

Phytochemical Nanomedicine, Targeted Delivery, and Stimuli-Responsive Therapies for PCOS

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Abstract:

Polycystic ovary syndrome (PCOS), now renamed polyendocrine metabolic ovarian syndrome (PMOS), is a common endocrine and metabolic disorder that affects fertility, metabolic health and quality of life. Available drugs treat isolated features of the syndrome and are often limited by side effects, incomplete response and poor adherence. Plant-derived compounds such as curcumin, quercetin, resveratrol, berberine and naringenin act on several pathogenic pathways at once, including insulin signalling, inflammation and oxidative stress, but their clinical use is restricted by low solubility, rapid metabolism and poor oral bioavailability. Nano-formulation is increasingly used to overcome these barriers. In the second generation of delivery systems is being developed that adds ovarian targeting, cell-membrane camouflage and release that is triggered by the diseased microenvironment, particularly by reactive oxygen species. This review covers the rationale for phytochemical nanomedicine in PCOS, the nanocarriers and stabilisation strategies used, the preclinical evidence, and the emerging targeted and stimuli-responsive approaches. Examine the local routes such as vaginal delivery, computational formulation design, and the safety, model and regulatory barriers that still separate these systems from the clinic. Most evidence comes from letrozole-induced rodents, and much of the stimuli-responsive design knowledge comes from cancer research rather than from PCOS itself. Standardised models, reproductive toxicology and early clinical trials are the priorities for the field.

Keywords: Polycystic Ovary Syndrome; Phytochemicals; Nanomedicine; Targeted Drug Delivery; Stimuli-Responsive Nanocarriers; ROS-Responsive Release; Vaginal Drug Delivery; Biomimetic Nanoparticles.

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Introduction

Polycystic ovary syndrome (PCOS) is defined by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology, and it is accompanied by insulin resistance, obesity, dyslipidaemia and psychological burden in many patients. Estimates of its prevalence differ with the diagnostic criteria used, ranging from about 4% to 21% of women of reproductive age [1,2]. The 2023 international guideline offers 254 recommendations and practice points and explicitly notes that the supporting evidence is still mostly of low to moderate quality [3]. In 2026 a global consensus renamed the condition polyendocrine metabolic ovarian syndrome (PMOS) to reflect its endocrine, metabolic and ovarian dimensions and to drop the misleading reference to cysts, with a three-year transition to the new term [4,5]. Because the studies cited here were published under the old name, this article uses PCOS.

Treatment today is largely directed at single features: insulin sensitisers for metabolic disturbance, ovulation-induction drugs for

infertility and hormonal agents for androgen excess and cycle control. No single agent corrects the interlinked insulin, inflammatory and oxidative abnormalities, and gastrointestinal intolerance of metformin, for instance, can reduce adherence [1]. This gap has led researchers to look at multi-target natural compounds and at better ways to deliver both natural and synthetic drugs.

Nanomedicine is attractive because nanocarriers can prolong drug half-life, raise bioavailability, deliver cargo to specific cells and reduce toxicity [6]. First-generation PCOS nanomedicine mainly focused on encapsulation: making an existing drug or extract more soluble, stable and absorbable.

Disease Biology as a Design Brief: Each pathological feature of PCOS suggests a design requirement for a delivery system. Hyperandrogenism and disturbed gonadotropin balance, with raised LH, low FSH and a high LH/FSH ratio, define the endocrine target and are readily reproduced in the letrozole rat model, in

which aromatase inhibition raises testosterone and lowers oestradiol [1,2]. Insulin resistance, driven by impaired PI3K/AKT signalling, links metabolic and ovarian dysfunction, and androgens and insulin reinforce each other in a vicious cycle [1]. Low-grade inflammation, with elevated TNF- α and other cytokines, disrupts folliculogenesis and ovulation [1,7]. Oxidative stress and mitochondrial dysfunction, shown by reduced ATP and membrane potential, add a further layer [1].

These features have three practical consequences for carrier design. First, because the syndrome is

multi-factorial, multi-target agents such as polyphenols are logical payloads. Second, because oxidative stress and inflammation are concentrated in the ovarian microenvironment, they can be used to guide drug release. Third, because PCOS is a chronic condition treated over long periods in young women, the carrier must be biodegradable and safe for reproductive tissues [6,8]. Table 1 summarises how these requirements translate into design choices.

Table 1: From PCOS pathophysiology to delivery-system design requirements

Feature	Key abnormality	Design implication	References
Hyperandrogenism	High LH, low FSH, high testosterone, low oestradiol	Carriers that restore hormonal balance and follicular development; ovarian exposure	1, 2
Insulin resistance	Impaired PI3K/AKT and GLUT4 signalling	Insulin sensitisers or phytochemicals with improved bioavailability; combination payloads	1, 9
Inflammation	Raised TNF- α and other cytokines	Immune-cell-directed or membrane-camouflaged carriers	2, 7
Oxidative stress	ROS excess, mitochondrial dysfunction	Antioxidant payloads; ROS-triggered release	1, 10
Chronic therapy in young women	Long-term exposure, fertility concerns	Biodegradable materials, low dose, local routes, reproductive toxicology	6, 8, 11

Phytochemicals in PCOS and Their Pharmaceutical Barriers: Phytochemicals have been studied in PCOS because they can act on several targets simultaneously. A recent review of nano-formulated phytochemicals in PCOS describes, among others, flavonoids such as quercetin and naringenin, the stilbene resveratrol, curcumin and berberine [12]. Naringenin, a citrus flavonoid, has been reported to improve insulin sensitivity by activating the PI3K/Akt pathway and AMPK and by promoting GLUT4 translocation, and in PCOS rats it restored the oestrous cycle and reduced IL-6 and TNF- α [12]. Resveratrol has been linked to lower testosterone, LH and DHEAS and to improved follicular development through effects on glycolysis and SIRT1 [12]. In a letrozole rat model, resveratrol at 20 mg/kg, alone or with a barberry extract, was compared with metformin over 42 days, illustrating both the interest in these compounds and the high doses of the unformulated agents that are often needed [13].

Why free phytochemicals fall short: Most phytochemicals are lipophilic, poorly water soluble and chemically unstable, and they are metabolised and cleared quickly, which restricts their bioavailability and therefore their pharmacological effect [14]. A frequently cited example is quercetin: after a single oral dose in rats, about 93% was reported to be metabolised within an hour [15]. Curcumin is a hydrophobic compound with similar problems, and it has motivated much of the formulation work in PCOS [16,17].

Nanoformulations: Nano-sized phytochemical particles show greater biological activity mainly because of longer circulation, easier attachment to membranes and cellular uptake, and longer retention [14]. Nano-vehicles can also improve solubility, lower systemic adverse effects and allow accumulation in a target organ [18]. In PCOS the evidence for this benefit is emerging: chitosan-based curcumin nanoparticles were more effective than free curcumin in restoring ovarian morphology in rats and produced effects on LH, prolactin, testosterone and insulin comparable to or better than metformin [16]. Nanocurcumin also modulated NF- κ B and the autophagy markers LC3-II and p62 in letrozole-treated rats, which suggests that formulation can change the molecular response as well as the exposure [17]. Combined daidzein and genistein nanoparticles at 25 and 50 mg/kg over 35 days outperformed the plain compounds and reached an effect similar to clomiphene citrate [19].

Nanocarrier Platforms and Formulation Strategies for Phytochemicals: The choice of carrier depends on the physicochemical nature of the phytochemical and on the intended route. The main families used with phytochemicals are described below, and Table 2 lists representative formulations.

Polymeric nanoparticles: Chitosan-based nanoparticles are widely studied because they are biodegradable and can efficiently deliver drugs and

phytochemicals. Metformin-loaded chitosan nanoparticles have shown improvements in insulin resistance, testosterone levels and ovarian morphology in PCOS models.

Lipid-based systems: Liposomes, phytosomes, solid lipid nanoparticles and ethosomes improve the solubility, stability and bioavailability of poorly soluble phytochemicals. Berberine and resveratrol lipid formulations have demonstrated beneficial effects on insulin sensitivity and ovarian function.

Inorganic and green-synthesised nanoparticles: Metallic and selenium nanoparticles have shown

potential for improving insulin resistance, hormonal imbalance, inflammation and oxidative stress in PCOS models. Plant-mediated synthesis provides a greener approach for preparing these nanoparticles.

Stabilisers and formulation quality: Stabilisers are essential for maintaining nanoparticle size, preventing aggregation and ensuring controlled drug release. Consistent reporting of particle size, loading, release and stability is needed to improve comparison and reproducibility among PCOS formulations.

Table 2: Representative phytochemical and related nano-formulations relevant to PCOS

Payload	Nano-formulation	Evidence and setting	References
Curcumin	Arg-CS-NAcHis chitosan nanoparticles	PCOS rats: lower LH, prolactin, testosterone, insulin; better ovarian morphology than free curcumin	16
Curcumin	SNEDDS, SPIONs, nanocurcumin	Reported in mouse and rat PCOS models; NF- κ B, LC3-II and p62 modulation	17
Daidzein + genistein	Nanoparticles (25, 50 mg/kg)	Letrozole rats, 35 days; better than plain compounds, comparable to clomiphene	19
Berberine	Phytosome; nano-ethosomal gel	PCOS models: better insulin sensitivity, lower testosterone; higher bioavailability	12
Quercetin	Macrophage membrane-cloaked ROS-responsive nanoparticles	PCOS model: low toxicity, controlled and relatively targeted release	10
Resveratrol derivative (DMU-212)	Liposomes	Granulosa cells in vitro: higher oestradiol and progesterone secretion	6
Selenium (+ metformin)	Selenium nanoparticles	Letrozole + high-fat diet rats: improved HOMA-IR, lipids, hormones, oxidative and mitochondrial markers	1
Quercetin, naringenin, berberine (non-PCOS)	PLGA, alginate-chitosan, SLN carriers	Diabetes and metabolic-syndrome models; indirect evidence for PCOS	18

Targeted Delivery to the Ovary: Second-generation systems aim to concentrate drug in the ovary or in ovarian immune cells. Three strategies are visible in the current literature.

Ligand and surface functionalisation: Nanoparticle surfaces can be modified with antibodies, peptides or polysaccharides to bind particular cells, which also lengthens circulation and lowers clearance [6]. Hyaluronic acid-coated liposomes of linagliptin, a DPP-4 inhibitor repurposed for PCOS, were designed for ovarian targeting. In PCOS rats the formulation improved insulin sensitivity and normalised lipids, and an artificial-intelligence model was used to predict encapsulation efficiency and optimise the liposomes [21].

Biomimetic camouflage: Cell-derived membranes give nanoparticles natural surface proteins, which can improve biocompatibility and homing. Macrophage membrane-cloaked quercetin

nanoparticles were developed for the ROS-rich ovarian lesion and were reported to combine low toxicity, controlled release and relatively targeted delivery; intermittent dosing was explored to reduce treatment burden and the risk of immunogenicity [10]. Mesenchymal stem cell-derived exosomes are natural lipid vesicles proposed to treat PCOS-related infertility by modulating immunity, limiting inflammation and reducing granulosa cell apoptosis [2].

Route-based (local) targeting: The route of administration is itself a targeting strategy. Vaginal delivery avoids first-pass metabolism and gastrointestinal side effects. Cationic noisome carrying metformin in a thermosensitive gel were developed for intravaginal PCOS therapy [11], and progesterone-loaded transethosomes designed to enhance vaginal permeation were optimised statistically and evaluated clinically in women with anovulatory PCOS, which makes this one of the few nanocarrier systems tested in patients [22].

Stimuli-Responsive Nanotherapies: Stimuli-responsive nanocarriers release their cargo in response to particular triggers, giving greater spatial, temporal and dose control than passive systems [23]. The triggers are usually divided into endogenous stimuli, such as pH, enzymes, redox gradients and ROS, and exogenous stimuli, such as temperature, light, magnetic fields and ultrasound [23–25]. Responsive systems allow on-demand and site-specific delivery and aim to improve efficacy while reducing systemic side effects [26]. Table 3 compares the main trigger types.

ROS-responsive release: relevant trigger for PCOS: Oxidative stress is a hallmark of the PCOS ovary [1], which makes ROS a natural trigger. ROS-sensitive chemical bonds or groups can be built into a carrier so that it releases cargo in an oxidising environment [24]. In cancer research ROS-responsive carriers have been found to be more selective than pH- or glutathione-responsive ones [24], and the same logic was applied to PCOS in the macrophage membrane-cloaked quercetin system, which was designed to release quercetin preferentially where ROS are high [10]. The design has an appealing feature: the drug, an antioxidant, is delivered where oxidative stress is greatest, and its action may in turn reduce the trigger.

pH-, enzyme- and redox-responsive systems: pH-responsive carriers rely on protonation or cleavage of acid-labile bonds in acidic

compartments such as endosomes and lysosomes, and they can stay stable in the circulation while releasing more drug after uptake [25]. Enzyme-responsive systems use substrate-specific linkers that are cleaved by overexpressed enzymes, such as matrix metalloproteinases, giving highly localised release, although enzyme expression is heterogeneous and peptide linkers can be immunogenic [26]. Redox-responsive carriers exploit differences in glutathione level. These strategies were developed mainly in tumour models, where the microenvironment is acidic and rich in ROS and enzymes [24,25].

Multi-stimuli and exogenous triggers: Single stimuli may not give sufficiently precise activation, and multi-stimuli systems, for example pH/ROS/enzyme triple-responsive designs, have been reported to give incremental and synergistic control of release [24,27]. Exogenous triggers such as light, magnetic field or ultrasound offer external control but add complexity and the need for equipment [23]. Magnetic iron oxide particles carrying curcumin have already been tested in a mouse PCOS model [17], and this may indicate a direction for externally guided systems. Responsive nanomedicines for inflammatory conditions have reached phase I and II trials, which suggests that the concept is translatable, although not yet for PCOS [26].

Table 3: Stimuli-responsive strategies and their relevance to PCOS

Trigger	Principle	Relevance to PCOS	References
ROS	ROS-cleavable bonds or groups release cargo under oxidative stress	Directly explored (quercetin nanocarrier); oxidative stress is a PCOS hallmark	1, 10, 24
pH	Acid-labile bonds cleave in acidic compartments	Mainly cancer data; ovarian pH gradients unverified	25
Enzyme	Substrate-specific linkers cleaved by overexpressed enzymes	Not yet tested in PCOS; enzyme heterogeneity and immunogenicity	26
Redox (glutathione)	Disulfide-type linkers respond to glutathione level	Not yet tested in PCOS	23, 25
Multi-stimuli	Combined pH/ROS/enzyme triggers for synergistic control	Concept only; potential for greater precision	24, 27
Exogenous (magnetic, light, ultrasound)	External field triggers or guides release	SPIOs used with curcumin in a mouse PCOS model	17, 23

Computational and Data-Driven Formulation Design: Formulation optimisation is normally slow, requiring many experimental batches. Machine-learning models can predict formulation properties such as encapsulation efficiency and thereby reduce the experimental workload, as shown for hyaluronic acid-coated linagliptin liposomes [21]. Statistical optimisation was likewise used in the development of progesterone transthesosomes [22].

Safety, Model Limitations and Translational Barriers

- Animal models: Letrozole models do not fully mimic human PCOS.
- Limited PCOS-specific research: Stimuli-responsive systems are mainly adapted from cancer research.
- Safety concerns: Long-term reproductive and nanoparticle toxicity remain uncertain.
- Limited clinical evidence: Most formulations are still in the preclinical stage.

Future Perspectives: Several developments seem most likely to advance the field. First, combination and co-delivery systems should be explored further, since selenium nanoparticles with metformin already outperform either component alone [1]. Second, phytochemicals with the best mechanistic evidence, such as quercetin, curcumin, resveratrol, berberine and naringenin, should be formulated in carriers that are matched to their properties and compared head-to-head with standard drugs using matched doses [19]. Third, ovary-directed carriers should be validated by biodistribution studies that show real accumulation, not only downstream efficacy, since many claims of targeting rest on indirect endpoints [21].

Fourth, the stimuli-responsive concept requires disease-specific characterisation: measurement of ROS, pH and enzyme levels in PCOS ovarian tissue would show which triggers are usable. Fifth, non-oral routes deserve more attention, including vaginal gels and potentially other local forms, because they can improve adherence and reduce systemic exposure [11]. Sixth, the change to PMOS terminology and its emphasis on metabolic and endocrine features may encourage carriers that treat the whole syndrome rather than the ovary alone [5]. Finally, harmonised preclinical protocols, fertility and offspring endpoints, and early-phase trials with patient-reported outcomes are needed to make progress credible [29].

Conclusion

Nanomedicine has moved from simple encapsulation to targeted and stimuli-responsive designs in PCOS. Phytochemical nanoformulations improve the bioavailability and potency of multi-target natural compounds, while ligand-coated, membrane-cloaked and ROS-responsive carriers begin to address where and when a drug acts. The preclinical results are encouraging across hormonal, metabolic, inflammatory and histological endpoints, but they rest mainly on short-term rodent studies, and important design concepts are borrowed from cancer research. Rigorous characterisation, reproductive toxicology, confirmation of ovarian targeting and clinical studies are the next steps. If these are achieved, next-generation nanocarriers could support safer and more effective multi-target management of PCOS/PMOS.

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