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Review Paper

Exploring Nanotechnology with Traditional Herbal Pharmacology: Nanocarrier-Based Phytochemical Delivery for The Management of Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine and metabolic disorder of reproductive-age women characterized by hyperandrogenism, ovulatory dysfunction and/or polycystic ovarian morphology, with frequent metabolic abnormalities including insulin resistance, dyslipidemia and obesity. Chronic low-grade inflammation and oxidative stress further contribute to ovarian and metabolic dysfunction. Conventional pharmacotherapy is selected according to reproductive and metabolic goals, but interest in complementary herbal approaches has increased because medicinal plants provide chemically diverse compounds with antioxidant, anti-inflammatory, insulin-sensitizing and hormone-modulating activities. Nevertheless, many phytochemicals exhibit poor aqueous solubility, instability, rapid metabolism and limited oral bioavailability. Nanotechnology offers a strategy to improve these pharmaceutical properties through liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, micelles, phytosomes and extracellular-vesicle-based systems. Important phytochemicals investigated in PCOS include curcumin, resveratrol, quercetin, berberine, epigallocatechin gallate, apigenin and ellagic acid. Nanocarrier incorporation may improve solubility, protect active molecules from degradation, enhance cellular uptake and enable controlled release. Proposed biological effects include modulation of PI3K/Akt and AMPK signaling, suppression of NF-κB-associated inflammation, activation of antioxidant defenses, improvement of insulin signaling and regulation of ovarian steroidogenesis. However, the PCOS nanomedicine field remains predominantly preclinical, and ovarian targeting, reproductive safety, long-term toxicity, formulation standardization, scale-up and clinical validation remain unresolved. This review integrates traditional herbal pharmacology with contemporary nanocarrier technology and critically discusses mechanisms, formulation strategies, evaluation parameters, safety considerations,

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research gaps and future translational opportunities.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common and clinically heterogeneous endocrine disorder affecting reproductive-age women. Its manifestations extend beyond ovarian morphology and include reproductive dysfunction, androgen excess and important metabolic consequences. The biological basis is multifactorial, involving interactions among genetic susceptibility, environmental factors, insulin resistance, altered steroidogenesis, chronic inflammation, oxidative stress and metabolic dysfunction. Contemporary reviews emphasize that PCOS should be considered a multisystem disorder rather than a condition restricted to the ovary [1,2].

Treatment is individualized according to symptoms, metabolic risk and reproductive objectives. Lifestyle intervention remains foundational, while pharmacological approaches may include combined oral contraceptives, insulin-sensitizing therapy, anti-androgenic treatment and ovulation-induction strategies. These interventions can be effective for selected outcomes but do not eliminate the complex underlying biology of PCOS. Consequently, there is continuing interest in multi-target approaches and natural products [1–5].

Traditional herbal pharmacology provides a large repertoire of phytochemicals with antioxidant, anti-inflammatory, metabolic and endocrine activities. Systematic reviews have identified clinical and preclinical evidence for several medicinal plants and compounds, although study heterogeneity, variable preparations, small sample sizes and incomplete safety data limit definitive conclusions [3–6]. A major pharmaceutical challenge is that many promising phytochemicals have low aqueous solubility, poor gastrointestinal stability, extensive first-pass metabolism or rapid systemic elimination. Advanced drug-delivery systems can potentially overcome some of these limitations [7,8].

Nanocarrier-based delivery is therefore an attractive intersection between traditional herbal pharmacology and modern pharmaceutics. By encapsulating or associating phytochemicals with nanoscale carriers, it may be possible to improve dissolution, protect labile molecules, modify pharmacokinetics, increase cellular uptake and provide controlled release. Recent PCOS-focused reviews indicate increasing interest in nanotechnology, particularly plant-derived nanoparticles, while emphasizing that most evidence is still preclinical [9,10].

Methodology

This narrative review was developed by searching PubMed/MEDLINE and publicly available scientific literature for publications concerning PCOS, medicinal plants, phytochemicals, nanotechnology, nanoparticle drug delivery and reproductive/metabolic mechanisms. Priority was given to recent reviews, systematic reviews and mechanistic studies, while foundational literature was retained where necessary. Search concepts included combinations of “polycystic ovary syndrome”, “PCOS”, “phytochemicals”, “herbal medicine”, “nanoparticles”, “nanocarriers”, “curcumin”, “resveratrol”, “quercetin”, “berberine”, “phytosome”, “liposome”, “solid lipid nanoparticle”, “nanostructured lipid carrier” and “targeted delivery”. The literature was synthesized thematically rather than by formal quantitative meta-analysis. Because this article is a narrative review, no human participants, animals or experimental interventions were directly studied.

Important note: claims of therapeutic efficacy are presented as preclinical or investigational where appropriate; nanocarrier-based phytochemical

therapy should not be interpreted as an established clinical treatment for PCOS.

PCOS: Pathophysiological Basis and Therapeutic Targets

Hyperandrogenism

Hyperandrogenism is a major biochemical and clinical feature of PCOS. Increased androgen exposure can impair follicular development, contribute to hirsutism and acne, and participate in ovulatory dysfunction. Ovarian and adrenal steroidogenic abnormalities may interact with insulin signaling and other endocrine pathways [1,2].

Insulin resistance and hyperinsulinemia

Insulin resistance is common in PCOS, although it is not universal. Compensatory hyperinsulinemia can promote ovarian androgen production and reduce hepatic sex-hormone-binding globulin, increasing free androgen availability. Metabolic dysfunction also contributes to long-term cardiometabolic risk [1,2].

Oxidative stress

An imbalance between reactive oxygen species generation and antioxidant defense has been reported in PCOS. Oxidative stress may influence steroidogenesis, follicular maturation, mitochondrial function and inflammatory signaling. This makes antioxidant pathways important targets for phytochemical investigation [4,11].

Chronic low-grade inflammation

Inflammatory mediators and signaling pathways such as NF-κB have been implicated in metabolic and ovarian abnormalities. Phytochemicals with anti-inflammatory activity may therefore act on mechanisms that overlap with insulin resistance and oxidative stress [5,12].

Abnormal folliculogenesis and steroidogenesis

Altered gonadotropin signaling and steroidogenic enzyme activity can disturb follicular selection and maturation. A successful multi-target strategy would ideally improve metabolic signaling while normalizing ovarian endocrine function rather than focusing on a single symptom.

Traditional Herbal Pharmacology in PCOS

Medicinal plants have been used historically for reproductive and metabolic disorders. Modern reviews report experimental and, for selected interventions, clinical evidence suggesting that herbal preparations can influence menstrual regularity, androgen status, glucose metabolism, oxidative stress and inflammatory pathways. However, evidence quality varies substantially and herbal products should not be assumed to be equivalent to standardized pharmaceuticals [3–6]. The most relevant phytochemicals for nanocarrier development are those with a strong mechanistic rationale but unfavorable pharmaceutical properties. Polyphenols and alkaloids frequently demonstrate biological activity in cell and animal models while suffering from limited oral bioavailability. This creates a logical opportunity for formulation-based improvement rather than simply increasing the dose of the conventional extract.

Major Phytochemicals of Interest

Curcumin

Curcumin, a principal polyphenol of Curcuma longa, has antioxidant and anti-inflammatory properties and has been investigated in metabolic and reproductive models of PCOS. Proposed effects include improvement of oxidative balance,

inflammatory signaling, insulin sensitivity and ovarian function. Its major pharmaceutical limitations include poor aqueous solubility, instability and extensive metabolism, making it a strong candidate for nanoformulation [13,14].

Resveratrol

Resveratrol is a stilbene polyphenol found in grapes and several other plants. Experimental PCOS studies have explored its effects on androgen excess, oxidative stress, insulin signaling and ovarian function. Poor water solubility, chemical instability and rapid metabolism can limit exposure, supporting investigation of lipidic, polymeric and other nanocarriers [15,16].

Quercetin

Quercetin is a flavonoid with antioxidant and anti-inflammatory properties. In PCOS-related experimental research, it has been investigated for effects on oxidative stress, insulin resistance, inflammatory signaling and ovarian steroidogenesis. Its limited water solubility and bioavailability provide a rationale for nano-enabled delivery [17].

Berberine

Berberine is an isoquinoline alkaloid found in several medicinal plants. Its pharmacology includes effects on glucose and lipid metabolism, inflammation and cellular energy pathways. AMPK-related signaling is frequently discussed in relation to its metabolic activity. Formulation approaches may help address its oral bioavailability limitations [18].

Epigallocatechin gallate

Epigallocatechin gallate (EGCG), a major green-tea catechin, has antioxidant and anti-inflammatory properties and has been investigated in metabolic disorders. Nanocarriers may protect EGCG against degradation and potentially enhance systemic exposure, although PCOS-specific clinical evidence remains limited [19].

Apigenin and ellagic acid

Apigenin and ellagic acid have attracted recent attention as natural compounds with antioxidant, anti-inflammatory and metabolic activities. Reviews of PCOS phytochemicals describe potential effects on insulin signaling, inflammatory pathways and steroidogenesis, but further pharmacokinetic, toxicological and clinical studies are needed [20].

Pharmaceutical Barriers to Phytochemical Therapy

The translation of phytochemicals from experimental findings into medicines is frequently limited by poor aqueous solubility, low permeability, chemical instability, extensive first-pass metabolism, rapid elimination and variable extract composition. These issues can lead to low and inconsistent concentrations at the intended site of action. Increasing dose is not necessarily an optimal solution because it may increase off-target exposure without proportionately improving efficacy.

Nanocarriers can address some, but not all, of these barriers. The carrier must be selected according to the physicochemical properties of the phytochemical, intended route, release profile, target tissue and safety requirements.

Nanocarrier-Based Phytochemical Delivery

Liposomes

Liposomes are phospholipid vesicles capable of accommodating hydrophilic and lipophilic compounds. They can improve the apparent

solubility and stability of phytochemicals and can be surface-modified for altered biodistribution. Limitations include possible leakage, oxidation of lipids and storage instability.

Polymeric nanoparticles

Biodegradable polymers such as PLGA, PLA and chitosan can form nanoparticles or nanocapsules with controlled-release characteristics. Polymeric systems can protect phytochemicals from degradation and allow modulation of release kinetics.

Solid lipid nanoparticles

Solid lipid nanoparticles use a solid lipid matrix stabilized by surfactants. They can enhance the delivery of lipophilic compounds and provide controlled release. Their limitations include drug expulsion during storage and polymorphic changes in the lipid matrix.

Nanostructured lipid carriers

NLCs combine solid and liquid lipids to create a less ordered lipid matrix. This can increase loading capacity and reduce the tendency of some active compounds to be expelled during storage.

Nanoemulsions

Nanoemulsions contain very small dispersed droplets and can improve the apparent solubility and gastrointestinal delivery of poorly water-soluble compounds. They are particularly attractive for oral phytochemical formulations.

Polymeric micelles

Micelles contain a hydrophobic core and hydrophilic corona and can solubilize poorly water-soluble molecules. Their small size may facilitate biological interactions, although dilution and stability after administration must be considered.

Phytosomes

Phytosomes are phospholipid complexes of plant-derived constituents. They are especially relevant to the present concept because they combine botanical active ingredients with a formulation strategy designed to improve membrane interaction and absorption.

Metallic nanoparticles

Plant-mediated synthesis of silver, selenium and other metallic nanoparticles has received increasing attention. Plant extracts may act as reducing and capping agents. Nevertheless, metallic systems require stringent characterization and reproductive toxicity assessment because biological activity does not imply safety [9,10].

Extracellular vesicles and exosomes

Exosomes are naturally occurring extracellular vesicles involved in intercellular communication. Their biological origin and potential cellular uptake make them attractive experimental carriers. However, scalable production, characterization, loading efficiency, targeting, purity and reproductive safety remain major challenges.

Mechanistic Basis of Nanocarrier-Based Phytochemical Action in PCOS

The proposed therapeutic framework is: phytochemical selection → nanocarrier encapsulation → improved stability/solubility → enhanced absorption and/or cellular uptake → controlled release → modulation of metabolic, inflammatory, oxidative and steroidogenic pathways → potential improvement in ovarian and metabolic phenotypes.

PI3K/Akt signaling

PI3K/Akt is a central insulin-signaling pathway. Phytochemicals that improve insulin sensitivity may influence glucose uptake and downstream metabolic processes through this pathway.

AMPK signaling

AMPK is a major cellular energy sensor. Compounds such as berberine and resveratrol have been investigated for AMPK-related metabolic effects, supporting interest in formulations that increase their effective exposure.

NF-κB and inflammatory signaling

Excessive NF-κB activation can promote inflammatory mediator production. Anti-inflammatory phytochemicals may attenuate this signaling, potentially reducing inflammatory contributions to metabolic and ovarian dysfunction.

Nrf2-mediated antioxidant defense

Nrf2 regulates antioxidant and cytoprotective genes. Enhancement of endogenous antioxidant defense may help counter oxidative stress associated with PCOS.

Ovarian steroidogenesis

Phytochemicals may affect steroidogenic enzymes and signaling pathways involved in androgen production. Whether a nanocarrier improves these effects in a clinically meaningful manner remains to be established.

Gut microbiota and metabolic signaling

Emerging research links PCOS to alterations in gut microbial composition and metabolite signaling. Natural products may interact with this axis, but the specific contribution of nanocarrier delivery remains an emerging research area [1,21].

Comparative Advantages of Nanocarriers

Nanocarrier	Suitable phytochemical profile	Potential advantage	Key limitation
Liposome	Hydrophilic/lipophilic	Versatile loading; biocompatibility	Leakage/oxidation
PLGA nanoparticle	Many small molecules	Controlled release; protection	Organic-solvent processing; scale-up
SLN	Lipophilic	Sustained delivery	Drug expulsion/polymorphism
NLC	Lipophilic	Higher loading potential	Formulation complexity
Nanoemulsion	Poorly water-soluble	Improved dispersion and oral delivery	Surfactant dependence
Micelle	Poorly water-soluble	Solubilization	Dilution stability
Phytosome	Botanical extracts	Improved membrane interaction	Complexity of extract standardization
Metallic nanoparticle	Selected phytochemicals/extracts	Experimental biological activity	Reproductive and systemic toxicity concerns
Exosome	Bioactive molecules	Natural vesicle biology	Manufacturing and characterization challenges

Green Nanotechnology and Herbal Nanoparticles

Green synthesis uses biological materials, including plant extracts, as reducing, stabilizing or capping agents in nanoparticle preparation. This approach may reduce reliance on some conventional chemical reagents and can incorporate phytochemical functionality into the nanoparticle surface. However, green synthesis should not be equated with inherent safety. Particle size, morphology, surface chemistry, residual materials, dose, biodistribution and reproductive toxicity must be systematically evaluated [9].

Formulation and Characterization Strategy

A candidate nanophytochemical formulation should be optimized using a quality-by-design mindset. Critical material attributes may include polymer/lipid composition, surfactant concentration, active-to-carrier ratio and surface charge. Critical process parameters may include mixing energy, solvent removal conditions, homogenization or sonication parameters and temperature.

Parameter	Purpose	Typical interpretation
Particle size	Confirms nanoscale distribution	Smaller, reproducible size is often desirable, but biological performance is context-dependent
PDI	Measures size distribution	Lower PDI generally indicates a more uniform population
Zeta potential	Assesses surface charge/stability	Magnitude can provide information about colloidal stability
Entrapment efficiency	Measures encapsulated active	Higher efficiency can reduce free active fraction
Drug loading	Measures active relative to carrier	Important for dose feasibility
FTIR	Chemical interaction	Identifies shifts or changes in characteristic bands
DSC	Thermal behavior	Assesses melting/transition changes
XRD	Crystalline structure	Identifies amorphous/crystalline changes
SEM/TEM	Morphology	Visualizes particle shape and structure
In-vitro release	Release kinetics	Compares burst and sustained release
Stability	Shelf-life assessment	Tracks size, PDI, active content and degradation

Preclinical Evaluation in PCOS

Preclinical studies should use well-characterized PCOS models and appropriate controls. Common induction approaches include letrozole or androgen exposure in rodents, depending on the scientific question. A robust design should compare healthy control, untreated PCOS, conventional phytochemical and nanocarrier formulation groups where feasible.

Endpoints may include body weight, food intake, glucose tolerance, fasting insulin, lipid profile, testosterone and other reproductive hormones,

estrous cyclicity, ovarian morphology, follicle counts, corpus luteum formation, oxidative-stress markers, inflammatory cytokines and histopathology. Pharmacokinetic studies are important for determining whether the nanocarrier actually improves systemic exposure. Toxicological and reproductive-safety studies should be integrated rather than treated as an afterthought.

Safety and Regulatory Considerations

The reproductive age of the target population makes safety a central consideration. Evaluation should include acute and repeated-dose toxicity, genotoxicity where appropriate, immunotoxicity, hepatotoxicity, nephrotoxicity, reproductive toxicity, biodistribution and potential tissue accumulation. Metallic nanoparticles require particular caution because their physicochemical properties can alter biological interactions [9,10].

For botanical formulations, botanical identity, extraction method, marker compounds, contaminants, pesticide residues, heavy metals, microbial quality and batch-to-batch consistency should be controlled. For nanomedicines, additional characterization of particle size distribution, surface chemistry, aggregation, residual solvents and release behavior is required. Regulatory classification can be complex when botanical actives and nanomaterials are combined.

Proposed Developmental Workflow

Medicinal plant selection → authentication → extraction → phytochemical profiling → selection of lead phytochemical → nanocarrier selection → formulation optimization → particle characterization → in-vitro release and stability → cellular/mechanistic studies → PCOS animal model → pharmacokinetics and biodistribution → reproductive and systemic toxicity → larger translational studies → clinical evaluation.

FUTURE PERSPECTIVES

Future development is likely to focus on rationally designed nanocarriers rather than simply producing smaller particles. Surface engineering, ligand-mediated targeting, stimuli-responsive release and combination delivery could potentially improve site-specific exposure. Co-delivery of complementary phytochemicals is conceptually attractive but requires careful investigation of compatibility, pharmacokinetic interactions and dose selection.

Personalized nanomedicine may eventually become relevant because PCOS phenotypes differ substantially in reproductive, metabolic and inflammatory characteristics. Integration of pharmacogenomics, metabolomics, microbiome profiling and advanced imaging could support patient stratification. Nevertheless, these approaches remain research concepts rather than established clinical practice.

CONCLUSION

Nanocarrier-based phytochemical delivery provides a scientifically attractive bridge between traditional herbal pharmacology and contemporary drug-delivery technology for PCOS. Phytochemicals such as curcumin, resveratrol, quercetin, berberine and EGCG have mechanistic properties relevant to oxidative stress, inflammation, insulin resistance and ovarian dysfunction, while nanocarriers may address important pharmaceutical limitations such as poor solubility and bioavailability. Current evidence supports continued investigation, but the field remains predominantly preclinical. Ovarian targeting, reproductive safety, long-term toxicity, standardization, scale-up and clinical efficacy are the major translational barriers. Future studies should therefore emphasize rigorous formulation characterization, pharmacokinetics, validated PCOS models, appropriate safety assessment and

well-designed clinical trials. The combination of traditional medicinal knowledge, phytochemical science and nanotechnology may ultimately contribute to more precise and bioavailable natural-product interventions, provided that efficacy and safety are established through high-quality evidence.

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