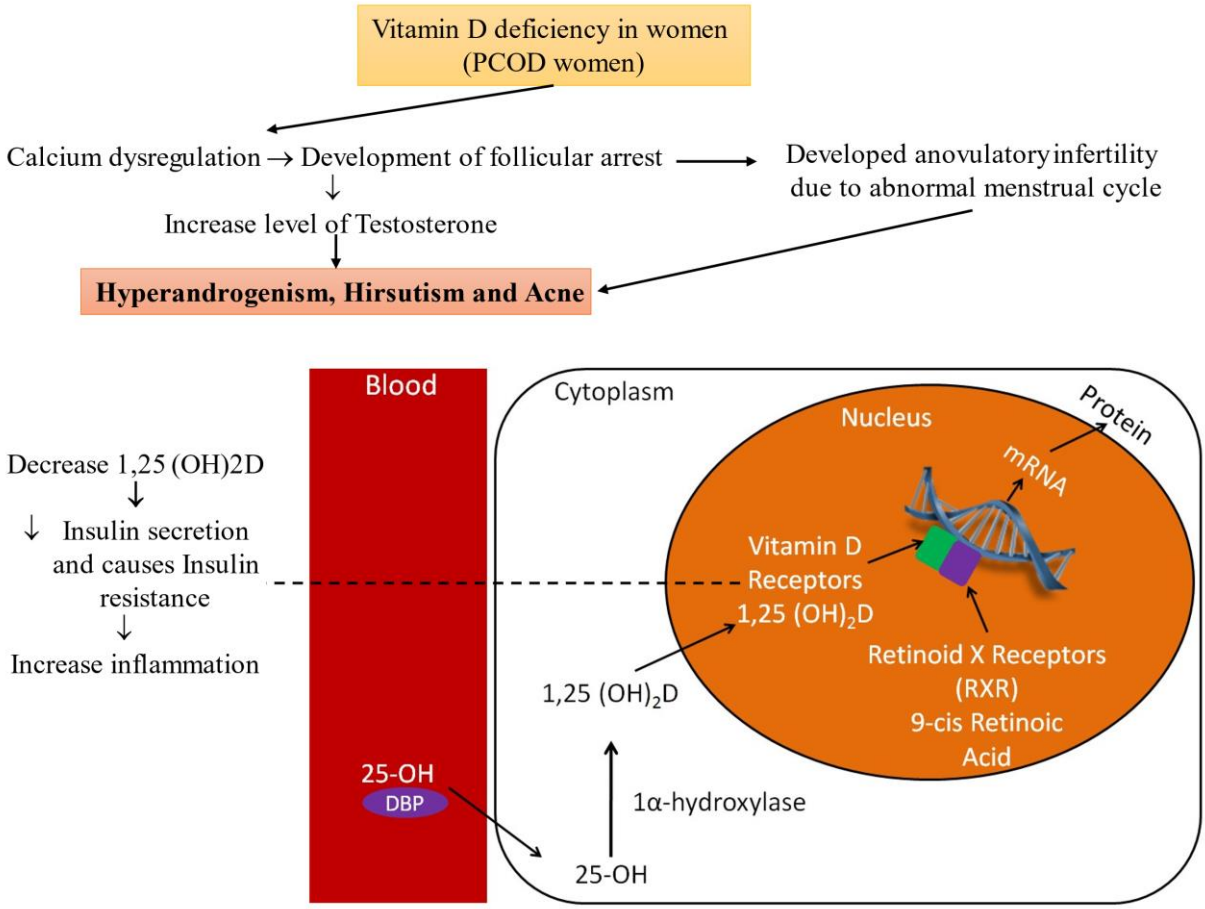

Figure 7: Vitamin D and PCOS

Vitamin A

Both the production of androgen and the synthesis of retinol depend on vitamin A. According to a study by M. Vindhya et al. (2023), obese women with PCOS have higher levels of RBP4, or retinol-binding protein 4, which is associated with obesity and poor glucose metabolism. It is thought that 17-estrodiol activates the RBP4 gene, which in turn influences the altered gonadal and adrenal steroid profiles [96].

Vitamin B

Vitamin B6, Folic acid and Vitamin B12 comes on focus due to its role of homocysteine and also helps in maintaining hormonal imbalance in polycystic ovarian syndrome **[97].** Homocysteine is associated with the risk for CVS and reproductive symptoms in PCOS. It was found in studies that Vitamin B is strongly linked with the pathophysiology of PCOS (Causing Insulin Resistance). *Kaya et al. (2009)* **[98]** showed that in PCOS-afflicted women, decreased serum insulin B12 concentrations were associated with IR, obesity, and elevated Hcy levels**.** Three months of folic acid treatment reduced increased blood Hcy levels successfully, especially in women without IR. It is unknown if supplementing with folic acid has a dose-dependent impact, though. In the pathophysiology of PCOS, it has also been proposed that regular exercise can lower plasma Hcy concentrations. According to research young obese and overweight women with PCOS who exercise regularly for six months had considerably reduced plasma Hcy levels **[98,99].**

Other supplements

Numerous research has also been conducted on supplements, which are important in maintaining polyovarian cyst syndrome in women. Additionally, carnitine has a critical function in promoting oocyte maturation and reducing oxidative stress. Numerous studies have also shown that probiotics, omega-3 fatty acids, melatonin, and N-acetyl-L-cysteine can prevent the development of hyperglycemia and glucose intolerance.

Furthermore, bioflavonoids have been shown to reduce female inflammation and improve the morphology of the ovaries and uterus in PCOS-affected women. Its anti-diabetic properties, which support insulin tolerance, have also been demonstrated.

Minerals (i.e., calcium, chromium, magnesium, selenium, and zinc) have been shown in studies to help in PCOS by lowering blood cholesterol, lowering LDL, improving lipid metabolism, and playing a part in insulin metabolism.

Herbal Therapy

An endocrine condition known as polycystic ovarian syndrome affects one in fifteen women worldwide [100]. The World Health Organization states that PCOS often affects women between the ages of 24 and 30 who are fertile [101]. Insulin resistance, miscarriages, and infertility in women are linked to long-term polycystic ovarian disease [102]. Its primary distinguishing characteristics are elevated testosterone levels, hirsutism, and acne. For PCOS, there are natural and allopathic treatments that interfere with the PCOS mechanism [103]. Over the past ten to fifteen years, women have utilized herbal medicines (HM) more often, with rates of usage ranging from 25% to 92% [104].

Herbal medicine is widely recognized for its pharmacologically active components that have physiological effects on female endocrinology and have been linked to a lower risk of osteoporosis, cardiovascular disease, and breast cancer [105]. Herbal medicines are complex therapies that might have both good and negative interactions among ingredients [106].

Curcumin

In the process of female reproduction, curcumin acts as a natural regulator and defender **[107].** Curcumin has been used to treat a variety of female reproductive disorders, such as PCOS, endometriosis, and ovarian failure, according to a study by Datu Agasi Mohd Kamal *et al.* Numerous in-vivo and in-vitro scientific trials on curcumin have demonstrated its effectiveness as a powerful component to lower elevated hormone levels and manage elevated insulin levels in women with PCOS **[108].** To increase curcumin's bioavailability, a variety of formulations are available, including subcutaneous injection, tropical application, structural analogues, inclusion of hydrophilic carriers, phospholipid complexes, nanoparticles, and liposome encapsulation **[109].**

A clinical trial of curcumin (1300 mg of curcumin three times per day) on women with PCOS (n = 72) was conducted by Heshmati J et al. and resulted in significantly higher gene expression of the glutathione peroxidase enzyme activity and peroxisome proliferator-activated γ receptor coactivator 1 α **[110]**. Similarly, Sohaei S et al. observed that curcumin lowers blood insulin and lipid levels in their research (n = 60) **[111].**

Mechanism:

Several preclinical and clinical investigations completed in the last few years have demonstrated that inflammatory-cytokines in PCOS patients might stimulate adipocyte proliferation by altering signal transducer and activator of transcription-3 (STAT3) signaling

pathway [112,113]. There is a connection between PCOS and persistent inflammation. Excessive inflammatory substances generate more reactive oxygen species (ROS), which throw off the body's natural ROS balance and damage insulin signaling and insulin-mediated glucose transport [114]. Lowering plasma insulin levels and treating insulin resistance may help PCOS women avoid future diabetes and cardiovascular disease in addition to correcting reproductive abnormalities [115,116].

It works by decreasing intestinal glucose absorption, increasing intestinal glucose metabolism, and inhibiting the synthesis of glucose in the liver [117]. Additionally, it functions by inhibiting the production of vascular endothelial growth factor (VEGF), a proangiogenic factor that delays ovarian fibrosis, promotes matrix breakdown, and inhibits ovarian angiogenesis. VEGF is intimately associated to the development of PCOS [118]. The following figure 8 describes the mechanism of curcumin.

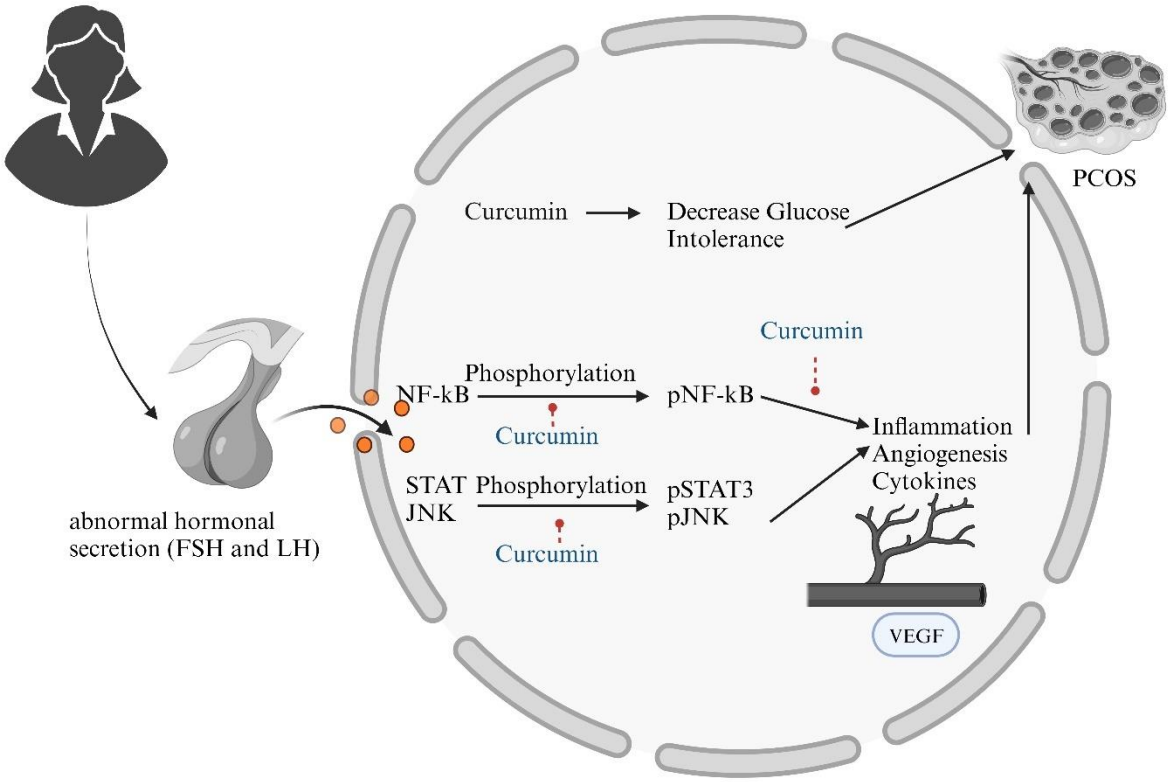

Figure 8: Curcumin treats polycystic ovarian syndrome (PCOS) by preventing phosphorylation, which in turn prevents inflammation and angiogenesis. Curcumin also helps to lower elevated glucose levels.

Liquorice

Licorice is a plant belonging to the Fabaceae family (scientifically known as glycyrrhiza glabra L.) and widely used for the wound healing, cough and pain relief. This plant is also reported for various medicinal properties like anti-proliferative, anti-bacterial, anti-viral, anti-oxidant and estrogenic activity. Licorice (glycerin active ingredient) is proven to lower blood sugar level by inhibiting 11 beta HSD2 enzyme **[119].**

It has been observed that licorice root extract lessens the negative effects of diabetes in PCOS-affected women. In addition, licorice extract has been shown to preserve ovarian morphology, oocyte maturation, and embryo development. According to the study, licorice extract reduces levels of estrogen and testosterone. It also improves egg fertilization rate and reduces ovarian cyst [120].

Mentha piperita

Peppermint (*Mentha piperita L.*) of Lamiaceae or Labiatae family have proven its androgenic activity in both animals and women in various letrozole induced PCOS model in animals. Peppermint is a common plant with a strong menthol flavour that is utilised in both culinary and medical uses. The antioxidant, anticancer, antiallergenic, anti-inflammatory, antiviral, antibacterial, and antifungal properties of peppermint have been studied [121].

Mechanism:

According to study *Maharjan et al. and Amoura et al,* **[121,122]** revealed that peppermint help in the reduction of estrogen level. Additionally, decreased estrogen lowers feedback system (negative) on LH synthesis from master gland, leading to higher amounts of LH, which further prompt theca cells to release testosterone.

Conclusion

Twenty percent of women who are of reproductive age have PCOS, a complicated endocrine, metabolic, and reproductive disorder. By 2025, it's expected that sedentary lifestyles and poor balance would cause the disorder to rise by 50% [123]. Modern treatments with long-term side effects include tamoxifen and clomiphene citrate [124]. There are several health advantages to non-pharmacological approaches, including as better insulin sensitivity, weight control, testosterone maintenance, symptom management, and dietary and acupuncturist modifications.

References

1. Saadia Z. Follicle Stimulating Hormone (LH: FSH) Ratio in Polycystic Ovary Syndrome (PCOS) - Obese vs. Non- Obese Women. Medical Archives. 2020;74(4):289. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7520057
2. Esmaeilzadeh S, Andarieh MG, Ghadimi R, Delavar MA. Body Mass Index and Gonadotropin Hormones (LH & FSH) Associate with Clinical Symptoms Among Women with Polycystic Ovary Syndrome. Global Journal of Health Science [Internet]. 2015 Mar 1 [cited 2023 Aug 10];7(2):101–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4796454/
3. Azziz R, Adashi EY. Stein and Leventhal: 80 years on. American journal of obstetrics and gynecology [Internet]. 2016 [cited 2023 Aug 10];214(2):247.e1–11. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26704896
4. Polycystic ovary syndrome | British Columbia Medical Journal [Internet]. Bcmj.org. 2018 [cited 2023 Aug 10]. Available from: https://bcmj.org/articles/polycystic-ovary-syndrome
5. De Leo, V., M. C. Musacchio, V. Cappelli, M. G. Massaro, G. Morgante, and F. Petraglia 2016. “Genetic, hormonal and metabolic aspects of PCOS: an update,” Reproductive Biology and Endocrinology, 14/1 (2016) https://doi.org/10.1186/s12958-016-0173-x

6. NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases. 2019 [cited 2023 Aug 10]. Available from: https://www.niddk.nih.gov/
7. Khan, M. J., A. Ullah, and S. Basit 2019. "Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives," The Application of Clinical Genetics, Volume 12/12 (2019), 249–260 (DOI: https://doi.org/10.2147/tacg.s200341)
8. Witchel, S. F., S. E. Oberfield, and A. S. Peña 2019. "Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls," Journal of the Endocrine Society, 3/8 (2019), 1545–1573 (DOI: https://doi.org/10.1210/js.2019-00078)
9. Deswal, R., V. Narwal, A. Dang, and C. S. Pundir 2020. "The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review," Journal of Human Reproductive Sciences, 13/4 (2020), 261–271 (DOI: https://doi.org/10.4103/jhrs.JHRS_95_18)
10. Bharali, M. D., R. Rajendran, J. Goswami, K. Singal, and V. Rajendran 2022. "Prevalence of Polycystic Ovarian Syndrome in India: A Systematic Review and Meta-Analysis," Cureus, (2022) (DOI: https://doi.org/10.7759/cureus.32351).
11. Repaci, A., A. Gambineri, and R. Pasquali 2011. "The role of low-grade inflammation in the polycystic ovary syndrome," Molecular and Cellular Endocrinology, 335/1 (2011), 30–41 (DOI: https://doi.org/10.1016/j.mce.2010.08.002).
12. Rudnicka, E., K. Suchta, M. Grymowicz, A. Calik-Ksepka, K. Smolarczyk, A. M. Duszewska, R. Smolarczyk, and B. Meczekalski 2021. "Chronic Low-Grade Inflammation in Pathogenesis of PCOS," International Journal of Molecular Sciences, 22/7 (2021) (DOI: https://doi.org/10.3390/ijms22073789).
13. Mohamed-Hussein ZA, Harun S. Construction of a polycystic ovarian syndrome (PCOS) pathway based on the interactions of PCOS-related proteins retrieved from bibliomic data. Theor Biol Med Model. 2009;6(1):18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743649/
14. Ndefo, U. A., A. Eaton, and M. R. Green 2013. "Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches," P & T: A Peer-Reviewed Journal for Formulary Management, 38/6 (2013), 336–355.
15. Polycystic ovary syndrome (PCOS) | National Health Portal Of India Nhp.gov.in (2015) https://www.nhp.gov.in/disease/endocrinal/ovaries/polycystic-ovary-syndrome-pcos , accessed 22 May 2023.
16. Sidra, S., M. H. Tariq, M. J. Farrukh, and M. Mohsin 2019. "Evaluation of clinical manifestations, health risks, and quality of life among women with polycystic ovary syndrome," ed. S. Garzon PLOS ONE, 14/10 (2019), e0223329 (DOI: https://doi.org/10.1371/journal.pone.0223329)
17. Jitendra Patel, A. and A. Pravin Thakor 2012. "Prospective use of Tephrosia Purpurea in Remedial Treatment of PCOS: Study in Wistar Rat," International Research Journal of Biological Sciences, 1/3 (2012), 1–6.
18. Pereira, S. S. and J. I. Alvarez-Leite 2014. "Low-Grade Inflammation, Obesity, and Diabetes," Current Obesity Reports, 3/4 (2014), 422–431 (DOI: https://doi.org/10.1007/s13679-014-0124-9)

19. Maiorino, M. I., G. Bellastella, D. Giugliano, and K. Esposito 2018. “From inflammation to sexual dysfunctions: a journey through diabetes, obesity, and metabolic syndrome,” Journal of Endocrinological Investigation, 41/11 (2018), 1249–1258 (DOI: https://doi.org/10.1007/s40618-018-0872-6)
20. Xiong, Y., X. Liang, X. Yang, Y. Li, and Li Na Wei 2011. “Low-grade chronic inflammation in the peripheral blood and ovaries of women with polycystic ovarian syndrome,” European journal of obstetrics, gynecology, and reproductive biology, 159/1 (2011), 148–150 (DOI: https://doi.org/10.1016/j.ejogrb.2011.07.012)
21. Boulman, N., Y. Levy, R. Leiba, S. Shachar, R. Linn, O. Zinder, and Z. Blumenfeld 2004. “Increased C-Reactive Protein Levels in the Polycystic Ovary Syndrome: A Marker of Cardiovascular Disease,” The Journal of Clinical Endocrinology & Metabolism, 89/5 (2004), 2160–2165 (DOI: https://doi.org/10.1210/jc.2003-031096)
22. Rudnicka, E., M. Kunicki, K. Suchta, P. Machura, M. Grymowicz, and R. Smolarczyk 2020. “Inflammatory Markers in Women with Polycystic Ovary Syndrome,” BioMed Research International, 2020 (2020), 1–10 (DOI: https://doi.org/10.1155/2020/4092470)
23. Gonen, Y., Casper, R. F. (1990). Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. Hum. Reprod. 5 (6), 670–674. doi: 10.1093/oxfordjournals.humrep.a137165
24. Legro, R. S., Barnhart, H. X., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., et al. (2007a). Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. New Engl. J. Med. 356 (6), 551–566. doi: 10.1056/NEJMoa063971
25. Legro, R. S., Zaino, R. J., Demers, L. M., Kunselman, A. R., Gnatuk, C. L., Williams, N. I., et al. (2007b). The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am. J. Obstetrics Gynecol. 196 (4), 402. e401–402. e411. doi: 10.1016/j.ajog.2006.12.025
26. Barrea, L., Arnone, A., Annunziata, G., Muscogiuri, G., Laudisio, D., Salzano, C., et al. (2019). Adherence to the mediterranean diet, dietary patterns and body composition in women with polycystic ovary syndrome (PCOS). Nutrients 11 (10), 2278. doi: 10.3390/nu11102278
27. Kwon CY, Cho IH, Park KS. Therapeutic Effects and Mechanisms of Herbal Medicines for Treating Polycystic Ovary Syndrome: A Review. Frontiers in Pharmacology. 2020 Aug 12;11. https://doi.org/10.3389/fphar.2020.01192
28. Raja-Khan NES-V, Wu XK, Legro RS. The physiological basis of complementary and alternative medicines for polycystic ovary syndrome. Am J Physiol Endocrinol Metab. 2011;301(1):E1–E10. doi: 10.1152/ajpendo.00667.2010.
29. Amini L, Tehranian N, Movahedin M, Tehrani FR, Ziaee S. Antioxidants and management of polycystic ovary syndrome in Iran: a systematic review of clinical trials. Iran J Reprod Med. 2015;13(1):1.
30. Arentz S, Smith CA, Abbott JA, Bensoussan A, et al. Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings. BMC Complement Altern Med. 2014;14(1):511. doi: 10.1186/1472-6882-14-511.
31. Goodarzi MO, Azziz R. Diagnosis, epidemiology, and genetics of the polycystic ovary syndrome. Best Prac Res Clin Endocrinol Metab. 2006;20:193–200. doi: 10.1016/j.beem.2006.02.005.

32. Kabel AM. Polycystic ovarian syndrome: insights into pathogenesis, diagnosis, prognosis, pharmacological and non-pharmacological treatment. Pharm Bioprocess. 2016 Jan 1;4(1):7-12.
33. Rojas, J., M. Chávez, L. Olivar, M. Rojas, J. Morillo, J. Mejías, M. Calvo, and V. Bermúdez 2014. "Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth," International Journal of Reproductive Medicine, 2014 (2014), 1–17 (DOI: https://doi.org/10.1155/2014/719050).
34. Lim, S. S., R. J. Norman, M. J. Davies, and L. J. Moran 2012. "The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis," Obesity Reviews, 14/2 (2012), 95–109 (DOI: https://doi.org/10.1111/j.1467-789x.2012.01053.x).
35. González, F., N. S. Rote, J. Minium, and J. P. Kirwan 2006. "Reactive Oxygen Species-Induced Oxidative Stress in the Development of Insulin Resistance and Hyperandrogenism in Polycystic Ovary Syndrome," The Journal of Clinical Endocrinology & Metabolism, 91/1 (2006), 336–340 (DOI: https://doi.org/10.1210/jc.2005-1696).
36. Anagnostis, P., B. C. Tarlatzis, and R. P. Kauffman 2018. "Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences," Metabolism, 86 (2018), 33–43 (DOI: https://doi.org/10.1016/j.metabol.2017.09.016).
37. Wu, Jielei MDa; Chen, Di MDb; Liu, Nenghui MDa,∗. Effectiveness of acupuncture in polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. Medicine 99(22):p e20441, May 29, 2020. | DOI: 10.1097/MD.0000000000020441
38. Ee C, Smith CA, Costello M, Moran L, Steiner GZ, Stepto N, et al. Acupuncture or auricular electro-acupuncture as adjuncts to lifestyle interventions for weight management in PCOS: protocol for a randomised controlled feasibility study. Pilot Feasibility Stud. 2020;6:53. doi: 10.1186/s40814-020-00591-4.
39. Acupuncture NINCDPo. Acupuncture. The Journal of the American Medical Association. 1998;280:1518–1524.
40. Zhang H, Bian Z, Lin Z. Are acupoints specific for diseases? A systematic review of the randomized controlled trials with sham acupuncture controls. Chinese Medicine. 2010;5, article 1
41. Moffet HH. Sham acupuncture may be as efficacious as true acupuncture: a systematic review of clinical trials. Journal of Alternative and Complementary Medicine. 2009;15(3):213–216.
42. Johansson J, Stener-Victorin E. Polycystic ovary syndrome: effect and mechanisms of acupuncture for ovulation induction. Evid Based Complement Alternat Med. 2013;2013:762615. doi: 10.1155/2013/762615. Epub 2013 Sep 2.
43. Lansdown A, Aled Rees D. The sympathetic nervous system in polycystic ovary syndrome: a novel therapeutic target? *Clinical Endocrinology.* 2012;77(6):791–801.
44. Sun J, Jin C, Wu H, Zhao J, Cui Y, Liu H, et al. Effects of electro-acupuncture on ovarian P450arom, P450c17α and mRNA expression induced by letrozole in PCOS rats. *PLoS One.* 2013;8(11):e79382. doi: 10.1371/journal.pone.0079382.
45. Mannerås L, Cajander S, Lönn M, Stener-Victorin E. Acupuncture and exercise restore adipose tissue expression of sympathetic markers and improve ovarian morphology in rats with dihydrotestosterone-induced PCOS. *Am J Physiol Regul Integr Comp Physiol.* 2009;296(4):R1124–31. doi: 10.1152/ajpregu.90947.2008.

46. Li J, Cui W, Sun W, Zhang QY, Guan Q. [Effect of electro-acupuncture on the spindle and oocytes quality in patients with PCOS] *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2015;35(3):304–9. Chinese.
47. de Oliveira NM, Machado J, Lopes L, Criado MB. A Review on Acupuncture Efficiency in Human Polycystic Ovary/Ovarian Syndrome. J Pharmacopuncture. 2023 Jun 30;26(2):105-123. doi: 10.3831/KPI.2023.26.2.105. PMID: 37405111; PMCID: PMC10315877.
48. Zhang HL, Huo ZJ, Wang HN, Wang W, Chang CQ, Shi L, et al. [Acupuncture ameliorates negative emotion in PCOS patients: a randomized controlled trial] *Zhongguo Zhen Jiu.* 2020;40(4):385–90. doi: 10.13703/j.0255-2930.20191231-k0005. Chinese.
49. Hickman FE, Stanley EM, Carter BD. Neurotrophin responsiveness of sympathetic neurons is regulated by rapid mobilization of the p75 receptor to the cell surface through TrkA activation of Arf6. *J Neurosci.* 2018;38(24):5606–19. doi: 10.1523/JNEUROSCI.0788-16.2018.
50. Zhao Z-Q. Neural mechanism underlying acupuncture analgesia. *Progress in Neurobiology.* 2008;85(4):355–375.
51. Lim CE, Wong WS. Current evidence of acupuncture on polycystic ovarian syndrome. Gynecol Endocrinol. 2010 Jun;26(6):473-8. doi: 10.3109/09513591003686304. PMID: 20230329.
52. Lim C, Ng R, Cheng N, Zhang G, Chen H. Acupuncture for polycystic ovarian syndrome. Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD007689. DOI: 10.1002/14651858.CD007689.pub4
53. Ye Y, Zhou CC, Hu HQ, Fukuzawa I, Zhang HL. Underlying mechanisms of acupuncture therapy on polycystic ovary syndrome: Evidences from animal and clinical studies. Front Endocrinol (Lausanne). 2022 Oct 24;13:1035929. doi: 10.3389/fendo.2022.1035929. PMID: 36353235; PMCID: PMC9637827.
54. Sandro Graca, Mike Armour, Lara McClure, Acupuncture for polycystic ovary syndrome – A cross-sectional survey of clinical practice amongst acupuncturists trained in reproductive medicine, European Journal of Integrative Medicine, Volume 54, 2022, 102161, ISSN 1876-3820, https://doi.org/10.1016/j.eujim.2022.102161.
55. Han Yang, Zhi-yong Xiao, Zi-han Yin, Zheng Yu, Jia-jia Liu, Yan-qun Xiao, Yao Zhou, Juan Li, Jie Yang, Fan-rong Liang, Efficacy and safety of acupuncture for polycystic ovary syndrome: An overview of systematic reviews, Journal of Integrative Medicine, Volume 21, Issue 2, 2023, Pages 136-148, ISSN 2095-4964, https://doi.org/10.1016/j.joim.2022.12.002.
56. Wal P, Gupta D, Wal A, Pandey SS, Krishnan K. A Wholistic Approach to Non-Pharmacological Intervention for Primary Dysmenorrhea. Current Women`s Health Reviews [Internet]. 2023 Feb 3 [cited 2024 Apr 17];20(1):21–34. Available from: https://benthamscience.com/article/128651
57. Cheryce L. Harrison, Catherine B. Lombard, Lisa J. Moran, Helena J. Teede, Exercise therapy in polycystic ovary syndrome: a systematic review, *Human Reproduction Update*, Volume 17, Issue 2, March-April 2011, Pages 171–183, https://doi.org/10.1093/humupd/dmq045
58. Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. Fatness on all-cause mortality: a meta-analysis. *Progress Cardiovascular Diseases*. 2014;56(4):382–90
59. Nicolucci A. Relationship of exercise volume to improvements of quality of life with supervised exercise training in patients with type 2 diabetes in a randomised controlled trial: the Italian Diabetes and Exercise Study (IDES). *Diabetologia*.2012;55(3):579–88.

60. Access Deloitte. Value of Accredited Exercise Physiologists in Australia. Australia: Exercise & Sports Science Australia; 2015. accessed on 10 August 2017 (https://www.essa.org.au/wp-content/uploads/2015/10/Deloitte-Report-2015_Value-of-AEPs-in-Australia.pdf).
61. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. *International evidence-based guideline for the assessment and management of polycystic ovary syndrome*. 2018.
62. Haqq L, McFarlane J, Dieberg G, Smart N. Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: a systematic review and meta-analysis. Endocrine Connect 2014;3(1):36–46.
63. Kite C, Lahart IM, Afzal I, Broom DR, Randeva H, Kyrou I, et al. Exercise, or exercise and diet for the management of polycystic ovary syndrome: a systematic review and meta-analysis. *Syst Rev*. 2019;8(1):51.
64. Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2011;96(1):E48–56.
65. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. *Fertil Steril*. 2010;93(7):2421–3.
66. (PDF) Exercise in polycystic ovarian syndrome: An evidence-based review. Available from: https://www.researchgate.net/publication/320211314_Exercise_in_polycystic_ovarian_syndrome_An_evidence-based_review [accessed Apr 15 2024]
67. Li Y, Xu S, Zhang X, Yi Z, Cichello S. Skeletal intramyocellular lipidmetabolism and insulin resistance. Biophys Rep 2015;1:90-8.
68. Harrison CL, Stepto NK, Hutchison SK, Teede HJ. The impactof intensified exercise training on insulin resistance and fitness inoverweight and obese women with and without polycystic ovarysyndrome. Clin Endocrinol (Oxf) 2012;76:351-7
69. Vigorito C., Giallauria F., Palomba S., Cascella T., Manguso F., Lucci R., De Lorenzo A., Tafuri D., Lombardi G., Colao A., et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2007;92:1379–1384. doi: 10.1210/jc.2006-2794.
70. . Orio F., Giallauria F., Palomba S., Manguso F., Orio M., Tafuri D., Lombardi G., Carmina E., Colao A., Vigorito C. Metabolic and cardiopulmonary effects of detraining after a structured exercise training programme in young PCOS women. Clin. Endocrinol. 2008;68:976–981. doi: 10.1111/j.1365-2265.2007.03117.x.
71. Almenning I., Rieber-Mohn A., Lundgren K.M., Shetelig Løvvik T., Garnæs K.K., Moholdt T. Effects of High Intensity Interval Training and Strength Training on Metabolic, Cardiovascular and Hormonal Outcomes in Women with Polycystic Ovary Syndrome: A Pilot Study. PLoS ONE. 2015;10:e0138793. doi: 10.1371/journal.pone.0138793.
72. Redman, L. M., Elkind-Hirsch, K., & Ravussin, E. (2011). Aerobic exercise in women with polycystic ovary syndrome improves ovarian morphology independent of changes in body composition. Fertility and sterility, 95(8), 2696–2699. https://doi.org/10.1016/j.fertnstert.2011.01.137
73. Shele G, Genkil J, Speelman D. A Systematic Review of the Effects of Exercise on Hormones in Women with Polycystic Ovary Syndrome. J Funct Morphol Kinesiol. 2020 May 31;5(2):35. doi: 10.3390/jfmk5020035. PMID: 33467251; PMCID: PMC7739243.

74. Stepto NK, Patten RK, Tassone EC, Misso ML, Brennan L, Boyle J, Boyle RA, Harrison CL, Hirschberg AL, Marsh K, Moreno-Asso A, Redman L, Thondan M, Wijeyaratne C, Teede HJ, Moran LJ. Exercise Recommendations for Women with Polycystic Ovary Syndrome: Is the Evidence Enough? Sports Med. 2019 Aug;49(8):1143-1157. doi: 10.1007/s40279-019-01133-6. PMID: 31166000; PMCID: PMC6905185.
75. Selvaraj V, Vanitha J, Dhanaraj FM, Sekar P, Babu AR. Impact of yoga and exercises on polycystic ovarian syndrome risk among adolescent schoolgirls in South India. Health science reports. 2020 Dec;3(4):e212.
76. Aili S. Role of Yogasana in prevention of Polycystic Ovarian Syndrome. Journal of Ayurveda and Integrated Medical Sciences. 2021 Feb 28;6(01):166-71.
77. Verma A, Kumar S, Dei L, Dhiman K. Management of PCOS: A psychosomatic disorder by yoga practice. Int J Innov Res Devel. 2015 Jan 31;4(1):216-9.
78. Kumari, Deepika; Kumar, Manoj; Tiwari, Prabhakar; Mahey, Reeta1; Malhotra, Neena1; Mishra, Richa; Dada, Rima. Impact of Yoga in Polycystic Ovary Syndrome. International Journal of Ayurveda Research 4(3):p 132-136, Jul–Sep 2023. | DOI: 10.4103/ijar.ijar_133_23
79. Pearson ACS, Cutshall SM, Hooten WM, Rodgers NJ, Bauer BA, Bhagra A. Perspectives on the use of aromatherapy from clinicians attending an integrative medicine continuing education event. BMC Complement Altern Med. 2019 Jul 12;19(1):174. doi: 10.1186/s12906-019-2572-y.
80. Olivia. How To Use Essential Oils For PolyCystic Ovary Syndrome (PCOS) Treatment | Essential Oil Benefits [Internet]. essentialoilbenefits.com. 2015 [cited 2024 Apr 17]. Available from: https://essentialoilbenefits.com/how-to-use-essential-oils-for-polycystic-ovary-syndrome-pcos-treatment/
81. Top 10 Essential Oils for PCOS and How to Use [Internet]. The Miracle of Essential Oils. 2017 [cited 2024 Apr 17]. Available from: https://www.themiracleofessentialoils.com/essential-oils-for-pcos/
82. Heydari, Naval1; Abootalebi, Mliheh1; Tayebi, Naeimeh2; Hassanzadeh, Fahimeh3; Kasraeian, Maryam4; Emamghoreishi, M.5; Akbarzadeh, Marzieh6,. The effect of aromatherapy on mental, physical symptoms, and social functions of females with premenstrual syndrome: A randomized clinical trial. Journal of Family Medicine and Primary Care 8(9):p 2990-2996, September 30, 2019. | DOI: 10.4103/jfmpc.jfmpc_452_19
83. Jones T, Purdy M, Stewart EA, et al. Lavender Aromatherapy to Reduce Anxiety During Intrauterine Insemination: A Randomized Controlled Trial. *Global Advances in Health and Medicine*. 2021;10. doi:10.1177/21649561211059074
84. Kianpour M, Mansouri A, Mehrabi T, Asghari G. Effect of lavender scent inhalation on prevention of stress, anxiety and depression in the postpartum period. *Iran J Nurs Midwifery Res*. 2016;21(2):197-201.
85. Nikjou R, Kazemzadeh R, Rostamnegad M, Moshfegi S, Karimollahi M, Salehi H. The effect of lavender aromatherapy on the pain severity of primary dysmenorrhea: a triple-blind randomized clinical trial. *Ann Med Health Sci Res*. 2016;6(4):211-215.
86. Salehi-Pourmehr H, Ostadrahimi A, Ebrahimpour-Mirzarezaei M, Farshbaf-Khalili A. Does aromatherapy with lavender affect physical and psychological symptoms of menopausal women? A systematic review and meta-analysis. *Complement Ther Clin Pract*. 2020;39:101150.

87. Alesi S, Ee C, Moran LJ, Rao V, Mousa A. Nutritional Supplements and Complementary Therapies in Polycystic Ovary Syndrome. Adv Nutr. 2022 Aug 1;13(4):1243-1266. doi: 10.1093/advances/nmab141. PMID: 34970669; PMCID: PMC9340985.
88. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2019;3:CD007506.
89. Günalan E, Yaba A, Yılmaz B. The effect of nutrient supplementation in the management of polycystic ovary syndrome-associated metabolic dysfunctions: A critical review. J Turk Ger Gynecol Assoc. 2018 Nov 15;19(4):220-232. doi: 10.4274/jtgga.2018.0077. Epub 2018 Oct 9. PMID: 30299265; PMCID: PMC6250088.
90. Szczuko M, Kikut J, Szczuko U, Szydłowska I, Nawrocka-Rutkowska J, Ziętek M, Verbanac D, Saso L. Nutrition Strategy and Life Style in Polycystic Ovary Syndrome-Narrative Review. Nutrients. 2021 Jul 18;13(7):2452. doi: 10.3390/nu13072452. PMID: 34371961; PMCID: PMC8308732.
91. O'Byrne SM, Blaner WS. Retinol and retinyl esters: biochemistry and physiology. J Lipid Res. 2013 Jul;54(7):1731-43. doi: 10.1194/jlr.R037648. Epub 2013 Apr 26. PMID: 23625372; PMCID: PMC3679378.
92. Mousa A, Naderpoor N, de Courten MP, Scragg R, de Courten B. 25-hydroxyvitamin D is associated with adiposity and cardiometabolic risk factors in a predominantly vitamin D-deficient and overweight/obese but otherwise healthy cohort. J Steroid Biochem Mol Biol. 2017;173:258–64.
93. Lathief, S., Pal, L. (2014). Emerging Concepts: Role of Vitamin D Deficiency in the Pathogenesis of PCOS. In: Pal, L. (eds) Polycystic Ovary Syndrome. Springer, New York, NY. https://doi.org/10.1007/978-1-4614-8394-6_19
94. Lin MW, Wu MH. The role of vitamin D in polycystic ovary syndrome. Indian J Med Res. 2015 Sep;142(3):238-40. doi: 10.4103/0971-5916.166527. PMID: 26458338; PMCID: PMC4669857.
95. Grzesiak M. Vitamin D3 action within the ovary - an updated review. Physiol Res. 2020 Jul 16;69(3):371-378. doi: 10.33549/physiolres.934266. Epub 2020 May 29. PMID: 32469224; PMCID: PMC8648308.
96. Vindhya, M., S. Bhumika, R. Mythreyi, K. Murugesan, G. G. Swamy, D. Kandaswamy, J. Valliyappan, B. Elango, K. M. Basalingappa, and M. Mathanmohun. “Role of Vitamin A and Vitamin D in Management of Polycystic Ovary Syndrome”. Journal of Medicine and Health Sciences Research, vol. 6, Dec. 2023, pp. 7-11, doi:10.21839/jmhsr.2023.v6.8730.
97. PCOS and B Vitamins | Conquer Your PCOS Naturally
98. Kaya C, Cengiz SD, Satiroglu H. Obesity and insulin resistance associated with lower plasma vitamin B12 in PCOS. Reprod Biomed Online. 2009;19:721–6.
99. Kondapaneni V, Gutlapalli SD, Poudel S, Zeb M, Toulassi IA, Cancarevic I. Significance of Homocysteine Levels in the Management of Polycystic Ovarian Syndrome: A Literature Review. Cureus. 2020 Oct 23;12(10):e11110. doi: 10.7759/cureus.11110. PMID: 33240706; PMCID: PMC7682539.
100. Eunice Kennedy Shriver National Institute of Child Health and Human Development - NICHD [Internet]. www.nichd.nih.gov. [cited 2023 Aug 10]. Available from: https://www.nichd.nih.gov/health/topics/factsheets/pcos

101. Polycystic ovary syndrome [Internet]. www.who.int. [cited 2023 Aug 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome
102. Bharali MD, Rajendran R, Goswami J, Singal K, Rajendran V. Prevalence of Polycystic Ovarian Syndrome in India: A Systematic Review and Meta-Analysis. Cureus. 2022;14(12):e32351. Published 2022 Dec 9. doi:10.7759/cureus.32351
103. Wardle JL, Adams J, Lui C-W. A qualitative study of naturopathy in rural practice: A focus upon naturopaths' experiences and perceptions of rural patients and demands for their services. BMC Health Serv Res. 2010;10(1):185. doi: 10.1186/1472-6963-10-185.
104. Williamson E. Synergy and other interactions in phytomedicines. Phytomedicine. 2001;8(5):401–409. doi: 10.1078/0944-7113-00060.
105. Ren MQ, Kuhn G, Wegner J, Chen J. Isoflavones, substances with multi-biological and clinical properties. Eur J Nutr. 2001;40(4):135–146. doi: 10.1007/PL00007388.
106. Wei W, Zhao H, Wang A, Sui M, Liang K, Deng H, Ma Y, Zhang Y, Zhang H, Guan Y. A clinical study on the short-term effect of berberine in comparison to metformin on the metabolic characteristics of women with polycystic ovary syndrome. Eur J Endocrinol. 2012;166(1):99–105. doi: 10.1530/EJE-11-0616.
107. Sirotkin AV. The influence of turmeric and curcumin on female reproductive processes. Planta Med (2022) 88(12):1020–5. doi: 10.1055/a-1542-8992
108. Kamal DAM, Salamt N, Yusuf ANM, Kashim MIAM, Mokhtar MH. Potential Health Benefits of Curcumin on Female Reproductive Disorders: A Review. Nutrients. 2021 Sep 7;13(9):3126. doi: 10.3390/nu13093126.
109. Heshmati J., Moini A., Sepidarkish M., Morvaridzadeh M., Salehi M., Palmowski A., Mojtahedi M.F., Shidfar F. Effects of curcumin supplementation on blood glucose, insulin resistance and androgens in patients with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial. Phytomed. Int. J. Phytother. Phytopharm. 2021;80:153395. doi: 10.1016/j.phymed.2020.153395.
110. Heshmati J., Golab F., Morvaridzadeh M., Potter E., Akbari-Fakhrabadi M., Farsi F., Tanbakooei S., Shidfar F. The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: A randomized placebo-controlled clinical trial. Diabetes Metab. Syndr. 2020;14:77–82. doi: 10.1016/j.dsx.2020.01.002.
111. Sohaei S., Amani R., Tarrahi M.J., Ghasemi-Tehrani H. The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled clinical trial. Complementary Ther. Med. 2019;47:102201. doi: 10.1016/j.ctim.2019.102201.
112. Rostamtabar M, Esmaeilzadeh S, Tourani M, Rahmani A, Baee M, Shirafkan F, et al. Pathophysiological roles of chronic low-grade inflammation mediators in polycystic ovary syndrome. J Cell Physiol (2021) 236(2):824–38. doi: 10.1002/jcp.29912
113. Zhuang ZH, Pan XH, Zhao K, Gao W, Liu J, Deng TQ, et al. The effect of interleukin-6 (IL-6), interleukin-11 (IL-11), signal transducer and activator of transcription 3 (STAT3), and AKT signaling on adipocyte proliferation in a rat model of polycystic ovary syndrome. Med Sci Monit (2019) 25:7218–27. doi: 10.12659/MSM.916385

114. Pan MD, Sun X. Chronic inflammatory mechanism of polycystic ovary syndrome and its research progress. J Reprod Med (2021) 30(8):1118–21. doi: 10.3969/j.issn.1004-3845.2021.08.025
115. Łagowska K, Bajerska J, Jamka M. The role of vitamin d oral supplementation in insulin resistance in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. Nutrients (2018) 10(11):1637. doi: 10.3390/nu10111637
116. Yang J, Guo YQ, Seo W, Zhang RH, Lu CJ, Wang YY, et al. Targeting cellular metabolism to reduce head and neck cancer growth. Sci Rep (2019) 9(1):4995. doi: 10.1038/s41598-019-41523-4
117. Jochmans S, Alphonsine JE, Chelly J, Vong LVP, Sy O, Rolin N, et al. Does metformin exposure before ICU stay have any impact on patients' outcome? a retrospective cohort study of diabetic patients. Ann Intensive Care (2017) 7(1):116. doi: 10.1186/s13613-017-0336-8
118. Wang LL, Li C, Meng JP, Yang X. Effect of curcumin on expression of VEGF in polycystic ovary syndrome rat models. J Shanghai Jiaotong University (Medical Science) (2014) 34(2):144–8. doi: 10.3969/j.issn.1674-8115.2014.02.004
119. Chen, Meimei, Jingru Zhu, Jie Kang, Xinmei Lai, Yuxing Gao, Huijuan Gan, and Fafu Yang. 2019. "Exploration in the Mechanism of Action of Licorice by Network Pharmacology" Molecules 24, no. 16: 2959. https://doi.org/10.3390/molecules24162959
120. Tanideh N, Zareian Z, Hosseinpour R, Tanideh R, Koohpeyma F, Koohi-Hosseinabadi O, Shekarkhar G, Irajie C, Taghi MM, Barhaghtalab MJY, Iraji A. Investigating the Effect of Hydroalcoholic Extract of Licorice Root to Prevent Ovariectomy-Mediated Complications. Biomed Res Int. 2022 Aug 10;2022:7879432. doi: 10.1155/2022/7879432.
121. Maharjan, R.; Nagar, P.S. and Nampoothiri, L. (2010): Effect of Aloe barbedensis Mill. formulation on letrozoleinduced polycystic ovarian syndrome rat model. J. Ayurveda Integr. Med.,1(4): 273-279
122. https://www.journalijar.com/article/6277/potential-effects-of-mentha-piperita-(peppermint)-on-letrozole--induced-polycystic-ovarian-syndrome-in-female-albino-rat/
123. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nature Reviews Endocrinology. 2018 Mar 23;14(5):270–84. https://pubmed.ncbi.nlm.nih.gov/29569621
124. Liu, J., Wu, Q., Hao, Y., Jiao, M., Wang, X., Jiang, S. and Han, L. (2021). Measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017. Human Reproduction, [online] 36(4), pp.1108–1119. doi: https://pubmed.ncbi.nlm.nih.gov/33501984/
125. Wal A, Dash B, Jaiswal V, Gupta D, Arun Kumar Mishra. Role of inflammation, oxidative stress, and angiogenesis in polycystic ovary syndrome (PCOS): Current perspectives. Elsevier eBooks. 2024 Jan 1;459–85. https://doi.org/10.1016/B978-0-443-13587-3.00018-7
126.