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Review Article

Advancement in Green nano-formulation for management of Gynaecological disorders: Emerging trends and Therapeutic insights

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Abstract

Objective: Considering environmentally friendly methods of synthesis, greater efficacy, and lower systemic toxicity compared to conventional therapies, this paper provides a critical review of recent advances in green nano-formulation approaches in treating gynaecological disorders.

Sources of Data: Comprehensive narrative literature as well as reliable pharmaceutical and biomedical resources was searched using PubMed, Scopus, Google Scholar and Science Direct. Studies related to green nanotechnology and gynaecological therapies, dated from 2010 to 2026, were prioritized.

Summary of Contents: Low drug solubility, potential for systemic side effects, and limited ability for target-specific administration have provided challenges to the successful therapeutic intervention of nano-formulations in gynaecological conditions such as PCOS, endometriosis, cervical cancer, and vaginal infections. Green nano-formulations that are produced through the use of biopolymers, plant extracts, and environmentally friendly techniques have emerged as alternative nanocarrier candidates. They consist of lipid-based systems, nano-emulsions, and nanoparticles created using environmentally friendly processes. The review demonstrates how the creation of nanoparticles by phytochemicals can positively influence drug delivery and drug efficacy. The clinical performance of the discussed systems is addressed based on certain parameters, including particle size, surface charge, encapsulation efficiency, and biocompatibility.

Conclusion: The integration of green chemistry and nanotechnology can be considered as an innovative strategy for treating diseases associated with gynaecology. The usage of nano-formulations is promising in terms of safety, efficiency, and patients' compliance, although additional studies are needed to ensure its successful implementation in medical practice.

Keywords: Green nanotechnology, nano-formulation, gynaecological disorders, drug delivery, bioavailability, sustainability

1. Introduction:

The concept of nanotechnology was introduced over 40 years ago; however, its application came into view in recent years. The Green chemistry integrated with nanotechnology gives a broad idea of green nanotechnology in the development of the economy, health and environment together. Green nano-formulation deliver bioactive phytocompounds as a therapeutic agent to the female reproductive system for treating associated disorders ¹. The formulation of nanoparticles heavily relies on nature rather than traditional, chemical and physical methods, an alternative to the conventional process ².

This sustainable methodology employs plant extracts and natural polymers as sustainable reducing and stabilizing agents to replace toxic chemicals used in conventional

synthesis. The green-synthesized nanocarriers offer excellent biocompatibility, stability and therapeutic efficacy. Phytochemicals with antimicrobial, antioxidant and anti-inflammatory properties delivered directly to target reproductive tissues. Overall, green nanotechnology offers a sustainable and effective treatment option for precision management of female reproductive health disorders ^{3,4}.

Nevertheless, traditional gynaecological therapies, particularly use vaginal drug delivery do possess serious limitations such as inadequate drug solubility, quick mucosal elimination, altered vaginal pH, and side effects, which results in decreased drug efficacy and compliance issues on the part of the patient. This routinely results in suboptimal therapeutic outcomes and increased

complexity of treatment⁵. Numerous systems of nanocarriers, including nanohydrogels, quantum dots, metal nanoparticles, nano-phytosomes, niosomes, dendrimers, nanosheets, nano-emulsions have demonstrated their capacity for application in drug delivery and delivery in women's health.

Green nanocarriers can help stabilize drug delivery, increase drug retention time at mucosal surfaces offer controlled and localized release while minimizing systemic toxicity. Thus, green nanotechnology-based drug delivery systems offer not just an effective strategy to move away from the disadvantages of conventional approaches, but also enhance therapeutic efficacy and sustainability for women's health⁶.

2. Classification and Design of Nano-formulations:

Green nano-formulations are categorized and engineered based on sustainable synthesis methods using biological resources (plant extracts, microorganisms, or biopolymers). Formulations focus on sustainability, biocompatibility, and low environmental toxicity while still ensuring high therapeutic efficacy⁷. In gynaecological contexts, green-designed nano-formulations promote safe, targeted, and effective delivery of bioactive phytochemicals for better management of fertility and reproductive health. These bio-based methods often employ plant extracts, microbial systems, enzymes, and bio waste to serve as reducing and stabilizing agents in mild reaction conditions, generally in aqueous or ethanolic media. Key phytochemicals involved include polyphenols, flavonoids, terpenoids and alkaloids, enabling eco-friendly nanoparticle synthesis with lower environmental footprints⁸.

Extracts from *Oxalis corniculata* and *Trianthema portulacastrum* have been effectively used to create silver (Ag) and copper oxide (CuO) nanoparticles with strong antibacterial and antioxidant activities⁹. Likewise, *Moringa oleifera* and *Eucalyptus globulus* extracts efficiently yield Ag nanoparticles applicable in environmental remediation and biomedicine^{10,11}. Microbial species including *Aspergillus niger* and *Bacillus subtilis* are also valuable for the biogenic synthesis of metal nanoparticles producing materials with enhanced stability and reduced toxicity compared to chemically synthesized counterpart¹².

Advancing sustainable nanomedicine, green nanotechnology incorporates eco-friendly nanocarriers and polymers that improve therapeutic delivery while adhering to environmental safety goals (Figure 1). Biodegradable and renewable polymers such as chitosan (derived from crustacean shells), alginate (from brown algae), cellulose, starch and poly (lactic acid)/ poly (lactic-co-glycolic acid) (PLA/PLGA) constitute commonly researched materials for nanoparticle fabrication¹³.

Chitosan nanoparticles exhibit mucoadhesive and antibacterial properties, making them ideal for oral and nasal drug delivery. Alginate forms ionic cross-linked gels useful in encapsulating proteins, enzymes, and probiotics with excellent biocompatibility and minimal immunogenicity, facilitating applications such as targeted drug delivery and wound healing. Plant-derived polymers like modified cellulose and starch improve drug release profiles and bioavailability, especially for hydrophobic compounds like curcumin¹⁴. PLA and PLGA are notable for their biodegradability into lactic and glycolic acid, naturally metabolized by the body, thus supporting safe excretion and controlled release formulations, including oncological therapies. Green manufacturing practices also emphasize the use of eco-friendly solvents such as ethanol, supercritical CO₂ and water along with natural surfactants like lecithin and saponin, reducing environmental impact and promoting circular economy principles¹⁵.

Additionally, hybrid nano-systems that combine organic and inorganic components represent an advanced frontier integrating multifunctionality, stability, and biocompatibility, while maintaining eco-friendly synthesis. Examples include polymer-metal oxide nanocomposites such as chitosan silver and alginate zinc oxide nanoparticles fabricated using plant extracts or microbes. These hybrids show potent antibacterial and wound-healing capacities without harmful chemical residues¹⁶. Silica gold nanoparticles merge silica's biocompatibility with gold's photo thermal and bio sensing functions for cancer treatment¹⁷. Polymer-lipid hybrid nanoparticles (PLHNs), combining biodegradable polymers such as PLGA with natural lipids, offer controlled release of hydrophobic drugs with reduced environmental footprint, epitomizing the fusion of functionality, safety, and sustainability in nanomedicine¹⁸.

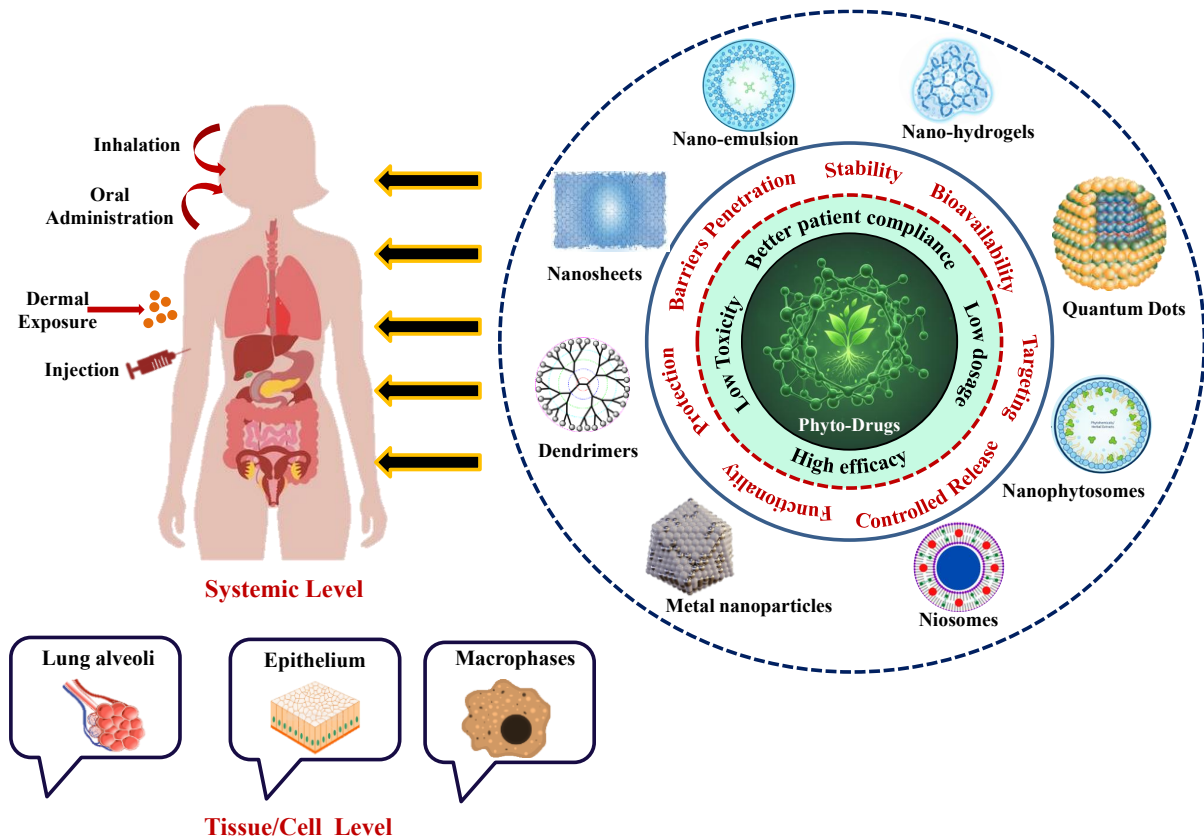


Figure 1: Schematic illustration of nanoparticle-based drug delivery system showing targeted delivery to diseased tissue, enhanced therapeutic efficacy, and reduced systemic toxicity

3. Therapeutic Applications in Gynaecological Disorders:

Nanotechnology based therapeutics have significantly enhanced treatments for gynaecological conditions by improving drug solubility, targeting efficiency, and sustained drug release (Figure 2). The major disease areas benefiting from these innovations are discussed below.

3.1 Leucorrhoea and Vaginal Infections

Leucorrhoea and vaginal infections are commonly caused by bacterial and fungal pathogens, including *Candida albicans* and *Gardnerella vaginalis*. Traditional topical drug administration often suffers from short residence time and poor mucosal absorption. Hydrogel-based delivery systems loaded with antimicrobial drugs, such as metronidazole and clotrimazole, offer sustained release and better mucosal penetration. These hydrogels maintain hydration, enhance adhesion to the vaginal epithelium, and provide effective local concentration¹⁹. Nanostructured lipid carriers and polymeric nanogels can encapsulate drugs for controlled delivery, reducing systemic side effects. Metronidazole-loaded nanogels have demonstrated prolonged activity against bacterial vaginosis, while clotrimazole nano systems improve antifungal action and minimize drug resistance²⁰. Likewise, advanced green-synthesized or plant-based green nano-formulations harness the phytochemicals derived from sources such as *Aloe vera*, *Curcuma longa* and

Azadirachta indica to promote a safe and environmental-friendly treatment solutions for vaginal infections. These nanocarriers with herbal components provide superior antimicrobial properties, allow for healing of the mucosal membranes and provide sustained, localized drug delivery, with minimal toxicity stimulant and restoration of the vaginal micro flora²¹.

3.2 Bacterial Vaginosis and Candidiasis

Bacterial vaginosis and vulvovaginal candidiasis involve microbial imbalance in the vaginal flora. Conventional therapy often leads to relapse due to low retention and incomplete eradication of pathogens. Bio adhesive nano-formulations, such as chitosan-based nanoparticles or mucoadhesive liposomes, provide prolonged contact with mucosal tissues, allowing sustained local drug release. These formulations can deliver antimicrobial or antifungal agents like metronidazole, fluconazole, or plant-derived antimicrobials with higher stability and controlled drug kinetics. Mucoadhesive nanoparticles exploit electrostatic interactions with mucin, enhancing local residence time and improving the overall therapeutic response while limiting systemic exposure^{22,23}.

Additionally, the incorporation of green synthesis into these mucoadhesive systems improves their therapeutic efficacy, safety, and biocompatibility. Green nano-formulations with natural antimicrobials and antioxidants, generated by plants, not only help with infection control,

but also assist with mucosal regeneration and restoration of microbiota equilibrium. Overall, the green synthesis method provides less irritation, more manageable drug release, and better patient tolerance. Therefore, green nanotechnology could be a significant step forward in local therapy for vaginal infections ²⁴.

3.3 Endometriosis

Endometriosis, driven by ectopic growth of endometrial tissue and chronic inflammation, often requires complex hormonal and anti-inflammatory interventions. Conventional oral therapies face challenges of poor bioavailability and systemic toxicity. Nano-formulations offer site-specific drug delivery using biodegradable polymeric nanoparticles, liposomes, or solid lipid carriers. Encapsulation of anti-inflammatory agents such as curcumin or non-steroidal drugs can inhibit prostaglandin synthesis and reduce lesion formation. Hormonal treatments, like nano-encapsulated progesterone, ensure controlled release and improved local efficacy. Moreover, siRNA-loaded nanoparticles targeting inflammatory mediators or angiogenic factors (e.g., VEGF, IL-6 pathways) demonstrate potential for genetic-level control of the disease, reducing recurrence and side effects compared to systemic drugs ^{24,25}.

3.4 Cervical Cancer

Cervical cancer therapy has greatly advanced with nanocarrier-assisted targeted chemotherapy and immunotherapy. Nanoparticles can preferentially accumulate in tumor tissue through the enhanced permeability and retention effect (EPR), minimizing damage to healthy cells. Common strategies include polymeric or lipid-based nanoparticles delivering paclitaxel, cisplatin or doxorubicin directly to cervical tumor cells. Surface modification with ligands like folic acid or antibodies enhances receptor-mediated

targeting²⁶. Additionally, immunotherapeutic nano-systems delivering siRNA or tumor-associated antigens can stimulate antitumor immune responses. Recent studies have demonstrated that green gold, silver and polymeric nanoparticles exhibit potent cytotoxicity against cervical cancer cells by inducing apoptosis, modulating oxidative stress and sensitizing tumors to chemo radiotherapy. When integrated with immunotherapeutic agents or siRNA, these green nano-systems can also enhance immune activation against tumor antigens. Thus, green nanotechnology provides a safer, sustainable, and multifunctional platform for advancing targeted, combinatorial and immune-based cervical cancer therapies ²⁷.

3.5 Polycystic Ovary Syndrome (PCOS)

PCOS management often involves hormonal regulation and metabolic control. However, oral bioavailability and first-pass metabolism limit efficacy for many therapeutic agents. Nano-formulations containing herbal bioactives such as curcumin, resveratrol, or berberine improve solubility and sustained plasma concentration. Similarly, nanoencapsulation of metformin or hormonal agents (like progesterone) provides controlled release and improved ovarian targeting. These herbal or hormonal nano-formulations reduce oxidative stress, modulate insulin resistance, and help restore normal ovarian function ²⁸. Recent research indicated that green-synthesized gold and silver nanoparticles are less toxic and more biocompatible than those produced chemically, while biopolymer-based green nanoparticles were also found to have superior stability, controllable drug release profiles and less inflammatory response in vivo. It has also been shown that green-synthesized nanocarriers have superior antioxidant activity, less environmental impact and validity in scientific and therapeutic safety in sustainable biomedical applications ²⁹.

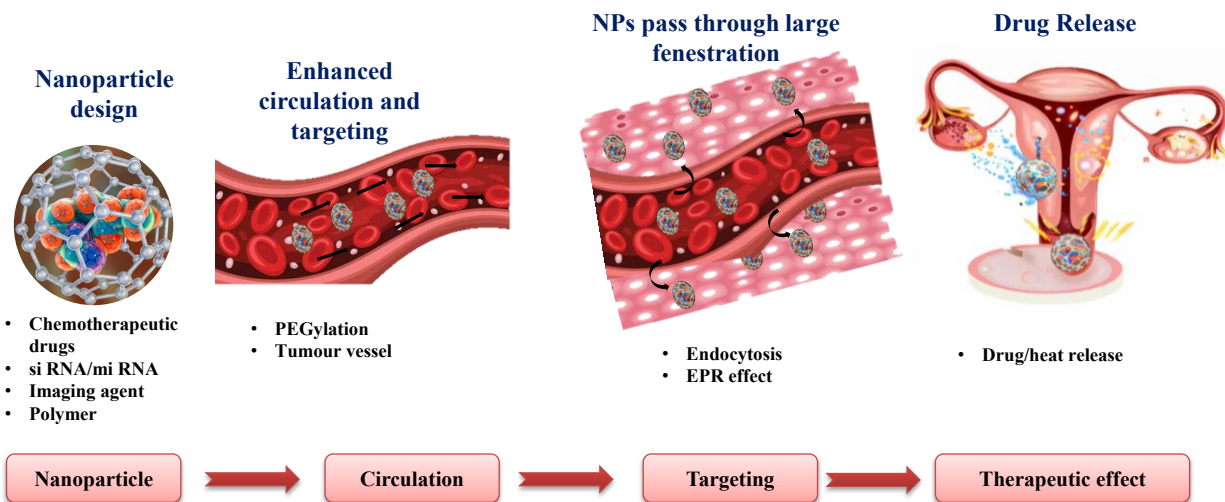


Figure 2: Schematic representation of Nanoparticle design, circulation, targeting and site-specific drug release leading to enhanced therapeutic efficacy

Table 1: Summary of therapeutic agents and corresponding nano-formulation approaches for managing major gynaecological disorders

Condition	Drug/Phytochemical	Nano-formulation Type	Key Outcomes	Ref
Leucorrhoea & Vaginal Infections	Metronidazole, Clotrimazole	Hydrogel, Nanogel	Sustained drug release, better mucosal adhesion, reduced recurrence	19,30
Bacterial Vaginosis/ Candidiasis	Metronidazole, Fluconazole, Chitosan	Bioadhesive nanoparticle, Mucoadhesive liposome	Prolonged retention, enhanced antimicrobial efficacy	30,31
Endometriosis	Curcumin, Progesterone, siRNA	Polymeric nanoparticle, Liposome	Localized anti-inflammatory and anti-angiogenic effect	32,33
Cervical Cancer	Paclitaxel, Cisplatin, siRNA	Lipid nanoparticle, gold nanoparticle, Polymeric micelle	Targeted delivery, reduced toxicity, immune activation	34,35
PCOS	Curcumin, Resveratrol, Metformin	Polymeric nanoparticle, Nano-emulsion	Improved bioavailability, hormone balance, metabolic regulation	36,37

4. Limitations, Challenges, and Future Trends in Green Nanotechnology:

Green nanotechnology provides sustainable solutions for medicine, energy, and environmental cleanup; yet it faces significant scientific and regulatory obstacles that hinder its comprehensive implementation. Its success depends on addressing persistent challenges such as nanoparticle stability, biocompatibility, large-scale synthesis, and ethical governance ³⁸.

Limitations

A major obstacle is nanoparticle stability, which dictates functionality and safety during storage and use. Green-synthesized nanoparticles frequently encounter agglomeration or oxidation as a result of their organic coats, leading to variable physicochemical properties. Furthermore, variability between batches in biological synthesis attributable to the composition of plant extracts, changes in microbial strains, and climatic factors undermines repeatability and constrains industrial scalability. Attaining consistent shape and enduring stability while ensuring environmentally sustainable synthesis is technically challenging ⁶.

The scaling-up challenge is equally pressing. Green synthesis utilizing plants or microbes is economically viable yet time-intensive and produces a limited yield of nanoparticles, rendering it impractical for industrial-scale manufacturing. The purification and quality standards of biologically produced nanoparticles require sophisticated filtration and automation systems, frequently increasing expenses and energy usage. Additionally, ensuring consistent biocompatibility poses difficulties, as natural stabilizers and bio-reducing agents may undergo unpredictable interactions with human cells or microflora, leading to variable toxicity or immunogenicity ³⁹. Ethical and environmental issues present another dimension of

concern. The unregulated utilization of biological resources for nanoparticle synthesis poses concerns regarding sustainability and biodiversity, particularly in areas where rare flora or marine biomaterials are utilized as raw materials. Moreover, despite the designation of "green," nanoparticle residues released into aquatic or terrestrial environments might modify microbial communities and trophic interactions ⁴⁰.

Clinical Translation and Regulatory Supervision

The progression from laboratory-scale research to clinical application is hindered by insufficient *in vivo* data and ambiguous regulatory frameworks. Limited green-synthesized nanoparticles have progressed to preclinical or clinical evaluation owing to inadequate pharmacokinetic and toxicological assessment ⁴¹. Regulatory bodies, including the FDA and EMA, underscore the necessity of thorough safety dossiers in accordance with rules such as FDA's 21 CFR §314 and EMA Directive 2001/83/EC, especially for nano-formulations intended for vaginal or mucosal administration. These frameworks require data regarding local tissue interaction, mucosal irritation, immunological activation, and reproductive safety to guarantee compliance. The lack of common international review standards results in delays in the approval and dissemination of eco-friendly nanomedicines ⁴².

Recent Advancements

Engineers have created stimuli-responsive and self-healing hydrogels from biodegradable polymers like chitosan and hyaluronic acid to mitigate functional restrictions. These hydrogels modify their structure in reaction to environmental stimuli (pH, temperature, light) and release therapeutic ingredients in a regulated manner essential for sustained drug delivery and tissue regeneration. Bio inspired nano-formulations utilizing

phytochemicals such as quercetin or curcumin exhibit enhanced biocompatibility and antioxidant efficacy, merging traditional medicine with nanomedicine ⁴³.

The recent combination of green nanotechnology, artificial intelligence (AI), and 3D bioprinting signifies a new frontier in innovation. AI-driven nano-design models forecast ideal synthesis conditions and toxicity profiles. Concurrently, 3D bioprinting utilizes nanocomposite bioinks infused with living cells to create tissue prototypes and customized drug carriers, propelling advancements in regenerative and reproductive medicine ⁴⁴.

Emerging Trends

The forthcoming years will prioritize responsible innovation that merges technical proficiency with ethical governance. Global initiatives like the UNESCO Green Nano Commons and the EMA "Regulatory Science 2025" agenda emphasize the necessity for interdisciplinary collaboration and open-access information dissemination. Future study will integrate AI-driven nano-informatics with lifetime risk assessment to guarantee standardized, reproducible, and sustainable design of nanomaterials ⁴⁵.

5. Conclusion:

Recent developments in environment friendly nano-formulations have stimulated a new direction in the treatment of gynaecological issues by integrating the principles of nanotechnology, natural product chemistry and personalized medicine. Traditional pharmacological approaches typically have challenges related to low solubility, poor tissue selectivity, limited decomposition and toxic side effects. In contrast, environment friendly and phytochemical-based nano-formulations are safer, more effective and more sustainable options that have the potential to improve therapeutic outcomes, while minimizing toxic effects. These new systems lead to improved drug stability, mucosal adhesion, cell uptake and release profiles for the treatment of localized and sustained desired effects in the female reproductive tract.

Green nano-formulations are synthesized using natural extracts, polysaccharides or bio-surfactants and avoid the harmful organic solvent and toxic reagents used with traditional approaches to nanocarrier formulation, thus providing eco-safety and reduction of potential cytotoxicity. Their antioxidant-rich phytochemical cores provide intrinsic therapeutic benefits by ameliorating oxidative stress, inflammation and microbial dysbiosis, contributing to common underlying factors in bacterial vaginosis, vulvovaginal candidiasis, pelvic inflammatory disease and endometriosis. The synergistic activity of natural bioactives such as curcumin, quercetin, resveratrol and berberine encapsulated in lipid, polymeric or metallic nanocarriers, provides benefits of not only protecting labile molecules from degradation but also enhanced bioavailability in tissue.

Moreover, green nanocarriers possess excellent mucoadhesive properties and have the ability to penetrate

the vaginal epithelium to facilitate deeper drug permeation and retention. The stimuli-responsive nature of green nanocarriers, which can respond to pH, enzymes, or redox gradients, can generate on-demand, site-specific drug release to maximize therapeutic efficacy while minimizing systemic exposure. Moreover, the anti-inflammatory and immune-modulatory properties of specific phytochemical nano-formulations can help restore vaginal microbiome homeostasis and promote healing of the mucosa, allowing for both symptom management and the correction of underlying pathophysiology.

Future interventions include smart vaginal rings and other intra-vaginal delivery platforms that integrate nanocarriers will transform sustained drug delivery to be patient friendly. Combination nano-therapies encapsulating multiple drugs including antimicrobial, hormonal and anti-inflammatory therapies into one comprehensive therapy will adequately address the complexity of multifactorial gynaecological disorders. The introduction of artificial intelligence and machine learning into the design and optimization of nano-formulations will readily predict optimal drug-carrier stability, drug bio distribution and potential therapeutic efficacy, paving the way for enhanced personalized medicine in women's health. Despite successful laboratory studies and fast-track regulatory approval for green nano-formulations, issues associated with large-scale synthesis and long-term biocompatibility and regulatory studies remain barriers to gain acceptance for use in health care. Robust translational and clinical studies will be required to assess pharmacokinetics, toxicology and efficacy in real-world practice. In addition, close collaborations amongst nanotechnologists, pharmacologists, gynaecologists and policymakers will be needed to implement these innovative technologies into standard clinical practice.

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