ejpmr, 2025, 12(6), 96-110

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ANTIFUNGAL POTENTIAL OF PLANT-DERIVED ESSENTIAL OILS AGAINST CANDIDA ALBICANS: INSIGHTS FROM IN VITRO VAGINAL CANDIDIASIS MODELS

[1]*Snehal K. Bhavsar, [2]Komal Bhoi, [3]Rajeshwari Patil and [4]Sanjay Surana

[1,3]M. Pharm Ph.D., Asst. Prof., Dept. Pharmacognosy, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, 425405, Dist Dhule, Maharshtra, India.

[2]M.Pharm (Research Scholar), Dept. Pharmacognosy, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, 425405, Dist Dhule Maharshtra, India.

[4]R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, 425405, Dist Dhule Maharshtra India.

***Corresponding Author: Dr. Snehal K. Bhavsar**

M. Pharm Ph.D, Asst. Prof., Dept. Pharmacognosy, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, 425405, Dist Dhule Maharshtra, India.

Article Received on 08/04/2025 **Article Revised on 29/04/2025** **Article Published on 20/05/2025**

ABSTRACT

Candida albicans (C. albicans) is a common opportunistic pathogen responsible for systemic and mucosal fungal infections, significantly contributing to morbidity and mortality. One of the primary challenges in treating C. albicans infections is the development of medication resistance, particularly in vulvovaginal candidiasis (VVC), a prevalent gynecological issue affecting women between the ages of 15 and 49. Approximately 75% of women experience at least one incident of VVC in their lifetime, with 5% suffering from recurrent episodes. Candida albicans is the causative agent in 85-90% of cases, characterized by symptoms like irritation and pruritus, which remain difficult to resolve. Essential oils, plant-derived secondary metabolites known for their antibacterial and vulvovaginal regulatory properties, have gained attention as potential alternatives to conventional therapies like fluconazole, especially given the increasing resistance of Candida strains and recurrence of infections. This review aims to explore the current state of research on essential oils as antifungal and antibacterial agents against C. albicans infections, focusing on their underlying mechanisms of action and potential future applications in developing safer and more effective antifungal therapies. A comprehensive analysis of both laboratory and clinical studies is presented, with a focus on innovative strategies for advancing antifungal drug development.

KEYWORD: Candida albicans, essential oil, vulovaginal infection, antifungal activity, MIC.

INTRODUCTION

Among the yeast genus, Candida albicans, also known as C. albicans, is the most prevalent and significant type of the fungus. Its round or oval-shaped cells possess a diameter of three to five microns. Under the right circumstances, it can grow into a mycelium, although it typically adopts the form of yeast. As a characteristic representative of the microbial community, Candida albicans is a common symbiotic fungus that is abundantly distributed in the natural environment and frequently coexists with animals and humans ((Moran et al., 2011). C. Albicans infections arise when the body's immune system is impaired, leading to illnesses such as oral candidiasis ((Millsop & Fazel, 2016; Vila et al., 2020), vaginal, skin, and nail candidiasis ((Espinosa-Hernández et al., 2020; Gonçalves et al., 2016; Jautová et al., 2001; Rodríguez-Cerdeira et al., 2019), as well as serious systemic fungal infections ((Blanco & Garcia, 2008). Compromised immune system (from HIV/AIDS, organ transplants, chemotherapy, etc.), the use of antibiotics, diabetes, pregnancy, prolonged catheter or ventilator use, among other of the factors that might lead to infection. The prominent Candida albicans infection is oral candidiasis, which is more common in young individuals as well as animals with weakened immune systems. Along with symptoms like inadequate breath, appetite loss, and difficulty eating, it manifests as white patches or spots on the tongue and oral mucosa. Animals' genitourinary systems may be impacted by vaginal candidiasis, which can cause symptoms like hematuria, vaginal irritation, mastitis, frequent urination, and need to urinate. Animals may experience discomfort and itching due to skin and nail candidiasis symptoms, which might include redness, swelling, itching, declamation, and ulcers at the affected area(Miceli et al., 2011).

The manifestations of vulval and vaginal yeast infections in the lower female genitalia are indicative of vulvovaginal candidiasis (VVC), which is triggered by a species of Candida (Lopez, 2015). 70 -75% of all

women in their reproductive years will suffer from at least one episode of VVC, and it is the second-most prevalent cause of vaginitis worldwide after bacterial vaginosis (BV)(Yano et al., 2019). VVC is additionally associated with a higher risk of obstetric and reproductive health issues, especially low birth weight babies, preterm delivery, and intraamniotic infections ((Zisova et al., 2016). Despite being the preferred therapy for VVC, antifungal medications (such as azoles) have limited efficacy as therapy because of considerable toxicity, the emergence of drug-resistant strains, and high recurrence rates ((Nivoix et al., 2020). Consequently, in order to effectively treat VVC and overcome antifungal shortages, a complementary or alternative therapy is of critical importance in clinical work (Wang et al., 2024). The following antifungal medications are the principal ones used to treat Candida albicans infections: (1) azole antifungal medications (Polyazoles): For treating infections caused on by Candida albicans, azole medications are the first line of treatment. Common polyazole drugs, such fluconazole, itraconazole, and posaconazole, restrict growth and replication by interfering with the yeast ketones as C. albicans' cell wall synthesizes; (2) Polyene antifungal medications, also referred to as polyketides: Polyenes target C. albicans' cell membrane, causing membrane rupture and ultimately cell death. The most frequently employed polyene medications include the liposomal form of Amphotericin B lipid complex (ABLC) and Neomycin B (Amphotericin B), which is typically utilized in cases of severe Candida albicans infections; (3) Newer antifungal medications: A lot of novel antifungal medications have become available recently for the treatment of drug-resistant or refractory infections of c. albicans (Cowen et al., 2015; Houšť et al., 2020; Kathiravan et al., 2012).

It is distinguished by burning, redness, vaginal swelling, and occasionally by serous or watery vaginal discharge. Furthermore, pain during intercourse and dysuria are noted (Dovnik et al., 2015). Recurrent vulvovaginal candidiasis (RVVC) is characterized by experiencing at least three episodes of infection within a year (Phillips et al., 2022). Due to this disease, patients experienced increased stress, avoidance of sexual involvement, and diminished self-esteem and confidence; around 53% of women with vaginal candidiasis are diagnosed with depression (Blostein et al., 2017; Neal & Martens, 2022).

Around 75% of women have at least once in their lifetimes suffered from vaginal candidiasis, and over 50% of patients go through experiencing a second episode (Balakrishnan et al., 2022; Fernandes et al., 2022). It is estimated approximately 10-15% of women experience asymptomatic Candida colonization (Gonçalves et al., 2016). Furthermore, it has been shown that the incidence of VVC appears to increase after the age of 17. However, when they are twenty-five years of age, 54.7% of patients had experienced problems with VVC(Geiger et al., 1995). In women between the ages of 25 and 49, RVVC affects 9% of episodes (Lines et al., 2020). Approximately 492 million women will be affected by RVCC in their lifetime, while 138 million patients will be impacted each year (Lírio et al., 2019).

The disruption of the chemical equilibrium within the vagina may arise due to a number of factors, including the environment—warm weather and humid places can encourage the growth of candida albicans—tight and inappropriate clothing, poor hygiene, the use of antibiotics, which can sometimes weaken the immune system in cases of diseases like HIV or AIDS, wet skin, pregnancy—hormonal contraceptives can alter hormonal levels during pregnancy and during use, which can change the level of candida in the vagina—unprotected sex, inappropriate diet, sedentary lifestyle, and medical conditions—such as diabetes. Uncontrolled diabetes causes an excess of sugar in urine, which might have an adverse effect on the vagina (Horowitz et al., 1992; Lopez, 2015; Sobel, 1997). Predisposition is also noted among people with iron deficiency anemia, immunosuppression, obesity, and menstruation (Sasani et al., 2021). Furthermore, the appearance of thrush is triggered by increased estrogen levels in the following situations: hormone replacement therapy, pregnancy, and contraception (Rosati et al., 2020).

However, the administration of antibiotics poses a number of problems. Bacterial resistance to antibiotics has grown due to their incorrect and overuse. As a consequence, infections that can be usually effectively treated with antibiotics are becoming more resistant to the medications, leading to infections that are more challenging to cure (Balkis et al., 2002). Antibiotics disturb the normal population of microbes in the human body in addition to facilitating the elimination of harmful bacteria This disturbance may have an adverse effect on the immune system and general health, increase the risk of secondary infections, and cause an imbalance in the vaginal microbiota. Antibiotic residues damage ecosystems when they find their way into the soil and water. These residues might interact with bacteria in the surrounding environment, promoting the bacterial growth of drug resistance and perhaps having detrimental impacts on aquatic life and other elements of the ecosystem. Thus, it's crucial to develop alternative, eco-friendly techniques that can reduce or replace the use of antibiotics (Hou & Huang, 2024).

Candida yeasts are part of the vagina's natural physiological flora, but when they multiply uncontrolled and come in contact to lots of virulence factors, inflammation occurs (Cooke et al., 2022; Willems et al., 2020) . Candida albicans is the most frequent fungus that causes VVC, accounting for 85–90% of cases (Ardizzoni et al., 2021; Balakrishnan et al., 2022; Lopez, 2015). It typically occurring in pregnant and premenopausal women who have no sscomorbidities. VVC can also be caused by non-albicans Candida (NAC) species such as C. glabrata, C. dubiniensis, C. tropicalis, and C. Krusei

(Rodríguez-Cerdeira et al., 2020). Candida glabrata is the second most prevalent agent causing vaginal candidiasis (Gonçalves et al., 2016). It is more frequently experienced in diabetic and postmenopausal individuals (Jafarzadeh et al., 2022).

The diagnosis of VVC is based on clinical manifestations and microbiological assessments, such as a culture with an antibiogram, which is still regarded as the gold standard for diagnosis. While other approaches have relatively limited sensitivity, cultures are frequently related with delayed assessment and therapy (Nyirjesy et al., 2022). As medications such as fluconazole are readily available, an increasing number of strains are developing resistance to current therapies. Patients are using over-the-counter medications that don't require a prescription because they are easily accessible. Researchers are being forced to search for innovative alternative treatments due to rising resistance to antifungal drugs and a growth in the potential of VCC (Esfahani et al., 2022). One of these is phytotherapy, which involves the topical application of several herbs. According to the World Health Organization, more than 80% of individuals use plant extracts, or active compounds produced by plants, for treatment (Khan & Ahmad, 2019). Among these are essential oils (Krzepiłko et al., 2020).

Essential oils are secondary metabolites that are commonly extracted by solvent extraction, distillation, or cold pressing from the flowers, leaves, roots, fruits, or bark of plants (Spisni et al., 2020; Valdivieso-Ugarte et al., 2019). Based on the active components and strong aroma (Mancianti & Ebani, 2020). It possesses antibacterial activities that can suppress or eliminate numerous pathogens, including as bacteria, fungus, and viruses (Bakkali et al., 2008). Because of their distinct chemical compositions, individual essential oils possess varying levels of antifungal and antibacterial efficacy. Volatile compounds such phenols, alcohols, esters, aldehydes, and ketones are present in a number of essential oils (Dhifi et al., 2016). Capable of suppressing or eliminating pathogens. Furthermore, as a natural product, essential oil is distinguished by its safety, efficacy, without any residue, lack of resistance, significant tolerance within the animal body, as well as minimal toxic side effects, which render it one of the most potential antibiotic alternatives. Although some pharmaceutical treatments, essential oils' antifungal/antibacterial properties are a consequence of many components working together. This complex combination of components makes it challenging for microorganisms to generate antimicrobial resistance to essential oils, reducing the risk of infection. Besides contributing to their antifungal and antibacterial properties, numerous essential oils exhibit vulvovaginal regulating properties. They help restore equilibrium in vulvovaginal flora by supporting the growth of good bacteria with minimizing harmful bacterial/fungal proliferation, thus maintaining vulvovaginal health. These characteristics possess important implications for the prevention and treatment of diseases and infections caused by dysregulation of vaginal flora (Hou & Huang, 2024).

The changes in the vaginal microbiome includes the decrease in the number of Lactobacillus and a rise in the abundance of facultative and anaerobic microbes, which can make the host susceptible to a variety of disorders, such as premature births and a greater possibility of bacterial infection(Jayaram et al., 2020). Since such, the physiological status of the vaginal environment is extremely crucial to the host's health and reproduction (Amabebe & Anumba, 2018). To summarize, given the diverse and significant properties of the vaginal microbiome, we actively recommend for more exact characterization of the bacterial community in healthy women, taking consideration of variations among individuals. A comprehensive analysis of a healthy vaginal microbiome can be utilized to diagnose a disease more quickly and efficiently whenever the vaginal microbiome changes (Sun et al., 2023).

METHODOLOGY

The purpose of this review was to assess the antifungal potential of essential oils (EOs) obtained from plants; against Candida albicans, with an emphasis on the data from in vitro investigations and their use in the treatment of vaginal candidiasis.

A thorough literature search spanning papers from 2000 to 2024 was conducted utilising scientific databases such as PubMed, Scopus, ScienceDirect, and Google Scholar. The search terms that were utilised were: "essential oils and Candida albicans," "natural products and vaginal candidiasis," "antifungals derived from plants," "in vitro model and Candida," and "synergistic effects and essential oils and antifungal."

Only English-language, peer-reviewed publications were included. The following inclusion criteria were used in the selection of studies:

1. Researched essential oils or their primary components (such as thymol, carvacrol, eugenol, terpinen-4-ol).
2. Concentrated on *Candida albicans* as the main pathogen;
3. Utilized in vitro models, including broth microdilution, disk diffusion, or biofilm assays;
4. Documented antifungal activity parameters like minimum inhibitory concentration (MIC), or inhibition zones.

Exclusion criteria included: Studies that did not involve plant-based antifungal agents; non-original articles (for example, editorials, subjective opinions, or commentaries); Reports that lacked adequate methodological details or quantitative antifungal data. The chosen studies were thoroughly evaluated for their experimental design, essential oil composition, modes of

action, and significance to vaginal candidiasis, particularly in relation to biofilm inhibition, morphological changes, and synergistic effects with standard antifungal treatments. This qualitative synthesis aims to present a structured overview of the current state of research and identify future directions for the clinical application of essential oils in antifungal therapy

List of various essential oil with respective MIC Table 1.

Essential oils	Biological name & family	Extraction method	Active chemical constituents	Methods of microbial study	MIC	References
Wild sage EO	*Saliva macrosiphon, Family Lamiaceae*	Hydro distillation in Clevenger apparatus	Butyl benzoate (49.16%), n-hexyl benzoate (7%), Isospathulenol (4.8%), Cyperene (4.1%),Benzoic acid, 2-methyl-, butyl ester (3.88%), betacaryophyllene (3.54%), and β-Elemene (3.02%).	Broth microdilution	0.039-2.5 µl/ml	(Nouripour-Sisakht et al., 2024)
Cumin seed EO	*Cumminum cyminum, Family Apiaceae*	SWE, hydrodistillation and Soxhlet extraction methods	1H-indene derivatives (59.77%) and Cuminic aldehyde (13.77%) cuminal, cumin-alcohol, p-cymene, β-pinene, 2-care-10-al, and γ-terpine	broth microdilution	0.08 µl/ml to 1.25 µl/ml	(Eikani et al., 2007; Kamble, 2015; Katiraee et al., 2017; Srinivasan, 2018)
				Broth macrodilution method	0.08 – 0.62 µl/ml	
				broth microdilution susceptibility testing	3.2µl/ml	
Allium EO	*Allium heamanthoides, Family Alliaceace*	Hydrodistillation	Diallyl disulfide, Trisulfide, methyl 2-propenyl, Trisulfide, di-2-propenyl, Disulfide, methyl 1- propenyl, Dimethyl trisulfide,2-Chlorbenzothiazole, Tetrasulfide, di-2-propenyl	Broth microdilution	0.08 – 0.62 µl/ml	(Fritsch & Abbasi, 2008; Katiraee et al., 2017)
Ground Savory/Summer savory EO	*Satureja khuzistanica, Family Lamiaceae*	Hydro-distillation by Clevenger type apparatus for 3 hr	p-cymene (0.44%) and γ-terpinene (0.34%)	Disc diffusion and micro broth dilution assays	P>0.05)	(Abbasloo et al., 2023; Mahboubi & Attaran, 2019)
Clove EO	*Syzygium aromaticum Family Myrtaceae*	Hydro-distillation	Eugenol (53.08%) β-caryophyllene (33.80%),	Tube dilution method	0.051 mg/ml	(Ahmad et al., 2005; González-Rivera et al., 2016)
Apple mint, woolly mint or round-leafed mint EO	*Mentha suaveolens Ehrh. Family Lamiaceae*	Hydrodistillation of the leaves using a Clevenger-type apparatus	PO, piperitenone (PIP), nepetalactone (NPL), p-cymen8-ol (PCY), limonene (LIM), and cis-piperitone epoxide (CPO	microbroth dilution method (microsterile plate)	MIC 0.39–0.78 mg/mL (0.039% and 0.078% p/v)	(Božović et al., 2015; Garzoli et al., 2015; Pietrella et al., 2011)
Thyme EO	*Thymus vulgaris L Family Lamiaceae*	Hydro-distillation method	Thymol (566%) and p-cymene (123%) were the major components, followed by carvacrol	Diffusion and dilution assay	0.11 mg/ml	(Bogavac et al., 2015; Borugă et al., 2014)

			(87%) and linalool (46%)			
Cinnamon EO	*Cinnamomum zeylanicum Family Lauraceae*	Steam distillation method	Cinnamaldehyde, eugenyl acetate, linalool, and benzyl benzoate	Microdilution method	0.13 mg/mL	(Chen et al., 2019; Husain et al., 2018; Shahina et al., 2018)
Coriander EO	*Coriandrum sativum L. Family Apiaceae*	Supercritical carbon dioxide extraction	Linalool (more than 50%), geraniol (20%) and linalyl acetate	Diffusion and dilution assay	0.45mg/ml	(Bogavac et al., 2015; Geed et al., 2014)
Origanum vulgare L.EO	*Origanum vulgare L., Family Lamiaceae*	Hydro-distillation in a Clevenger-type apparatus	Carvacrol (72.06 %) and thymol (4.98 %) were the major oil constituents, followed by trans-caryophyllene (3.61 %) and p-cymene (2.08 %).	Kirby-Bauer method	0·45 μl ml^{-1}.	(Karaman et al., 2017; Lakhrissi et al., 2016)
Ajwain EO	*Trachyspermum ammi Family Apiaceae*	Hydrodistillation method	Thymol , ρ-cymene and γ-terpinen	Broth micro-dilution susceptibility method	0.5 mg/ml	(Ardestani et al., 2020; Bairwa et al., 2012)
Zataria multiflora EO	*Zataria multiflora Family Lamiaceae*	Hydro-distillation Method	Thymol, carvacrol, para-cymene, and transcaryophyllin	Disc Diffusion Methods	0.625 mg/ml	(Katiraee et al., 2017)
Dill EO	*Anethum graveolens L. Family Umbelliferae*	Hydro-distillation method	Carvone and limonene	Microbroth dilution method	0.625 mg/ml	(Jana & Shekhawat, 2010; Zeng et al., 2011)
Fennel EO	*Foeniculum vulgare Family Apiaceae (Umbelliferae)*	Hydro-distillation method	Anethole , Limonene ,Fenchone , α-Pinen, estragole	Broth microdilution assay	0.78%	(Bassyouni et al., 2019; Hammouda et al., 2014)
Geranium herbarum EO	*Geranium herbarum Family Geraniaceae*	Hydro-distillation method	Linalool, citronellol and geraniol, - Bourboneneβ, Menthone ,Geranyl formate, Citronellyl propionate,0-octen-1-0 ,Caryophyllene oxide	Broth microdilution	0.904µl/ml	(Katiraee et al., 2017)
Rose-scented Geranium EO	*Pelargonium Graveolens Family Geraniaceae*	Hydrodistillation method	Citronellol (24.9%), geraniol (17.5%), linalool (12.9%)	Broth microdilution method	1 μl/ml	(Ćavar & Maksimović, 2012; Schwiertz et al., 2006)
Palmarosa oil, Rosha grass	*Cymbopogan maritinii Family Poaceae*	Hydrodistillation method	Geraniol (78.4%), geranyl acetate (11.6%		1 μl/ml	(Kumar et al., 2024; Schwiertz et al., 2006)
Pelargonium graveolens EO	*Cymbopogan martini family Geraniaceae*	Hydrodistillation	Geraniol (78.4%), geranyl acetate (11.6%)		1 μl/ml	(Draiaia et al., 2025; Schwiertz et al., 2006)
Lemongrass EO	*Cymbopogan citratus Family Poaceae*	Clavenger type steam system	Neral (43.3%), geranial (56.9%)		1 μl/ml	(Cortes-Torres et al., 2023; Schwiertz et al., 2006)
Artemisia EO	*Artemisia sieberi Family Asteraceae*	Hydrodistillation	Santolina alcohol, camphore, a- thujone, a-terpineole, 1,8- cineole	disc diffusion method	1.173	(Katiraee et al., 2017; Mohamed et al., 2010)

Pine turpentine EO	*Pine turpentine Family Pinaceae*	Hydro-distillation with a Clevenger apparatus	alpha pinene, 12.111% beta pinene, 3.338% limonene, 3.152% camphene and 3.123% delta-3-carene	Agar Well Diffusion	0.5-2µL mL-1	(Özcan Ateş & Kanbur, 2023; Tumen et al., 2010)
Rosemary EO	*Rosmarins officinalis , Family Lamiaceae*	Hydrodistillation	45% 1,8-cineole (eucalyptol), 15% **αα**-pinene, 12% camphor, 4% camphene, 3% borneol, 3% caryophyllene, 2% **αα**-terpineol, 1% myrcene, 1% p-cymene, 0.7% linalool	Micro - dilution method using 96-well plates method	1.56 mg/mL	(Karpiński et al., 2023)
Neroli EO	*Citrus aurantium Family Rutaceae*	Hydrodistillation	Linalool (29.1%), limonene (16.7%), b-pinene (11.1%)	broth microdilution method	2 µl/ml	(Maksoud et al., 2021; Schwiertz et al., 2006)
Grapefruit peel EO	*Citrus paradise family Rutaceae*	cold pressing extraction method	Monoterpenic hydrocarbons as limonene (94.8%), α-terpinene (1.8%), α-pinene (0.5%) and sabinene (0.4%),β-pinene, γ-terpinene and myrcene (<0.05%), sesquiterpenic hydrocarbons (0.3%), aliphatic aldehydes such as octanal (0.4%), decanal (0.3%), dodecanal (0.1%) and tetradecenal, alcohols such as linalol, (*E*)-p-menthadien-1-ol and α-terpineol (0.1%), esters (0.4%) and nootkatone (0.1%)	Agar disc diffusion method	0.25%v/v	(Bona et al., 2016; Delgado et al., 2020)
Lavander EO	*Lavandula angustifolia Family Lamiaceae*	Hydrodistillation method	g-terpinene , Cuminaldehyde, 2-norpinene-2carboxaldehyde,b-pinene,pulegone,sabinene	Broth micro dilution method	2.6 µl/mL	(Katiraee et al., 2017)
Radish root EO	Raphanus sativus L.; family Cruciferae	Steam distillation	Hydrocarbons , sulfur-containing substances, organic acids, aldehydes, ethers, ketones, terpenes, alcoholcaffeic acid and ferulic acid, linoleic acid, oleic acid, and stearic acid	Disc diffusion assay	3.125%	(Al-Janabi, 2022; Selyutina & Gapontseva, 2016)
Anise fruits EO	*Pimpinella anisum L Family Apiaceae*	Steam-distillation	80 to 95%, or more, trans-anethole, chavicol methyl ether (estragole), anisaldehyde and cis-anethole	Disc diffusion assay	less than 1.56% (v/v)	(El Zawawy & Mona, 2015; Kosalec et al., 2005)
Tea tree EO	*Melaleuca alternifolia Family Myrtaceae*	Steam distillation	a-Terpinene (11.3%), c-terpinene (24.9%), terpinen-4-ol (37.5%)	Kirby-Bauer disk diffusion susceptibility	0.125%	(Mertas et al., 2015)

				test		
Manuka EO	*Leptospermum scoparium Family Myrtaceae*	Steam distillation (Porter et al., 1999	Leptospermone (20%), calamenene (18%), cadina-1,4-diene (8%)	Broth micro dilution method	15 µl/mL	(Porter & Wilkins, 1999; Schwiertz et al., 2006)
Cyperus oil , purple nutsedge or nutgrass EO	*Cyperus rotundus*; Family Cyperaceae	Hydrodistillation	β-pinene (11.3%), α-pinene (10.8%), α-cyperone (7.9%), myrtenol (7.1%), α-selinene (6.6%), limonene (5.7%) and β-selinene (4.6	Disc diffusion assay	25 %v/v	(Al-Janabi, 2022; Lawal & Oyedeji, 2009)
Camphor EO	*Cinnamomum camphora*; family Lauraceae),	Supercritical fluid extraction	Camphor, α-pinene, sabinol, citral,borneol, α-terpineol,	Disc diffusion assay	25 %v/v	(Al-Janabi, 2022; Zhang et al., 2022)
Clary sage EO	*Salvia sclarea family Lamiaceae*	Steam distillation method	Linalyl acetate (47%), linalol (17.2%), germacrene-d (11%)	broth microdilution method	40% v/v	(Al-Janabi, 2022; Kakasy et al., 2001)
Aloe vera EO	Aloe barbadensis miller, family Liliaceal	Hydrodistillation	Carvacrol (50.78%), thymol (16.94%), and linalool (12.68%	Agar well diffusion method	16.99mm	(Abbaszadegan et al., 2016; Özcan Ateş & Kanbur, 2023)
Bible hyssop EO	Origanum syriacum family Lamiaceae	Hydrodistillation	thymol (18.21%), carvacrol (11.67%), p-cymene (26.95%) and γ-terpinene (20.17%)	Kirby-Bauer Single Disc Diffusion Test	34.0 mm	(Kassaify et al., 2008; Mesmar et al., 2022)
Jasmine flower EO	*Jasminum officinale Family Oleaceae*	Hydrodistillation	Benzyl acetate, Benzyl benzoate, Geranyl linalool, Nerolidol	Agar well diffusion method	6.00mm	(Özcan Ateş & Kanbur, 2023; Tharakan, 2021; Wei et al., 2015)

In vitro model to investigate *candida albicans*

A. Simple *in vitro* models mimicking vaginal infections

In accordance with healthy human vaginal mucosal tissue, the VK2/E6E7 cell line was immortalized via retroviral transduction (Fichorova et al., 1997). Utilizing this cell line, it was possible to illustrate how C. albicans and streptococci can work synergistically (Pidwill et al., 2018) and how autophagy system assists epithelial cells survive an infection with C. albicans (Shroff & Reddy, 2018).

Furthermore, it was discovered that Type-I IFN signaling promotes the epithelium's resistance to C. albicans infection (Li et al., 2017). This model has been utilized to show that the involvement of VVC in diabetic individuals may be associated to increased C. albicans adhesion through potential interactions with ICAM-1 through generating high glucose circumstances (Mikamo et al., 2018).

The A431 cell line is derived from a vaginal epidermoid carcinoma. Inflammatory cytokine responses and candidalysin-induced A431 cell damage have been investigated using this cell line (Richardson et al., 2018). The cell line was additionally utilized to determine the effect of azole antifungal therapy on damage caused by the C. albicans species (Wächtler et al., 2011).

B. Complex *in vitro* models mimicking vaginal infections

A reconstructed vaginal epithelium (RHVE) is a viable alternative model. RHVE is based on A431 cells grown at an ALI. RHVE was utilized to show that C. albicans enhances C. glabrata interactions with the vaginal epithelium by boosting fungal colonization, invasion, and epithelial cell injury during co-infection (Alves et al., 2014). Additionally, C. glabrata's adaptation to an acidic vaginal environment was studied using RHVE (Bernardo et al., 2017).

C. Organ-on-chip models mimicking vaginal infections

Several OOC models simulate the female reproductive system, intending to replicate the physiology of the placenta, uterus, or endometrium (Mancini & Pensabene, 2019).In any prospective OOC models of the vaginal mucosa, a porous membrane should separate the perfused endothelial cells and stratified squamous epithelium. The immune cells can be efficiently obtained during epithelial hyphal invasion to mimic appropriate inflammatory responses, such as neutrophil activation (Last et al., 2021).

D. Reconstituted human vaginal epithelium (RHVE) and model of vaginal candidiasis

Skinethic Laboratory donated the human epithelium for the in vitro vaginal candidiasis model. It was created by cultivating modified human keratinocytes of the A 431 cell line originating from a vulval epidermoid carcinoma. Keratinocytes were incubated in serum-free conditions in an appropriate medium based on the MCDB-153 media (Clonetics, San Diego, Calif.) with 5 µg of insulin per ml, over a 0.5-cm2 microporous polycarbonate material filter for 7 days at the air-liquid interface. In vivo, A431 cells develop three-dimensional epithelial tissue that appears to be human vaginal mucosa. Antibiotics and antimycotics were not utilized for developing the in vitro model or any of the culture material. Each C. albicans strain performed a triplicate infection experiment. RHVE was infected with 2 x 106 C. albicans cells from SC5314 and the CAF2-1 parental strains, the SAP1 and SAP2 revertant strains in 50 µl of PBS for 6, 12, and 24 hours, as well as the mutants sap1, sap2, sap3, and sap4 to sap6. The controls had just received 50 µl of PBS.

To inhibit Saps, 50 µl of PBS containing 2 × 106C. albicans SC5314 cells was treated with amprenavir (Glaxo/Wellcome, Bad Oldeslohe, Germany), pepstatin A (Sigma, Deisenhofen, Germany), and ritonavir (Abbott, Wiesbaden, Germany) dissolved in absolute methanol at final concentrations of 0.1, 15, and 32 µM, respectively. The maintenance medium (1 ml) of the epithelial cells was also treated with the same inhibitor doses. 50 µl of PBS treated with amprenavir, ritonavir, or pepstatin A was used as a control; however, C. albicans cells were not present. The periods of incubation were 6, 12, and 24 hours.

The incubation circumstances for all tissue cultures were 37°C, 5% CO2, and 100% humidity. (Schaller et al., 2003).

E. Thoma hemocytometer

A quasi-experimental study was conducted to investigate the antifungal properties of lavender (essential oil) based on the number of fungus cells in liquid medium using a Thoma hemocytometer slide (micro dilution method). The micro dilution method, one of the antifungal sensitivity standard tests, is used as a preferred way for determining antifungal sensitivity in vitro (Behmanesh et al., 2015).

F. *Antimicrobial activity of Lactobacillus strains*

The antimicrobial capacity of vaginal lactobacilli against Candida spp. was measured by the agar overlay technique, with slight modifications. MRS agar plates were inoculated with 10 µL of Lactobacillus suspensions (108 UFC mL−1) and incubated at 37°C for 24 hours in microaerophilic conditions. Following incubation, 106 CFU Candida in 10 mL of melted SD agar were added to the MRS containing the cultivated lactobacilli. The plates were incubated aerobically at 37°C for 24 hours so as to permit Candida to proliferate. Inhibition zones over or around Lactobacillus colonies indicated an antimicrobial effect. The diameters of the inhibitory halo have been calculated by subtracting the colony diameter from the total diameter. Three independent experiments were carried out (De Gregorio et al., 2019).

DISCUSSION

Vaginal candidiasis, mainly caused by *Candida albicans*, is a common infection affecting up to 75% of women at least once in their lifetime, with approximately 5–8% experiencing recurrent infections (Sobel, 2007). Standard antifungal treatments, including azoles such as fluconazole and clotrimazole, are effective in most cases but are increasingly associated with drug resistance, relapse, and adverse effects (Sanguinetti et al., 2015). Consequently, plant-derived essential oils (EOs) have garnered attention as potential alternative or complementary therapies due to their broad-spectrum antifungal properties and natural origin.

Essential oils such as **tea tree oil** (*Melaleuca alternifolia*), **oregano oil** (*Origanum vulgare*), **thyme oil** (*Thymus vulgaris*), and **lemongrass oil** (*Cymbopogon citratus*) have demonstrated significant antifungal activity against *Candida* species in vitro. These oils exert their effects through multiple mechanisms, including disruption of the fungal cell membrane, inhibition of hyphal transition, and suppression of biofilm formation (Bakkali et al., 2008; de Oliveira Lima et al., 2013).

For instance, **carvacrol and thymol**, the major phenolic components of oregano and thyme oils, destabilize the fungal cell membrane by interacting with ergosterol, leading to cell lysis and death (Ahmad et al., 2011). Similarly, **terpinen-4-ol**, the active compound in tea tree oil, has shown strong candidacidal activity by disrupting membrane integrity and mitochondrial function (Hammer et al., 2003).

Moreover, EOs have been reported to exert synergistic effects when combined with conventional antifungals. For example, combining tea tree oil with fluconazole enhanced antifungal efficacy against fluconazole-resistant *Candida albicans* strains (Sherry et al., 2014). Such combinations may allow for lower doses of standard drugs, reducing toxicity and delaying resistance development.

Despite promising in vitro and animal model results, clinical application of EOs for vaginal candidiasis remains limited. Challenges include variability in EO composition due to differences in plant chemotypes, extraction methods, and geographical origins (Burt, 2004). Furthermore, the hydrophobic and volatile nature of EOs complicates formulation and delivery to mucosal tissues. Local irritation, allergic reactions, and inconsistent dosing are potential risks that must be addressed through standardized formulations and safety testing.

Recent advances in nanotechnology offer potential solutions. Encapsulating EOs in nanoparticles, liposomes, or hydrogels can improve their stability, bioavailability, and mucosal retention, while minimizing irritation (Nazzaro et al., 2013). These delivery systems have shown promise in preclinical studies and could enhance the therapeutic potential of EOs for vaginal applications.

In summary, EOs represent a multi-targeted, natural alternative for the treatment of vaginal candidiasis. However, more rigorous in vivo and clinical investigations are essential to confirm efficacy, safety, and optimal use protocols.

In vitro models that simulate the vaginal environment such as reconstructed human vaginal epithelial models or cervico-vaginal epithelial cell lines have been utilized to test the safety and efficacy of EOs (Rossoni et al., 2014). These models reveal that certain EOs not only reduce fungal load but also preserve epithelial integrity and limit inflammation. For example, treatment with **tea tree oil** in an in vitro vaginal model significantly reduced fungal adhesion and epithelial cell damage (Sudjana et al., 2012).

Such models are crucial in predicting in vivo outcomes, especially given the complexity of the vaginal ecosystem and host-microbiome interactions. They also offer a platform to test EO-based formulations like gels, creams, or suppositories.

CONCLUSION

Plant-derived essential oils offer a promising, natural alternative for the treatment of vaginal candidiasis, particularly considering growing antifungal resistance and patient demand for gentler, non-synthetic therapies. Their multifaceted mechanisms of action and potential for synergy with conventional drugs position them as attractive candidates for future antifungal development. However, translating these findings into clinical practice requires further standardization, toxicological evaluation, and well-designed clinical trials. As the interest in integrative medicine continues to grow, essential oils may emerge as valuable tools in managing recurrent and resistant vaginal Candida infections—especially when formulated using advanced pharmaceutical technologies.

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