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Chapter 2: Role of Nanocarriers (Liposomes, SLNPs, Niosomes and Dendrimers) in Reproductive Health: An Emerging Paradigm

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Abstract

The revolution of nanotechnology in medical sciences and in drug delivery system provided targeted and controlled therapeutic interventions with maximum efficacy. Of these advancements, nanocarriers including liposomes, niosomes, SLNPs and dendrimers are of great interest in the field of reproductive healthcare. These nanomedicines improve bioavailability, decrease toxicity, and achieve more efficient organ targeting compared with clinical medication. The Polycystic Ovary Syndrome (PCOS) is one of the reproductive disorders that involve both human and animal reproductive health. PCOS endometriosis, infertility, and hormone-related imbalances. Their biocompatibility and tunable structure, liposomes and niosomes have been widely studied as vehicles for hormones and antioxidants. SLNPs provide the advantages of stability and controlled release, and dendrimers, well-defined architecture and surface modifiability, are good for encapsulation of hydrophobic drugs and for targeted therapy. Altogether, these nanocarrier platforms serve as the hopeful new era and provide a path toward more specific and personalized reproductive health care.

Keywords: *Polycystic Ovary Syndrome (PCOS), Nanocarriers, Targeted drug delivery, Controlled release, Bioavailability, Organ targeting.*

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is, hence, very often diagnosed and the most widely spread one amongst the hormonal dysfunctions in women, penetrating about 5% to 21% of the female population across the globe. Although described first by Stein and Leventhal in 1935, PCOS is still the main reason of infertility today. By the presence of at least two of the following doctors most likely will confirm the condition: either irregular or absent ovulation, or symptoms of excess male hormones, or characteristic changes in the ovaries after excluding other causes [1-3].

PCOS is a very complex mix of disorders affecting hormones, reproduction and metabolism. Hormonal imbalance is a common issue in women having PCOS, for instance, they may have high levels of luteinizing hormone (LH) and low levels of follicle-stimulating hormone (FSH) together with insulin resistance and increased production of androgens which can block the regular ovulation cycle resulting in irregular periods, cyst formation in the ovaries and infertility [4-6]. Apart from reproductive problems, PCOS is also associated with increased risk of long-term health problems. It causes diabetes mellitis type 2, endocarditis, and even some types of cancers like the breast or uterine cancer, among others. The psychological effect is also considerable as many people experience stress, depression, and low life satisfaction [7].

Treatment usually focuses on

- Managing symptoms rather than providing a cure.
- Options may include hormonal therapies, lifestyle changes such as diet and exercise, and medications that improve insulin sensitivity.
- However, these treatments can sometimes have limited effectiveness or cause unwanted side effects [8].

In recent years, advances in nanotechnology and therapy. Nanomedicine offers improved drug delivery, increased bioavailability, targeted delivery, and deeper tissue penetration which have opened promising new avenues for PCOS diagnosis. Additionally, emerging nanoscale imaging and biosensing techniques may enable earlier detection and more accurate monitoring of PCOS (Figure 2.1)[9].

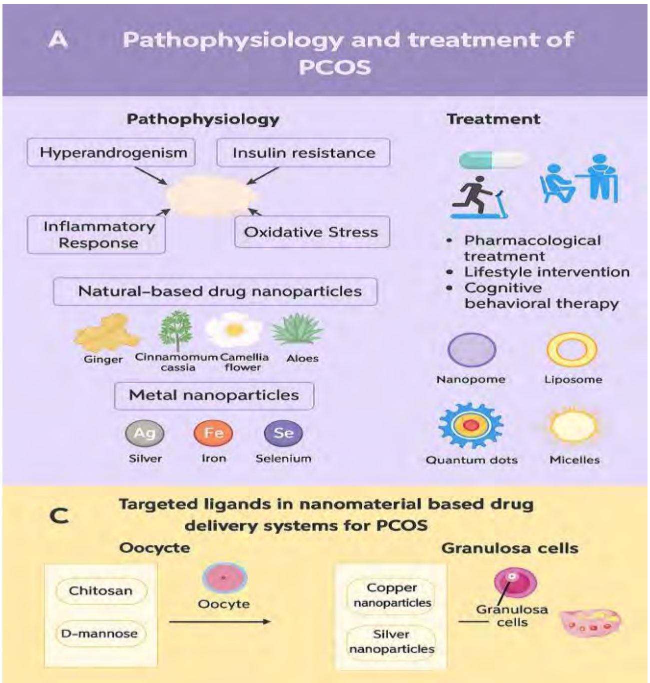

Figure 2.1: Pathophysiology and targeted drug delivery for treatment of PCOS

A. Liposomes for treatment of PCOS

Liposomes are tiny, spherical vesicles made of one or more layers of phospholipids. Both water-soluble and fat-soluble drugs can be incorporated in the liposomes. Because of their flexible structure and compatibility with biological systems, liposomes are used as an effective drug delivery system for managing PCOS [10].

Advantages:

- They improve drug absorption,
- target specific tissues,
- and sustained release, making them especially helpful for delivering treatments like metformin, resveratrol, inositols, and hormonal therapies.
- low toxicity in the body, better drug metabolism (in PCOS treatment), and protection for fragile bioactive compounds from breaking down [11].
- By directing drugs straight to the ovaries or insulin-sensitive areas, liposomes create localized treatment effects while reducing side effects. This approach enhances the overall effectiveness of the therapy [12].

I. Industrial Applications

• **Pharmaceutical Industry:** Researchers are looking into liposomal formulations to improve how insulin sensitizers and anti-androgens work in treating PCOS [13].

• **Nutraceuticals and Dietary Supplements:** Natural bioactives like curcumin, quercetin, and vitamin D have antioxidant and anti-inflammatory properties. They are being added to liposomal carriers to make them more effective for managing oxidative stress and inflammation related to PCOS[14].

• **Cosmeceuticals:** Researchers are studying topical liposomal formulations for treating skin problems associated with PCOS, such as acne and hirsutism which improve drugs penetration and support better local treatment effects [15].

II. Research and Diagnostics

Emerging studies are exploring liposome-based biosensors and imaging systems to detect ovarian changes associated with PCOS which may aid in the early diagnosis and precise monitoring of the syndrome.

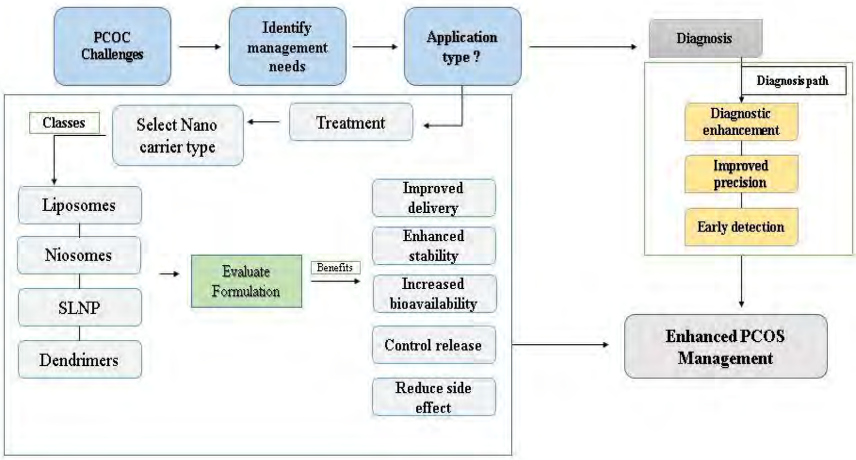

Figure 2.2: Schematic representation of challenges faced in PCOS

B. Nanocarriers in Reproductive Health

In recent years, nanocarriers have emerged as a game changer in reproductive health, Among the most studied nanocarrier systems are liposomes, niosomes, solid lipid nanoparticles (SLNPs), and dendrimers. Each of these offers unique structural and functional benefits [16-17].

Advantages of Nanocarriers [18]:

- Targeted Delivery
- Improved Therapeutic Bioavailability
- Decreases side-effects

It reduces off-target effects especially in Hormone -sensitive and metabolic tissues which are common in reproductive disorders. Nanocarriers can carry different types of therapeutic agents (hormonal drugs, phytoconstituents, and gene drug therapy which makes them versatile [19-20].

The following parts of the article will go into more detail about their specific mechanisms, applications, and clinical prospects in managing reproductive health, as shown in fig. 2.2

Diagnosis of PCOS

The diagnosis of PCOS should rely on a combination of clinical assessment and diagnostic tests.

This generally includes

- A thorough review of medical history,
- A physical exam, and
- Lab tests to check hormone levels, such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), insulin, and anti-Müllerian hormone (AMH) [20].
- Transvaginal ultrasound (US) is also used to evaluate the ovaries, cyst formation, and other features characteristic of polycystic ovaries (PCO) [21].

C. Nanotechnology: Key Features and Applications

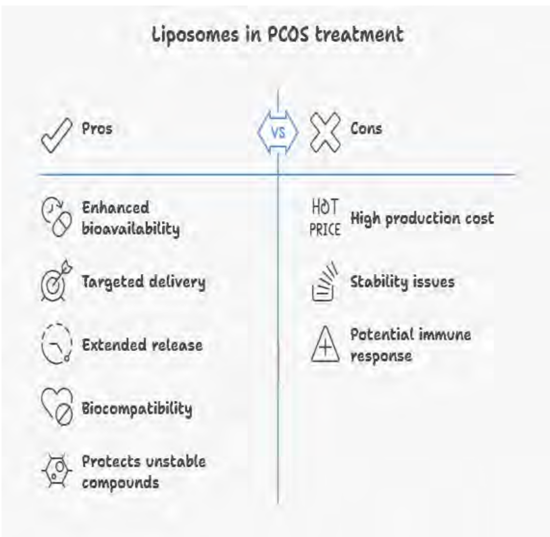

Figure 2.3: Representation of advantage and disadvantage of nanocarriers in PCOS

In medicine, nanotechnology plays a significant role in managing PCOS which improves diagnostic accuracy and treatment outcomes. Notably, nanocarriers like nanoparticles and liposomes have attracted considerable interest [22].

These carriers provide a promising way

- To enhance the delivery, and bioavailability of drugs typically used for PCOS.
- Many medications for PCOS struggle with poor solubility and bioavailability or susceptible to breakdown in the body; using nanoformulations protects these drugs and allows for controlled release mechanism in the body [23], as illustrated in fig. 2.2.
- This approach not only improves treatment effectiveness but also reduces side effects, making the therapy safer and more efficient [24].

2. NANO-BASED DRUG DELIVERY SYSTEMS

Nanotechnology involves the deliberate design and manipulation of materials at the nanoscale, which is typically between 1 and 100 nanometers with improved functional properties [25-26]. Through this process, researchers created nanoparticles that have remarkable features, such as self-stabilization and the ability to change structure on their own and have a high surface-to-volume ratio, providing distinct benefits compared to conventional micron-sized materials [27]. Nanomaterials display unique behaviours because of quantum effects and significant surface interactions. These effects enhance their thermal, mechanical, catalytic, electronic and optical properties [28] which changes the physical as well as the chemical properties of nanomaterials, leading to lower binding energy per atom and reduced melting points [29].

The ability of nanomaterials to disperse is key for maximizing their uptake in biological systems. However, strong attractions between particles reduces their effective surface area by forming clumps together. Factors which are important and crucial to optimize are

- zeta potential,
- pH,
- ionic strength, and the balance between hydrophilic and hydrophobic properties of the suspension medium can help address this issue [30].

Importantly, the properties of particles in the nanoscale range depend on their size. Quantum effects at smaller sizes become more noticeable, causing changes such as inducing magnetism in materials that weren't magnetic before and altering catalytic performance due to changes in electron affinities [31]. Figure 2.3 outlines the pros and cons of liposomes. Nanoparticles can differ in size, structure, and surface characteristics, all of which significantly affect drug release patterns, targeting capabilities, and biological stability. Important physical and chemical qualities, like

- shape,
- charge,
- hydrophobicity,

- roughness, and mechanical strength,

These above qualities impact the accuracy and effectiveness of drug delivery [32]. The composition and surface charge of the nanoparticles also plays a crucial role in this interaction [33]. Figure 2.4 shows the different types of nanocarriers.

Research reveals that spherical nanoparticles penetrate cells more effectively than rod-shaped ones. The entry into endosomes, which is crucial for successful delivery inside cells, is also influenced by charge. For instance, uterine-targeted exosomes with a negative charge showed better uptake in uterine tissue, indicating that particles with mildly negative or neutral zeta potentials than positively charged ones [34].

The stability and biological response of nanoparticles depend on factors such as surface chemistry, hydrophobicity, and how they are administered. A stable protein corona can improve how well nanoparticles work and how compatible they are [35]. Moreover, how nanoparticles behave in living systems is largely determined by their design and biological interactions [36].

In regenerative medicine, these nanostructures also show potential as scaffolds for tissue repair or as carriers for biological signals that promote healing [37]. Although this field is still developing, and under research, nanomedicine holds considerable promise for diagnosing and treating disorders of the female urogenital tract (UGT). Increasingly, literature supports the idea that nanosystems can enhance early detection and targeted treatment of these conditions. [38].

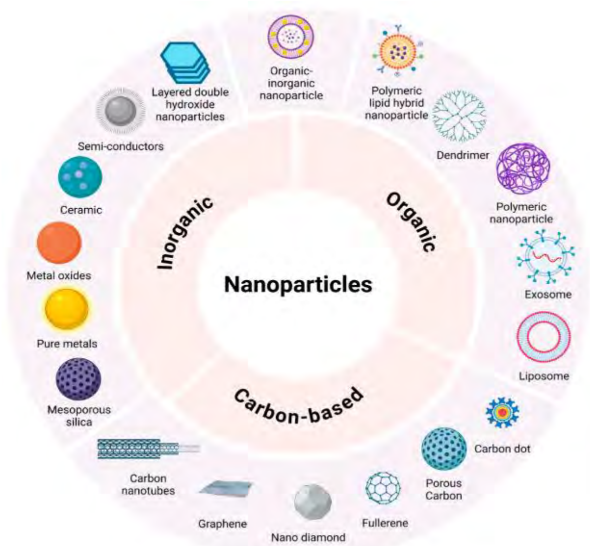

Figure 2.4: Representation of types of nanocarriers

Case : Steroidogenic activity of liposomal methylated resveratrol analog 3,4,5,4′-tetramethoxystilbene (DMU-212) in human luteinized granulosa cells in a primary three-dimensional *in vitro* model.

- Granulosa cells (GCs) are a crucial part of the ovary, as they significantly contribute to the synthesis of steroid hormones, particularly estradiol.
- Hormone production involves an organized co-operation of granulosa cells (GCs) with theca cells.
- Stimulated by the LH, theca cells synthesize androgens which penetrates into the granulosa.
- an enzyme named aromatase (CYP19A1) (On receipt of signals from the follicle-stimulating hormone (FSH), located in the granulosa cells, transforms these androgens into estrogen, a necessary precursor for the development of the follicle and body-readying for future reproduction [39].
- When these finely tuned hormonal processes are disrupted, it can lead to imbalances in steroid production. Which plays a key role in the development of polycystic ovary syndrome (PCOS)-a common condition marked by elevated androgen levels and the interruption of normal follicle maturation, ultimately affecting a woman's reproductive health and overall well-being [40].
- Resveratrol (3,4',5-trans-trihydroxystilbene) is one of the phytoalexins, belong to a class of natural polyphenol, widely occurring in grape skin. It has super anti-oxidant and the anti-aging features which makes as a popular amazing supplement for overall well-being.
- More recently, its potential use in the treatment of ovarian dysfunction is under consideration [41-45].

Structure–activity relationship (SAR) studies have shown that replacing the hydroxyl (-OH) groups in resveratrol with methoxy (-OMe) groups can enhance its lipophilicity, which may lead to better bioavailability in the body. It also influences the molecule's solubility-highlighting the delicate balance between chemical modification and biological performance [46].

Therefore, liposomes are capable of encapsulating compounds with varying lipophilic-hydrophilic characteristics offer a viable approach to enhance the therapeutic efficacy of methoxy derivatives. Among the many methoxy-modified forms of resveratrol, 3,4,5,4′-tetramethoxystilbene (commonly known as DMU-212) stands out for its strong anticancer potential. Studies have shown that DMU-212 exhibits notable activity against a wide range of cancer cell lines, making it a promising candidate for further investigation in cancer therapy.[47][48][49]. Additionally, the cytotoxic effects of DMU-212 have been found to the anticancer effects of DMU-212 have been closely linked to its interaction with the cytochrome P450 enzyme CYP1A1.

This enzyme is often found to be overexpressed in various human cancers compared to normal tissues, suggesting that the heightened presence of CYP1A1 may enhance the bioactivation or effectiveness of DMU-212 in targeting cancer cells [50][51]. Research conducted by Piotrowska-Kempisty et al. indicated that DMU-212 does not exhibit cytotoxic effects against noncancerous ovarian HOSE cells lacking CYP1A1, in contrast to their cancerous ovarian counterparts that express this protein [52]. Consequently, it can be inferred that DMU-212 may not demonstrate any cytotoxicity in human noncancerous granulosa cells [53].

Considering the potential clinical value of DMU-212-loaded liposomes-particularly due to their improved pharmacokinetic properties-it becomes essential to gain a deeper understanding of the mechanisms driving DMU-212's effects on steroid hormone production in human granulosa cells. Uncovering these pathways could pave the way for more targeted and effective treatments for ovarian dysfunction.

Purpose

Granulosa cells (GCs) play a vital role in the production of steroid hormones, which are essential for normal ovarian function. Resveratrol, a naturally occurring polyphenol, has garnered attention for its broad health benefits-especially its potential to support and improve reproductive health by influencing hormone regulation and ovarian activity [54]. Nonetheless, its use is constrained by its low bioavailability [55].However, modifying the stilbene structure of resveratrol by adding methoxy groups has significantly reduced its water solubility. As a result, to improve its delivery and therapeutic potential, DMU-212 must be encapsulated in liposomes-an approach that enhances its solubility, stability, and bioavailability in biological systems [56]. This research aimed to assess the effects of the liposomal formulation of DMU-212 (lipDMU-212) on the secretion of estradiol and progesterone by human ovarian GCs within a primary three-dimensional cell culture system [57].

Results

Liposome-encapsulated DMU-212 (lipDMU-212) has demonstrated a marked increase in estradiol and progesterone output depending on the dose. The effect is likely due to the molecule's action of raising the expression levels of crucial genes involved in steroidogenesis, such as CYP11A1, HSD3B1, StAR, CYP17A1, CYP19A1, and HSD17B1, which are genetically responsible for the production and control of ovarian steroid hormones [58]. Moreover, we showed that lipDMU-212 by itself or in conjunction with follicle-stimulating hormone (FSH) administration did indeed result in the upregulation of HSD3B1 and CYP11A1 protein levels in the GCs. This indicates a potential synergistic or additive effect and thus underlining its capability to promote the production of steroid hormones by directly regulating the activity of key enzymes in the steroidogenic pathway [59-61].

Nanoliposomes

Nanoliposomes are nanoscale unilamellar vesicles made of phospholipid bilayers. Which are capable of carrying both hydrophilic and lipophilic drugs. Nanoliposomes are particularly beneficial in oncology and antiviral therapies due to their potential for sustained drug release and improved pharmacokinetics parameters [62]. They can achieve both passive target as well active target through the enhanced permeability and retention (EPR) effect in tumor tissues abd by surface modification with ligands or antibodies respectively [63]. PEGylated nanoliposomes exhibit prolonged circulation time, which enhances therapeutic outcomes [64-67] (as mentioned in **Table 1**).

Table 2.1: [68][69][70][71][72]

Drug	Purpose / Mechanism	Status	Remark
Liposomal Metformin	Improves insulin sensitivity, reduces androgen levels	Investigational	Enhances bioavailability, reduces GI side effects
Liposomal Letrozole	Aromatase inhibitor for ovulation induction	Under Development	Improves ovarian targeting, reduces systemic exposure
Liposomal Curcumin	Anti-inflammatory and antioxidant, reduces cyst formation	Preclinical/Experimental	Improved stability and sustained release observed
Liposomal Resveratrol	Reduces oxidative stress, improves insulin sensitivity	Preclinical	Enhances therapeutic activity in animal PCOS models
Liposomal DCI	Regulates insulin signaling and ovulation	Under Development	Improves metabolic and reproductive outcomes
Liposomal Myo-Inositol	Regulates hormonal imbalance and follicular development	Preclinical	Enhances absorption and cellular uptake
Liposomal Quercetin	Anti-inflammatory, reduces ovarian inflammation	Experimental	Promising in reducing follicular cysts in PCOS rats
Liposomal Berberine	Insulin sensitizer, reduces androgen levels	Under Investigation	Liposomal form improves GI tolerance and efficacy
Liposomal Vitamin D	Modulates insulin resistance and ovulatory function	Supplemental Strategy	Liposomal form improves absorption in deficiency cases
Targeted Nanoliposome	Targets leukemic or overexpressed cells in PCOS + co-morbidities	Research-level	Ligand-targeted for specific cellular uptake

Solid lipid nanoparticles (SLNPs)

Among the most studied nanocarriers are **solid lipid nanoparticles (SLNPs)** which are submicron colloidal carriers with particle sizes typically below 1000 nm and remain solid at body temperature (37°C). These carriers are composed of physiological lipids like mono-, di-, and triglycerides, fatty acids, and waxes. Stabilized with surfactants, SLNs provide a lipophilic matrix ideal for incorporating therapeutic agents. They have shown promise in the treatment of various cancers, including colon and breast cancers, due to their controlled drug release capabilities and biocompatibility [73][74][75].

SNLP in Hirsutism

Hirsutism is a dermatological condition that refers to the excessive growth of hair in androgen-sensitive areas in women. Recently, the enhancement of the visible signs of a hairy female has taken special concern that affected the quality of life. The present study was developed to compare the follicular targeting effect of topical spironolactone (SP) or progesterone (PG)-loaded nanostructured lipid carrier (NLC) on the management of hirsutism. Four NLC formulations were prepared using cold homogenization techniques and pharmaceutically evaluated. SP-NLC and PG-NLC topical hydrogels were prepared to explore their pharmacological effect on letrozole-induced polycystic ovarian syndrome (PCOS) in rats. Inflammatory mediators, antioxidant, and hormonal parameters were assayed. Additionally, histopathological examination was carried out to confirm the successful induction of PCOS. Results confirmed that all NLC formulations have a spherical shape with particle size ranged from 225.92 ± 0.41 to 447.80 ± 0.66 nm, entrapment efficiency > 75%, and zeta potential (−31.4 to −36.5 mV). F1 and F3 NLCs were considered as selected formulations for SP and PG, respectively. Female Wistar rats treated with F1 formulation for 3 weeks displayed better outcomes as manifested by the measured parameters as compared to the other tested groups. A significant reduction in hair follicle diameter and density was observed after topical application of SP or PG nano-gels. Finally, the outcomes pose a strong argument that the development of topically administered SP-NLC can be explored as a promising carrier over PG-NLC for more effectual improvement in the visible sign of hirsutism.

Hyperandrogenism

Hyperandrogenemia refers to a condition characterized by increased levels of androgens circulating in the body. In individuals with polycystic ovary syndrome (PCOS), this imbalance often arises due to disrupted steroid hormone production within ovarian cells. Key androgens typically elevated in PCOS include testosterone (T), dehydroepiandrosterone (DHEA), its sulfate form (DHEAS), dihydrotestosterone, and androstenedione (A). Overproduction of these hormones results in abnormal follicle development, increased numbers of small antral follicles, and a lack of ovulation. Additionally, enhanced cortisol breakdown at the peripheral level is believed to exacerbate hyperandrogenemia.

When cortisol levels are low, negative feedback on the hypothalamic–pituitary–adrenal (HPA) axis is reduced, prompting the pituitary to secrete more adrenocorticotropic hormone (ACTH). This stimulates adrenal glands to produce more steroids, including androgens. Consequently, various physiological routes converge to raise androgen levels, making hyperandrogenemia a central aspect of PCOS pathophysiology. Emerging evidence also links elevated androgens to insulin resistance (IR) in women with PCOS. According to findings by Paolo et al., individuals showing hyperandrogenic traits also exhibit insulin resistance. Moreover, antiandrogen treatments may help improve insulin sensitivity in these cases [76][77].

Insulin Resistance (IR)

IR is highly prevalent in PCOS, affecting approximately 75% of patients. It contributes significantly to the metabolic disruptions seen in this condition. Studies from the 1990s suggest that insulin interacts with its receptors in PCOS patients, enhancing not only steroid hormone production in the ovaries and adrenal glands but also luteinizing hormone (LH) release from the pituitary [78]. The resulting hyperinsulinemia feeds into the core mechanisms driving PCOS. Additionally, IR influences signaling in tissues not typically reliant on insulin, such as the ovaries and the pituitary, disrupting the hypothalamic–pituitary–ovarian (HPO) axis and exacerbating hyperandrogenemia [79].

Inflammation and Oxidative Stress

Research has shown that PCOS is associated with elevated inflammatory and genetic markers. Women with the condition tend to exhibit increased levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-18 (IL-18), tumor necrosis factor-alpha (TNF-α), and ferritin compared to control subjects of similar age and body mass index (BMI). In PCOS, hyperandrogenemia and IR both trigger inflammation, increasing reactive oxygen species (ROS) and leading to oxidative stress [80]. This oxidative stress impairs normal follicular development, potentially damaging oocytes and granulosa cells and compromising fertility. Elevated ROS production is linked with key PCOS features, including IR, hormonal imbalance, inflammation, and obesity. Moreover, defects in mitochondrial function and oxidative phosphorylation can disrupt insulin signaling and glucose metabolism. Antioxidant defenses, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), are often reduced in obese individuals, compounding these effects [81].

3. NATURAL-BASED DRUG NANOPARTICLES

Natural remedies, derived from plants, animals, and minerals, have long been used for their therapeutic potential. Modern scientific studies have increasingly validated the bioactive compounds found in these sources, particularly those from plants, for their medicinal benefits. Recently, there has been a growing interest in herbal medicines for managing conditions such as PCOS, especially due to the limitations and side effects of conventional treatments. A study by Arentz et al. highlighted that over 70% of women with PCOS used complementary therapies, reflecting dissatisfaction with mainstream pharmaceutical options [82].

Several botanicals have been explored for their multifaceted roles in improving symptoms of PCOS, including hormonal imbalances, ovulation issues, insulin resistance, and weight management. For instance, *Aloe barbadensis* gel has shown promise in animal models by improving ovarian function, while chamomile extract supports healthy follicular development. Clinical studies suggest compounds like curcumin-a bioactive from turmeric-can safely help reduce hyperandrogenism and high blood sugar levels [83]. To overcome the poor solubility and pH stability of curcumin, researchers have turned to nanoparticle formulations. Natural nanoparticles mimic the properties of extracellular vesicles and are suitable for drug delivery due to their surface chemistry and size. Chitosan (CS), a biodegradable polysaccharide, is one of the most commonly used biopolymers for encapsulating active compounds. Although CS has limited solubility in water, chemical modifications can improve its performance. Functionalized CS nanoparticles have been used to deliver curcumin effectively, with one study reporting reductions in LH, prolactin, testosterone, and insulin levels in PCOS-affected rats [84].

Other natural nanoparticles consist of vesicles obtained from ginger which are composed mainly of 6-gingerol and thus they not only enhance the insulin sensitivity but also regulate the expression of specific genes that are related to glucose metabolism [85]. Additionally, one more popular and frequently used spice in the kitchen is cinnamon which has also been the subject of researches regarding the management of PCOS. Animal and clinical trials, by granting it around the ballpark of normal hormone levels and menstrual regularity, give it a score as its positive effect on the endocrine system and menstrual cycle, respectively. Nanoparticle silver derived from Cinnamomum cassia, for example, is one of the innovative formulations that come with the added advantage of the antioxidant effect, especially in the case of a diabetic model. Moreover, the same goes for the plant-sourced nanoparticles from Aloe vera and Camellia where they have shown anti-inflammatory and antioxidant effects which have consequently made them potential candidates for PCOS therapy.

Niosomes

Niosomes are vesicles composed of non-ionic surfactants and cholesterol which makes them stable bilayer structures in aqueous environments. These vesicular nanocarriers self-assemble through the hydration of non-ionic surfactants and cholesterol, and have been utilized in cancer therapy, peptide delivery via the oral route, treatment of leishmaniasis, ophthalmic formulations, dermal drug delivery, and haemoglobin transport. They are biodegradable, relatively nontoxic, more stable, and cost-effective alternatives to liposomes in drug delivery applications [86-88].

Niosomes offer versatility in structure-forming unilamellar, oligolamellar, or multilamellar vesicles-which can encapsulate both hydrophilic and lipophilic compounds [88][89] making them strong candidates for clinical translation because of their long shelf life, ease of large-scale manufacturing, and physical stability [89].

Advantages of Niosomes

1. Improved patient compliance.
2. Minimized side effects with prolonged action.
3. Efficient dosing due to localized delivery.
4. Encapsulation protects the active ingredient from degradation.
5. Controlled release.
6. Avoids gastrointestinal breakdown and first-pass metabolism.
7. Maintains structural integrity in emulsified forms.
8. Suitable for Oral, parenteral, and topical administration [86][89].

Composition of Niosomes

1. **Surfactant:** Typically non-ionic (Spans, Tweens), these amphiphiles are biodegradable, biocompatible, and self-assemble into vesicles above their gel-to-liquid transition temperature [86][87].
2. **Surfactant Structure (CPP)**:The critical packing parameter (CPP)-a function of the hydrophobic tail volume, head-group size, and tail length-determines vesicle shape [89][90].
3. **Cholesterol**: Enhances bilayer rigidity, reducing drug leakage, and stabilizing the vesicle [89].

4. **Encapsulated Drug:** The drug's physicochemical properties influence vesicle charge, membrane rigidity, and size due to interactions with the surfactant head groups [89].

5. **Hydration Conditions**: Hydration temperature and duration (above transition temperature) critically affect vesicle size, lamellarity, and drug retention [88][89].

6. **Osmotic Stability**: Exposure to hypertonic or hypotonic environments alters vesicle size and can impact release kinetics [90].

Table 2.2: Herbal phytoconstituents in nanoformulations for enhanced efficiency

Nanocarrier	**Key Ingredient**	**Therapeutic Agent**	**Mechanism**
Chitosan nanoparticles	Chitosan	Curcumin	Reduce the levels of serum luteinizing hormone, prolactin, testosterone, and insulin
Ginger nanoparticles	Lipid	Ginger	Elevated the expression of forkhead transcription factor (Foxa2) to mitigate insulin resistance induced by intestinal epithelial cell (IEC) exosomes
Liposomes	Glycerol phospholipid	Methoxy derivatives of resveratrol (DMU-212)	Increase the secretion of estradiol and progesterone
Quantum dot	Polyethylene glycol (PEG)	Metformin	Restore glucose uptake and reverse insulin resistance

4. INTRAVAGINAL ADMINISTRATION OF METFORMIN–LOADED CATIONIC NIOSOMES WITH THERMOSENSITIVE GEL FOR PCOS

Among various treatment modalities, metformin hydrochloride (MTF–HCl) is extensively recommended by physicians for PCOS due to its superior therapeutic efficacy compared to other drugs [91]. Mechanistically,

- MTF–HCl activates the AMP-dependent kinase-α (AMPK-α) pathway
- to suppress hepatic glucose production, enhance fatty acid oxidation, and increase tissue glucose uptake.
- However, despite favorable physicochemical properties, oral administration suffers from impaired bioavailability (50–60%), risk of lactic acidosis, and requires frequent dosing (500 mg 2–3 times/day), which negatively affects patient compliance [91]. These limitations support the need for customized dosage forms to maximize therapeutic outcomes in PCOS.

The vaginal route is preferred because it offers large surface area, rich vascularization, bypasses first-pass metabolism, and allows for high permeability and drug residence time. Consequently, mucoadhesive delivery systems have been explored for vaginal drug delivery (including colloidal vesicular systems such as liposomes and niosomes), which enhance drug permeation [91]. Cationic nanovesicles provide increased stability, mucoadhesion, and improved tissue penetration. Mucin-a key glycoprotein in vaginal mucus-facilitates cell adhesion, aiding mucoadhesion and controlled drug delivery.

Thermosensitive gels that undergo sol–gel transition under physiological conditions represent a significant advancement in drug delivery [91].

[1]. Unmodified and cationic small unilamellar niosomes containing metformin (MTF–HCl SUNs and MTF–HCl C–SUNs) were prepared via reverse-phase evaporation. These nanoformulations were then mixed with chitosan/β-glycerophosphate gel and evaluated in vitro for gelation time, temperature, viscosity, mucoadhesiveness, and drug release profile. Their therapeutic efficacy was validated in a mifepristone-induced PCOS model in Wistar rats through intravaginal administration, demonstrating encouraging normalization of ovarian histology and hormonal profiles [91].

[2]. Formulation and Evaluation of Ginger & Cinnamon–Loaded Niosomes for PCOS

[3]. The bioavailability and stability of phytoconstituents (phytochemicals) from Zingiber officinale (ginger) and Cinnamomum zeylanicum (cinnamon) are limited and less niosomal encapsulation provides a viable solution for these issues [92].

[4]. The recent clinical trial showed that orally administered metformin, cinnamon, and ginger supplementation produced similar effects, as the improvement of insulin resistance and testosterone levels for metformin was also for cinnamon, while ginger significantly reduced LH and FSH but had lesser metabolic impacts [92]. These findings support the view that niosomal ginger/cinnamon formulations can be used as alternative or adjunctive therapies for PCOS which are high in the list of Table 2.2.

[5]. Impact of Phytoniosome Tinospora cordifolia Leaf Extract and Its Loaded on Mifepristone-Induced Polycystic Ovarian Syndrome (PCOS):

[6]. The LH/FSH ratio in women with PCOS is increased due to rise in the frequency of GnRH pulses, leading to reproductive and metabolic complications like disturbances in estrogen and FSH levels, as well as increased production of androgens and insulin. Low estrogen and high androgen levels in granulosa and theca cells hinder follicle maturation, thus causing ovulatory failure.

5. ROLE OF NANOCARRIER IN DRUG DELIVERY

1. Dendrimers not only increase drug solubility by encapsulating poorly soluble drugs within their branched structures but they also promote the drug's distribution in the body through a little amount and thus the drug's bioavailability is enhanced [114].

2. The pH, enzymes, or oxidative stress can be considered as some of the factors that cause drug degradation, however, dendrimers can protect drugs through their unique structure by keeping them in their inner cavities, thus the active ingredients are still there and are effective for a longer time [115].

3. Dendrimers that are targeted at particular cell types or tissues can be designed by adding specific ligands to their surfaces, which means that the drug will not only go to the right place but also have less impact on the surrounding healthy tissues [116].

4. Dendrimers' size and structure make them very similar to a drug and thus able to penetrate the cells; in this way, they can be viewed as drug delivery systems or enhancers of the therapeutic performance of drugs by granting them access to the cells, where the different pharmacological actions take place.

5. The usage of PAMAM or Poly(amidoamine) dendrimers in the field of nanoparticle synthesis is a classic example of their utility. The branching structure of the dendrimer contains tertiary amine groups which can complex with metal ions in aqueous solutions. Upon the chemical reduction of these ions, they turn into nanoparticles which eventually get entangled within the dendrimer framework, thus opening avenues for drug delivery and diagnostics [117].

7. The use of dendrimer in drug delivery is gaining popularity. For instance, polylysine dendrimers with sulfonated naphthyl groups have already been identified with antiviral activity.Cytotoxicity and Biomedical Applications of Dendrimers

8. Dendrimers, which are frequently referred to as starburst polymers or cascade molecules, have become very attractive candidates for the delivery of drug and gene due to their defined structure, small size, and surface properties that can be changed. They have the same size, they are monodisperse, there are cavities inside for drugs to be; the peripheries are customizable, the internal for drug release is controlled and the delivery is targeted [119].

9. The most popular dendrimers are PAMAM (polyamidoamine) and PPI (polypropylene imine), mainly because they are available commercially and have a good structural appearance. These carriers have been used in various biomedical

applications such as drug delivery, imaging, microbial therapy, gene transfection, and even as curative agents for neurodegenerative diseases [120].

10. The cytotoxicity of dendrimers is a major barrier despite their great therapeutic potential. Generous size, concentration, and especially surface charge are the factors most responsible for their toxicity. The case is the same with cationic dendrimers, especially those with terminal amine groups, which usually have very tight interactions with negatively charged cell membranes and may lead to the global destruction of the cell through membrane rupture and loss of cellular contents [121]. On the other hand, there is a tendency for dendrimers bearing neutral or anionic surfaces to have much lower toxicity [122]. To allow for the masks or gating techniques not to be very effective while the efficacy of the therapy is kept, surface modification methods have been introduced. These methods include conjugation with polyethylene glycol (PEG), acetyl groups, or carbohydrates, which cause a significant reduction in toxicity by neutralizing the surface charge or promoting biocompatibility [126, 127].

CONCLUSION

The use of nanocarriers such as liposomes, solid lipid nanoparticles (SLNPs), niosomes, and dendrimers for drug delivery is revolutionizing the whole procedure that drug release, targeting, and efficiency have previously adjusted in reproductive healthcare. These drug carriers at the nanoscale not only reduce systemic side effects and enhance therapeutic effectiveness but also improve the solubility and stability of the drugs, allow for sustained or controlled release, and facilitate delivery to the reproductive-linked areas where the drugs are needed. Dendrimers are the ones that can make multivalency possible on their surfaces and very accurately pick the target cell, while lipid-based carriers (liposomes, SLNPs, and niosomes) are the ones that are most attractive due to their biocompatibility and readiness for clinical use. These systems could be turned into diagnostic and therapeutic agents for conditions such as PCOS with superior therapeutic outcomes, fewer side effects, and the ability to use natural ingredients in order to develop a more sustainable intervention. Just a few of the issues that must still be resolved before these technologies can be applied to clinical practice with greater success include the toxicity of nanoparticles, the safety of the reproductive systems (germ cells/embryos and placental transfer), consistency of manufacturing processes for production, and regulatory approvals. Standardized labeling schemes and well-designed reproductive toxicology investigations Strong reproductive toxicology experiments, standardized characterization schemes, and meticulously planned clinical trials are just a few of the obstacles that still need to be overcome.. In conclusion, if nanocarriers are developed collaboratively across disciplines, safely, and with thorough safety evaluation, they represent an exciting and promising new frontier in reproductive health with rapid progress.

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