Bioscene

Bioscene
Volume- 21 Number- 02
ISSN: 1539-2422 (P) 2055-1583 (O)
www.explorebioscene.com

A Systemic Review on Natural Products and Nanotechnology used in Vaginal Infections

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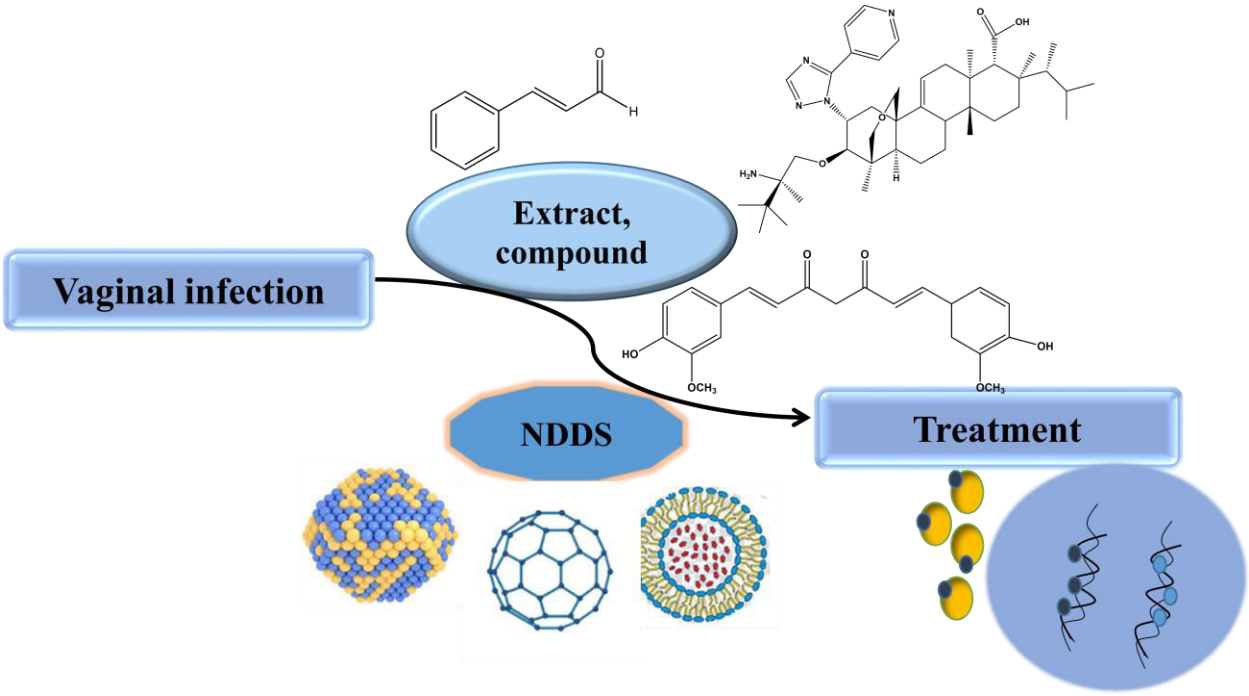
Abstract:

Objectives: Vaginal infections affect about fifty percent of all women get, whereas AIDS-affected women experience greater severity. Medical intervention might be necessary for the candida-caused infection or vulvavaginal infection. Improved effective therapy can be achieved by carefully selecting polymers to create novel delivery featuring certain characteristics including stimulus responsiveness, antibacterial activity, and muco-adhesiveness., **Methods:** Based on the publications that were issued in English between 2007 and 2024, we created a systematic review. We used syntax and database-specific tags to guide our search approach for Science Direct, PubMed, Scopus and Cochrane, among other databases. The papers with inclusion criteria were chosen, and their data was retrieved and examined., **Results:** The goals of the present review is to illustrate reported extract, conventional formulations and various new strategies for local administration for the treatment of disease as well as to evaluate various optimisation parameters critically based on their physicochemical characteristics., **Conclusions:** Here, we review the natural extract, formulation and novel therapies (nanoparticles, liposomes, hydrogels or microsphere) for treatment. These may improve the safety and efficacy of the drug. Novel approaches are catching attention of researcher for local delivery of drug now a days by utilizing cellular or intrinsic targeting.

Keywords: Vaginal infections, Candida albicans, Vulvavaginal infection, Natural extract, Novel approaches

Graphical Abstract:



Various Approaches for Management of Vaginal infection

1. Introduction

Vaginal infections are exceedingly common, especially in women who are fertile. Such cases don't have a high death rate, but they are linked to increased discomfort and a decline in the standard of life [1]. After Candida albicans, Candida glabrata is frequently the next second leading root of candidiasis having an elevated mortality rate in people with impaired immune systems are challenging to cure, as well as frequently resistant to several azole antifungal medications [2]. To get rid of these infections, both local and systemic therapies are options. Local therapy can be achieved through the use of innovative vaginal medication delivery. Vaginal medication administration can enable long-term drug release in the vaginal region and reduce systemic negative effects [3]. The disease has been linked to frequent and widespread behaviours among women, like wearing tight or synthetic pants, which creates an environment conducive to the growth of C. albicans, as well as using systemic or topical antibiotics, which lessen the protective effects of the vaginal flora and facilitate the colonisation of C. albicans [4]. The vaginal mucosal membrane of healthy women is coated with a diverse microbiota that is primarily lactobacilli. The first line of defence against genital diseases is this ecosystem's

equilibrium, which makes it crucial. Certain vaginal infections, such as trichomoniasis, vulvovaginal candidiasis, and bacterial vaginal candidiasis, have been well-characterized to yet [5]. Womens get vaginal infections experience more serious cases. Medical treatment may be necessary for the candida-caused infection vulva vaginitis. Under a microscope, the doctor looks at vaginal secretions and does a pelvic check. Candida yeast presence can be increased by antibiotics, nutrition, or immune system suppression [5]. Trichomonas vaginalitis (TV), vulvovaginal candidiasis (VVC), and bacterial vaginosis (BV) are among the most prevalent causes of contagious conditions [6]. Ovulation, the luteal phase, puberty, pregnancy, and oestrogen-based medicines including combination of hormonal contraception and hormone-replacement therapy can all cause a rise in vaginal discharge. Ten percent of women have normal vaginal discharge [7]. The aggressive yeast C. albicans is responsible for over 90% of vulvovaginal illnesses. The primary treatment approach for treating and preventing these kinds of infections is thought to be the hunt for anti-C. albicans medicines with novel pharmacological targets. In this regard, natural products provide a potentially useful source of antimicrobial chemicals [8]. Throughout the years 1981 to 2006, natural substances were the source, inspiration, or derivative of more than 40% of newly registered medications. Natural products have a significant impact on the anti-infective field since a large portion of pharmaceuticals are produced from or extracted from them. One of the most frequent causes of gynaecological consultations for women is vaginal infections. It is crucial for women's healthcare practitioners to be aware of natural remedies since they are quite popular among women who have chronic infections. Furthermore, several phytotherapeutic items have been proposed as organic sources of antibacterial substances [9]. Spices have long been used to improve taste and aroma as well as preserve food. Spice oils have been linked to antibacterial action due to the presence of substituted aromatic compounds, including eugenol, carvacrol, and cinnamon aldehyde [10]. This review's objective is to offer an overview of the range of phytochemical extract, formulation and nanoplatforms for antimicrobial agent administration by vaginal delivery. There is also a brief information on polymers used in vaginal drug delivery.

2. Material and Method

We conducted a thorough search of the databases MEDLINE (PubMed) and Embase considering the following search parameters to find publications published between 2007 and 2024. Candida species, especially C.albicans, vulvovaginal candidiasis. PRISMA Flow Diagram **Fig. (1).**) showed how reports moved through the various phases of the systematic review. It plotted the variety of data that had been found, whether they had been incorporated or not, and the justifications for the omissions.

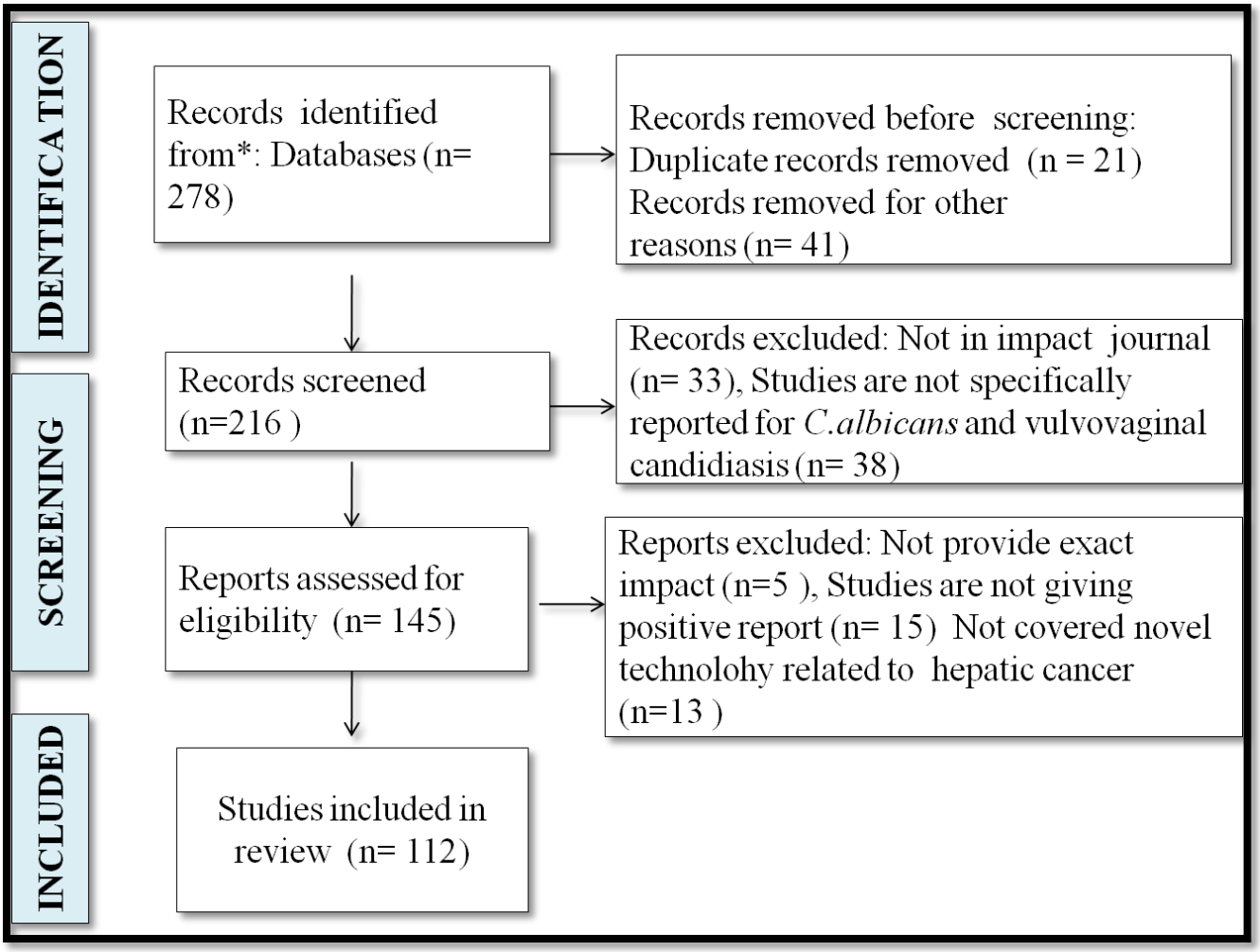


Fig. (1). PRISMA diagrammatic representation

3. Epidemiology

In rural Maharashtra, Bang et al. identified vulvovaginal candidiasis in 35% of 650 adult women, whereas Prasad et al. found the disease in 10% of 451 married women aged 16 to 22 in rural Tamil Nadu state [11, 12]. VVC incidence ranged from 29% to 49% in a global research included 6000 women from the US and the UK, including 9% of those women experiencing recurrent VVC and Investigation from India revealed that amongst adult women in the age of reproduction range, the incidence of confirmed VVC ranged from 10% to 35% [13]. In India, women who were evaluated to be negative for bacterial vaginosis also had a greater frequency of vulvovaginal candidiasis than those who were clinically diagnosed with the disease [14]. A research conducted in Estonia using barcoded pyrosequencing technique discovered Candida in 67.6% of the asymptomatic women, indicating a more diversified mycobiome. According to recent research, there are around 138 million women globally who are affected by RVVC annually, and an additional 372 million

throughout the course of a lifetime [15]. VVC is the second most prevalent cause of vaginal infections in the US, accounting for 1.4 million outpatient visits annually and impacting 70–75% of women at some point in their lives. At a minimum $368 million yearly treatment cost for VVC [11]

4. Etiology

Candida albicans is responsible for more than 90% of infections, with non-albicans species (such as C. glabrata, C. tropicalis, C. krusei, and C. parapsilosis) coming in second [2]. One of the main reasons for gynaecological consultations in the globe, it has significant direct and indirect financial consequences [13]. There isn't a single cause for candidiasis episodes, but a number of internal and exogenous host virulence variables are being found to be important contributors. Inherited, immune-mediated, physiological, metabolism, sanitary, antibiotic/corticosteroid usage, and lifestyle-related variables are examples of inbuilt variables [16]. Reduced acidity in the vagina may result in the reduced Lactobacilli to become even more alkaline, and the proliferation of pathogens including G. vaginalis, Mobiluncus, Prevotella, Prophyromonas, Peptostreptococcus, Mycoplasma hominis, and Ureaplasma and others. On the other hand, glycogen loss may result from a decrease in vaginal oestrogen. The pH will increase in the absence of glycogen because Lactobacilli won't have a substrate to produce lactic acid [12].

5. Pathogenesis

Candida species are the main pathogens in vaginal colonisation (VVC). They most likely originated in the gastrointestinal tract and first colonised the vagina as commensals, causing no symptoms. The vagino-protective microbiota creates a regulated, non-adversarial environment in which Candida microbes thrive. Specifically, lactic and acetic acids are organic acids that help make Candida spp. more tolerant in the vagina [17]. Acute symptoms Candida vulvovaginitis is an abrupt shift that can be caused by a variety of variables however it requires prior colonisation of the vaginal yeast. This is characterised by the growth of yeast blastospores, the development of hyphae, and the production of several fungal virulence variables. These modifications to the microbiome lead to incursions of the outer vaginal epithelial surface and proinflammatory response in the vaginal epithelial cells. Soon after come the numerous concomitant signs and symptoms of acute vulvovaginitis. An elevated level in IL-1β and IL-6 is a component of the proinflammatory cytokines as discussed in **Fig. (2).** [18]. causes and consequences of CVV is examined with regard to host predisposition variables (gestation, contraceptive pills, type 2 diabetes, cell-mediated the immune system, vaginal flora, and other), vaginal defence systems (humoral arrangement, phagocytic system, cell-mediated defences, vaginal flora, and other), pathogenesis of recurrent and

chronic CVV (inner reservoir, sexually transmitted infections, vaginal recurrence, and clinical models) [19].

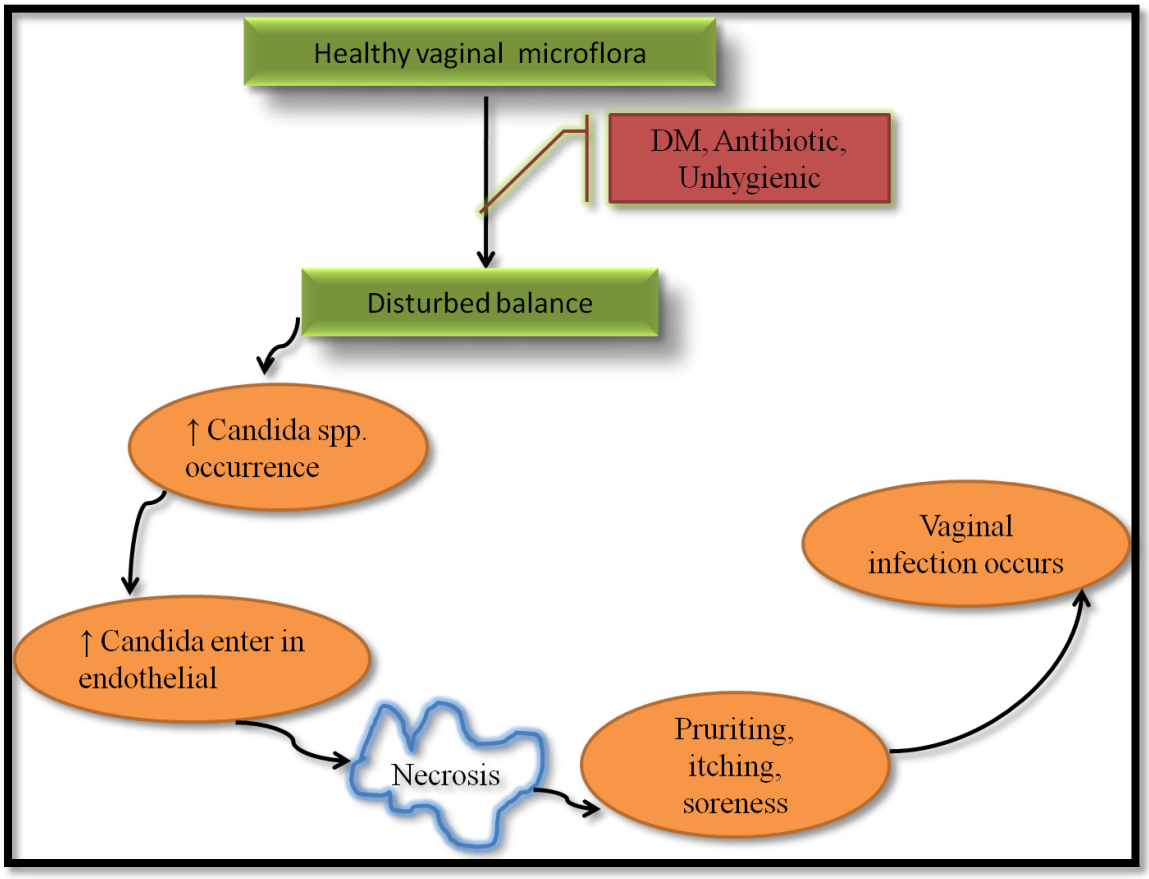


Fig. (2). Pathogenesis of vaginal infection.

5.1. Symptoms

Vaginal discharge, irritation, discomfort, and edema are among the signs and indications of VVC. Furthermore, vulvar erythema and inflammation with excoriations are often seen conditions. It is said that the normal vaginal discharge in VVC has a character similar to cottage cheese [20].

6. Treatment

Physical checkup, and the biological testing performed in the laboratory are frequently used to make the final determination [5]. The accessible medication is limited by therapeutic restrictions such as low bioavailability, excessive vaginal discharge volume that flushes the individual, low adherence to the vaginal mucosa, frequent dosage, protracted therapy duration, and reduced therapeutic effectiveness that may cause relapse [21]. It may be necessary to use systemic and intravaginal treatment in conjunction for a complex or recurring VVC [4] and

including more cereals rice, wheat, and veggies in the diet. Maintaining the right amount of yeast may be achieved by eating a half-cup of yoghurt every day. To ease digestive issues, use two or three Acidophilus pills per day [22]. Ureaplasma sp. infection patient was advised to treat the condition with an incised clove of garlic after receiving inadequate local therapy with antibiotics and antifungals. Gynecologist's control checkup verified that the infection had been successful treatment and did not encounter any negative consequences [23].

6.1. Extracts and phytoconstituents

Ethanol extract of S. khuzistanica boosted the anti-candidal effects of ketoconazole and amphotericin B, but it showed no synergistic impact on clotrimazole when used against clinical isolates of C. albicans. Thus, ethanol extract from S. khuzistanica can be used as a novel anti-candidal drug against clinical isolates of C. albicans. The MIC and MFC against clinical isolates were 299.4 and 722.6 (μg/mL), respectively [24]. Heracleum persicum fruit extracts, both methanolic and ethanolic, showed anti-Candida properties against Candida albicans, Candida tropicalis, and Candida glabrata. The ethanolic extract of the studied plant exhibits higher anti-Candida effects at 0.625 μg/μL compared to the methanolic extract at 2.5 μg/μL [25]. Clinical isolates of C. albicans, E. platyloba ethanolic extract had a strong synergistic impact with itraconazole ($P<0.01$) and fluconazole ($P<0.001$), but it also had an antagonistic effect with clotrimazole and miconazole [26]. C. glabrata strains exhibiting slightly greater MIC and MFC values. By 21 days after 5% hexane and butanol exhibit equivalent to the activity of fluconazole [27]. It is possible replacement of antifungal drugs with essential oils of C. cyminum and L. binaludensis as herbal inhibiting agents to manage the most significant pathogenic species of Candida and alternative treatments for recurrent vulvovaginal candidiasis [28]. Essential oil of C. cyminum and alcoholic extract of S. persica were able to inhibit Candida species and can be used as adjunctive therapy for candidiasis [29]. Azole-resistant strains of Candida were examined against echinocandin showed strong efficacy. The obtained MIC values were remained considerably lower. After topical application, despite a little decrease in activity at pH 4 compared to 7 [30]. Cyclamen coum tuber extracts of n-butanol and aqueous fractions exhibited significant activity at 2-32 μg/mL of saponin was seen in the MIC and MFC of varying Candida strains. The extract's aglyconic aqueous phase exhibited the strongest anticandidal properties like strains of C. albicans and C. tropicalis, respectively [31]. Significant alterations are brought about in all fungal cell membranes by Solanum chrysotrichum, with somewhat less impact on the cell wall [32]. Broad-spectrum antifungal action is exhibited by Rhizome and Root of Smilacina japonica . MICs against Candida albicans reported [33]. The most effective treatments were eugenol and cinnamonaldehyde, which inhibited every strain of Candida and had a highly additive impact (FICI 0.625). The

means of the MIC, MFC, and cinnamonaldehyde inhibition zone were 69 mm, 50.05 mg/L, and 109.26 mg/L, respectively. In less than four hours, all viable Candida cells were destroyed by cinnamon aldehyde. The corresponding means for eugenol IZ, MIC, and MFC were 35.2 mm, 455.42 mg/L, and 690.09 mg/L [34]. Various mechanism involved in the management of disease is mentioned in **Fig. (3).**

Proanthocyanidin polymeric tannins from S. adstringens have demonstrated efficiency in controlling candidiasis in a mouse model and exhibit antifungal effects in in-vitro against C. albicans. It provides intriguing substitutes for the antifungals that are currently used for the management of vaginal candidiasis [35]. Via focusing on sterol production and plasma membrane ATPase activity, cinnamonaldehyde demonstrates its antifungal action by Cell death and intracellular acidification result from H^+-ATPase suppression and encountered fungicidal properties that preferentially affect fluconazole-resistant Candida isolates [10] and eugenol and cinnamon aldehyde showed excellent antibiofilm action and fluconazole synergistically in vitro [36]. Cymbopogon citratus and Syzygium aromaticum showed encouraging in-vitro anti-biofilm action, confirming the ethnopharmacological usage of oils in mucocutaneous infection with Candida [37]. Demonstrates the substantial anticandidal action of methyl cinnamondehyde and curcumin against clinical isolates that are both sensitive and azole-resistant; methyl cinnamondehyde is shown to be beneficial [38]. For acute VVC, Ibrexafungerp is a potentially effective oral medication that is safe and works differently from the other azole treatments [39]. When treating acute vulvovaginal candidiasis infections, oteseconazole proved to be both safe and effective in preventing repeated episodes. Additionally, it showed no discernible inferiority to fluconazole, the conventional therapy for vulvovaginal candidiasis [40].

In C. albicans, ROS buildup was brought on by malfunctions in the mitochondria. The addition of cysteine stopped in the Anethum graveolens seed essential oil-induced drop in cell viability and the rise in ROS generation, suggesting that ROS play a key role as a mediator of antifungal effect. These results suggest that the primary anti-Candida targets of A. graveolens are the mitochondria and the cytoplasmic membrane [41]. By obstructing the vital PM-ATPase enzyme and interfering with ergosterol production, geraniol compromises the integrity of cell membranes. As a result, it may be utilised to control and treat invasive as well as superficial candidiasis [2], for C. albicans strains, coriander oil and amphotericin B also had a synergistic impact; however [42]. Buchenavia tomentosa extracts shown encouraging antifungal effectiveness against low-cytotoxic Candida species. On Candida glabrata, gallic acid, corilagin, and ellagic acid all shown encouraging inhibitory action [43]. M. titans' aqueous extract had great potential as an antifungal agent [44]. The proliferation of the microbes was suppressed by formononetin, with a minimum inhibitory dose of 200 μg/mL. In addition, five out of the six yeasts that

were examined showed fungicidal activity against formononetin. When combined, our findings show that Red propolis purported antibacterial effect is related to the isoflavone formononetin [45]. Extracts from O. vulgare and essential oils derived from Portugal are promising substitutes for the industry's usage of synthetic chemicals [46]. 67% ethanol, the bark of G. glabra, the stem of F. religiosa, and the husk of P. major were showed to possess adequate effectiveness against C. albicans to that of synthetic antifungal drugs [47]. An in-vivo study showed the effectiveness of the free and loaded extracts when applied topically in a rodent model of vaginal candidiasis, and Artemia salina L. validated a satisfactory safety profile of extract [48]. Tea tree oil and its constituents change the characteristics of membranes and disrupt processes related to membranes in order to produce their antifungal effects [49]. The effect of aloe vera ethanol extract on the Candida albicans preventing growth region ($p<0.005$).Comparable to conventional antifungal medications, aloe vera ethanol extract has concentration-dependent efficacy over Candida albicans and many more are listed in **Table 1.** [50].

Table 1. List of plant extract and phytoconstituents reported for control of vaginal infection.

Botanical source/compound	**Part used**	**Extract type**	**Organism/pathogenic condition**	**Ref.**
Geraniol	-	Compound	C. andidiasis	[2]
cinnamaldehyde	-	Compound	C. glabrata, C. krusei, C. albicans and C. parapsilosis	[10]
S. khuzistanica	Aerial parts	Ethanol	C. albicans	[24]
Heracleum persicum	Fruit	Methanolic	C. albicans C. tropicalis, C. glabrata	[25]
Echinophora platyloba	Dried aerial parts	Ethanolic	C. albicans	[26]
Sapindus saponaria	Dry pericarps of the fruits	Hydroalcoholic and n-butanol	C. albicans, C. glabrata	[27]
Cuminum cyminum	Seed	Essential oils	C. albicans	[28]
L. binaludensis	Seed	Essential oils	C. albicans	[28]
Salvadora persica	Chewing sticks	Alcoholic	C. albicans, C. dubliniensis	[29]
Echinocandin (CD101)	-	Compound	C. albicans, C. glabrata, C. parapsilosis, C.	[30]

			tropicalis	
Cyclamen coum	Tuber	Aqueous	C. albicans, C. tropicalis and C.krusei	[31]
Solanum chrysotrichum	Leaves	Saponin-standardized	C. albicans, C. glabrata, C. parapsilosis, C. krusei, C. lusitaniae, C. tropicalis	[32]
Smilacina japonica	Dried rhizome and root	Hydroalcoholic	C. krusei, C. albicans	[33]
Stryphnodendron adstringens	Stem bark	Proanthocyanidin polymeric tannins	C. albicans	[35]
eugenol and cinnamaldehyde	-	Compound	C. albicans	[36]
Cymbopogon citratus and Syzygium aromaticum	Leaves and buds	Essential oils	C. albicans	[37]
α-methyl cinnamaldehyde and curcumin	-	Compound	-	[38]
Ibrexafungerp	-	Triterpenoid	Vulvovaginal candidiasis	[39]
oteseconazole	-	Compound	Vulvovaginal candidiasis	[40]
Anethum graveolens L	Seed	Essential oil	C. albicans	[41]
Coriander and amphotericin B	Seed	Essential oil	C. albicans	[42]
Buchenavia tomentosa	Leaves	Gallic acid, corilagin and ellagic acid	C. glabrata.	[43]
Macrocybe titans		Aqueous	Candida albicans	[44]
Red propolis	Formononetin	Methanolic	C. albicans , C . albicans, C. tropicalis , C. tropicalis	[45]

Origanum vulgare	Whole herb	Essential oil and ethanol extracts	C. albicans	[46]
G. glabra, F. religiosa, and P. major	Bark +stem and husk	Ethanol	C. albicans	[47]
A. urundeuva,	Leaves	Hydroethanolic	C. albicans, C. glabrata	[48]
Melaleuca alternifolia	Leaves	Oil	C. albicans, C. glabrata	[49]
Crossandra infundibuliformis	Leaves	Alkaloids, saponins, phytosterols, phenolic flavanoids, tannins, terpenoids	C. kruseii, C. gullirmondi	[51]
Aloe vera	Ethanol	Ethanol	C. albicans	[50]
Rosmarinus officinalis	Leaves	Essential oil	C. albicans, C. glabrata	[52]
Punica granatum	Pericarp and peel extracts	Ethanolic	C. albicans, C. krusei	[53]
Morinda citrifolia	Fruit	Juices	C. albicans	[54]

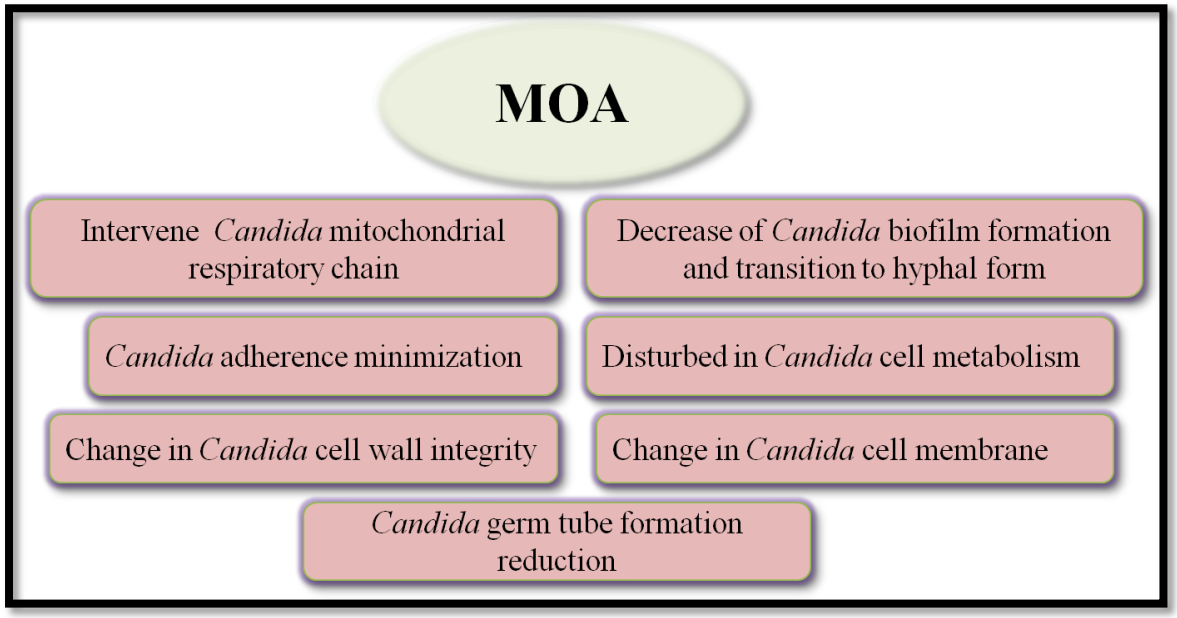


Fig. (3). Mechanism involved in the treatment of vaginal infection.

6.2. Formulations

Conventional herbal dosage forms are effective in the treatment like vaginal creams including 10% Ziziphus Spina are just as efficient in getting rid of Candida albicans as Clotrimazole [55] whereas female rats with C. albicans infections may be treated with L. inermis (henna) vaginal cream; however, 4% henna was more successful and had a result comparable to clotrimazole [56]. Arnebia euchroma containing vaginal cream may help lessen vulvovaginal candidiasis problems. However, it is advised that further research be done with bigger sample numbers and varied doses [57]. The findings indicated that using a vaginal lotion containing A. millefolium helped lessen vulvovaginal candidiasis problems, the minimum inhibitory concentration of the extract was 37.5 mg/mL [58]. The treatment of VVC by Althaea officinalis appears to have been significantly aided as compared to standard vaginal cream, with no notable adverse effects [59]. A research indicated that the therapeutic effects of vaginal cream, yogurt and honey is not only similar with clotrimazole vaginal cream but more effective in relieving some symptoms of vaginal candidiasis, results showed that the "yoghurt and honey" significantly outperformed the clotrimazole group in terms of symptom improvement ($P<0.05$). Additionally, the first culture (one week after treatment) and second culture (14 days after treatment) of the combination showed positive results (20% versus 8.6%) [60]. The use of N. sativa honey may be given as supplemental therapy in the treatment of VVC because the study's findings demonstrated that it considerably reduced the condition [61]. Effectiveness of the intravaginal therapy using a cream containing the extract at dosages of 0.5, 1.0, and 2.0% in the in-vivo model of VVC. After eight days of therapy, the vaginal fungus load in infected rats was completely eliminated. For the treatment of vulvovaginal candidiasis, S. nitens extract is safe, natural antifungal drug that works well [62]. There was a gradual decrease in the fungal load after using vaginal curcumin cream. In the 1.0% cream-treated group, there was a decrease in the inflammatory infiltrate. When treating vulvovaginal candidiasis, vaginal cream containing curcumin may be a promising and successful antifungal medication [9]. The essential oil of Thymbra capitata had a significant impact on Candida biofilms. It's suggested as a useful antifungal medication to treat resistant mucocutaneous candidosis when combined with a suitable pharmaceutical formulation [63]. When it comes to treating vaginal candidiasis, chamomile is similarly efficient as clotrimazole [64]. A greater proportion of women reported that curcumin was also potentially helpful in treating the clinical symptoms [65] and the curative value of a Q. brantii fraction vaginal douche was comparable to that of clotrimazole vaginal cream [66]. The vaginal tablet made from S. officinalis is effective in treating vulvovaginal candidiasis both on its own and in combination with clotrimazole [67]. Comparing calendula vaginal cream to clotrimazole, it seems to possess a more durable but more significant impact on the management of

vaginal Candidiasis [68]. Gynaecologists and obstetricians might recommend dill as a helpful substitute for pharmaceutical medications, particularly for women who are frequently interested in natural remedies. [69] and cream with 1% clotrimazole and ginger was superior to clotrimazole in terms of effectiveness and potential utility for treating vaginal candidiasis [70]. For the management of vulvovaginal candidiasis, S. nitens extract may be a safe, natural antifungal drug that works well. [71] formulations reported for control of vaginal infection listed in **Table 2.**

Table 2. List of formulations reported for control of vaginal infection

Source	**Formulation**	**Composition**	**Organism/pathogenic condition**	**Ref.**
curcumin	Cream	-	Vulvovaginal candidiasis.	[9]
Cinnamaldehyde and eugenol	Cream	-	C. albicans, 2 C. glabrata, and 1 C. 6lusitaniae	[34]
Ziziphus Spina-Christi (ZSC)	Leaves	Hydro-alcoholic	Candida albicans	[55]
Lawsonia inermis	Leaves	Hydro-ethanolic	Candida albicans	[56]
Arnebia euchroma	Root	Ethanol	Candida vaginitis (Clinical)	[57]
Achillea millefolium		Aqueous	Candida albicans	[58]
Althaea officinalis	Cream	Aqueous extract 4% + clotrimazole 1%	VVC(clinical)	[59]
yogurt and honey	Cream	Yogurt and honey	VVC(clinical)	[60]
N. sativa-honey	Cream	N. Sativa-honey	VVC(clinical)	[61]
Syngonanthus nitens	Stem	Methanol:water	C. albicans	[62]
Thymbra capitata EO	Biofilms	Essential oil	VVC	[63]
Chamomile extract	Cream	Water extract	VVC(clinical)	[64]
Curcuma longa	Cream	Curcumin	VVC(clinical)	[65]
Quercus Brantii	Cream	Hydroalcoholic	vaginal candidiasis	[66]

Salvia officinalis	Tablet	-	VVC(clinical)	[67]
Calendula officinalis	Vaginal cream	-	Vaginal Candidiasis	[68]
Anethum graveolens	Suppository	Aqueous	Vulvovaginal candidiasis	[69]
Ginger-clotrimazole	Vaginal cream	Aqueous	Vulvovaginal candidiasis	[70]
Syngonanthus nitens	Cream	Methanol	Vulvovaginal candidiasis	[71]
Melaleuca alternifolia	Cream	Aqueous	Human papillomaviruses	[72]
Zataria multiflora	Cream	-	Acute vaginal candidiasis	[73]
E. camaldulensis + V. odorata + M. piperita	Cream	Ethyl acetate+ water+ hydroalcoholic	Anti-trichomonas	[74]

6.3. Novel therapies

Numerous benefits are associated with vaginal nano-based administration, including prolonged delivery, improved bioavailability, effective penetration through the vaginal epithelium, systemic absorption, and greater effectiveness [75]. Vaginal fluids quickly eliminate or dilute the medicinal formulations, making it difficult to achieve therapeutic effectiveness with traditional formulations. A lot of research has been done on the specific delivery of medications straight into vaginal mucous using hydrogels. Selecting natural, synthetic, or semisynthetic polymers is mentioned in **Fig (4).** [76]. Development of nanoparticle (100 nm -1 μm) for delivery of drug to vagina is focused on two significant factors; vaginal mucus barriers and drug retention. To achieve drug retention in vaginal area mucus penetrating particle are preferred and also improve the above mentioned problems [77]. Polyethylene glycol-polystyrene nanoparticles, polymeric nanoparticles were utilized as delivery systems of drug at the particular site [78]. Many polymers like polysaccharides come via plants, but some are proteins, like glutein, zein, etc. These macromolecules are important components of pharmacological dosage forms and are often utilised in formulations, especially for controlled drug-release systems. Still, there is not much data available on their usage in the synthesis of polymeric nanoparticles for vaginal systems [79]. Using Eudragit® RS 100 and medium-chain triglycerides, scientists created a mucoadhesive gel of pemulen/pullulan that

included cationic nanocapsules loaded with clotrimazole. This gel demonstrated sufficient mucoadhesion and vaginal penetration for the oil-core [80].

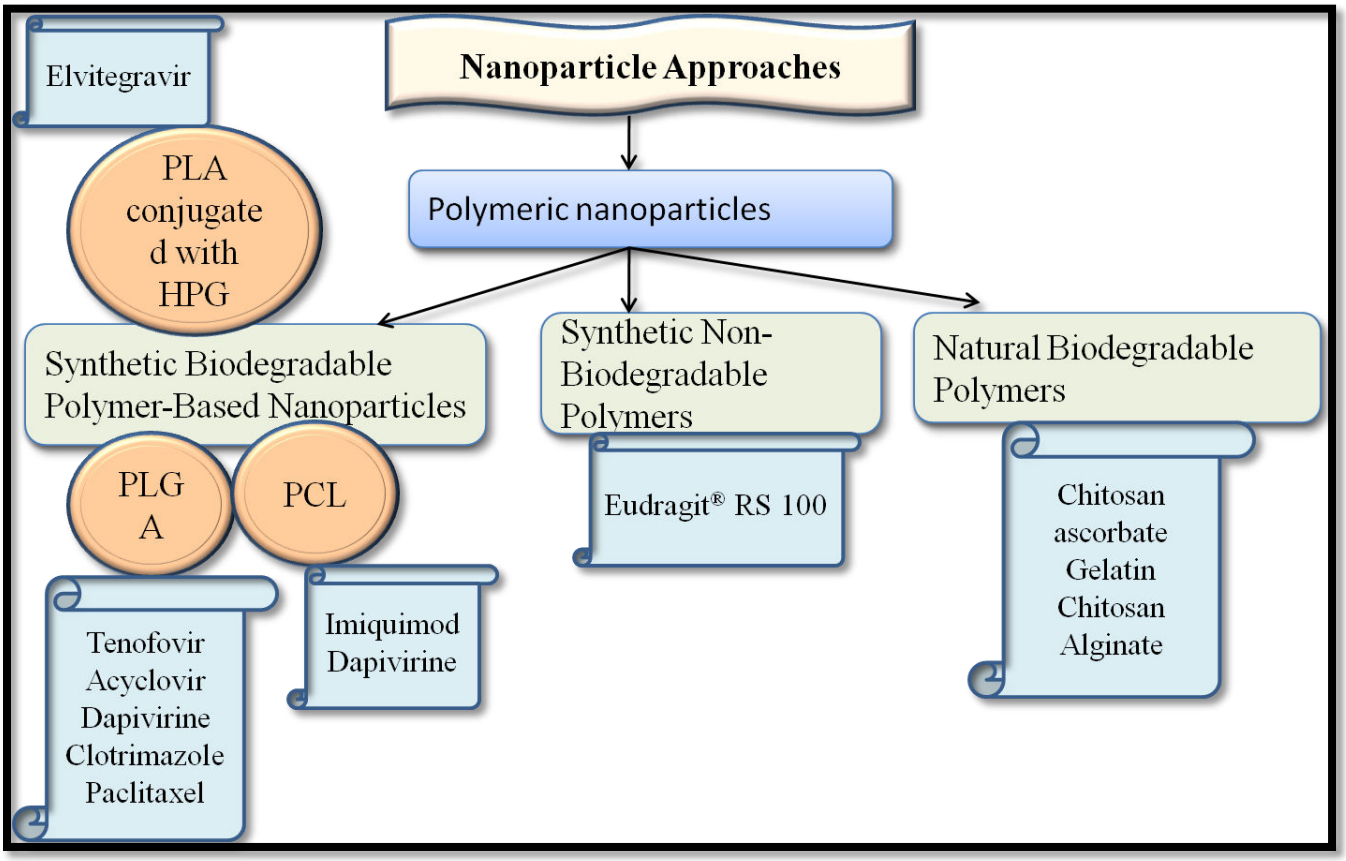


Fig. (4). List of polymers used in the management of vaginal infection

The drug-loaded nanofiber adhered to the vaginal mucosa without tearing because of its strong tensile strength and acceptable mucoadhesive properties. luliconazole (LCZ) drug was mixed into different concentrations (2.5, 5, 7.5, and 10%) of tea tree oil and loaded into the PCL/gelatin nanofibrous mats. The antifungal activity of the drug-loaded nanofiber was seen to have a synergistic impact with the modest ZOI of 4.3 ± 0.30 mm displayed by the oil-loaded nanofiber. LCZ-loaded nanofibers may be a unique therapeutic delivery method for vaginal infection with candida therapy [81]. Dried extract of S. baicalensis radix combined with a carrier gave rise to binary systems that exhibited more antifungal activity than the pure extract as novel approaches to the cure of vulvovaginal candidiasis [82]. Nanostructured lipid systems was found significant role in the biological effectiveness particularly for the relief of acute VVC, and that luteolin-rich fraction may be employed as an antibiotic in the management of vaginal infections [83]. Hydro-ethanolic extracts of Astronium sp. have been shown to have improved anti-C. albicans activity both in-vitro and in-vivo when utilising a nanostructured lipid framework [84]. Fibres and lotions filled

with benzydamine and benzydamine nanoparticles may used as a medication delivery method for relieving vaginal infections. As a substitute to controlled-release vaginal compositions for vaginal infections, chitosan nanoparticle laden nanofiber formulations are provided. [85]. Histology and cytology from the vagina revealed that L-carnitine can lessen the tissue destruction brought on by vaginitis [86]. When it came to curing vaginal trichomonad infection in mice, intravaginal auranofin-loaded nanoparticles gel significantly surpassed oral auranofin with no adverse effects on the body or the environment. These findings demonstrate the hydrogel formulation potential for efficient topical treatment of vaginal infections [87]. Silver colloidal nanoparticles could prove to be a useful substitute for traditional antifungal medications in the treatment of Candida-associated denture stomatitis [88]. Clinical implications regarding the management of denture stomatitis may arise from a combination of silver nanoparticles with nystatin and chlorhexidine digluconate, further research is required before it is advised that these medications be used safely in clinical settings [89], antibacterial properties of Bismuth nanoparticles, showed promising result against a range of harmful microbes [90]. In comparison to free anidulafungin, the liposome preparations enhanced anidulafungin solubility showed encouraging activity against planktonic and biofilm C. albicans [91]. Investigations on anti-candida activity Clotrimazole-loaded nanostructured lipid carrier gel was found four times more effective against Candida albicans than Fungizone(®). These positive findings imply that the hydrogel containing Clotrimazole-loaded nanostructured lipid carrier can be suggested as a novel way to give Clotrimazole for the treatment of vaginal infections [92]. Itraconazole-Loaded Polycaprolactone-Nanoparticles and Itraconazole solution, exhibited elevated TNF-α and IL-1β levels as well as normal tissue inflammation, animals received Itraconazole-Loaded Polycaprolactone-Nanoparticles had lower cytokine levels and healthy tissue features [93]. Coconut oil-core nanocapsules filled with clotrimazole provide interesting substitutes for treating vulvovaginal candidiasis [94]. Both investigation in-vitro and in-vivo antifungal efficacy of olive leaves gold nanoparticle minimal inhibitory concentration for the suppression of Candida albicans 40.77 ng/ml [95] and combined effects of quercetin and gallic acid enhanced the antioxidant properties. Compared to free polyphenols, polyphenol-liposomes showed greater anti-inflammatory effects and were non-cytotoxic and C. albicans growth was significantly inhibited [96]. β-microseminoprotein as a significantly affect innate immunity against Candida albicans and might possess potential therapeutic effect [97], whereas mucoadhesive liposomal gel increased drug tissue penetration and enhanced sertaconazole tissue persistence when contrasted with traditional gel, the mucoadhesive liposomal gel demonstrated a minimal histopathological alteration and a considerable decrease in the microbial population, which in turn led to a decrease in inflammatory reactions [98]. Rats

administered terpesomes loaded fenticonazole nitrate gel, antifungal efficacy with the lowest histopathological heterogeneity was observed. Obtained results confirmed the effectiveness of using this gel for managing vaginal candidiasis [99]. Only the microemulsion of Cymbopogon nardus essential oil increased the elimination of the fungal vaginal infection on the third day of therapy, according to an in-vivo VVC test, indicating that the addition of the microemulsion considerably boosted the efficacy of the essential oil [100], and metronidazole encapsulation in chitosomes may enhance the healing process of complicated vaginal infections [101]. Ketoconazole nanoparticles possess the potential to manage Candida albicans-related vaginal infections [102]. Topical gel therapy for vaginal candidiasis containing sertaconazole microemulsion offers promising effect [103]. In comparison to the commercial gel, miconazole nitrate-loaded solid lipid nanoparticles combinations had a much improved skin-targeting ability and thus dramatically raise the overall absorption of miconazole nitrate in epidermis. These findings suggest that the investigated miconazole nitrate-loaded solid lipid nanoparticles combination with skin targeting might be a viable vehicle for miconazole nitrate topical administration [104]. When tested on human skin cell models, the produced Chitosan nanoformulations demonstrated non-toxic fungicidal efficacy against Candida albicans. The findings of this investigation mark the beginning of the process of creating a pharmaceutical dosage form that may be utilised for treating vaginal candidiasis [105]. In a different investigation, lyophilized sponges made of cellulosic derivatives were created to administer cidofovir, and the results showed high mucoadhesive strength, adequate mucoadhesive capacity, and a dry solid form that can preserve the medication contained [106]. List of novel approaches in the management of vaginal infection are illustrated in **Table 3.**

Table 3. List of plant extract and phytoconstituents reported for Noval Drug Delivery of Vaginal infection.

Compound	**Nanoformulation**	**Disease type**	**Polymer**	**Ref.**
Benzydamine	Nanoparticles	Vaginal infections	Hydroxypropyl methylcellulose + polyvinylpyrrolidone	[3]
Lycopene	Nanoparticles	Vulvovaginal candidiasis	Sodium dihydrochloride 2,2'- Azobis (2-methylproprylnamide)+ octane	[4]
Luliconazole	Nanofibers	Candida infection.	Polycaprolactone (PCL)/gelatin	[81]

Scutellarie Baicalensis Radix	Nanoparticles	Vulvovaginal candidiasis	Chitosan	[82]
Syngonanthus Nitens	Nanoemulsion	Vulvovaginal Candidiasis	Cholesterol + polyoxyethylene 20-cetyl ether	[83]
Astronium Fraxinifolium, Astronium Graveolens, and Astronium Urundeuva	Nanostructured lipid system	C. albicans	SPC/Brij®	[84]
Amphotericin –B	Nanoparticle	C. albicans	PEGylated PLGA	[85]
L-carnitine	Nanoparticles	C. albicans	Silver	[86]
Auranofin	Nanoparticles	Vaginal trichomonad infection	Vaginal trichomonad	[87]
Silver nanoparticles	Nanoparticles	C. albicans C. glabrata	Sliver nitrate+ Sodium citrate + Ammonia	[88]
Nystatin or chlorhexidine digluconate	nanoparticles	C. albicans C. glabrata	Silver	[89]
Bismuth	nanoparticles	C. albicans	Polyvinylpyrrolidone	[90]
Anidulafungin	liposome	C. albicans	-	[91]
Geraniol	Nanoemulsions	C. albicans	Cholesterol+ polyoxyethylene 20-cetyl ether + soy phosphatidylcholine	[107]
clotrimazole	Hydrogels	C. albicans	Poloxamer p407, poloxamer p188 , tristearin, carbopol	[92]
	Nanocapsule suspensions	C. albicans C. glabrata	Eudragit	[95]
	Microspheres	Vaginal candidiasis	Hydroxypropylmethylcellulose, sodium carboxymethylcellulose and Carbopol.	[108]
Itraconazole	Nanocapsules and	Vulvovaginal candidiasis	-	[93]

	nanospheres			
Olive leaf extract	Nanoparticles	Cutaneous candidiasis	Hydrogen tetrachloroaurate	[95]
Quercetin, , and gallic acid,	Liposomes	Vulvovaginal candidiasis	Soybean lecithin+	[96]
β-Microseminoprotein	Liposomes	Vulvovaginal candidiasis	Ergosterol	[97]
Sertaconazole Nitrate	Liposomes	Vaginal Candidiasis	Soy phosphatidylcholine, cholesterol and the cationic surfactant	[98]
Fenticonazole nitrate+Terpesomes	Liposomes	Vaginal Candidiasis	L-α phosphotidylcholine + ß-estradiol-17-valerate	[99]
Cymbopogon nardus Essential Oil	Microemulsion	Vulvovaginal candidiasis	Polyoxyethylene (23) lauryl ether (Brij35®) + soy phosphatidylcholine	[100]
Metronidazole	Liposomes	Vaginal infections	Chitosan	[101]
Ketoconazole	solid lipid nanoparticles	Candida albicans.	Polyoxyethylene-40 stearate	[102]
Resveratrol (RES) or epicatechin	liposomal	Vaginal Infections	Chitosan	[110]
Sertaconazole	Micro emulsion	Vaginal candidiasis	Carbopol 940	[103]
Miconazole nitrate	Micro emulsion	Vaginal candidiasis	Polycarbophil	[104]
Tioconazole (TIO) and Econazole	Nanocapsule	Vaginal candidiasis	Chitosan	[105]
Econazole nitrate	Mucoadhesive cellulosic	Vaginal candidiasis	Poloxamers/Gelucire	[109]

7. Conclusion

Plants having therapeutic qualities have been studied and employed for centuries to treat a range of infectious illnesses. Vaginal disorders have an elevated risk of recurrence, which is frequently brought on by ineffective management of complicated infections involving many pathogens, including bacteria and fungi [101]. Among C. albicans cells and biofilms, the majority of the mentioned

nanoparticles demonstrate significant potential for antifungal action through multi-target mechanisms that potentially reduce the formation of antifungal resistance. Concerns has been raised about the cytotoxicity of metal nanoparticles, and changes in synthesis or coating methods have been made to get around these restrictions, with a focus on green synthesis [95]. The benefits of nanomedicines included enhanced drug delivery, bioavailability, dissolution, penetration, and persistence. The use of nanoparticles in healthcare is deemed necessary in the quest for improved therapeutic procedures [111]. It might not be possible to produce complex formulations that react to several triggers on a big scale. In addition, differences in the vaginal environment among women at different phases of their lives point to the need for greater study as more individualised regimens are being developed to treat vaginal problems. To evaluate the efficacy, biocompatibility, and acceptability of stimuli-responsive formulations in treating various vaginal conditions at preclinical and clinical phases, more experimental research is needed [112]. However, more research with a bigger sample size and varied doses is advised to evaluate the effects of this novel medication.

Abbreviation

VVC= Vulvovaginal candidiasis
MFC= Minimum Fungal Concentration
mg/L= Milligrams per liter
μg/Ml= Microgram per milliliter
ZOI= Zone of Inhibition
IL-1β = Interleukin-1 beta
IL-6 = Interleukin-6
PCL= Polycaprolactone
IZ = Inhibition Zone
MIC = Minimum Inhibitory Concentration

Conflict of Interest

The author(s) have no conflict of interest.

Acknowledgement

The author like to thank Mr. Pranveer Singh, Chairman PSIT for providing facility and encouragment.

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