Review Article

Herbal Nanomedicine For Polyendocrine Metabolic Ovarian Syndrome: Targeted Ovarian Delivery and Future Perspectives

Geetharani Narayanan[1*], Kumar Mohan[2], Margret Chandira Rajappa[3]

[1.] Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation, (Deemed to be University), Yercaud main road, Salem, Tamil Nadu, India. ORCID: 0000-0001-9952-6050
[2.] Department of Pharmaceutical Chemistry, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation, (Deemed to be University), Yercaud main road, Salem, Tamil Nadu, India. ORCID: 0000-0002-3513-2383
[3.] Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation, (Deemed to be University), Yercaud main road, Salem, Tamil Nadu, India. ORCID: 0000-0001-6364-2340

Corresponding Author: Dr. Kumar Mohan , Email ID: kumarvmcp@yahoo.co.in

Abstract

The complicated endocrine and metabolic disorder that causes ovarian dysfunction, insulin resistance and hyperandrogenism is known PMOS (Polyendocrine metabolic ovarian syndrome) which effects up to 20% of reproductive age of women. This biological mechanism includes impaired metabolic function of hepatic and adipose tissue, persistently increased inflammation, irregular ovarian steroidogenesis, and changes to insulin function along with changes in follicular maturation. While conventional treatments generally manage symptoms, there are significant side effects and poor efficacy, thus prioritizing a safer and more targeted, more individualized approach. Herbal phytochemicals in preclinical and early clinical trials display insulin sensitizing properties, anti inflammatory properties, anti-oxidant properties and anti-androgenic effects. However, they are relatively poorly soluble and have low bioavailability and have a high rate of metabolism which limits their use. Various nanotechnologies are emerging as options for delivering the particles in nanoscale size and for being a potential vehicle to improve the stability of phytochemicals, their bioavailability, and ovarian-specific targeting. Based on preclinical data chitosan, selenium, and copper based nanocarriers could be beneficial for the recovery of ovulation, oxidative stress reduction, and recovery of the function of oocytes and granulosa cells; but, to date, no human clinical trial has been reported on the combination of these herbal nanomaterials in the treatment of PMOS. The obstacles of long-term toxicity, reproductive safety, standardization of herbal extracts and complexity of regulation for combined products of botanicals and nanomedicines are still significant. The aim of this review is to briefly summarize the pathophysiological mechanisms of PMOS, review relevant phytochemicals and nano-tech delivery systems and investigate safety, regulatory, and standardization issues, specifically highlighting the delivery to the oocytes and granulosa-cells. To effectively implement the initial hinges of these strategies will need to involve human cohorts with PMOS in standardized phenotyped clinical trials.

Keywords: Nanoparticles, Oocyte, Granulosa cell, Herbal, Targeted drug delivery.

1. INTRODUCTION

Polyendocrine metabolic ovarian syndrome (PMOS) is considered the most prevalent endocrine/metabolic disorder of women of all ages, having a substantial impact on cardiovascular risk, metabolic health and infertility. The disorder is very complex with clinical issues ranging from chronic inflammation to menstrual problems, to obesity and insulin resistance and to hyperandrogenism. PMOS is not just a reproductive issue and is now considered as a systemic metabolic disorder. PMOS is caused by a number of overlapping pathophysiological processes such as the dysregulated activity of enzymes involved in steroidogenesis (CYP11A1 and CYP17A1), the overproduction of ovarian androgens, insulin resistance and hyperinsulinemia, oxidative stress and inflammation due to NF-κB signaling, excess anti-mullerian hormone (AMH) influencing attenuated follicular maturation, and metabolic disturbances in adipose tissue and the liver. Collectively, these alter the metabolic and endocrine state of the body, creating a vicious cycle of metabolic and endocrine dysfunction. Despite being effective sometimes and not other times, and having side effects, conventional treatments such as hormonal contraceptives, insulin sensitizers (metformin), and ovulation-induction drugs (letrozole, clomiphene citrate) only offer comfort in the form of symptoms. With a chronic illness like PMOS, there is a growing trend in the use of supplementary therapies like herbal medicines have more than one mechanism of action; anti-androgenic, anti-inflammatory and insulin sensitizing. Phytochemicals with beneficial effects in preclinical and early clinical research include curcumin, berberine, resveratrol and quercetin. But their physiologic high metabolism, low oral bioavailability, poor tissue solubility and lack of tissue selectivity restrict their therapeutic applications. Nanotechnology is a possible solution to these restrictions – phytochemicals can be encapsulated in polymeric, lipid-based or inorganic nanoparticles and these properties such as solubility and stability, circulatory times and site-specific targeting are increased. Granulosa- and oocyte-targeted nanocarriers could especially limit the effects of the nano drugs to the system, simultaneously restoring reproductive function in PMOS. Despite its promising preclinical results [1-5], there are still considerable difficulties to overcome in

areas of toxicity, regulatory approval, and standardization of herbal-nano formulations. This review was conducted using the literature search of PubMed, Science Direct, and Google Scholar (2020–2026); with the keywords such as granulosa cell, oocyte, phytochemical, herbal, nanoparticle, nanomedicine and PMOS. Articles were selected for being included if they dealt with mechanisms relevant to PMOS, phytochemical pharmacology, or nanocarrier based delivery, with preference being given to articles published in the last 5 years, and mechanistic studies relevant to PMOS or closely related reproductive and toxicological studies were included if they were unavailable and are specifically identified when discussed.

There are, however, a number of recently published reviews that cover similar topics: herbal-based approach with nanotechnology in PMOS [6,7] and a mechanistic basis for nanomedicine in PMOS [8]. The present review is designed to build on these by dealing specifically with mechanisms to target the oocyte and granulosa cells; by representing only as much evidence as pertains to PMOS; by explicitly separating out the evidence that can be directly extrapolated between non-PMOS models of reproductive and toxicological uses; and by explicitly synthesizing the standardization and regulatory hurdles of combined herbal nanomedicines. So far, no human clinical trials of herbal-phytochemical nanoformulation in PMOS have been reported and this should be kept in mind throughout the following portions.

2. PMOS PATHOPHYSIOLOGY

2.1. Ovarian Androgen Synthesis (CYP11A1, CYP17A1 Enzymes)

Imbalanced ovarian steroidogenesis is a key feature of PMOS pathogenesis. Within the theca cells of PMOS ovaries they tend to have an excess of steroidogenic enzymes like CYP17A1 and CYP11A1, these enzymes push excess amounts of androgen. This hyperactivity causes the release of more androstenedione and testosterone, and approximately 2/3 of women with PMOS also experience functional ovarian hyperandrogenism (FOH). An excessive insulin and androgen result in early luteinization of granulosa cells inhibits the growth of follicles and the conversion of androgens to estrogens. Intriguingly, high LH levels will further stimulate the production of androgen in the theca cells, but long term exposure of the theca cells to LH will also produce some desensitization of the cells over time; however, over time the positive feedback between LH and theca cell androgen levels can keep the system abnormal. In addition, the polycystic ovarian morphology (PCOM) observed in women is the result of hyperestrogenemia, hyperandrogenemia, (the production of androgens) which increased the recruitment of primordial follicles into the development zone, and also induce inhibition of the selection of a dominant follicle [9-12].

2.2. Insulin Signalling and Glucose Metabolism (IR, PI3K/Akt Pathways)

This insulin resistance result in nearly 70% of women with PMOS having hyperinsulinemia, even in lean women. Interestingly, the ovaries are unable to become insulin resistant, but remain steroidogenically insulin sensitive when insulin resistance impairs glucose uptake and PI3K/Akt signaling in other tissues. The hyperinsulinaemia that occurs in CAS syndrome co-drives ovarian androgen production by antagonising the desensitising effect of LH on the ovary. Insulin has also an action on granulosa cell follicular maturation and steroidogenesis through actions with insulin-like growth factors (IGFs). The rise of free blood androgen is also caused by the loss of production of sex hormone-binding globulin (SHBG) and changes in levels of IGF signalling. Metabolic inflexibility, a sign of insulin resistance is one of the earliest.Early insulin resistance sign there is impaired sensitivity to catecholamines in the process of lipolysis as part of metabolic inflexibility in PMOS. Hyperinsulinemia and hyperandrogenism interact with each other, resulting in a vicious cycle that contributes to the maintenance of PMOS pathology, and to systemic metabolic impairment [9, 10, 13-15].

2.3. Inflammation and Oxidative Stress (NF-κB, Cytokines, ROS)

PMOS is now known to be an inflammatory and metabolic disorder. Women who are PMOS, including those who are not obese, have higher levels of C-reactive protein (CRP), which is a marker of low grade chronic inflammation. These include pro-inflammatory cytokines (IL-6, TNF-α) which affect the function of the ovary (insulin resistance) and are produced as a result of NF-κB activation. Too many reactive oxygen species (ROS), a key component of oxidative stress, exacerbate the follicular environment, deplete the quality of the oocyte and stimulate androgen production. Recent animal studies also have demonstrated that autoimmune pathways could play a role in the development of a disease and on reproductive outcomes. Inflammation has been shown to interact with oxidative stress to constitute a pathogenic axis that correlates PMOS reproductive abnormalities with metabolic abnormalities [9, 10, 16-19].

2.4. Follicular Maturation Regulators (AMH, FSH Responsiveness)

Hyperresponsiveness of the granulosa cells to FSH and anti-Müllerian hormone (AMH) production by increased numbers of small antral follicles accounts for dysregulated folliculogenesis, a hallmark of PMOS. This leads to FSH hyporesponsiveness due to inhibition of aromatase activity that decreases conversion of androgen to oestradiol. LH predominance is another important aggravating factor, because it makes theca cells to produce more androgens, thus reinforcing the hyperandrogenic state. This is

due to a LH/FSH imbalance caused by HPO axis dysfunction and the result is the selection of a dominant follicle is not possib le and causes a manifestation of oligo-ovulation or anovulation in the horses. Relative FSH deficiency is a major factor in these women with high AMH who suffer from infertility [1, 9, 10, 20-22].

2.5. Adipose Tissue and Hepatic Lipid Metabolism

There is a strong relationship between PMOS and liver disease and fat mass. Too much androgen in the fat cells results in changes in adipokine production and a decrease in lipolysis leading to insulin resistance throughout the body. The conversion of androgens to estrogens increases in stromal adipocytes, especially when obese, which leads to increased estrone levels. While physiological changes in estradiol have an inhibitory effect on LH, this leads to sustained excessive LH secretion and may even disrupt ovulatory cycles through its effect on hepatic SHBG production creating a rise in the bioavailability of free androgens, and through its effect on other IGF-binding proteins, modifying follicular maturation. Women with PMOS also tend to have dyslipidaemia, fatty liver disease and cardiometabolic risk as a result of another disturbance of lipid metabolism in the liver and in circulation. Given the many systemic metabolic disruptions, it is becoming clearer that PMOS is actually a metabolic disorder rather than just a disorder of the reproductive system [9, 10, 23-26].

Table 1a: Evidence Tiers for Herbal Management of PMOS

Evidence Tier	Effects Reported	Limitations	Ref. No
Clinical (systematic & narrative reviews)	Improvements in menstrual regularity, androgen levels, ovulation rates, and some metabolic markers	Heterogeneity in preparations, small sample sizes, variable doses, and inconsistent endpoints; need for standardized RCTs	27
Preclinical studies (curcumin, berberine, quercetin, resveratrol, cinnamaldehyde, artemisinin derivatives)	Anti-androgenic, insulin-sensitizing, anti-inflammatory, antioxidant effects; improved follicular function in animal/cell models	Translational gap to human studies; most work limited to animals or cell lines	28

Table 1b: Individual Phytochemicals Studied for PMOS

Phytochemical	Source	Effects	Limitations	Ref. No
Curcumin (Turmeric)	Polyphenolic compound from Curcuma longa	Anti-inflammatory, insulin-sensitizing, antioxidant, androgen-lowering; nano-formulations improve bioavailability	Poor oral absorption, rapid metabolism	29
Berberine	Isoquinoline alkaloid from Berberis spp.	Improves insulin sensitivity, reduces androgen excess, comparable to metformin in some studies	Low oral bioavailability; GI side effects	30
Quercetin	Flavonoid found in onions, apples, berries	Improves insulin resistance, reduces inflammation, restores ovarian morphology in rats	Limited human trials; dose standardization required	31
Resveratrol	Polyphenol from grapes, berries, peanuts	Reduces androgen levels, improves insulin sensitivity, suppresses theca cell steroidogenesis	Mixed results in clinical trials	32
Cinnamaldehyde	Active component of cinnamon bark	Improves menstrual cyclicity, insulin sensitivity, reduces oxidative stress	Variable results; few high-quality RCTs	33
Fagonia indica (nanoparticle form)	Fagonia-coated chitosan nanoparticles	Reduced androgen levels, restored estrous cycles in PMOS rat models	Preclinical only; no human trials	34

3. NANOTECHNOLOGY APPROACHES FOR HERBAL PHYTOCHEMICALS IN PMOS

The integration of nanotechnology into herbal therapy has opened new opportunities for overcoming phytochemical constraints such as poor solubility, limited oral bioavailability, rapid metabolism, and lack of site specificity. Nanodelivery systems can generally be divided into several functional platforms, each with distinct benefits and applications for PMOS-relevant phytochemicals.

3.1 Polymeric Nanoparticles

Polymeric nanoparticles provide controlled and prolonged release, increase stability, and protect sensitive phytochemicals from premature degradation [6, 7 35-40].

A. Poly-lactic-co-glycolic acid (PLGA): Both hydrophilic and hydrophobic phytochemicals may be encapsulated in PLGA nanoparticles, which are FDA-approved, biodegradable, and allow for long-term release. PLGA systems have been investigated for the delivery of antioxidant and anti-inflammatory compounds relevant to PMOS.

B. Chitosan: Mucoadhesive, biocompatible polysaccharides used for oral and mucosal administration. Chitosan nanoparticles avoid first-pass metabolism and enhance intestinal absorption. In preclinical PMOS models, chitosan nanoparticles coated with plant extract have demonstrated a notable improvement in ovarian histology, a decrease in androgen levels, and a restoration of estrous cycles.

C. Alginate: To improve encapsulation efficiency and pH-responsive drug release, chitosan is frequently combined with another natural polymer, alginate, to form hydrogel matrices. Alginate-based nanoparticles have been incorporated into formulations to increase circulation time and bioactivity.

3.2. Lipid-Based Systems

Lipid-based nanocarriers are particularly useful for hydrophobic phytochemicals with limited water solubility, such as curcumin, resveratrol, and cinnamaldehyde.

A. Liposomes: Spherical vesicles with hydrophilic and hydrophobic contents (surrounded by a phospholipid-bilayer and called lipid vesicles if hydrophobic content dominates spherical vesicles containing only hydrophobic substances are called liposomes). Liposomal curcumin is thought to be a promising platform for the management of metabolic dysfunction in PMOS due to its greater bioavailability and anti-inflammatory action

B. Solid lipid nanoparticles (SLNs): These are carriers which have the properties of solid particle stability along with lipid biocompatibility. SLNs can also help to control oxidative stress and promote lymphatic absorption. In animal models of PMOS, curcumin enriched SLNs were found to have greater insulin sensitivity and ovarian functions.

C. Nanoemulsions: Dispersions of oil in water with nanoscale droplet sizes. They are effective in increasing the solubility and absorption of lipophilic substances. Nanoemulsified cinnamaldehyde has shown benefit for PMOS-associated metabolic syndrome by enhancing glucose tolerance and lowering inflammatory markers.

3.3. Inorganic Nanoparticles

The distinctive physicochemical and biological characteristics of inorganic nanoparticles can be used for both treatment and diagnosis.

A. Selenium nanoparticles: Selenium is involved in insulin regulation and antioxidant defense. Compared with inorganic selenium salts, SeNPs show increased antioxidant efficacy and decreased systemic toxicity. SeNPs combined with metformin have demonstrated a synergistic improvement in ovarian morphology, hormonal balance, and insulin sensitivity in PMOS rat models.

B. Gold nanoparticles: Herbal phytochemicals can be used to functionalize AuNPs for theranostic, targeted-delivery, or imaging applications. AuNP-based resveratrol and quercetin carriers have demonstrated anti-inflammatory and antioxidant benefits in metabolic-disease models, though they have not yet been extensively investigated specifically in PMOS.

C. Silver nanoparticles (AgNPs): AgNPs are commonly known for their antibacterial activity and it is getting more research into their application in metabolic issues. Use of granulosa cells in long term conditions, such as PMOS, however, is still limited by the evidence of oxidative stress and apoptosis induced by AgNPs (given in sections 6 and 8), and thus there is a need for the cells to be further evaluated for safety before use.

3.4. Nanoscale Natural Drug Delivery Systems (NNDDS)

A newer and more innovative approach is the use of natural plant based scaffolds or self organization of phytochemical as nanocarriers.

A. Self-assembled phytochemical nanoparticles: Flavonoids and polyphenols like quercetin and resveratrol are able to produce nanoparticles without the need of artificial excipients, thus reducing the amount of excipients and their potential toxicity.

B. Plant-derived nanocarriers: Plant derived nanocarriers imply the discovery of exosome like vesicles from food plants like grapefruit and ginger that can be used for encapsulation of bioactive compounds to cross biological barriers. These technologies are being explored to better target delivery of phytochemicals such as berberine or curcumin into the ovarian tissue of PMOS.

C. Biogenic nanoparticles: These are the nanoparticles that are prepared by plant extracts that have both phytochemical and therapeutic potential as well as being nanosystem. In one such example, the green synthesized selenium nanoparticles using moringa extract have shown a higher antioxidant activity.

3.5. Nanotechnology-Based Drug Delivery and Ovarian Targeting in PMOS

Conventional pharmacological therapies for the endocrine, metabolic, and reproductive problems caused by PMOS sometimes have low efficacy or are associated with undesirable side effects. Nanotechnology provides an alternative way to overcome these challenges by improving the pharmacokinetics, bioavailability, and tissue-specific distribution of both conventional drugs and herbal phytochemicals. When used to treat PMOS, nanocarriers may enhance reproductive efficacy, reduce systemic side effects, and restore ovarian function [41, 42].

4. ADVANTAGES OF NANOMATERIALS IN PMOS THERAPY

Several drawbacks of conventional therapies have been overcome using nanoparticles [41–43]:

1. Enhanced stability and solubility: Encapsulating hydrophobic medications, such as resveratrol or curcumin, guarantees increased drug stability, improves water solubility, and protects against gastrointestinal tract enzymatic breakdown.
2. Improved pharmacokinetic characteristics: Nanocarriers can lower clearance rates and lengthen circulatory half-lives by altering absorption, distribution, metabolism, and excretion (ADME) profiles. This helps sustain therapeutic levels and lower the frequency of dose.
3. Targeted delivery: By modifying the surfaces of nanoparticles with ligands that target certain ovarian receptors, drugs can concentrate specifically in the ovaries, minimizing systemic exposure and adverse consequences.
4. Ovarian and follicular barrier penetration: Nanoparticles are tiny enough to penetrate through cellular membranes, follicular barriers, and stromal tissue, allowing therapeutic concentrations to reach oocytes and granulosa cells.
5. Reduced systemic toxicity: Nanocarriers might enhance safety by limiting off-target distribution to other organs including the liver or kidneys by concentrating therapeutic action inside the ovaries.

5. OOCYTE TARGETED NANODELIVERY

The oocyte is the primary functional unit of female reproduction, located within the ovarian follicle and supported by somatic granulosa and theca cells. An unfavorable microenvironment marked by persistent low-grade inflammation, oxidative stress, and hormonal imbalance impairs oocyte quality in PMOS. Increased levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, impede fertilization potential and interfere with maturation processes [21, 44].

Nanotechnology-based strategies proposed to enhance oocyte functionality include [21, 44-48]:

1. Selenium nanoparticles (SeNPs), which have strong anti-inflammatory and antioxidant properties. SeNPs preserve oocyte maturation capacity and restore redox balance in PMOS models by lowering IL-6, TNF-α, and IL-1β.
2. Chitosan nanoparticles (ChNPs): a naturally occurring, mucoadhesive, biocompatible polysaccharide. Flaxseed extract, rich in lignans and phytoestrogens, is encapsulated into ChNPs to improve stability, transport, and permeability, supporting LH/FSH modulation, folliculogenesis, and ovulation.
3. Bilirubin-grafted ChNPs, an advanced nanocarrier reported to preserve mitochondrial activity in oocytes by lowering intracellular ROS and calcium excess, with potential to support fertilization and embryonic development.
4. Ligand-directed targeting via mannose-binding receptors on oocyte membranes, proposed as docking sites for ligand-functionalized nanoparticles to deliver hormonal modulators or antioxidants directly to oocytes.

By these strategies, SeNP and ChNP effects (SeNPs, ChNPs) have been evaluated directly in PMOS animal models. Bilirubin-grafted ChNP effects (Bilirubin-grafted ChNPs) are drawn from general oocyte-toxicology and cumulus-oocyte-complex studies that are not specific to PMOS. Mannose-receptor-mediated targeting (Ligand-directed targeting) remains a conceptual strategy that has not yet been validated in any PMOS model (given in Table 2).

Overall, oocyte-targeted nanomedicine offers a strategy to improve fertility outcomes for PMOS patients, particularly those using assisted reproductive technologies though this remains a preclinical prospect at present.

6. GRANULOSA CELL-TARGETED NANODELIVERY

Granulosa cells play an essential role in oocyte maturation, steroidogenesis, and follicular development. They release important growth factors and use aromatase to convert androgens into estrogens. Excess androgens, insulin resistance, and inflammation damage granulosa cells in PMOS, resulting in aberrant folliculogenesis and anovulation [49-55].

Nanotechnology approaches proposed for granulosa cells include [55-59]:

1. Copper nanoparticles (CuNPs): reported to improve granulosa cell activity and restore ovarian endocrine function by regulating the release of steroid hormones such as progesterone, estradiol, and testosterone.

2. Silver nanoparticles (AgNPs): possess antioxidant and antibacterial qualities, but research shows AgNPs can cause oxidative stress and cell death in granulosa cells, raising concerns about reproductive safety; their use in PMOS therefore remains restricted pending careful assessment.
3. Polymeric nanoparticle systems: quercetin and resveratrol encapsulated in chitosan or PLGA nanoparticles show increased antioxidant activity, lower inflammation, and restored granulosa cell steroidogenic function, supporting oocyte function and follicular health.
It should be noted that the copper and silver nanoparticle findings summarized above (CuNPs) are drawn substantially from bovine, porcine, and rodent reproductive-toxicology studies rather than PMOS disease models specifically, and should be interpreted as mechanistic evidence pending confirmation in PMOS-specific systems.
Granulosa cell-targeted nanomedicine therefore offers a potential dual therapeutic advantage supporting oocyte growth and restoring normal hormone production both of which are compromised in PMOS, though direct clinical validation is still lacking.

7. Clinical Implications and Future Perspectives

In the context of PMOS, nanomedicine may have encouraging preclinical potential for the management of PMOS through targeted granulosa cell and oocyte therapy and ultimately impact the way PMOS is managed if proven effective in clinical trials. These strategies could be useful for normalizing the development of follicles, promoting ovulation, and optimizing reproductive success through direct preservation of functional integrity of oocytes and granulosa cells. Unlike traditional pharmaceutical products, nanoparticulate-delivered tumor therapy enables targeted delivery within the ovary, where less exposure of the drug is required to non-reproductive tissues. This targeted approach can help minimize the potential for adverse systemic reactions that can be associated with chronic medication use, including gastrointestinal problems, nephrotoxicity and hepatotoxicity. Anothe r advantage of nanocarriers is their ability to enhance the therapeutic potential of phytochemicals found in herbs, for example , curcumin, resveratrol, and quercetin, are poorly soluble, unstable, and have low bioavailability when present in their natura l state, but can become more soluble, stable, and bioavailable when encapsulated with nanoscale delivery systems. Advances in the use of ligand-functionalized nanocarriers also have the potential to move toward a more individualized approach to treatment; for instance, targeting FSH receptors on granulosa cells could allow for the use of specific nanocarriers for different types of patients where hyperandrogenism, insulin resistance, or chronic inflammation predominates. This is because it has not yet been proven to have clinical disease-modifying effects as yet, but may eventually prove to be good for symptom control and disease modification, given the combination of nanomedicine with herbal remedies, and tested in human PMOS trials [60-64, 68, 69].

Table 2: Types of Nanocarriers and Targeted Cells

Target Cell	Nanocarrier Type	Therapeutic Agent	Observed Effect in PMOS	Safety Considerations
Oocyte	Selenium nanoparticles (SeNPs)	Selenium (antioxidant)	Reduces IL-6, TNF-α, IL-1β; mitigates oxidative stress and inflammation; improves oocyte maturation	Requires reproductive toxicology studies before clinical use
Oocyte	Chitosan nanoparticles (ChNPs)	Flaxseed extract (FSE)	Stabilizes and enhances bioavailability of phytoestrogens; regulates LH and FSH; supports folliculogenesis	Biocompatible, but long-term safety still under study
Oocyte	Bilirubin-grafted ChNPs	Bilirubin (antioxidant)	Reduces intracellular ROS and Ca2+ overload; preserves oocyte quality and fertilization potential	Early preclinical evidence only; not PMOS-specific
Oocyte	Ligand-functionalized nanoparticles	Mannose-binding receptor targeting	Potential for selective delivery of therapeutic molecules to oocytes	Conceptual; not yet validated in any model
Granulosa cells	Copper nanoparticles (CuNPs)	Copper ions	Modulates steroidogenesis; increases progesterone, estradiol, testosterone regulation; improves follicular function	Must monitor oxidative stress risk; largely non-PMOS toxicology data
Granulosa cells	Silver nanoparticles (AgNPs)	Silver ions	Antioxidant and antimicrobial properties, but induces apoptosis and oxidative stress in granulosa cells	Safety concerns limit clinical use

Granulosa cells	Polymeric nanoparticles (PLGA, Chitosan)	Quercetin, Resveratrol, Curcumin	Restores granulosa cell function; reduces inflammation; enhances steroid hormone balance	Considered safer than inorganic NPs; requires GMP-standardized formulations

8. Toxicology and Safety of Nanomaterials

One factor to consider when using nanotechnology to treat PMOS is safety. Inorganic nanoparticles like gold (Au) and selenium (Se) have been found to be therapeutic due to their anti-inflammatory and antioxidant attributes. However, little is known about their long term toxicological consequences, especially in women of reproductive age. Reproductive safety evaluations are essential prior to clinical translation, since PMOS mostly affects women who are fertile. Additional research needs to be conducted on placental transfer, bio-distribution, accumulation in reproductive organs and potential effects on pregnancy outcomes and fertility. Establishing accurate safety limits, like maximum tolerated doses and no observed adverse effect levels (NOAELs) is important to make sure that a treatment is not harmful but that it does have advantages. More in-depth therapeutic application of inorganic nanoparticles in PMOS is premature without such information [65-69]. Safety evaluation should not be limited to the encapsulated phytochemical or metal ion, but include the carrier materials themselves, such as chitosan and PLGA degradation products and potential immunogenicity, as this is rarely assessed in the PMOS-specific literature reviewed here.

9. Standardization and Quality Control

Herbal based nanomedicine presents an extra challenge for standardization. The chemical properties of herbal extracts can vary significantly depending on factors such as plant species, geographic location, extraction period and extraction method, which can dramatically affect treatment efficacy and safety. As such, the phytochemical quality must follow strict requirements and so does the nanoparticles themselves; that's why, when used in nanocarrier systems, they are subject to regulatory analysis. By address this, manufacturing needs to adhere to strict quality control procedures and Good Manufacturing Practices (GMP) such as the validation of batch-to-batch uniformity, identification and quantification of components of the herbal extract and verification of the repeatability of the nanoparticle formation process. Standardized evaluation methods such as determination of kinetics, encapsulation efficiency, Zeta potential and particle size distribution are the required protocols for regulatory approval of the nano-formulated product, and are utilized to maximize stability and safety, whilst minimising variability. The current relevant pharmacopoeial and regulatory standards for nanomedicine characterization offer a partial basis for such standards but to date there is no guidance for the combined botanical-nanocarrier product for PMOS. Without such methodical standardization, the development of herbal nanomedicine from preliminary investigations to reliable clinically approved treatments cannot be reached.

10. Conclusion

A PMOS is a complicated affliction that is associated with both metabolic and reproductive endocrinology. Conventional treatment with pharmaceuticals only treats a small aspect of the disease and often doesn't lead to lasting, patient-centered improvements. Despite their proven multi-targeted effects against hyperandrogenism, insulin resistance, inflammation and oxidative stress, the poor pharmacokinetics and inconsistent clinical effects of herbal medicines and phytochemicals remain to be a limitation in their therapeutic applications. Nanotechnology offers a potential solution to improve the solubility, stability, bioavailability and tissue-specific delivery of herbal phytochemicals: a solution still being studied in the preclinical setting and yet to be proven in human PMOS trials. Preliminary findings of chitosan administration and selenium/copper-based nanoparticles demonstrate promising results for enhancing the quality of oocytes, modulation of granulosa cell function, and restoration of ovarian function in PMOS models, and ligand-directed targeted strategies suggest the potential for more personalized ovarian-specific treatment. However, there are important gaps that need to be addressed before herbal nanomedicine can be integrated into routine care for PMOS: standardization of the manufacturing of herbal extracts and nanocarriers, characterization of their long-term reproductive toxicity (including that of the carrier materials), and a regulatory pathway specific to integrated botanical-nanomedicine products is a need. Further studies should focus on well-designed and well-powered clinical trials with human PMOS population phenotypically stratified to validate safety and efficacy. To conclude, the nanotechnology and herbal medicine might be a promising way forward in the treatment of PMOS, transitioning from symptom management to disease modification and fertility restoration, if these findings can be replicated in clinical trials that show their efficacy and safety.

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