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Review

Endowed Polyphenols in Advanced Delivery Systems for Vaginal Infections

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Abstract: Vaginal infections (VIs) are the result of the nefarious vaginal polymicrobial universe (i.e., *Gardnerella vaginalis*, *Prevotella* spp., *Staphylococcus* spp., *Candida albicans*, etc.), the inhabitants of which multiply and infect the surface of the vaginal epithelium, which serves as a scaffold for the adhesion of pathogenic poly-complexes with interactive abilities. VIs affect over 1 billion women per year and have a stunning annual relapse rate of 30%. These conditions impact women's quality of life and fertility and cause oncogenic Human Papillomavirus (HPV) persistence. VIs are typically treated with oral (i.e., Flagyl®) and localized drug tablets and creams/gels (i.e., Clindesse®), with potential leakage from the vaginal tract upon administration leading to the failure of the treatment. This study intends to highlight polyphenols as potential therapeutic agents in terms of their benefits and limitations and suggest strategies to increase their effectiveness. Polyphenols are natural compounds rich in phenolic structures which have an impact on this type of pathology and deserve the utmost attention from researchers. Natural polyphenols have several advantages: renewability, biodegradability, low environmental impact, biocompatibility, application versatility, bioactive properties, and the potential for sustainable applications. These compounds, formulated in advanced delivery systems, may natively exhibit antioxidant, anti-inflammatory, and antimicrobial activities. The main objective of this review is to highlight the importance of researching new and effective formulations to prevent and treat VIs based on natural, controlled, and sustainable systems.

Keywords: bioactive compounds; sustainability; encapsulation; vaginal infections

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1. Introduction

The persistence of oncogenic HPV infection contributes to the development of cervical cancer (CC), which is the fourth most common among women, with a 50% mortality rate [1]. Current vaccines may prevent this cancer type. However, they are not accessible to most girls and young women in low- and middle-income countries, and the number of infections is still devastating. Withal, pathophysiological changes in the cervicovaginal microbial communities are HPV-partakers and are largely neglected worldwide. In the vaginal ecosystem, health is associated with low microbial diversity and the prevalence of *Lactobacillus* species. Vaginal infections (VI) result in pathogenic microbial overgrowth, such as *Gardnerella vaginalis*, *Atopobium* spp., and *Prevotella* spp., species also closely related to multiple sexually transmitted infections (STI) (i.e., HPV, herpes, and human immunodeficiency virus (HIV) [2].

Polyphenols are bioactive compounds derived from plants which have multiple functional properties, making them extremely valuable in pharmacology [3]. Particularly, in VIs, the impact of polyphenols is striking. This is related to the following vital biological properties: (i) antimicrobial properties, since these compounds may help inhibit the growth

and adherence of harmful bacteria in the vaginal environment; (ii) anti-inflammatory properties, which may help modulate the inflammatory process, potentially reducing symptoms associated with VIs; (iii) vaginal microbiota modulation, since polyphenols may influence the composition of the vaginal microbiota by promoting the growth of beneficial bacteria and inhibiting the proliferation of pathogenic bacteria, which could contribute to restoring a healthier balance in the vaginal microbiota; (iv) immunomodulatory effects, which may contribute to a more effective immune response against bacterial infections, including those associated with VIs [4]; and (v) the prevention of biofilm formation, which may interfere with the formation of bacterial biofilms. Biofilms can protect bacteria from antibiotics and the immune system, so inhibiting their formation may enhance the effectiveness of VI treatments [5]. In recent years, there has been a growing focus on the properties and extraction methods of certain molecules that can be used as safe and cost-effective alternatives to synthetic compounds [6,7]. This increased attention has resulted in the identification of numerous plant sources rich in polyphenols, including grapes [8], cranberries [9,10], black currants [11,12], chokeberries [10,13], and olives [14], among others.

Nevertheless, despite all its benefits and functional activities, the industrial production and commercialization of polyphenol-based products face numerous challenges. Due to the rapid degradation of polyphenols, advanced techniques such as nano- and microencapsulation are required to preserve their health benefits. These challenges are compounded by the high costs of extraction and purification, as well as the limited amount of research on their long-term stability. Additionally, regulatory hurdles stemming from their natural origins further impede market advancement. These factors complicate the commercial development of polyphenol-containing products, despite their recognized health value. However, future advancements in encapsulation technologies and a better understanding of polyphenol bioavailability may offer solutions to these issues.

In this review, the authors will provide an overview of what is currently known regarding the vaginal microbiome and the application of polyphenols in the treatment of vaginal-associated infections, making use of advanced delivery systems.

A PubMed search was conducted to determine the number of articles published under the following entry words: "(vaginal infections) AND (polyphenols)". The search results are presented in Figure 1. According to the data collected, there has been an increase in research involving polyphenols and their applications in vaginal-related infections. Nevertheless, if all papers on this subject are considered, the number is still low, with 19 publications since 2011. Another search was carried out regarding the number of publications that included the words "(vaginal microbiome) AND (polyphenols) AND (infections)", with a total of zero entries, which provides a good indication that this subject is still quite unexplored. Therefore, this review provides background insight into a subject that can soon be widely studied.

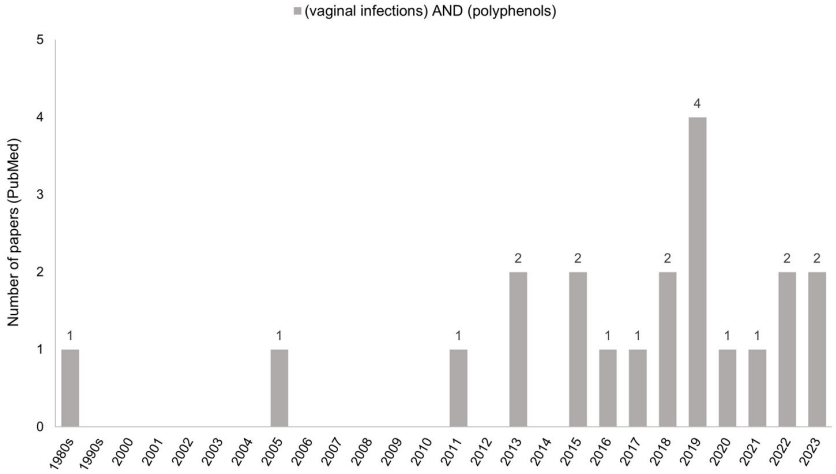

Figure 1. Number of papers included in the PubMed database related to VIs and polyphenols, according to the presented search words (search date: July 2024).

Integrating polyphenols into delivery systems aligns with the growing demand for sustainable healthcare solutions. This review emphasizes the potential of polyphenols, not just for their direct therapeutic benefits, but also for their role in pioneering environmentally friendly and patient-centered approaches. By exploring controlled and innovative delivery mechanisms, such as nanoparticles, liposomes, and hydrogels, the review aims to highlight the importance of continued research in developing next-generation formulations that are both natural and effective for managing VIs.

2. Methodology

2.1. Study Design

This review offers a comprehensive examination of the different types of VIs and their most used treatments. The primary aim of the review is to highlight the known potential of polyphenols and suggest their use, particularly when encapsulated, as a novel treatment option for these infections.

2.2. Data Collection

Data were gathered through an organized exploration of English-language publications in databases such as PubMed, Scopus, Google Scholar, and Web of Science. The following keywords were employed during the search: "Phenolic compounds", "Circular economy", "Sustainability", "Vaginal infections", "Encapsulation", "Vaginal microbiome", "Antimicrobial activity", and "Advanced systems". All relevant articles and abstracts published within the last five years were included in this review. The selection was based on their alignment with the review's scope and objectives, with an emphasis on studies offering detailed insights into polyphenols, their pharmacological effects, and mechanisms of action. In total, about 100 articles were incorporated into the analysis.

Furthermore, the key polyphenols discussed in this review are listed below in Figure 2. This figure provides a visual representation of the primary polyphenols analyzed, tannic acid ($C_{76}H_{52}O_{46}$), quercetin ($C_{15}H_{10}O_7$), gallic acid ($C_7H_6O_5$), (-)-epicatechin ($C_{15}H_{14}O_6$) and trans-resveratrol ($C_{14}H_{12}O_3$).

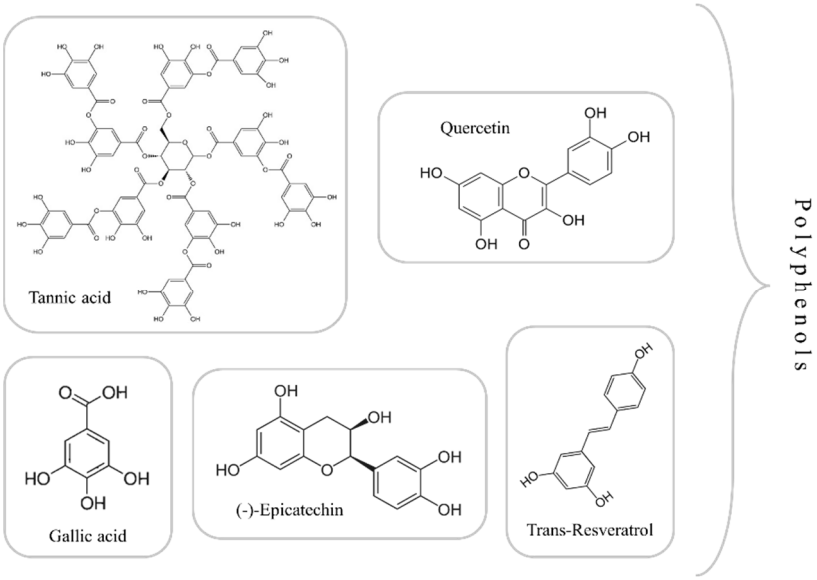

Figure 2. Main polyphenols covered in this review.

3. Vaginal Microbiome

The vaginal microbiome is a crucial component of the female body's microbiome and plays a significant role in maintaining vaginal and reproductive health [15]. It is involved in maintaining its homeostasis and equilibrium. The species within the vaginal microbiome are mutually interdependent and controlled by various factors, such as local immunity, the

endocrine system, and the internal environment [16]. Disruption in this balance can lead to dysbiosis, which is associated with various adverse health outcomes, including bacterial vaginosis (BV), preterm birth (PTB), and increased risk of STIs [17,18]. The vaginal microbiome consists of a diverse array of microorganisms, where the host provides the bacteria with nutrients needed to support their growth, and, in exchange, they play a protective role in preventing colonization of the host by potentially pathogenic organisms [19].

Culture-independent methods primarily relying on the examination of 16S rRNA gene sequences are employed to identify microbial diversity [20]. By utilizing this approach, researchers have been able to determine that vaginal communities are primarily governed by *Lactobacillus* spp., responsible for around 73% of its microbiota, and the more prevalent species were *L. crispatus*, *L. iners*, *L. gasseri*, and *L. jensii* [19].

Lactobacilli convert glycogen from exfoliated epithelial cells into lactic acid, keeping the vaginal pH of healthy women of reproductive age acidic (pH between 4 and 5), which inhibits the growth of pathogenic microorganisms [19,20]. They also exhibit antimicrobial properties beyond the effect of lactic acid production, such as producing target-specific bacteriocins. The vaginal microbiome, and consequently the pH, varies by age, menstrual cycle stage, the occurrence of infection, and sexual arousal. Menstrual, cervical, and uterine secretions, and sperm act as alkalizing agents and raise the pH. Changes in hormone levels (particularly estrogenic) during the menstrual cycle cause changes in epithelial cell layer thickness, intercellular channel width, pH, and secretions [21].

Contrary to previous beliefs associating a "healthy" and "normal" vaginal microbiome with the predominance of *Lactobacillus* spp. [22], recent studies have revealed that 20% to 30% of healthy women carry vaginal communities where lactobacilli are not significantly present. Instead, these communities consist of a diverse range of facultative or strictly anaerobic bacteria, such as *Atopobium*, *Corynebacterium*, *Anaerococcus*, *Peptoniphilus*, *Prevotella*, *Gardnerella*, *Sneathia*, *Eggerthella*, *Mobiluncus*, and *Finegoldia*, among others [19,23]. These microorganisms possess the ability to sustain functional vaginal ecosystems by preserving lactic acid production, and some of them can engage in either homolactic or heterolactic acid fermentation [24].

Understanding the vaginal microbiome and its role in maintaining vaginal equilibrium is crucial for promoting women's health and reproductive well-being.

4. Vaginal Infections

VIs are highly prevalent among adult women, specifically of reproductive age, ages varying between 15 and 49 years old [25,26], and are frequently encountered in clinical practice. Most women experience symptoms associated with vaginal problems, including discharge, itching, and odor. These symptoms can be distressing and embarrassing, often prompting women to seek healthcare assistance. Worldwide, it is estimated that approximately 5-10 million medical appointments per year are specifically attributed to vaginal symptoms. The primary culprits behind these symptoms are typically three types of infections: BV, trichomoniasis, or vulvovaginal candidiasis (VVC). These account for over 90% of vaginitis cases and the remaining cases are due to other poorly defined entities [26].

4.1. Bacterial Vaginosis

BV is the most common VI among women of childbearing age and the prevalence of symptomatic and asymptomatic BV varies depending on the population studied. It is commonly diagnosed in women seeking gynecologic care, especially in STIs. Pregnant and sexually active women also have a higher risk [26].

The exact cause of BV remains uncertain, but it is widely recognized that the primary factor is an excessive proliferation of anaerobic bacteria such as *Gardnerella*, *Mycoplasma*, and *Mobiluncus* species [26]. This overgrowth occurs due to factors like increased substrate availability, elevated pH, and, most importantly, the absence of the normal *Lactobacillus* bacteria that typically inhabit the vagina. The absence of *Lactobacillus* leads to reduced hydrogen peroxide production, which normally helps inhibit the growth of harmful pathogens [27].

There is a correlation between the excessive proliferation of anaerobic bacteria and elevated production of trimethylamine, the specific compound responsible for the unpleasant fishy odor commonly associated with BV [28].

Clinical features of BV include vaginal malodor and an abnormal discharge, especially noticeable after intercourse [29]. Nonetheless, up to 50% of women with BV may be asymptomatic [30]. Diagnosis is based on objective criteria, including the presence of clue cells on microscopy (exfoliated epithelial cells covered with *G. vaginalis*), a positive sniff/whiff test on the addition of 10% KOH, vaginal pH above 4.5, and an adherent greyish-white discharge [29]. Wet-mount examination and Gram staining are also useful in confirming the diagnosis [30].

4.2. Vulvovaginal Candidiasis

VVC is the most common clinical disease caused by *Candida* spp. and the second most common VI after BV [31]. VVC is thought to affect around 75% women of childbearing age [32], and around half of all college women by age 25, with 50% having a second reoccurrence [31,32]. Also, it has been reported that around 7% of women will develop recurrent VVC [33], defined as three or more symptomatic episodes within 1 year [34]. VVC includes the spectrum of symptomatic and asymptomatic patients, both fostering the development of positive cultures. The symptoms vary with the host's response and the infectious organism [31].

Between 85 and 90% of yeasts isolated from women with VCC are *Candida albicans* strains [35]. This highly versatile pathogen can adapt its growth to several physiological extremes, and it also possesses several genes that encode proteins that increase its virulence through host recognition and binding to the host cells, such as ALS1, HWP1, and INT1, whose proteins provide adherence, and MTN1; strains without this gene in vivo were avirulent [36]. Another protein with significant virulence is candidalysin toxin, which is encoded by the ECE1 gene. Previous research has shown that this gene is regulated in a highly complex way by multiple transcription factors. However, intraspecies heterogeneity is extremely significant to strain-dependent pathogenicity and the virulence mechanisms employed by natural isolates are neglected. Data from previous reports underlined that the capacity to induce damage is linked to neutrophil migration. The *ECE1* expression alone does not serve as a substitute of a pathogenicity indicator, as ineffective candidalysin secretion would likely impact pathogenicity. Therefore, the variant of ECE1 may also contribute to the reduced pathogenicity associated with *C. albicans* [37]. The remainder is other species, the most common of which are *C. glabrata* (formerly known as *Torulopsis glabrata)* and *C. tropicalis* [38]. Some of these species possess the ability to cause vaginitis, often more resistant to conventional therapy than *C. albicans* [30].

VVC is more common and harder to eradicate during pregnancy [31], due to the higher incidence of vaginal colonization, increasing from 9% in the first trimester to 54% in the third trimester [39]. This is most likely due to the higher contents of glycogen and carbon derived from higher levels of reproductive hormones, which are valuable resources for *Candida* growth and germination [30]. Other factors that increase the prevalence of VCC are high-estrogenic-containing oral contraceptives [31], the use of tight, poorly ventilated clothing, which increases perineal moisture and temperature [30], and the systemic use of antibiotics, mainly tetracycline, ampicillin, and cephalosporin, which end up eliminating the protective vaginal microbiota [30].

As stated before, the symptoms of VCC vary, but some clinical signs and symptoms include vulvovaginal pruritus, irritation, soreness, burning or micturition, and whitish, cheesy discharge. Most cases of VCC are detected by self-diagnosis, which is the basis for purchasing over-the-counter antimycotics [31]. Laboratory diagnosis methods include a latex agglutination slide technique, microscopic examination of vaginal secretions, or a 10% KOH preparation (whiff test) [30].

4.3. Trichomonal Vaginitis

Trichomoniasis is a common global infection, with an estimated annual distribution of approximately 170 million cases of trichomonal vaginitis. In the United States, it is estimated that 2 to 3 million women contract symptomatic trichomoniasis each year [40].

The disease is caused by the pathogenic parasite *Trichomonas vaginalis*, an anaerobic protozoa, which can cause cervicitis and urethritis [40]. The parasite is primarily transmitted through sexual activity, causing around 70% of male sexual partners of infected women to show its presence [41]. Thus, the use of non-barrier methods of contraception is significantly associated with trichomoniasis [42]. This parasite requires many essential nutrients for growth, and these are found in the vagina and vaginal secretions [43], e.g., an increase in iron salts (largely present in menstrual blood) facilitates overgrowth and clinical worsening of trichomoniasis symptoms [44]. The parasite can also obtain nutrients by digesting bacteria, such as through phagocytosis of *Neisseria gonorrhoeae* [45].

Due to the vague character of the clinical presentation and its overlap with the clinical signs of other STIs, the diagnosis of trichomoniasis based solely on clinical features is insufficient. It ranges from asymptomatic, up to 50%, to severe acute inflammatory disease. Most common symptoms that affect up to half, and sometimes more, women that report having trichomoniasis include vaginal discharge, malodorous or not, pruritus, dyspareunia, and dysuria. Less common symptoms are lower abdominal discomfort, vulvar erythema, and "strawberry cervix" (punctate hemorrhages visible to the naked eye) [30].

As previously mentioned, trichomoniasis is difficult to diagnose through clinical features, as they are not specific only to this infection. pH values greater than 4.5 are present in 90% of cases, and a fishy odor after the smell test is present in 50% of cases, but these are not specific symptoms of trichomoniasis. A better solution to differentiate this pathology from BV is through polymorphonuclear cells (PMNs). The ratio of PMNs to vaginal epithelial cells in BV is less than 1 in over 90% of cases, while for trichomoniasis, this ratio is greater than 1 in 75% of infections. Additionally, a microscopic evaluation is another valuable approach, as the direct observation of *Trichomonas* can detect 60–80% of cases. However, the standard method for diagnosis is Diamond's media culture, which can detect 95% of cases [46,47].

4.4. Aerobic Vaginitis

Aerobic vaginitis (AV) is a more recently discovered non-classifiable pathology that differs from BV [48]. Similar to other VIs, AV is characterized by an imbalance in the vaginal microbiota, leading to a change in the environment pH. However, it is unclear if this is the cause or a derivation of AV. Some studies propose that the disease is an immunological disorder due to the existence of inflammation and the presence of immature epithelial cells. Overall, the microbiota present in AV consists of commensal aerobic microorganisms originating from the intestines, which include *Escherichia coli*, *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus agalactiae*, and *Enterococcus faecalis*. The prevalence of AV ranges between 7 and 12% [49].

Despite being comparable to BV, these two should not be confused. AV is characterized by an objective abnormal yellow vaginal discharge, foul smell, elevated pH (>5), vaginal dyspareunia, vulvovaginal itching, and cervical erosion [48].

Diagnosis is made through microscopic examinations with fresh wet mounts and the severity of AV is defined using five different criteria, each rated as absent (0 points), moderate (1 point), or severe (2 points), and the sum of the points determines the diagnosis of AV. These criteria are lactobacillary grades (LBG), number of leukocytes, proportion of toxic leukocytes, background microbiota, and proportion of parabasal epitheliocytes [50].

4.5. Microbial Biofilm

The relapse of these conditions in an individual is a common occurrence, where even after multiple cycles of antibiotic therapy, the infections are not completely irradicated. This is primarily caused by the main pathogens in the diseases, such as *C. albicans* in VCC

and *G. vaginalis* in BV, which use biofilm formation as a major strategy in initiating and maintaining infections [51,52].

A microbial biofilm is formed when a surface is colonized by microorganisms which then produce an extracellular matrix that provides resistance, faster signalling among cells, and better nutrient circulation [53]. This makes it much harder for the antimicrobials to kill the biofilm [54]. After increasing in size, the biofilm's inner cells disperse and establish themselves in other locations, beginning new infections.

There have been many studies performed on novel treatments for these biofilms due to the low efficacy of Food and Drug Administration (FDA)-approved therapies [53]; however, more research is needed to expand these treatment options.

5. Oral Medication Versus Topical Application

Contrary to urinary infections, in which the first line of medication is oral antibiotics (i.e., nitrofurantoin, fosfomycin or trimethoprim/sulfamethoxazole) [55], topical treatments of VI have shown to be at least as effective as an oral treatment in most cases, thus resulting in higher local drug concentrations and fewer drug interactions and adverse effects (Table 1) [56]. However, for recurrent symptoms, oral antibiotics, and maybe simultaneously medication, are inevitable.

Each of the most common VIs has different clinical and pathological characteristics that have a significant impact on the efficacy of topical treatments and the development of effective topical approaches. A common occurrence is infection with several pathogenic microorganisms. This not only causes diagnostic difficulties, but also increases the risk of failure to treat a hidden overlapping problem, explaining the persistence of symptoms after a supposedly adequate treatment regimen for the identified clinical entity. Furthermore, the emergence of chemotherapeutic-resistant bacteria and the difficulties in managing infection recurrence underscore the need for more effective local treatments [56].

The therapeutic efficacy of conventional drugs can be improved by using formulation strategies that improve drug retention, solubility, and distribution in the vaginal tract, while also promoting drug interaction with pathogens and aiding in the recovery of the regular vaginal environment. To achieve these objectives, researchers must consider not only the physical and chemical properties of the drug and the overall formulation but also the specific features of the physiological environment that will be met after administration [56]. The amount, composition, microbiome, and pH of vaginal fluid are expected to influence the performance of vaginal drug delivery systems, as demonstrated in formulations subjected to physiologically simulated conditions [57–59].

There are several types of treatments for VIs (Table 1), including short-duration therapies. Yeast infections are often treated effectively with antifungal agents over a period of three to seven days. Common antifungal treatments include miconazole and clotrimazole, which are available in various forms such as creams, suppositories, and tablets. Some of these medications, like miconazole creams and clotrimazole pessaries, are available over the counter, while others, like fluconazole or butoconazole, may require a prescription. Brands like Vagisil® and Gino-canesten® also offer widely used products containing these active ingredients. The rise of resistance to existing antifungal and antibacterial treatments underscores the growing need for new therapeutic approaches in managing VIs.

Table 1. Active ingredients for VI treatment.

Active Ingredient	Indications	Dosage Form	Mechanism of Action	Reference
Clotrimazole	VVC	Cream, Tablet, Pessary	Inhibits ergosterol synthesis in fungal cell membranes, disrupting cell integrity.	[60,61]
Miconazole	VVC	Cream, Suppository	Inhibits fungal cell membrane synthesis by blocking ergosterol production.	[62,63]
Metronidazole	BV, Trichomonal vaginitis	Gel, Oral, Tablet	Disrupts DNA synthesis in anaerobic bacteria and protozoa.	[64,65]
Tinidazole	BV, Trichomonal vaginitis	Oral Tablet	DNA synthesis inhibition in anaerobic organisms.	[66,67]

Table 1. *Cont.*

Active Ingredient	Indications	Dosage Form	Mechanism of Action	Reference
Fluconazole	Recurrent VVC	Oral Tablet	Inhibits ergosterol synthesis, leading to fungal cell death.	[68,69]
Butoconazole	VVC	Cream	Inhibits fungal cell membrane ergosterol production, disrupting fungal growth.	[70,71]
Nystatin	VVC	Vaginal Tablet, Cream	Binds to sterols in the fungal cell membrane, causing leakage of cell contents.	[72,73]
Clindamycin	BV	Cream, Gel, Oral Tablet	Inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit.	[74,75]
Boric Acid	Recurrent VVC	Vaginal Suppository	Acidifies the vaginal environment, making it hostile to fungal growth.	[76,77]
Estradiol/Conjugated Estrogens	AV	Cream, Tablet, Ring	Restores vaginal tissue by increasing epithelial cell growth and pH balance.	[78,79]

Recent research on VI treatment strategies includes the development of more appropriate drug delivery systems for well-established drugs, with a special focus on improving the distribution, retention, and acceptability of formulations [80,81], some of which allow modulation of drug release, prolonged activity and reduced toxicity [56].

Antimicrobial-resistant bacteria are of high concern and earmarked for surveillance, according to the Centre for Intervention Science in Maternal and Child Health (CISMAC). Those include extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant bacteria, macrolide-lincosamide-streptogramin B-resistant, vancomycin-resistant *S. aureus* (VRSA). Suppose these bacteria are present in the female vaginal tract; in that case, they can be passed to newborns, resulting in local or systemic infections that are difficult to treat with currently available antimicrobials. Up-to-date information on the prevalence of colonization with major antimicrobial-resistant organisms is required to design successful treatment options [82].

6. Polyphenols as Antimicrobial Agents

Over the last 70 years, antibiotics have proven to be valuable drugs in treating bacterial infections [83]. However, their great availability has caused a general misuse, most commonly, extensive and unregulated use. This behavior, in turn, has given rise to new strains of multi-drug-resistant organisms (MDR), more problematic than the original ones [84]. These include methicillin-resistant *S. aureus* (MRSA), whose incidence in US intensive care units rose from 2% in 1974 to 64% in 2008 [85]. Regarding multi-drug-resistant *E. coli*, in a 2012 study, MDR was present in 92.2% of *E. coli* (n = 232) isolates from Khartoum state, Sudan [86]; in a previous study in 2000, it was 58% [87]. This bacterial resistance normally occurs by genomic mutation or through the acquisition of new genetic information that encodes resistance elements [84]. Almost 20 years after the discovery of penicillin, 50% of all *S. aureus* were penicillin-resistant, and around 10 years later, that number rose to almost 80%. Methicillin was released in 1960, and only one year later, the first strains of MRSA were discovered [88,89]. Clindamycin, an antibiotic used to treat BV, has been shown to create a path for clindamycin-resistant anaerobic bacteria; in a study performed on 48 women, from whom 1059 anaerobic bacteria isolates were obtained, 53% of these demonstrated resistance after therapy [90].

Thus, with an ever-growing concern over antibiotic-resistant microorganisms, the scientific community started researching new compounds with antimicrobial activity. Plant extracts have been part of human health for centuries, with the earliest findings of the use of medical plants dating up to 4000 B.C. Although these medicines may be efficient for the treatment of diseases such as urinary tract infections (e.g., *Arctostaphylos uvaursi*) and tuberculosis infections (e.g., oils of *Hydrastis canadensis)*, very few are regulated as antimicrobials [84].

Plants, when under stress, on tissue disruption or pathogen attack, produce various phytochemical compounds as a defense mechanism. These secondary metabolites include

phytoalexins, polyphenols such as alkaloids, flavonoids, phenolic acids, and other products [84]. Polyphenols, or "plant phenols", are divided into many classes, with the main ones being phenolic acids, flavonoids, stilbenes, phenolic alcohols, and lignans [91]. Each of these classes has its base molecular structure and therefore its mechanism of action against microorganisms. These include binding to cell wall proteins, leading to loss of functions, enzyme inhibition, and interaction with substrates, leaving them unavailable to the microorganism, among other effects [92].

The number of plant species that exist and the number of plants to be described is not agreed upon, but speculations lie around 250,000–280,000 of the former and 50,000–70,000 of the latter [93]. Additionally, with different secondary metabolites produced by each plant species ranging from 500 to 800, the world of potential therapeutic products derived from these compounds is very large [84]. Several studies are being conducted on polyphenols and their correlation with antimicrobial and antioxidant activities [94–96]; however, more discoveries must be made.

6.1. Quercetin

Quercetin (3,3,4,5,7-pentahydroxyflavone), first isolated in 1936 by Szent-Gyorgyi, belongs to the flavonoid subclass of flavonols, and it is found in several fruits and vegetables. The highest quantities of quercetin can be found in onions, asparagus, and red-leaf lettuce, while the lower ones are found in broccoli, green peppers, peas, and tomatoes [97,98]. Various medicinal plants, like *Hypericum perforatum* and *Ginkgo biloba*, also contain quercetin [99]. This polyphenol is one of the most studied [97], mainly due to its identified biological properties, such as antioxidant, anticancer, antimicrobial (antiviral, antibacterial, antifungal), and anti-inflammatory activities [97–100]. Furthermore, and highly relevant, the United States FDA has granted quercetin GRAS (Generally Recognized As Safe) status [99].

Particularly, regarding antimicrobial activity, a large variety of bacterial strains are susceptible to quercetin. Its solubility and interaction with the bacterial cell membrane have both been connected to this biological property [99]. The bactericidal action of quercetin is generally less effective against Gram-negative bacteria than against Gram-positive [101]. Similar results have been observed for some quercetin derivates [102]. A study by Shu et al. (2011) showed that *Streptococcus mutans*, *Streptococcus sobrinus*, *Lactobacillus acidophilus*, *Streptococcus sanguis*, *Actinobacillus actinomycetemocomitans*, and *Prevotella intermedia* were inhibited by quercetin, with minimum inhibitory concentrations (MICs) ranging from 1 to 8 mg/mL [103]. *S. aureus* (including MRSA and MSSA (methicillin-sensitive *S. aureus*) [104]) and *Pseudomonas aeruginosa* were likewise susceptible to the inhibitory effects of quercetin at MIC levels of 20 μg/mL [105]. Moreover, *Candida* spp. [106], *C. albicans* and *Saccharomyces cerevisiae* [104] have all been shown to be susceptible to quercetin antifungal effects.

6.2. Resveratrol

Resveratrol (3,4′,5-trihydroxystilbene), first isolated in 1939 by Takaoka from *Veratrum grandiflorum* O. Loes (root of the white hellebore) [107], is a member of the stilbene family [4], and it is commonly found in red fruits and berries, specifically in grape pulp, skin, seeds, and stems [108], being produced in response to environmental stress [109]. Its basic structure is composed of two phenolic rings linked together by a double styrene bond, with the molecular formula $C_{14}H_{12}O_3$, which results in 3,5,4′-trihydroxystilbene. This double bond is responsible for resveratrol isomeric cis- and trans-forms. It is worth noting that the trans-isomer is the more stable form from a steric point of view [110]. This polyphenol is widely explored due to its biological properties, such as antioxidant, antimicrobial (antiviral, antibacterial, antifungal), anti-inflammatory, immunomodulatory, antidiabetic, wound healing, and neuroprotective activities [4,108,109,111,112]. Furthermore, resveratrol's anticancer effects have been extensively explored since the initial report in the prestigious journal 'Science' in 1997 [113]. The accumulated results indicate that it might be a potential agent for the prevention and treatment of numerous cancers, including breast, cervical, uterus, skin, stomach, kidney, and liver cancers [112,114–116]. Moreover, this polyphenol is considered safe and well-tolerated [111,117].

Regarding resveratrol's antimicrobial activity, its antifungal effect is generally stronger than its antibacterial action [117]. For example, it inhibited the fungal species *C. albicans*, *Saccharomyces cerevisiae*, and *Trichosporon beigelii*, with MICs ranging from 10 to 20 μg/mL [118]. For some bacteria species, resveratrol only has a growth inhibitory effect at doses > 100 μg/mL. For instance, Gram-positive pathogens such as *S. aureus* [119–122] and *Enterococcus faecalis* [119,121] present MICs around 100–200 μg/mL, while Gram-negative ones, such as *E. coli*, *Klebsiella pneumoniae*, and *P. aeruginosa* [119,121,122], being less susceptible, present MICs superior to 200 μg/mL.

6.3. Gallic Acid

Gallic acid (3,4,5-trihydroxybenzoic acid), first discovered in 1786 by Carl Wilhelm [123], is a secondary metabolite that occurs in several plants, vegetables, nuts, and fruits. It has the chemical formula $C_7H_6O_5$, and it is composed of one benzene ring with three contiguous OH groups at the 3, 4, and 5 positions, as well as one carboxyl group at position 1. This polyphenol is nowadays considered of great importance due to its vast range of biological properties [123], mostly imparted by the hydroxyl groups [100], comprising antioxidant, anti-inflammatory, anti-dengue, anti-platelet, anti-apoptotic, antimicrobial, anti-arteriosclerosis, anti-tumor and anti-cancer activities [100,123–125]. Gallic acid was also found to decrease melanogenesis to overcome pigmentation and protect cells from UV-B or ionizing irradiation, which is why it is employed as an essential ingredient in many cosmetic formulations [126]. Furthermore, this compound also holds GRAS status, granted by the FDA [127].

Concerning the antimicrobial properties of gallic acid, it is thought to be active against microorganisms due to the three hydroxyl groups in its molecule, as mentioned before. It was demonstrated [128,129] that this polyphenol has antimicrobial action against the following bacteria: *Salmonella typhimurium*, *E. coli*, *S. aureus*, *Listeria innocua*, *Helicobacter pylori*, *Campylobacter* spp., and *Pseudomonas*. According to these studies, gallic acid has the capacity to degrade bacterial cell membranes, which leads to irreversible permeability alterations, rupture, hole formation, and a decrease in negative surface charge. The leakage of vital intracellular components is a result of this activity. Moreover, some reported MICs range from 0.5 to 8 mg/mL for *E. coli*, *Streptococcus mutans*, *P. aeruginosa*, *S. aureus* and *Listeria monocytogenes* [130–132].

6.4. Tannic Acid

Tannic acid, first identified in 1795, is a hydrolyzable polyphenolic molecule found in almost every aerial plant tissue, both herbaceous and wood types [133]. The molecular structure is not yet fully clarified; it is described as consisting of a central glucose molecule with ten gallic acid molecules attached to it [134]. It is worth noting that the natural source of the compound has a big impact on its phenolic composition, i.e., tannic acid from oriental nutgalls has less penta- and hexagalloyl esters, leading to higher molecular weight, while tannic acid from Turkish nutgall has a predominance of penta- and hexa-esters, and thus a lower molecular weight [135].

For the last century, this phenolic acid has been used for a variety of applications, such as the manufacture of ink, printing fabrics, photography, or as a coagulant in rubber production [135]. Due to its various unique properties, this compound has been subjected to extensive research, including its antiviral and antimicrobial activities. It can inhibit the adhesion of viruses and bacteria to surfaces, as well as interfere with the metabolism of both Gram-negative and Gram-positive bacteria and viruses [136]. Some of the microorganisms for which tannic acid has antimicrobial activity include *E. coli* [95,137], *S. aureus* (MSSA and MRSA) [138,139], and *C. albicans* [140]. Furthermore, it also possesses antioxidant properties, as demonstrated by the formation of complexes with Fe(II), inhibiting the participation in Fenton reactions [141].

6.5. Epicatechin

(-)-Epicatechin ((2R,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol) is part of the flavonoid subclass of flavon-3-ols [142,143]; it was discovered in 1948 and it is primarily found in both green and black tea. It is present in lower amounts in berries, common fruits, cocoa, and many non-alcoholic drinks [144]. Its molecule is composed of two benzene rings, with two hydroxyl groups each, and a dihydropyran heterocyclic ring with a hydroxyl group in carbon 3 [144,145]. The presence of a chiral center in positions two and three of the plant-derived flavon-3-ol led to four diastereoisomers: (+)-epicatechin, (-)-epicatechin, (+)-catechin, and (-)-catechin [142,146]. The compound has drawn considerable attention, and it has been explored for its biological properties, such as antioxidant, antimicrobial, anti-inflammatory, anti-tumor, anti-diabetic, and cardioprotective activities [4,142,144].

Regarding antimicrobial activity, epicatechins originating in the plant *Saraca indica* have shown antibacterial activity against a variety of multidrug-resistant pathogens, including *S. aureus* [147]. This polyphenol and its derivates inhibit antibiotic efflux pumps in *S. aureus*, which is resistant to penicillin, erythromycin, methicillin, and clindamycin, with MIC values between 32 and 512 μg/mL, according to different publications [147–149]. Another study by Li et al. (2022) [150] reported the antimicrobial activity of (-)-Epicatechin-3-gallate (a derivate) against *L. monocytogenes*, *P. aeruginosa*, *Bacillus cereus*, and *S. aureus*, with MICs ranging from 375 to 500 μg/mL.

7. Polyphenols in Advanced Systems

As mentioned previously, pathogens such as bacteria, fungi, parasites, and viruses cause infectious diseases, and the number of patients identified with resistant microbial infections is increasing [151]. Unfortunately, bacteria that are resistant to standard antibiotics have emerged rapidly over the past few decades, resulting in 700,000 global annual deaths, of which over 200,000 are infants [152]. In this regard, alternative bio-derived products have been employed as a potential strategy to fight infectious diseases. Specifically, polyphenolic compounds have been explored as antibacterial agents, and previous reports indicate efficacy for treating several of these microbial infections (reviewed in [153]). However, due to their physicochemical features and typically limited water solubility, polyphenolic delivery has been challenging. In this context, several innovative drug delivery methods can provide some advantages, such as improved bioavailability and controlled release of polyphenolic compounds [154]. Drug delivery systems can be defined as techniques where materials are employed to deliver therapeutic agents to specified targets in a regulated or controlled manner [155].

Joraholmen et al. (2020) [111] developed an advanced delivery system consisting of resveratrol-loaded liposomes incorporated in a chitosan hydrogel, for the treatment of *Chlamydia trachomatis* infection. In this study, both free resveratrol and resveratrol liposomes inhibited *C. trachomatis* proliferation. Nonetheless, the effect was higher when incorporated into the mentioned delivery system, with inhibition of 78% and 94% for 1.5 and 3 g/mL resveratrol, respectively, compared to 43% and 72%, for free resveratrol at the same concentrations. Furthermore, resveratrol liposomes in hydrogel demonstrated a potent anti-inflammatory effect in vitro, inhibiting nitric oxide (NO) generation in LPS-treated macrophages (RAW 264.7 cells), in a concentration-dependent manner.

In 2019, Joraholmen and colleagues [4] performed similar work, developing a delivery system comprising resveratrol- or epicatechin-loaded liposomes formulated in a chitosan-based hydrogel for vaginal application. In this work, liposomes presented an approximate size of 200 nm and entrapment efficiencies of 81 and 77% for resveratrol and epicatechin, respectively, and medium molecular weight chitosan at 2.5% *w*/*w* concentration has been shown to exhibit optimum textural features and mucoadhesiveness in ex vivo conditions. This system was non-toxic, and epicatechin-loaded liposomes exhibited superior radical scavenging activity at lower concentrations than vitamins C and E. This epicatechin superiority was also demonstrated with the higher inhibitory effect on the NO production by RAW 264.7 cells (higher anti-inflammatory activity), compared to the resveratrol-loaded formulation.

Giordani et al. (2020) [100] produced novel liposomes for the simultaneous administration of two polyphenols, quercetin and gallic acid, that, when released into the vaginal cavity, functioned to eliminate infection, while reducing VVC symptoms. Quercetin was chosen for its anti-itching and anti-inflammatory effects, whereas gallic acid was chosen for its anti-*Candida* activity. Quercetin-, gallic acid- and (quercetin + gallic acid)-loaded liposomes with a 200 nm size were developed. Quercetin entrapment efficiency was 85% in both quercetin liposomes, whereas gallic acid was less efficiently entrapped, with 30 and 25% in (quercetin + gallic acid) and gallic acid liposomes, respectively. Liposomes, particularly (quercetin + gallic acid) ones, promoted the prolonged release of both polyphenols, and their joint administration improved the antioxidant activity. Also, liposomes were non-cytotoxic and had greater anti-inflammatory effects than free polyphenols. Finally, gallic acid and (quercetin + gallic acid) liposomes significantly inhibited *C. albicans* growth. In another study, Ci et al. (2017) [156] constructed an in situ thermosensitive hydrogel delivery system based on amino-functionalized poloxamer 407 (F127-NH_2) for vaginal administration of acetate gossypol, a polyphenolic aldehyde. This hydrogel exhibited controlled release while having mucoadhesive properties, which derived from the amino (NH_2) functionalization of poloxamer 407 (F127). As seen above, the research on the administration of polyphenols using advanced delivery systems for vaginal applications (Figure 3) is still limited.

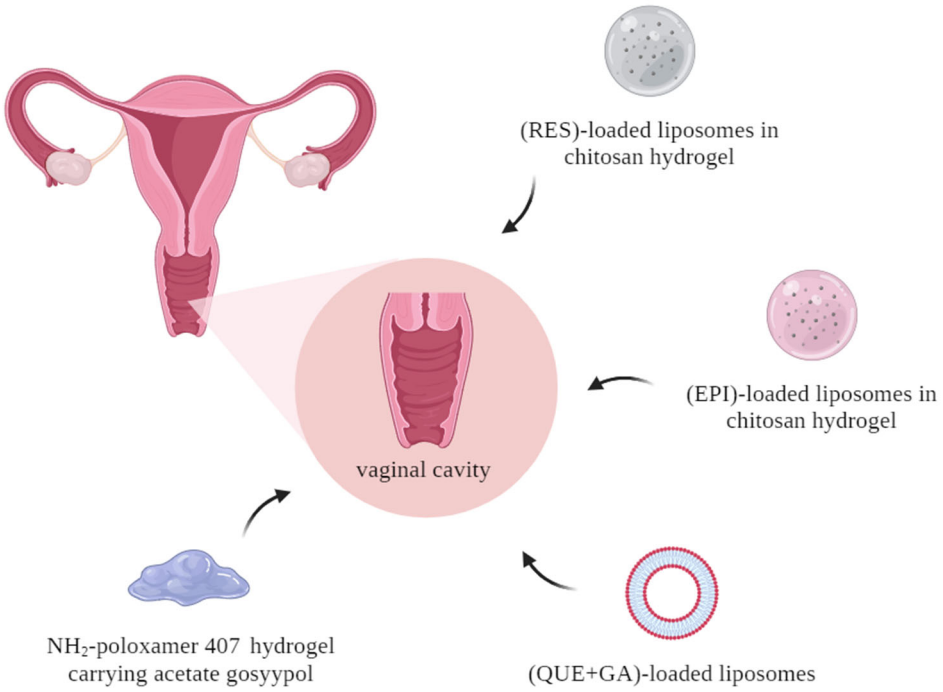

Figure 3. Polyphenols in advanced delivery systems for vaginal administration.

In this context, an analysis of other delivery systems with polyphenols, with distinct applications, can give suggestions for the development of novel forms for vaginal administration. Most of those other systems comprise protein-, metal-, polymer-, small molecule-, and nucleic acid-polyphenol-based nano delivery systems [157,158]. These include nanoparticles (solid lipid nanoparticles, nanostructured lipid carriers), nanoemulsions, nanocapsules, liposomes, and nano hydrogels, among others [159–161]. Also, a recently published paper by our group [155] reported some more examples of potential nano delivery systems (e.g., dendrimers, niosomes) for polyphenols, summarizing their advantages. For example, Joraholmen et al. [162] concluded that chitosan-based liposomes successfully loaded resveratrol with an encapsulation efficiency of approx. 75% for topical treatment of vaginal inflammation and infection. Furthermore, Schlich et al. [163], for nutraceutical purposes, prepared resveratrol-loaded niosomes composed of Tween 20/Span 60 and cholesterol. These compounds showed minimal cytotoxicity for intesti-

nal cells, displaying potential for oral intake. Imran et al. [164] developed a dual drug-loaded nanostructured lipid carrier (NLC) gel, with resveratrol and quercetin for improved disposition in skin layers, obtaining a resveratrol encapsulation efficiency of almost 90%. Tsai et al. [165] created resveratrol-loaded nanoemulsions using Caproyl 90 or isopropyl myristate as the oil phase, and propylene glycol and ethanol as cosurfactants. After 24 applications, the particles increased transdermal penetration and resveratrol deposition in the skin by 896.2- and 10.2-fold, respectively, when compared to the drug solution group. An in vivo study found that resveratrol plasma concentrations remained high for a long period following topical emulsion application. Pentek et al. [166] found that using polyamidoamide dendrimers improved resveratrol solubility and stability in aqueous and semisolid dose forms. Furthermore, the dendrimer enhanced resveratrol loading and skin penetration. Minnelli et al. [167] encapsulated resveratrol in bovine serum albumin-coated layered double hydroxide (LDH–BSA), allowing a better encapsulation efficiency when compared to only LDH. Moreover, Li et al. [168] showed that resveratrol-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles functionalized with red blood cell membranes have a better half-life and mean residence time when compared to simple resveratrol-loaded PLGA nanoparticles. Table 2 summarizes the examples mentioned above. Such knowledge can be transferred towards new forms for the treatment of VI.

Table 2. Drug delivery systems used for the delivery of polyphenols and their advantages/applications.

Drug Delivery System	Material	Loaded Compound	Advantages/ Application	Experiment Type	Reference Source
Liposomes	Chitosan	Resveratrol	Approx. 75% encapsulation efficiency; Topical treatment of vaginal inflammation and infections	In vitro	Joraholmen 2015 [162]
Niosomes	Tween 20/Span 60 (surfactants) and cholesterol	Resveratrol	Minimal cytotoxicity	In vitro	Schlich 2020 [163]
Nanoparticles	NLC: 1% lipid mix (Labrafil M 2125CS and Labrafil M 2130CS); Aqueous phase (5% Cremophor RH40 in distilled water)	Resveratrol and quercetin	Improved disposition in dermal and epidermal layers; resveratrol encapsulation close to 90%	In vitro; Ex vivo	Imran 2020 [164]
Nanoparticles	PLGA; red blood cell membranes	Resveratrol	Increased half-life and mean residence time	In vitro	Li 2019 [168]
Nanoemulsions	Caproyl 90/isopropyl myristate (oil phase); Propylene glycol and ethanol (cosurfactants)	Resveratrol	Increased transdermal and deposition in skin	In vitro; In vivo	Tsai 2016 [165]
Dendrimers	Polyamidoamide	Resveratrol	Enhanced solubility and stability; more efficiency in loading and skin penetration	In vitro; Ex vivo	Pentek 2017 [166]
Nanocomposites	bovine serum albumin-coated layered double hydroxide (LDH–BSA)	Resveratrol	Better encapsulation efficiency	In vitro	Minnelli 2020 [167]

8. Conclusions and Future Perspectives

The environment of the typical vaginal microbiota is continually evolving due to a wide range of physiological and environmental variables. Vaginal dysbiosis is characterized by changes in the variety or number of microorganisms, mainly by the reduction in *Lactobacillus* sp. and increases in certain pathogenic anaerobic bacteria, which promote inflammation. Vaginal dysbiosis has been linked to a significant rise in the incidence of STIs, preterm delivery, and infertility.

High rates of treatment failure and recurrence are linked to VIs. These can be attributed to the inability of antibiotics to effectively treat VI, as well as to failures in the restoration of the physiologic vaginal environment following antibiotic therapy. The conception of novel diagnostic and prognostic microbiological indicators, as well as of reasonable targets for

the development of novel preventative and therapeutic drugs, may be aided by a better knowledge of the microbiome roles.

The scientific literature supporting the positive effect of some polyphenols in treating VIs is still limited. To validate the effectiveness and safety of these alternative therapeutic agents, which might be used in place of or in addition to the conventional therapies, more studies, including in vivo ones, need to be carried out.

In conclusion, while polyphenols have been extensively researched, their application in encapsulation for vaginal treatments presents significant untapped potential. Looking ahead, there is a promising future for exploring advanced delivery systems to further enhance the therapeutic efficacy of polyphenols in addressing VIs. Continued innovation in this area could open new avenues for more targeted and effective treatments, expanding the scope and impact of polyphenol-based therapies in women's health.

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Abbreviations

AV, aerobic vaginitis; BV, bacterial vaginosis; CC, cervical cancer; CISMAC, Centre for Intervention Science in Maternal and Child Health; ESBL, extended-spectrum beta-lactamase; FDA, Food and Drug Administration; GA, GRAS, Generally Recognized As Safe; HIV, Human immunodeficiency virus; HPV, Human Papillomavirus; LDH-BSA, bovine serum albumin-coated layered double hydroxide; LGB, lactobacillary grades; LPS, lipopolysaccharide; MDR, multi-drug-resistant organisms; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NLC, nanostructured lipid carrier; NO, nitric oxide; PLGA, poly(lactic-co-glycolic acid); PMNs, polymorphonuclear cells; PTB, preterm birth; STI, sexually transmitted infections; VI, vaginal infections; VRSA, vancomycin-resistant *Staphylococcus aureus*; VVC, vulvovaginal candidiasis.

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