INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Role Of Nutraceuticals in The Management of Polycystic Ovarian Syndrome – Exploring Potential Benefits

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ARTICLE INFO

Published: 08 Sept 2026
Keywords:
Polycystic ovarian syndrome, hyperandrogenism, nutraceuticals etc
DOI:
10.5281/zenodo.22655682

ABSTRACT

Polycystic ovarian syndrome (PCOS) is one among the most common endocrine-reproductive disorder affecting women of reproductive age. It is mainly characterized by hyperandrogenism, cystic ovaries as well as oligo-anovulation. The diverse features of the syndrome have led to a number of diagnostic criteria over the years. Women with PCOS also frequently suffer from metabolic dysfunction, obesity, infertility and are at an increased risk of pregnancy complications and long-term cardiovascular disease. Reproductive, endocrine, and metabolic symptoms are highly variable, with heterogenous phenotypes adding complexity to clinical management of symptoms. Current pharmacological therapies have been limited because of many factors like hormonal irregularities, weight gain, gastro-intestinal issues etc. This review aimed to summarize and collect evidence about different nutraceutical approaches towards the management of PCOS

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an environmental multifactorial endocrine disorder that primarily affects women of reproductive age. It is a condition in which ovaries produce excessive amount of androgens (hyperandrogenism). In case of PCOS hormonal balance is fully disrupted. PCOS is pathologically caused by misdirected intracellular signaling, which can result from causes outside or inside the ovary that stimulate androgen synthesis from theca cells, which are ovaries' endometrial cells. The prevalence of the condition varies between 4 and 26% depending on the population and geographical area [1][2]. A complicated disorder known as polycystic ovarian syndrome (PCOS) is typified by high testosterone levels, irregular menstruation, and/or tiny cysts on one or both ovaries. The condition may primarily be biochemical (hyperandrogenaemia) or morphological (polycystic ovaries). Anovulation,

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

microcysts in the ovaries, follicular development suppression, and menstrual abnormalities are all possible outcomes of hyperandrogenism, a clinical feature of polycystic ovary syndrome (PCOS) [3].

One prevalent reason of infertility is PCOS. The etiology of PCOS has not been elucidated well and a proper management is not established yet. Increased luteinizing hormone (LH), elevated insulin, or decreased follicle-stimulating hormone (FSH) are examples of extra-ovarian variables [4].

Through a reduction in mitogen-activated protein kinase 1, elevated LH levels can directly increase theca androgen biosynthesis (MAPK). Furthermore, an elevated insulin level tends to interact with an elevated LH level, aggravating the intrinsic steroidogenic deficiency and raising the activity of phosphoinositide 3 kinase (PI3K) and inositol phosphoglycan (IPG), which in turn promotes the generation of androgens from theca cells. Indirect effects on androgen production may result from reduced FSH levels (when compared to LH levels). Decreased free sperm serum levels block aromatase action, which lowers androgen-to-estrogen conversion and raises androgen levels in the ovaries, which increases androgen production [5].

Increased levels of inhibins and anti-Müllerian hormone (AMH) are among the intraovarian factors. In concert with FSH, the elevated AMH action will decrease aromatase activity [6]. Inhibins and AMH can accomplish this purpose directly by stimulating androgen synthesis in theca cells, or indirectly by suppressing FSH. Reduced aromatase activity impedes the conversion of testosterone to estrogen, which adds to the excess androgen in the ovaries. As a result, increased testosterone levels maintain the inhibition of aromatase activity [7].

PCOS does not presently have a universally effective treatment. Because of this, each patient's treatment is unique and tailored to their needs. The focus of treatment is on symptoms, and it might not be required [8]. Particularly for obese PCOS individuals, lifestyle changes, dietary changes, and exercise programs are implemented. However, medication is required for severe clinical symptoms such hirsutism, acne, irregular periods, and anovulation. These include oral contraceptives that contain only progestin or in conjunction with it (COCPs), metformin, spironolactone, and either letrozole or clomiphene, which are all used to treat infertility [9]. Eflornithine (13.9%) cream administered topically, as well as waxing and bleaching, are cosmetic operations that can be done right away. The frequency of pharmaceutical failure, the possibility of severe side effects, and the prevalence of contraindications among PCOS women limit the effectiveness of current PCOS treatment strategies [10]. The percentage of women who accept and use complementary medicine has risen from 26 to 91% over the past ten years [11].

ABOUT NUTRACEUTICALS

The concepts of "nutrition" and "pharmaceutical" have been combined to form the word or phrase "nutraceutical." A vital part of healthy physiological function is played by nutraceuticals, which support human well-being. Everyone these days has concerns about their daily nutrition and overall health. Due to their safety profile, therapeutic effects, and dietary benefits, nutraceuticals have gained widespread acceptance. Nutraceuticals are defined as "specially designed preparations" that are made to meet nutrient requirements and/or provide preventive healthcare. From anticipating vitamin deficits to taking a prominent role in human health and the prevention and treatment of chronic illnesses, the science of nutrition has progressively expanded its purview. Nutraceuticals comprise single or mixed meals for pro- and pre-biotic goals as well as foods for specific medical applications; food supplements comprise single or mixed forms of

vitamins, minerals, protein supplements, functional foods, and herbal items [12].

The benefits of nutraceuticals can be found in a broad range of therapeutic areas, including the treatment of cancer, depression, diabetes, blood pressure, cholesterol, cough and cold, anti-arthritis, digestion, sleeping difficulties, and pain relief [13].

The nutraceutical research and development industries are placing out their best effort to ascertain how different nutraceuticals may prove to be significant in the pharmaceutical sector. The knowledge of nutraceuticals and their potential as potent therapeutic supplements has increased significantly throughout the past ten years. Nutraceuticals' dual therapeutic and nutritional actions have made them more popular than pharmaceuticals with both the general public and healthcare professionals.

ROLE OF NUTRACEUTICALS IN THE MANAGEMENT OF POLYCYSTIC OVARIAN SYNDROME

The complexity and lifetime negative biopsychosocial repercussions of PCOS, along with its incurable nature, highlight the significance of creating symptomatic alleviation and component-specific therapy plans that work. There has been an increase in interest recently on the potential benefits of using complementary therapies, vitamin supplements, and minerals or nutrients that resemble vitamins, treatments (CM) may improve PCOS patients' health outcomes [14].

By modulating important pathways believed to produce PCOS (e.g., insulin signaling, IR, lipid metabolism, etc.), supplements containing specific nutrients and complementary therapies may help improve health outcomes for women with PCOS and change the symptomatology and severity of it.

1. Vitamin supplements (Vitamin D, Vitamin B, Vitamin A, Vitamin E)
2. Bioflavonoids
3. Alpha-lipoic acid
4. Carnitine
5. Probiotics
6. Melatonin
7. Co-enzyme Q10
8. Omega-3-fatty acids

1. VITAMINS

Vitamin D: A steroid hormone, vitamin D is mostly obtained from sunlight and can also be obtained in small amounts through diet, such as fatty fish and fortified dairy products. In addition to its suggested role in skeletal homeostasis and calcium metabolism, vitamin D is also involved in several other metabolic and endocrine processes [15]. Through modifying progesterone production in human granulosa cells, follicle-stimulating hormone sensitivity, and anti-Mullerian hormone (AMH) signaling, vitamin D has a physiological function in reproduction, including ovarian follicular development and luteinization [16].

It has numerous roles that impact glucose homeostasis as well. The presence of particular vitamin D receptors (VDR) in skeletal muscle and pancreatic β-cells, the expression of the enzyme 1-α-hydroxylase, which can catalyse the conversion of 25-hydroxy vitamin D to 1,25-dihydroxyvitamin D, and the presence of a vitamin D response element in the human insulin gene promoter are some of the possible effects of vitamin D on glucose homeostasis [17].

It was also discovered that progesterone, oestradiol, and estrone could be produced in vitro by means of the active form of vitamin D. Vitamin D is necessary for the normal production of oestrogen in females [18]. Through the upregulation of both aromatase and dehydroepiandrosterone sulfotransferase (DHEAS), an enzyme that facilitates the sulfo-conjugation of endogenous hydroxysteroids, Vit D promotes ovarian steroidogenesis [19].

One of the main hall marks of PCOS pathophysiology is oxidative stress. Patients with PCOS have elevated levels of important oxidative stress indicators, including xanthine oxidase, advanced glycosylated end products (AGEs), nitric oxide (NO), and malondialdehyde (MDA). Being able to regulate oxidative stress, respiratory function in the mitochondria, and systemic inflammation in humans makes vitamin D an important antioxidant.

Vitamin B: The majority of research on vitamins in the B group focuses on folic acid, B6, and B12 because homocysteine (Hcy) is becoming more and more associated with PCOS. According to this mechanism, the risk of cardiovascular and reproductive symptoms in PCOS is enhanced by raised total plasma Hcy levels. Hcy is an important amino acid that is produced from dietary methionine [20]. Vitamins B6, B12, and folic acid are important players in the regulation of homocysteine. Reports have indicated a positive association between increased homocysteine levels and IR in the physiopathology of PCOS.

Vitamin E: Vitamin E is a scavenger of free radicals and a lipid-soluble vitamin that balances the functions of the oxidant and antioxidant systems. Furthermore, recent data demonstrated that the anticoagulant and antioxidant properties of Vit E could increase endometrial thickness in infertile women [21].

Vitamin A: Vitamin A is a fat-soluble vitamin that is essential for metabolic processes as well as healthy development and growth. Lipid-soluble vitamin A is helpful for antioxidant activity and is known to stop PCOS by promoting steroid production. Retinoids are a family of small organic chemicals that are essential for morphogenesis, growth, and cell differentiation, among other biological processes related to development. Numerous processes, such as reproduction (the generation of sexual steroids, spermatogenesis, conception, and placenta formation), cellular epithelium differentiation, cell division control, bone remodelling, genetic regulation, immune system stimulation, and lung development at all stages, are essentially dependent on vitamin A.

Retinoids, retinoic acid, and retinol have antioxidant properties as well as impacts on steroid metabolism, nuclear maturation of oocytes, and the prevention of cumulus cell death [22].

2. BIOFLAVONOIDS

A class of naturally occurring benzo-γ-pyran derivatives found in many fruits and vegetables are called bioflavonoids. Flavonoids are secondary metabolites mostly produced by plants. There are six subclasses: anthocyanins, flavones, flavan-3-ols, isoflavones, flavonols, and flavanones.

They benefit the gastrointestinal (GI) tract and nervous system, regenerate mitochondria, operate as chemical messengers and cell cycle inhibitors, and have anti-inflammatory, antiallergenic, anticlotting, germicidal, and chelating activities. The participation of chelating ions, such as iron or copper, has been demonstrated to enable bioflavonoids to protect DNA against damage induced by hydroxyl radicals.

According to reports, flavonoids are currently considered medications of choice due to their therapeutic potential against hyperlipidaemia, hyperglycaemia, oxidative stress, and hyperandrogenism [23].

Polyphenols are broadly classified into three main groups:[24]

- Polyphenols → Phenolic acids, Flavonoids, Non-flavonoids
- Phenolic acids → Hydroxycinnamic & Hydroxybenzoic acids
- Flavonoids → Anthoxanthins & Anthocyanins
- Non-flavonoids → Stilbenes & Lignans

3. ALPHA-LIPOIC ACID (ALA)

ALA is a naturally occurring amphipathic molecule that has potent anti-inflammatory and antioxidant properties. It is derived from octanoic acid in both plants and mammals. In the insulin metabolic pathway, ALA is first and foremost important because it improves glucose absorption. By activating AMPK, it promotes the translocation of the glucose transporter proteins GLUT4 and GLUT1 to the plasma membrane in adipocytes, simulating the action of insulin and so raising insulin sensitivity.

By promoting the synthesis of antioxidant enzymes like glutathione peroxidase and superoxide dismutase inside mitochondria and the endoplasmic reticulum through the translocation of nuclear factor erythroid-2–related factor 2 (Nfr–2), ALA and its reduced form, dihydro-lipoic acid (DHLA), act as scavengers of reactive oxygen species (ROS). This prevents the decreasing of PPARγ protein and shields the cell from oxidative damage.

Treatment with ALA also improves menstrual regularity and ovulation rhythm by having positive effects on endocrine patterns, particularly when paired with myo-inositol [25].

4. CARNITINE

The amino acids lysine and methionine are converted by the body into the quaternary amine known as carnitine. This chemical agent is capable of carrying fatty acids from the cytosol to the mitochondria in living cells, from where they can be transformed to energy. L-carnitine, which is the active form, and D-carnitine, which is the inactive form, are the two forms of carnitine that are commonly utilized as micronutrients. L-carnitine is crucial for the metabolism of glucose and the prevention of oxidative damage. Additionally, L-carnitine can stop cell death and maintain the mitochondrial membranes.

Recently, obese patients have employed L-carnitine supplements to improve the metabolic cascade. The evidence suggests that insulin resistance and hyperandrogenism may be linked to low serum levels of L-carnitine, even in non-obese women [26]. The use of L-carnitine (LC) and/or acetyl-L-carnitine (ALC) has been shown in numerous clinical studies to mitigate certain symptoms of PCOS, leading to improved reproductive outcomes [27]. In reproductive science, both LC and ALC are often utilized to enhance mitochondrial function in the management of female infertility [28]. In particular, LC is utilized to support the body's ability to oxidize fat cells to produce energy and burn fat, whereas ALC is mostly employed for its antioxidant and anti-aging effects. Moreover, LC stops DNA fragmentation brought on by the negative effects of free radicals [29].

Numerous studies have shown that administering L-carnitine (LC) or its acetylated version, acetyl L-carnitine (ALC), improves conditions such as PCOS, endometriosis, and amenorrhea. Furthermore, carnitines enhance gonadotropin and sex hormone levels while also improving oocyte health.

5. PROBIOTICS

The gut microbiome consists of many bacteria, archaea, viruses, fungi, protozoa, and their metabolites that have gradually adapted to reside on the mucosal surface of the intestine or in its lumen. The four most common bacterial phyla are Bacteroidetes and Firmicutes, Actinobacteria, and Proteobacteria. Beneficial bacteria such as Lactobacilli and Bifidobacteria are frequently reduced in PCOS, indicating a decrease in microbial diversity. Pathogenic bacteria, such as Escherichia and Shigella, are frequently seen to rise. Certain bacterial species, notably Bacteroidetes and Firmicutes, have also been seen to change their balance, resulting in altered short-

chain fatty acid synthesis and a deleterious influence on metabolism, gut barrier integrity, and immunity [30][31].

Fermented foods naturally include probiotic microbes, which have a number of health benefits. They have the capacity to enhance metabolic indices, alter the makeup of the gut microbiota, and control the immune system in addition to their antioxidant, antibacterial, and anti-inflammatory qualities. The bacterial genera Lactobacillus, Bacillus, Bifidobacterium, Streptococcus, and Enterococcus are among the most often used as probiotics. Numerous studies have been conducted on these probiotic strains, and their ability to support gut health and general wellbeing has been demonstrated [32].

With a significant decrease in the free androgen index and malondialdehyde, an increase in SHBG and nitric oxide, and improvements in weight, BMI, insulin, HOMA-IR, hirsutism, and total testosterone of PCOS patients, probiotic supplementation has a significant effect on the regulation of hormonal and inflammatory indicators [33].

6. MELATONIN

The indolamine hormone melatonin (N-acetyl-5-methoxytrypamine) was identified for the first time in the 1950s. Since light can inhibit melatonin secretion, photoperiod regulates melatonin levels by promoting its creation and secretion at night in response to darkness. Other organs that produce melatonin include the skin, bone marrow, gastrointestinal system, retina, and lymphocytes. It appears that melatonin production occurs in mitochondria within cells. Furthermore, follicular cells, oocytes, and cytotrophoblasts are all components of the female. Melatonin appears to shield follicles from oxidative stress and rescue them from atresia, which in turn appears to increase follicular maturation and ovulation [34].

Melatonin is a useful treatment for PCOS patients because it lowers oxidative stress, promotes oocyte maturation, and luteinizes GC. It has been demonstrated that giving melatonin to PCOS women, either by alone or in conjunction with other medications, raises the intrafollicular melatonin concentration, lowers intrafollicular oxidative stress, and increases the rates of fertilization and conception. Additionally, melatonin helps PCOS patients' corpus luteum produce more progesterone. The main shift seen in PCOS patients is an increase in the synthesis of LH, which is heightened in melatonin-deficient individuals, whereas gonadotrophin production is altered and FSH synthesis is decreased [35].

Melatonin inhibits the release of hormones like FSH, which reduces the number of cystic follicles and so modifies the hypothalamic axis. Additionally, melatonin can control the synthesis of GnRH by blocking the expression of GnRH receptors in the granulosa-luteal cells and maintaining the corpus luteum, which in turn sustains progesterone secretion [36].

7. CO-ENZYME Q10

The human body naturally produces coenzyme Q10, sometimes referred to as ubiquinone, which is an antioxidant and a metabolic cofactor. Additionally, food sources include meat, seafood, vegetables, seed oils, and nutritional supplements can provide it. Numerous species, including bacteria and animals, contain CoQ10.

CoQ10 is often taken as a dietary supplement to help prevent or treat illnesses like cardiovascular disease. The body naturally produces coenzyme Q10, which is essential for cell growth and defense.

Fat-soluble vitamin Coenzyme Q10 (CoQ10) functions as an efficient antioxidant that can shield ovaries from oxidative damage [37]. It has a constant oxidation-reduction cycle. Research indicates that administering CoQ10 as a dietary

supplement can enhance the metabolic and endocrine indices, insulin resistance, and endothelial cell function in individuals with PCOS [38].

8. OMEGA-3-FATTY ACIDS

Natural sources of omega-3 fatty acids include flaxseed oil, chia seeds, echium seeds, and walnuts. Marine oily fish are also good sources of omega-3 fatty acids. They are regarded as essential fatty acids that must be obtained from diet because humans lack the enzymes that add the ω-3 double bond at the methyl ends of fatty acids, which is the end opposite the carboxylic acid moiety [39].

Antioxidants can maintain female fertility by lowering ROS levels and oocyte apoptosis caused by oxidative stress. Follicle dysplasia and hyperinsulinemia in PCOS women resulting from severe oxidative stress can be treated with n-3 PUFAs, a traditional antioxidant [40]. Research indicates that through stimulating the PI3K/AKT pathway, n-3 PUFAs support the manufacture of progesterone and estradiol in PCOS granulosa cells.

FUTURE PROSPECTIVES

As per now, there is no universal treatment for PCOS and the treatment is always personalised. There is only symptomatic treatment and it only provides relief to certain symptoms. If we move ahead based on a symptomatic approach it may lead to certain lifelong complications like cardiovascular disorders, diabetes mellitus, etc. All the medications which have been currently prescribed have many limitations including side effects like weight gain etc. So, there is a rising tendency to turn into nutraceuticals and herbal approaches for the management of the PCOS. By affecting important pathways assumed to cause PCOS (e.g., insulin signaling, IR, lipid metabolism, etc.), supplements containing specific nutrients and complementary therapies may help improve health outcomes for women with PCOS and change the symptomatology and severity of the condition.

CONCLUSION

This review of the evidence suggests that some of the negative health effects linked to PCOS may be mitigated by supplementing with vitamins, vitamin-like substances, and complementary therapies.

In addition to conventional pharmacological therapy for PCOS, nutraceuticals represent a promising alternative approach, offering therapeutic benefits with a lower risk of adverse effects compared to many standard medications.

To ascertain the effectiveness of these supplements and their actions and interactions with the biological processes underlying PCOS, more study is thus required, especially through the use of well-designed, appropriately powered RCTs in addition to mechanistic studies.

The use of different nutraceuticals listed above can be used in the management of polycystic ovarian syndrome.

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HOW TO CITE: Nayana Shaji, Sri Suku J, Role Of Nutraceuticals in The Management of Polycystic Ovarian Syndrome – Exploring Potential Benefits, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 881-890, https://doi.org/10.5281/zenodo.22655682