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Chapter 4: Silencing Inflammation: Nano-Antioxidants and Immunomodulators in PCOS Management

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Abstract

Polycystic ovary syndrome (PCOS) is a hormonal disorder that primarily affects women's reproductive organs and endocrine system; it occurs mainly in women aged 18 to 44 years. Its characteristics include the formation of many cysts in the ovaries, changes in hormonal levels, and irregular ovulation. PCOS is a worldwide problem affecting more than 116 million women. The main risk factors include being overweight, heredity, the way one lives, tension, eating habits, and exposure to toxins in the environment. Among internal factors that aggravate the condition are oxidative stress, inflammation, and hyperandrogenism.The field of nanotechnology has recently opened up new avenues for treatment in terms of using metal nanoparticles (Ag, ZnO, Cu, Se) and biocompatible nanocarriers for drug delivery that also reduce oxidative stress, enhance insulin sensitivity and normalize hormone levels. Moreover, antioxidants like curcumin, quercetin, and resveratrol not only participate in the support of follicular maturation, but also take part in metabolic regulation and the provision of long-term reproductive health. Additionally, immunomodulatory nanoparticles can weaken chronic inflammation through the adipose tissue-mediated immune pathways. The present chapter showcases the contribution of nanotechnology applied to the areas of antioxidants and immunomodulators in the treatment of PCOS, as well as its inflammatory and immunological aspects.

Keywords: *Polycystic ovary syndrome (PCOS), Nanotechnology, Phytochemicals, Inflammation, Nano-antioxidants, Immunomodulators*

1. INTRODUCTION

Polycystic ovarian syndrome, a common metabolic and reproductive disorder, was previously considered a purely reproductive condition, but its association with insulin resistance and hyperandrogenism pointed to a metabolic disorder with long-term health risks, including cardiovascular disease and type 2 diabetes, which are now often overlooked (Allen et al., 2022). These risks are accompanied by reports of reduced quality of life and negative mental health outcomes. Polycystic ovarian syndrome has a strong impact on the healthcare system and results in high expenses and a significant consumption of resources. Surveys conducted worldwide have indicated a high level of dissatisfaction with care, which can be attributed to the fact that existing treatments usually take a small toll on long-term hazards and barely symptom-aided. The global guidelines do not deny the poor quality of the data but declare the urgent need for more comprehensive research. A few of the most common PCOS symptoms are shown in Fig. 4.1 (Balkrishna et al., 2023). The root causes of PCOS are shown in Fig. 4.2

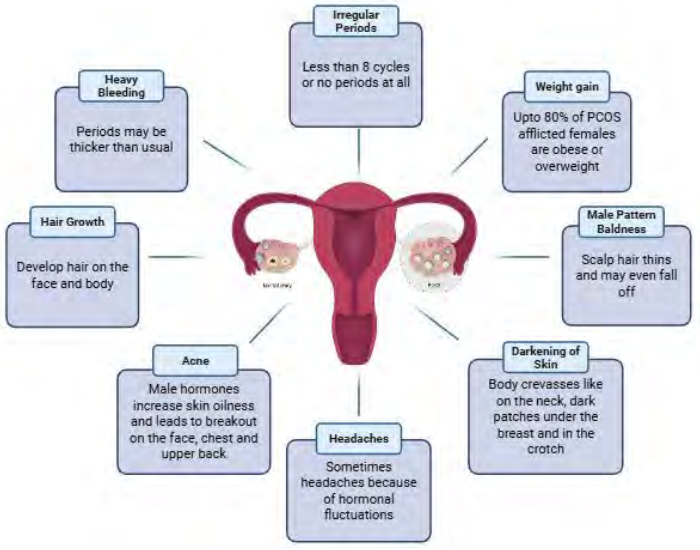

Figure 4.1: Polycystic Ovarian Syndrome Symptoms

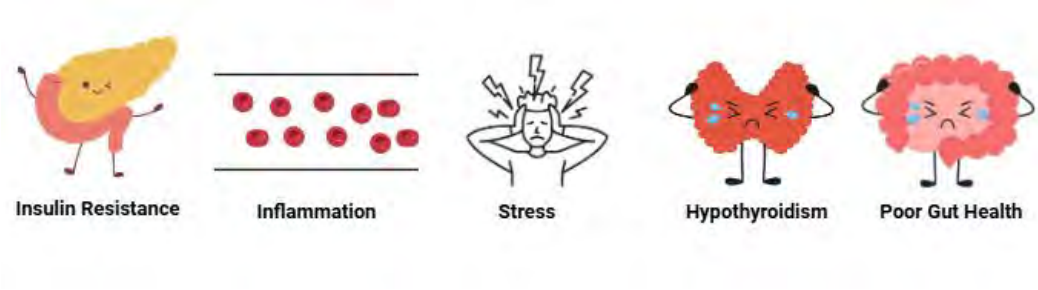

Figure 4.2: Root causes of PCOS

1.1 Epidemiology

Polycystic ovarian syndrome, which is a common endocrine disorder in women who are capable of having children, has a prevalence that varies between 4% and 21% depending on the criteria used for diagnosis. The disease is apparently spreading much faster than before and the distribution of its incidence is almost global. According to data from 204 countries, the age-standardized point prevalence in 2019 was high at 1677.8 per 100,000 and the annual incidence was effectively 59.8 per 100,000 representing increases of 30.4% and 29.5%, respectively since 1990. So it is time to recognize polycystic ovarian syndrome as a global public health issue taking into account its increasing incidence and related morbidity (Dong & Rees, 2023).

2. PATHOPHYSIOLOGY OF PCOS

2.1 PCOS is a complicated disorder that manifests itself with the presence of multiple cystic ovaries, disturbed menstrual cycles, and elevated androgen levels. One of the several mechanisms that are complex and involve the whole body and called the hypothalamic-pituitary-ovarian (HPO) axis dysfunctions is hyperandrogenism, insulin resistance (IR), reduced steroidogenesis, and excess fat around the belly (Siddiqui et al., 2022). At the center of the HPO axis is the hypothalamus that releases gonadotropin-releasing hormone (GnRH) which thus governs both insulin resistance and &rogens' production. If the release of GnRH is impeded, then the levels of luteinizing hormone (LH) may rise while those of follicle-stimulating hormone (FSH) may drop. In other words, prior research has indicated that by the pairing of insulin with LH, follicular membrane cells are able to produce higher amounts of androgens (Andrade et al., 2016). An excess of

ACTH might lead to the adrenal cortex's overproduction of androgens as well. This in turn causes one of the critical factors for the ovulation process, i.e. hyperandrogenism, to remain predominant and thus prevents the follicle from maturing. Studies aimed at identifying the pathogenic factors of PCOS are still scarce. A recent study reported hyperandrogenism, insulin resistance, and hyperinsulinemia as the main causes of the female reproductive dysfunctions. In addition, the so-called oxidative stress and inflammatory reactions that damage blood supply and the cells quality of the oocyte can act as risk factors for the development of PCOS (Doh et al., 2016).

2.2 Hyperandrogenism

Hyperandrogenemia is a systematic disorder that presents with a high level of androgens in the body. One possible explanation for the occurrence of PCOS is the poor production of steroids from ovarian cells. The major androgens in the blood of women include androstenedione (A), testosterone (T), dehydroepiandrosterone (DHEA), dihydrotestosterone, and dehydroepiandrosterone sulfate (DHEAS) (Burger, 2002). The excessive secretion of DHEAS, T, DHEA, and A in the case of PCOS leads to anovulation, the development of many small antral follicles, and the premature growth of ovarian follicles. Another hypothesis for hyperandrogenism is the increased metabolism of peripheral cortisol. Decreased cortisol levels disturb the negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to an increase in the production of ACTH by the pituitary gland and the stimulation of adrenal steroidogenesis (Moghetti et al., 2013). The mechanisms that produce excess androgen androgens, Hyperandrogenemia being one, constitute the main influences of the pathology of PCOS. In addition, hyperandrogenism is a factor that may contribute to the development of insulin resistance in patients with PCOS.

2.3 Insulin Resistance

To maintain a balanced ratio of nutritional availability to requirement, insulin carries out a number of functions in different tissues. Elevated blood glucose levels under normal physiological settings result in increased insulin secretion, which inhibits hepatic gluconeogenesis while promoting peripheral tissues' absorption of glucose. Compensatory hyperinsulinemia, which happens when insulin's capacity to perform

specific metabolic functions is compromised, is referred to as insulin IR. IR is a highly frequent ailment among PCOS patients, with estimates indicating that over 75% of them have it (Moghetti & Tosi, 2021). The condition is closely related to PCOS-related metabolic abnormalities. According to research from the 1990s, insulin activates a particular receptor in PCOS, which stimulates the pituitary organ's production of LH as well as ovarian and adrenal steroidogenesis. The pathophysiology of PCOS is fundamentally based on the hyperinsulinemia caused by tissue IR. Furthermore, in non-traditional insulin-responsive tissues including the pituitary gland and ovaries in PCOS patients, IR influences metabolic or mitogenic pathways. Moreover, there is compelling evidence that IR increases hyperandrogenism, which throws off the HPO axis and accelerates the onset of PCOS (Nestler et al., 1998).

Inflammatory Response and Oxidative Stress

Studies done so far show that there are genetic and inflammatory markers going up in the population of women with PCOS. One study states that women with PCOS had a very high level of a wide range of substances-C-reactive protein (CRP), interleukin-18 (IL-18), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and ferritin-when compared to women in the control groups matched for age and BMI (Rudnicka et al., 2020). It is the hyperandrogenism and insulin resistance that together cause an inflammatory reaction in PCOS by stimulating the production of reactive oxygen species (ROS) to a high level and, consequently, causing oxidative stress.It has been established that the entire oxidative stress process hampers the smooth follicular development and maturation. The presence of an excess of ROS can, in fact, result in cell death of oocytes and granulosa cells in the follicle which can further lead to degeneration of follicles and ultimately can affect fertility. Interestingly, oxidative stress is implicated in the pathological conditions such as obesity, inflammatory reactions, hyperandrogenism, and insulin resistance-conditions that are associated with PCOS. In a way, Frank González et al. suggested that high blood sugar levels can be a source of ROS which, in turn, create a pro-inflammatory milieu thus impacting IR and hyperandrogenism in women with PCOS. Mitochondrial dysfunction and impaired oxidative phosphorylation, which are hurdles in insulin signaling pathways and glucose metabolism, are also believed to be contributors to insulin resistance. Even though obesity conditions are marked by low antioxidant activity, signals like glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) are, nonetheless, drastically reduced in such people (Shi et al., 2024).

3. **IMBALANCE BETWEEN INFLAMMATORY MARKERS**

An inflammatory marker is a biomarker that is used in clinical settings to identify inflammation brought on by different diseases. According to some, these also affect the reproductive health of women. Inflammatory markers are critical to the ovary's functioning effectively. Pro-inflammatory and anti-inflammatory cytokines

Table 4.1: Relationship between inflammatory markers and PCOS

Sample	Effect	Inflammatory Markers	Observation
Serum and endometrial tissue	Increase	TNFα	When obesity exacerbates PCOS, an inflammatory state result
Serum	Increase	IL-6	IR and androgens are linked to elevated IL-6 levels, but not BMI
Adipose tissue of rat	Increase	IL-6	When treated with resveratrol, IL-6 mRNA expression decreased compared to normal treatment
Serum and follicular fluid	Increase	IL-8	IL-8 mRNA expression increased in GCs with higher BMIs, while serum concentrations eventually dropped.
Follicular fluid	Decrease	IL-10	Decreased IL-10 causes oxidative stress in PCOS, which triggers androgen production and inflammation
Serum and pooled follicular fluid	Increase	IL-18	Increased IL-18 levels impact the ovary, disrupting folliculogenesis
Serum	Increase	CRP	Obese PCOS females are at IR risk where oxidative stress does not cause obesity

3.1.1 Tumor Necrosis Factor-α (TNFα)

TNFα is produced by fibroblasts, neutrocytes, and activated macrophages in the ovaries. Human follicular fluid contains TNFα during ovulation, which prevents the phosphorylation of the insulin receptor tyrosine kinase. Obesity-related IR is linked to TNFα (Abraham Gnanadass et al., 2021). This cytokine influences the glucose process by decreasing the function of the glucose transporter type-4 (GLUT-4). TNFα and HA are correlated, according to another study. Obesity exacerbates PCOS and causes inflammation as a result.

3.1.2 IL-6

All cell types include the pleiotropic signaling inflammatory marker IL-6. The production of sex hormones, fetal development, and corpus luteum activity are all impacted by this cytokine. TNF-α, IL-1, and interferon-γ (IF-γ) are said to induce IL-6.

Serum levels of IL-6 were shown to be elevated in PCOS patients with IR. It has been investigated whether androgens trigger immunological reactions in female PCOS patients who are obese (Kim et al., 2019). According to a study, PCOS women with infertility have greater levels of IL-6 than healthy controls, which can have negative repercussions. While IR and androgens are linked to elevated IL-6 levels, BMI is not. Patients with PCOS had higher amounts of IL-6 mRNA, and when they were treated with an anti-inflammatory drug like resveratrol, their expression appeared to decline, lowering their risk of developing diabetes [Ghowsi et al., 2018].

3.1.3 IL-8

This inflammatory cytokine aids in follicular development and ovulation. It has been discovered that IL-8 promotes vascularization during follicular growth. According to a study, IL-8 is related to melanoma, angiogenesis, and metastasis. In one clinical experiment, IL-8 expression increased at first, but it fell after pioglitazone and metformin were administered [Ali et al., 2019]. While IL-8 levels in the serum declined, GCs' IL-8 levels increased as BMI increased when compared to obese PCOS and non-PCOS individuals [Rai et al., 2025].

3.1.4 IL-10

An immunosuppressant called IL-10 is essential to the body's defense system. IL-10 is thought to be linked to Th2 cells inhibiting Th1 cell activation. By producing progesterone and corpus luteum, Th1 cells reduce and sustain pregnancy. Obesity and metabolic diseases are associated with lower levels of IL-10. In PCOS, decreased IL-10 causes oxidative stress, which in turn triggers inflammation and androgen production (Artimani et al., 2018). Patients with PCOS syndrome had lower levels of plasma IL-10. However, Sylus et al. observed that in women with PCOS symptoms, clomiphene citrate enhances ovulation and conception rates and controls IL-10 (Sylus et al., 2018).

3.1.5 IL-18

It is a signaling cytokine molecule that triggers the activation of TNFα receptors, IL-1β, IL-2, and IL-6 inflammatory cytokines. After pro-IL-18 is cleaved by caspase-1, IL-18 triggers NF-kB and inflammatory cytokines. Atresia, steroidogenesis, and ovarian maturation all depend on this molecule. According to a study, the ovary is

impacted by high IL-18 levels, which disrupts folliculogenesis (Zhang et al., 2020). The fact that IL-18 is a crucial component that predicts fatalities from cardiovascular illnesses is intriguing. Serum concentrations of IL-18 are higher in those who exhibit signs of obesity. However, in cases of normal weight, the IL-18 was lower. In a similar vein, PCOS patients with obesity had higher endometrial IL-18 levels than those with normal weight. According to recent research, patients with PCOS complications and serum IL-18 have a close correlation (Sathyapalan & Atkin, 2010).

3.1.6 C-Reactive Protein

In the liver, the blood generates a protein known as CRP. This protein is controlled by the inflammatory factors TNF-α and IL-6. It is believed to be a crucial indicator of inflammation. The main reasons why CRP is released into the bloodstream are tissue damage and inflammation. CRP levels, which are associated with cardiovascular risk in PCOS patients, were greater in both obese and nonobese persons with PCOS symptoms. Regardless of their degree of obesity, women with PCOS had higher CRP levels, according to a research. Another study found that women with PCOS who are obese and had elevated CRP levels are more likely to have elevated blood lipid or cholesterol levels. CRP drop-off endothelial function was shown to be higher in PCOS individuals (K et al., 2016). In response to pro-inflammatory agents such as TNF-α and IL-6, a protein known as CRP is produced during the acute phase of the immune response. It is the most important indicator of long-term outcomes in inflammatory diseases. When there is cell damage or inflammation, CRP is released into the bloodstream. A higher CRP is indicative of systemic inflammation. Type 2 diabetes and cardiovascular disease may be more common in PCOS patients with elevated C-reactive protein levels (Cakal et al., 2011). Elevated CRP levels in PCOS-affected women are inflammatory and increase the risk of T2D. Research on persistent low-grade inflammation and PCOS has mostly focused on CRP levels (Pal et al., 2023). During the acute phase, the liver produces this protein in response to TNF-α and IL-6 activation. Another source of CRP generation is adipose tissue. There is growing evidence that CRP may be a gauge of the intravascular inflammatory process and is a critical predictor of the beginning of cardiovascular diseases. Kelly et al. [Kelly et al., 2001] compared 17 PCOS patients with 14 healthy controls to provide the first proof of

elevated CRP in PCOS patients. They found a statistically significant rise in serum CRP among the study group even after adjusting for age and BMI.

3. ANTIOXIDANTS AND IMMUNOMODULATORS IN PCOS

3.1 Alpha Lipoic Acid (ALA)

One of the strongest natural antioxidants is ALA, 1, 2-dithiolane-3-pentanoic acid, sometimes known as "the universal antioxidant." LA is a necessary cofactor for the pyruvate dehydrogenase complex and a member of the class of metabotropic antioxidants. It exhibits antioxidant activity in both its reduced (di-thiol: dihydro-lipoic acid) and oxidized (disulfide) forms. Furthermore, by increasing the expression of glucose transporter 4 (GLUT-4), which can start glucose transfer, LA reduces blood glucose levels (Rochette et al., 2013). Genazzani et al. (Genazzani et al., 2018) research demonstrated that obese PCOS individuals could have improved insulin sensitivity with low-dose integrative ALA supplementation. Additionally, triglycerides and glutamic oxaloacetic transaminase levels were lower in PCOS individuals with diabetes relatives levels, indicating that ALA's integrated treatment decreased metabolic impairment, particularly in people with familial diabetes, who are more likely to develop non-alcoholic fatty liver disease and acquire diabetes. In both obese and nonobese PCOS patients, ALA therapy is effective in postponing the development of problems like atherosclerosis and chronic liver injury, according to the results of these trials. For the treatment of PCOS and hyperinsulinemia combined with liver disease (cirrhosis, hepatitis, and decompensated steatosis), ALA is therefore anticipated to be the medication of choice. Inositol and LA can synergistically affect GLUT-4. Patients suffering from PCOS were administered ALA in the amounts of 400 mg/day, 800 mg/day, and 600 mg/day by the studies of Genazzani et al. (Genazzani et al., 2019) and Fruzzetti et al. (Fruzzetti et al., 2020). They concluded that the treatment together was better than single molecules, however, more studies are needed to find out the perfect doses.

4.2 Vitamin C and vitamin E

Vitamin E, which belongs to the group of fat-soluble vitamins, is known for its antioxidant activity and it is also able to stimulate “radicals scavengers.” These enzymes are vital for cell protection as they minimize the process of lipid peroxidation.

Similarly, vitamin C, another strong antioxidant, is often called the “vitamin of the century,” a required nutrient for humans, and a cofactor on some enzyme activities. Moreover, it can interfere directly with the aqueous peroxyl radicals and thus its antioxidant effects are through two different paths—it can either indirectly restore the levels of fat-soluble antioxidant vitamins or directly neutralize them—the first one being less noisy than the second (Traber & Atkinson, 2007). In their study, Olaniyan et al. (2019) used a PCOS mouse model that was induced by DHEA and they checked the effects of vitamin C on the different groups. The animals that received both DHEA and vitamin C showed significantly higher levels of antioxidants and metabolic enzymes, and lower levels of MDA and cytokines compared to the group that received DHEA only. The histological studies further revealed a decline in the number of atretic and cystic ovaries and confirmed through a marked downregulation of androgen receptor mRNA gene expression that the antioxidant properties of vitamin C are indeed capable of countering DHEA-induced PCOS. The 43 women with PCOS were chosen by Shirazi et al. (2021) and they were randomly assigned to two groups. Throughout the eight-week period, the vitamin E and the placebo group got 400 IU/day of vitamin E in cellulose (n = 21) and alpha tocopheryl acetate (n = 22) capsules, respectively. The changes due to vitamin E supplementation in weight loss, fat mass reduction, Ang-1, Ang-1/Ang-2 ratio, and VEGF levels were all found to be significant after controlling for potential confounders. This led to an improvement in the overall metabolic health of the subjects.

4.3 Resveratrol (RSV)

Resveratrol is a naturally occurring polyphenol that is composed of phenolic units among others, and it is mainly recognized for its strong antioxidant activity but also possesses many other properties such as anti-inflammatory, anti-coagulant, anti-aging, and even anticancer. It is present in the diet through sources like grapes, red wine, peanuts, and selected kinds of berries. It is indeed proposed that resveratrol's action against oxidative stress is by trapping free radicals as well as boosting the endogenous antioxidant enzymes (Tung et al., 2014).

Ergenoglu et al. (2015) first generated a PCOS rat model through subcutaneous administration of dihydrotestosterone for 14 days. Afterward, the animals were divided into two groups and treated with either isotonic saline (1 mL/kg/day) or resveratrol (10 mg/kg/day). It was found that there was a significant decrease in the number of antral follicles, plasma levels of AMH, IGF-1, and SD activity in the group receiving resveratrol, but there was a great increase in GP activity. This finding made it possible to recommend the antioxidant effect of resveratrol as a useful one in improving the treatment of PCOS.

4.4 N-Acetylcysteine (NAC)

At high doses, NAC, a safe and widely used mucolytic medication, lowers glutathione levels and raises cellular antioxidant levels (Thakker et al., 2015). 37 PCOS patients received oral NAC at a dose of 1.8 g/day for up to six weeks in research by Fulghesu et al. (Fulghesu et al., 2002) subjects who were noticeably obese were randomly assigned to a dose of 3 g/day. They discovered that all patients tolerated NAC well, and no negative side effects were noted. T levels and the free androgen index significantly decreased after hyperinsulinemic patients' insulin sensitivity significantly increased and their circulating insulin levels decreased concurrently at the end of the treatment. Normoinsulinemic patients, however, did not show comparable outcomes. Furthermore, research on how insulin-sensitizing drugs affect lipidic patterns revealed that NAC-mediated insulin-level reduction significantly reduced plasma lipid levels, including cholesterol, triglyceride, and LDL levels, suggesting that this medication may also have a positive long-term impact on PCOS patients' health outcomes.

4.5 Melatonin

The pineal gland secretes melatonin, a chemical having pleiotropic properties derived from tryptophan. It has a circadian pattern, peaking at night and falling throughout the day. Early life forms like unicellular organisms used melatonin primarily for its antioxidant and free radical scavenging properties. It differed from traditional antioxidants in a number of ways, such as its capacity to induce under moderate OS conditions and its ability to undergo cascade reactions with free radicals (Cheng & He, 2022). In a study by Pai et al., (Pai & Majumdar, 2014) daily subcutaneous testosterone injection (20 mg/kg) for 35 days caused PCOS in female rats that were 21 days old.

Over the course of 36 days, the PCOS mice received 500 mg/kg of metformin, 1 mg/kg of melatonin, or 2 mg/kg of melatonin in conjunction with testosterone.66 Body weight, body mass index, intra-abdominal fat (IAF), insulin, and CRP levels were all markedly decreased by both melatonin dosages; also, a positive lipid profile was noted. Furthermore, histological analysis of the tissues of the ovary, uterus, and IAF showed adipocyte hypertrophy, a reduction in cystic follicles, and cancerous endometrial glands, respectively.

4. NANOTECHNOLOGICAL APPROACHES IN PCOS MANAGEMENT

Nanotechnology has been used to aid in the diagnosis, treatment, and prevention of disease, making it a fresh hope for resolving today's human issues. Due to their small sizes (1 and 100 nm), nanotechnology uses structures and materials with novel features and applications in biology and medicine at the supramolecular, molecular, and atomic levels. High solubility, enhanced reactivity, faster passage across biological barriers, and desired size are just a few of the intriguing qualities and capabilities of nanomaterials. Innovative FDA-approved concepts have made the groundbreaking use of nanotechnology in medicine an exciting development in recent years. Because of this advancement, numerous nano-therapeutics for a range of human diseases have been created (Javid-Naderi et al., 2023). A number of factors, including hyperandrogenism, insulin resistance, oxidative stress, and inflammatory response, are important pathways via which PCOS causes anovulatory infertility and metabolic dysfunction. Therapy based on nanomaterials can affect these processes in a number of ways. Drugs that address these diseases are transported via nanocarriers. Currently, we treat PCOS-related disorders with various nanocarriers. These consist of micelles, carbon nanotubes, liposomes, nanoparticles, and quantum dots (Gupta et al., 2025).

4.1 Nanoparticles

4.1.1 Natural-Based Drug Nanoparticles

A variety of therapies originating from plant, animal, and mineral sources are included in the category of natural medicines; all have been confirmed to have certain bioactive qualities by modern pharmacological research. The use of medications produced from plants has significantly increased recently because their potential uses in herbal medicine for prevention, treatment, and rehabilitation. Arentz et al. (Arentz et al.,

2014) found that women with PCOS were dissatisfied with Western medications, and that over 70% of them used supplemental medications, indicating that patients preferred alternative therapy. Furthermore, conventional drugs used to treat PCOS issues can have negative side effects and fail in certain situations. Recent research has focused on the potential benefits of several herbs for PCOS, as they contain several active ingredients that may yield synergistic effects. Previous studies have shown that a significant number of botanicals have pharmacologically active ingredients that can positively affect insulin sensitivity, ovulatory function, obesity, and hormone levels. For instance, in a letrozole-induced animal model, Maharjan et al. (Nampoothiri et al., 2010) showed that Aloe barbadensis gel had a favourable effect on PCOS, while in rats with PCOS, chamomile extract promoted normal follicular development. According to a clinical study by Javad Heshmati et al., curcumin may be a safe and useful adjuvant treatment for reducing hyperandrogenism and hyperglycemia associated with PCOS (Heshmati et al., 2021).

Natural drug nanoparticles have shown promise in recent years for therapeutic uses; their size distribution and surface charge are similar to those of extracellular microbubbles found in mammals. These nanoparticles have structural and functional characteristics that increase their clinical value and function as natural nanocarriers for vesicle transport. This enables these nanovesicles to develop next-generation biotherapeutics and drug delivery systems in response to pressing clinical demands. Curcumin, a phenolic molecule with anti-inflammatory and antioxidant properties, has demonstrated potential in reducing hyperandrogenism, insulin resistance, and hyperglycemia in PCOS patients (Akter et al., 2023). However, its practical utility is limited by issues with solubility and poor pH stability. Researchers are becoming increasingly interested in biocompatible polymeric nanoparticles like chitosan (CS) that dissolve quickly and are simple to work with. Although CS is poorly soluble in water, this disadvantage can be mitigated with chemical modifications. The pharmacokinetic properties of the active components can be enhanced by functionalizing CS to encapsulate various pharmacological compounds (Shelma & Sharma, 2013). Because CS nanoparticles are cationic polysaccharides, they can be used to embed a range of chemicals, including antimicrobials, analgesics, and anti-

inflammatory medications. In comparison to controls, Raja et al. (Raja et al., 2021) successfully created nanoparticles with curcumin-embedded arginine and N-acetylhistidine-modified CS that efficiently inhibited serum levels of prolactin, testosterone, insulin, and LH in a rat model. This study is a promising first step in using nanoparticles as a powerful curcumin delivery system to treat PCOS(Rai et al., 2025).

Ginger stems from the rhizome of Zingiber officinale, which contains volatile oils, terpenes, and phenols, among other bioactive substances. In addition to improving insulin sensitivity and reducing insulin levels, the bioactive ingredient 6-gingerol adds a strong flavor. Ginger-derived nanoparticles have also been shown by Anil Kumar et al. (Kumar et al., 2022) to counteract insulin resistance, potentially by upregulating Foxa2 expression and so reducing IEC exosome-mediated insulin resistance. Cinnamon is a member of a broad genus that has been used for ages in spice, cooking, and medicine. Cinnamaldehyde, eugenol, manganese, iron, calcium, dietary fiber, and other associated substances are found in all species of cinnamon. Clinical and animal studies have examined the therapeutic benefits of cinnamon for PCOS. Cinnamon has been demonstrated to increase LH levels, lower insulin and testosterone, and restore the estrous cycle in animal models of PCOS. Short-term cinnamon supplementation has a positive impact on metabolic risk factors in 84 overweight women with PCOS, according to a clinical investigation by Borzoei et al. (Borzoei et al., 2018). Koffi Kouame et al. found that silver nanoparticles generated from cinnamomum cassia (CcAgNPS) exhibit antioxidant properties that may enhance renal function in diabetic mice (Kouame et al., 2019). Additionally, the anti-inflammatory and antioxidant qualities of nanoparticles derived from camellia, aloe vera, and other natural extracts may make them future therapeutic targets for PCOS treatment.

5.1.2 Metal Nanoparticles

Historically, scientists have produced nanoparticles via physical and chemical techniques, which provide a variety of challenges. Recent studies have focused on innovative therapeutic nanoparticles, such as selenium and silver, to treat PCOS. Silver nanoparticles show promise in reducing inflammatory markers and treating inflammation in rats with PCOS. Reducing inflammation may alleviate symptoms

commonly associated with elevated inflammatory cytokines in PCOS patients, which suggests a gradual approach. Current research mostly employs metal nanoparticles through natural compounds to maximize therapeutic benefits. Silver nanoparticles exhibit remarkable antibacterial properties and exhibit efficacy against cinnamon extracts that have been demonstrated to have anti-inflammatory and anti-cancer properties (Liu et al., 2017). Studies have demonstrated that curcumin-loaded iron nanoparticles effectively stop ovarian damage cells from dying, which may aid in the treatment of PCOS. Selenium nanoparticles have also shown promise in treating PCOS by reducing androgen production and disrupting the excessive androgen cycle through reduced androgen receptor expression. Additionally, it has been demonstrated that selenium nanoparticles lower insulin sensitivity indicators, sex hormone levels, inflammation, and mitochondrial function in PCOS models (Rabah et al., 2023). Furthermore, research indicates that carbon nanoparticles selectively boost follicle-stimulating hormone (FSH) levels, whilst copper nanoparticles increase ovarian cell survival and steroid release.

Metal and natural nanoparticles differ in terms of biocompatibility, immune response potential, and degradation rates. Natural nanoparticles often have superior biocompatibility, little immunological reactivity in biological systems, and rapid biodegradation because they resemble biological tissues. On the other hand, the biocompatibility and rates of metal nanoparticle disintegration depend on the specific metal used and any surface modifications performed to it. Surface-modified metal nanoparticles are effective vaccine delivery vehicles that can elicit a robust immune response (Hoseini et al., 2021). As a result, while selecting nanoparticles, it's critical to consider their rate of disintegration, potential immunological response, and biocompatibility.

5.1.3 Liposomes

Liposomes are lipid bilayers, consisting of one or more phospholipids, that self-assemble into spherical structures. These non-toxic and environmentally friendly structures are an excellent method for administering a myriad of drugs. Apart from chemical compounds, they can also carry proteins, nucleic acids, and the like. Due to the reasons mentioned above, liposomal delivery has become a prominent technique in

pharmacology, overcoming the drawbacks of minor drug toxicity and providing wider therapeutic areas (Guimarães et al., 2021). Resveratrol is a polyphenol that occurs naturally and has potential reproductive health-improving properties, but its use is limited owing to its poor bioavailability. DMU-212, a resveratrol methoxy derivative, has a greater bioavailability owing to its lipophilic nature. Lipid nanoparticles (LNPs) aid in drug translocation through gastrointestinal barriers; thus, they increase drug permeability, optimize transport kinetics, and enhance bioavailability tremendously. Integration of computational tools is a present-day challenge and opportunity for oral drug delivery systems. Nanoparticle drug delivery systems (NDDSs) play a vital role in the enhancement of oral bioavailability as they not only improve drug absorption but also facilitate intracellular penetration. The effectiveness of the nanoparticles is determined by their size, shape, and surface properties in spite of the oral drug delivery facing physiological and biochemical barriers.

5.1.4 Nanotubes

Carbon nanotubes are a novel class of materials that find extensive use in biomedical applications due to their unique structure, attractive properties (like size and aspect ratio of covering surface area to length), and mechanical, electrical, and thermal capabilities (Prajapati et al., 2022). Compared to other nanocarriers, carbon nanotubes can be more readily modified to bind bioactive materials and ligands for targeting. The application of carbon nanotube-based nanomedicine is therefore very alluring and promising. By decreasing fasting blood glucose and increasing serum biomarker levels associated with inflammation and oxidative stress, carbon nanotubes may contribute to insulin resistance, according to Miey Park et al. (Park et al., 2022). Carbon nanotubes are employed in diagnostics as well as drug delivery. One biomarker associated with both PCOS insulin resistance and the inflammatory process of type 2 diabetes is human fetuin A (HFA). Using magnetic multi-walled carbon nanotubes (m-MWCNTs) as nanocarriers, Esther Sánchez-Tirado et al. measured HFA (Sánchez-Tirado et al., 2018). The assay performed significantly better than ELISA kits and chronoimpedance immunosensors. Multi-walled carbon nanotubes have the ability to load silver nanoparticles and may one day be used to diagnose infertility, per a study by Pradeep K. Jha et al. (Jha et al., 2017). The toxicity of carbon nanotubes must also be taken

into account. According to Jianbin Zhao et al., prolonged exposure to multi-walled carbon nanotubes (MWCNTs) impairs X. tropicalis growth and development and may cause reproductive issues (Zhao et al., 2021). In humans, MWCNTs may also inhibit the production of progesterone by ovarian granulosa cells, possibly by blocking the expression of steroid acute regulating proteins.

5.1.5 Quantum Dots

Quantum dots are much brighter and more photostable than traditional fluorescent dyes. Numerous antibody-based immunoassays rely on them. Kunal Sarkar et al. described a nanodrug delivery system based on pegylated graphene oxide quantum dots (GOQDs) (Sarkar et al., 2024). Because GOQD-PEG can enhance glucose absorption and decrease insulin resistance in an in vitro model, this technology facilitates the continuous release of metformin. Moreover, the combination of quantum dots and nanoparticles can result in multisensing effects. In mammalian systems, quantum dots usually pierce cell membranes to regulate the flow of substances across the cell barrier. This is largely due to mechanisms like micropinocytosis, clathrin-mediated endocytosis, and caveolae-mediated endocytosis. Recent studies have shown that quantum dots can accurately detect and pinpoint specific markers of ovarian cancer metastases, opening the door to more specialized treatment strategies. A study by Vimal Singh et al. (Singh et al., 2019) demonstrated the safety and non-toxicity of carbon quantum dots in mice and cervical cells, confirming their suitability for use in biomedical applications.

5.1.6 Micelles

Micelles are commonly used molecular assemblies that have attracted a lot of attention in contemporary medicine due to their remarkable stability. Polymeric micelles are less immunogenic to drugs and have a longer half-life than conventional micelles. Co-delivery micelles have the potential to decrease reproductive toxicity and fertility loss while simultaneously increasing the efficacy of chemotherapy. Micellar nanoparticles are specific drug delivery vehicles that are produced when amphiphilic polymers or surfactants self-assemble in aqueous solutions. Research shows that curcumin and nano-membicellated curcumin (NMC) effectively inhibit the reproductive toxicity caused by chlorpyrifos (Pal, R et al., 2025). This is most likely because oxidative

damage and inflammatory reactions have decreased. Interestingly, another study suggests that NMC may impact embryonic development and lower oocyte quality. Interestingly, a newly developed siRNA nanoparticle called self-assembled micellar inhibitory RNA (SAMiRNA) shows promise in treating androgenetic alopecia linked to hyperandrogenism. Malabsorption and enzyme instability result in decreased bioavailability of oral insulin, a potential treatment for PCOS patients. Micelles are a promising new drug delivery method for oral insulin because of their enhanced sensitivity to glucose levels and rapid responses to glucose changes.

CONCLUSION

Polycystic Ovary Syndrome (PCOS) is frequently recognized as a complex inflammatory and immunometabolic disorder and thus it is not just an endocrine problem. In reality, chronic inflammation, oxidative stress, and immune dysfunction are the primary causes of hormonal imbalance, insulin resistance, dysfunctional ovaries, and, finally, metabolic diseases. The latter is the context in which the chapter "Silencing Inflammation: Nano-Antioxidants and Immunomodulators in PCOS Management" presents innovative and promising treatment methods based on nanotechnology that are capable of treating these interconnected disease pathways with higher precision and efficacy. Nano-antioxidants primarily aim at selectively removing the uncontrollable reactive oxygen species, that is restoring redox balance, and protecting the ovaries and metabolic tissues from damage due to oxidative stress. In parallel, the nano-engineered immunomodulators can maintain the inflammatory signaling pathways and immune cell responses very well and therefore alleviate chronic inflammation without extenuating exercises of total immunosuppression in the body. Nanocarriers have the ability to enhance bioavailability, stability, and tissue specificity; thus, they can significantly reduce the drawbacks of the traditional antioxidants and anti-inflammatory agents and this leads to better therapeutic outcomes with fewer side effects. Overall, the adoption of both nano-antioxidants and immunomodulators is making the management of PCOS, which has been traditionally on a trial-and-error basis, into one that is more science-savvy and individualized. The preclinical data are highly encouraging but further translational research and rigorously designed clinical trials will still be required in order to ascertain the safety for the long term.

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