International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1399-1406 www.ijprajournal.com ISSN: 2456-4494

Medicinal Plants for Management of Candida Albicans Biofilm Formation

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Submitted: 05-08-2022 Accepted: 14-08-2022

ABSTRACT:
Herbal products are natural products that have been very useful for humans to cure various ailments and as an alternative medicine for conventional therapy. However, bacteria in natural environments exist mainly in biofilm formation and are more likely to cause severe infections than their planktonic counterparts. Biofilm is associated with impaired epithelization and granulation tissue formation and also promotes a low-grade inflammatory response that interferes with wound healing. Since the infection caused by biofilm is often very difficult to treat, it is necessary to find a new active anti-biofilm agent. In the recent past, interest in the therapeutic and nutritional properties of various medicinal plants and their natural photochemical compounds established because of their anti-biofilm activities has gradually increased. In this review, we described different aerial parts of medicinal plants that have the anti-biofilm effect, which was evaluated against biofilm-producing different bacterial pathogens and antimicrobial agents that are responsible for wound healing.

KEYWORDS: Medicinal Plants, Phytochemical, Antibiofilm activity.

I .NTRODUCTION

A biofilm consists of a community of microorganisms that are irreversibly attached to a given surface, inert material, or living tissue, producing extracellular polymers that provide a structural matrix.Microorganisms in this type of community show lower growth rates and higher resistance to antimicrobial treatment, behaving very differently from planktonic cells. The ability to adhere to different types of surfaces allows microorganisms to form biofilms on medical devices, such as such as intravascular catheters, and cardiac prostheses.[1] valves and joint replacements or in various host tissues. linking biofilms to persistent colonization and infection. A single microbial species is capable of biofilm formation, although a mixture of bacterial and fungal species underlies biofilm formation in vivo. Having considered that 80% of all microorganisms living in this form, biofilm formation becomes an irrevocable field to explore. Due to these general characteristics, biofilms potentiate the establishment of unyielding infections in the human host. This is the case of biofilms formed by Candida species, which cause superficial and systemic fungal infections in immunocompromised patients.[2]These infections are very difficult to treat due to the characteristics of these species: resistance to antifungal drugs, expression of virulence factors, and the ability to form biofilm. Indeed, mucosal infections involve biofilm formation.[8] typically includes interaction with commensal bacterial flora and host components. Candida species are the fourth most common cause of nosocomial bloodstream infection in the United States. These infections are associated with a high mortality rate of approximately 50%. Biofilms are an additional problem because they are commonly found in medical devices such as prostheses, cardioverter defibrillators, urinary and vascular catheters, and cardiac devices that prevent the eradication of infections. with Candida.[3]

Candida infections

Candida species can cause superficial and local mucosal infections and the best known of these is commonly called thrush. Such infections generally affect gastrointestinal, vaginal, esophageal, and oral pharyngeal mucosal. Besides, most of women suffer from vulvovaginal candidiasis (VVC) at least once in their lives.[4]

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Some women experience repeated recurrences of this infection and it is known as recurrent vulvovaginal candidiasis (RVVC, oropharyngeal candidiasis (OPC) is common in HIV-infected patients and is also considered an important marker for the onset of AIDS. OPC also affects patients with oral diseases, cancer, and debilitated patients who produce less saliva However, it can cause a severe, life-threatening infection that leads to colonization of internal organs with Candida (disseminated candidiasis), which is a serious health problem in these individuals. The mortality rate in these patients is between 30% and 50% Candida infections in the United States are the fourth most common hospital-acquired infection and the second leading cause of such infections. Among Candida species, C. albicans causes most candidemia, followed by non-albicans strains such as Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei .C. glabrata is responsible for approximately 16% of all bloodstream infections, while C. krusei accounts for 2% of all clinical Candida isolates[5]

These challenging infections can be caused by different Candida species. C. albicans is the most common pathogen responsible for Candida infections, followed by Candida glabrata. Candida tropicalis is particularly relevant in urinary tract infections. while Candida parapsilosis is frequently found in the skin of healthy hosts and is the causative agent of catheter-related infections. Each species of Candida presents differences in terms of biofilm formation, namely at the level of their morphology, the characteristics of the extracellular matrix (ECM), and the ability to confer antifungal resistance. This variability increases the challenge of finding an effective solution to address Candida biofilm threats as a unique problem. In fact, due to the emergence of these fungal infections, there is an urgent need to find appropriate therapeutic approaches that may be able to treat patients more effectively. The path to finding these therapies certainly involves studying the various pathogenic traits of these species, such as biofilm formation.[6]

Biofilm formation

Biofilm formation, although a process present in all Candida species focused on above, differs significantly from species to species and is dependent on surface, host niche, and other factors. For example, mature C. albicans biofilms show a more heterogeneous structure, composed of blastophores and hyphae surrounded by an ECM of polysaccharide materials ECM provides structural scaffolds for adhesion between cells and with different surfaces and a barrier between biofilm cells and the neighboring environment. In the structure of these biofilms there are usually water channels that surround the microcolonies. In the case of C. glabrata, the biofilm is composed exclusively of yeast-like cells in an intimately packed multilayer structure or in groups of cells. In turn, the biofilm of C. tropicalis corresponds to a network of yeasts, pseudohyphae, and hyphae, with intense budding of hyphae. while C. parapsilosis presents a biofilm consisting of groups of yeast cells adhered to the surface, with minimal ECM.[7] differences highlight the complexity of the processes underlying biofilm formation and the difficulty of finding a single way to eradicate all Candida biofilms.Candida biofilms occur mostly in the mucosa or endothelium involved in the development of common candidiasis, such as vaginal and oral candidiasis, but are also associated with medical devices, such as catheters and vascular and urinary prostheses. Interestingly, however, in all cases, biofilm formation compromises antifungal treatment, and when it occurs in implanted medical devices such as central venous catheters, implant replacement is often necessary.This review highlights the main challenges found in the process of developing effective therapy against Candida biofilms, taking into account the differences found in biofilm formation. and its regulation, as well as antifungal resistance found in biofilms and mixed-species biofilm establishment. The currently proposed promising strategies are also discussed here.[8]

II.PROMISING STRATEGIES FOR BIOFILM FORMATION

Biofilm formation by fungal and bacterial pathogens on implanted medical devices causes major patient morbidity and mortality and leads to billions of dollars in healthcare costs. It is estimated that there are more than 45 million medical devices implanted each year in the United States. Infection of these devices occurs in 60% of patients, and Candida species are responsible for up to 20%, and the accumulation of biofilm on substrates in the oral cavity is the main etiological factor of oral diseases, candidiasis being one of the most common oral fungal infections diagnosed in humans, with one of this infections. Biofilms are complex structures that are highly resistant to antimicrobial agents and the host's immune system. These cellular biofilms have an altered phenotype in terms of growth rate and gene transcription.

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Studies have shown that microorganisms are almost non-existent in their free planktonic form in host tissues, but are grouped together, forming a multicellular community, both in tissues and on prostheses, catheters, and other surfaces . Transplant procedures, immunosuppression, the use of residual devices, and prolonged stay in intensive care units increased the prevalence of fungal diseases Availability inside medical devices, such as central and peripheral catheters, hemodialysis, and peritoneal dialysis units, and intracardiac prosthetic valves, facilitates biofilm formation. Biofilm present in dental plaque was first recognized by the medical community in the 1960s . Prevalence of the formation up to 75% in denture users Patients who have undergone hemodialysis and peritoneal dialysis are frequently affected by infections caused by the presence of biofilm.[9]

Candida yeasts are among the main microorganisms isolated from cancer patients, possibly due to infection with the use of implanted intravenous access devices. Biofilm resistance mechanisms include extracellular matrix (ECM), efflux pump activity, persisters, cell density, overexpression of drug targets, stress responses, and general cell physiology Thus, to increase the effectiveness of new treatment strategies against bacterial and fungal infections , factors leading to biofilm growth inhibition, biofilm destruction, or biofilm eradication are sought. These factors could include enzymes, sodium salts, metal nanoparticles, antibiotics, acids, chitosan derivatives, or plant extracts. Thus, strategies aimed at eradicating biofilms are needed . More recently, the use of silver nanoparticles (AgNPs) has been suggested to coat medical titanium implants in the hope of inhibiting biofilm formation and thereby reducing the incidence of microbial infections and rejection Anti-Candida antibodies can reduce the binding of Candida to various surfaces. Antibody studies have been performed by various authors to test their effects on various fungal and bacterial organisms. The application of photodynamic therapy has been investigated in terms of its inactivation of microorganisms that are pathogenic to the human host. Several authors have associated light-emitting diodes (LEDs) with other substances. Several studies have been performed with gold nanoparticles and enhanced photodynamic therapy, including the use of methylene blue against recalcitrant pathogenic C. albicans biofilms [10]

Traditional herbal medicinal plants have antibiofilm activities with bioactive compounds.[11-13]

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Plant	Parts used	Family	Types of plant extract	Pathogens used for biofilm	Bioactive compounds
Licinia regida	Leaf	Chrysobalanaceae	Ethanolic extract	candida albicans (ATCC90028)	Phenolic compounds such as flavonoids gallocatechin and epigallocatechin.
Helicteresisora Linn.	Fruits	Malvaceae	methanol and petroleum ether extracts	C. albicans. (ATCC 90028)	phytochemical constituents such as alkaloids, terpenoids, and flavonoids
Zingiber officinale	Root	Zingiberaceae	Toluene and water extrat	Pseudomonas aeruginosa PA14	gingerols, shogaols, and paradols
Azadirachta indica	Leaf	Mahogany	aqueous, ethanolic, and ethyl acetate extracts	Aspergillusflavus, Aspergillus fumigatus, Aspergillus niger, Candida abicans etc.	Nimonol
Allium sativum	Leaf	Amaryllidaceae	Ethanol, methanol	Escherichia coli, Salmonella typhi, Staphylococcus aureus and Bacillus cereus	alliin, allicin, ajoenes, vinyldithiins, and flavonoids such as quercetin.
Mentha piperita	Essential oil from the leaf	Lamiaceae	-	Aggregatibacteractinomycetemcomitans, Candida albicans, Candida dubliniensis	Menthol, menthone menthofuran
Lavandula angustifolia	Essential oils	Lamiaceae	-	Escherichia coli, Staphylococcus aureus	linalool, alpha terpineol
Ficus sansibarica	Fruitsleavs, stem barks	Moraceae	Cold extract methanol, hexane, dichloromethane, ethyl acetate, and methanol	Escherichia coli, , Staphylococcus aureus	stearic and palmitic acids α-parinaric acid and cerium C

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Vitex negundo	Leaves	Lamiaceae	Methanol, ethyl acetate, petroleum ether, and hexane	Escherichia coli	viridiflorol (26.52%), p-caryophy/lene (13.20%), 4-terpineol (4.46%), linalool (2.04%),
Artocarpus lakooch	Bark	Moraceae	Aqueous extracts	Candida albicans, Candida tropicalis, Candida dubliniensi	rutin (4.61 min), pyrogallol (7.22 min), gallic acid (8.39 min), resorcinol (10.33 min), quercetin (14.29 min), catechin (31.32 min) and caffeic acid (36.96 min)
Murraya koenigii	Leaves, essential oil	Rutaceae	Ethanol, aqueous	Pseudomonas aeruginosa	β-Pinene, Myrcene, p-Cymene, Limonene
Euphorbia hirta	Aerial	Euphorbiaceae	Methanol	Pseudomonas aeruginosa	quercitrin, myricitrin , euphorbin-A , gallic acid
Ocimum tenuiflorumi	Leaves	Lamiaceae	Methanol	Escherichia coli	Oleanolic acid, Ursolic acid, Rosmarinic acid, Eugenol, Carvacrol, Linalool, and β-caryophyllene
Vinca minor	Leaves	Apocynaceae	Aquatic, acetone, and ethyl acetate	Proteus mirabilis, Pseudomonas aueroginasa	minovincine, methoxyminovincine, minovincinine, vincadifformine, desoxyvincaminol, and vincamajine.
Leucas aspera	Whole Plant	Lamiaceae	Methanol, ethyl acetate, petroleum ether, and hexane	Streptococcus pyogenes, Pseudomonas aeruginosa, Staphylococcus aureus	β-caryophyllene (34.2%), 1-octen-3-ol (14.8%), α-humulene (6.3%), α-pinene (5.8%), epi-α-bisabolol (4.6%) and limonene (4.5%).
Herniaria glabra	Leaf	Caryophyllaceae	Aqueous	Escherichia coli	medicagen, gypsogen, 16-hydroxy-medicagen

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Saliva triloba	Leaves, volatile oil	Lamiaceae	Ethanol	Staphylococcus aureus, Escherichia coli, and Candida albicans	camphor (4.5-24.5 %), cineole (5.5-13 %), humulene (0-12 %), trans-thujone (3-8.5 %)
Andrographis paniculata	Leaves	Acanthaceae	Ethanol, methanol, chloroform, aqueous, and hexane	Pseudomonas aeruginosa	diterpenoids, flavonoids, and polyphenols.
Lagenaria siceraria ta	Fruit	Cucurbitaceae	Organic and aqueous	Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Streptococcus pnueumoniae, Streptococcus pyogenes	Triterpenoids, flavonoids, and sterols
Buchania lanzan	Root	Anacardiaceae	Methanol	Escherichia coli, Pseudomonas aeruginosa	vitamin B, calcium, chlorine, copper, iron, magnesium, phos phorus, potassium, sodium,
Calendula officinalis	Flowers	Asteraceae.	Water	Salmonella, Shigella dysenteriae, Shigella flexneri, Shigella sonnei and Escherichia coli	flavonoids, carotenes, saponin, resin, and volatile oils
Rosa canina	Leaf	Rosaceae	Methanol	Pseudomonas aeruginosa, Salmonella typhimurium	sugars, organic acids, pectins, flavonoids, tannins, carotenoids, fatty acids, vitamins
Rhodomyrtus tomentosa	Leaf	Myrtaceae	Ethanol	Streptococcus pyrogens	potassium (221.76 mg/150 g fruit), calcium (73.65 mg/150 g fruit), manganese (3.23 mg/150 g fruit),
Aegle marmelos	Leaves	Rutaceae	Ethyl acetate	Salmonella typhi, Escherichia coli, Pseudomonas aerugonisa	coumarin, xanthotoxol, imperatorin, aegeline, and marmeline.
Kaempferia rotunda	Rhizome	Zingiberaceae	Ethanol	Pseudomonas aeruginosa, Staphylococcus aureus	sopimarane, abietane, labdane and clerodane

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Aerva lanata	Leaves	Amaranthaceae	Methanol, petroleum ether	Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Proteus vulgaris	Sitosteryl palmitate, hentriacontane, β-sitosterol and its D-glucoside, α-amyrin and betulin

III.BIOACTIVE COMPOUNDS OF PLANTS

Folk knowledge about the use of medicinal plants has been passed down for centuries. In recent years, much of the than pharmaceutical research has focused on more specific approaches to evaluate and understand the biological and pharmaceutical effects of medicinal and aromatic plants.Plants are rich in a wide variety of secondary metabolites that play an important role in the defense against numerous pathogens. These molecules are also involved in adaptation to biotic and abiotic stress, protection against ultraviolet radiation, oxidation of molecules, and nutritional and water stresses, at the same time they perform functions at the level of tissue structure, being able to add flavor and color to vegetable products.Currently, approximately 200,000 different plant secondary metabolites have been isolated and identified They can be classified based on their chemical structures and/or biosynthetic pathways A simple classification includes three main groups: terpenoids (polymeric derivatives of isoprene and biosynthesized from acetate through the mevalonic acid pathway), biosynthesized from the shikimate pathways, containing one or more hydroxylated aromatic rings) and alkaloids (nitrogen-containing non-protein compounds, biosynthesized from amino acids, such as tyrosine[14]

Terpenoids, the condensation products of C5 isoprene units, are the main components of plant volatiles and essential oil They exhibit many important properties, including anti-insect, antimicrobial, antiviral, and anti-herbivore properties.Phenolic compounds are widely found in fruits, seeds, leaves, roots, and stems and are known for their strong antioxidant capacity and their anticancer, anti-inflammatory, hypolipidemic, and hypoglycemic properties.They have at least one aromatic ring with one or more hydroxyl groups attached, ranging from the low molecular weight. molecules to large and complex ones. Alkaloids are usually cyclic organic compounds containing at least one nitrogen atom in an amine-type structure. These compounds are known to possess varied biological activities such as antimicrobial and antimalarial properties, among others. Many studies have been published on bioactive properties such as anti-inflammatory/anti-inflammatory antioxidants, antifungal, antiseptics, and antimicrobials. The antimicrobial and/or antibiofilm activity of some of these compounds is closely related to their ability to inhibit nucleic acid synthesis, disrupt the plasma membrane, inhibit efflux pumps, cause mitochondrial dysfunction, affect division, and/ or cell growth and affect. cell wall formation as shown in Figure 1.[15]

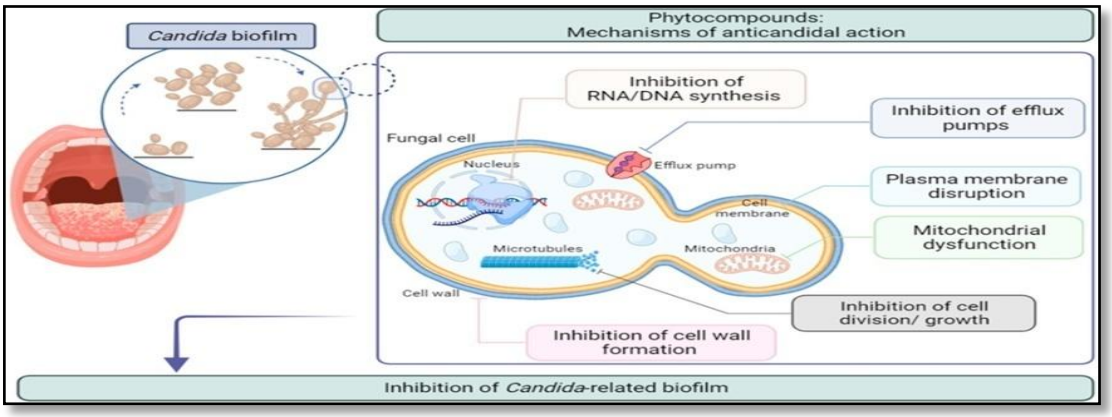

Figure 1. Mechanisms of action of phytocompounds against Candida spp. (Created with BioRen-der.com).

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IV.CONCLUSION AND FUTURE PERSPECTIVES

This review highlights the overwhelming complexity of the intracellular mechanisms leading to the formation of Candida biofilms, including those controlling adhesion, changes in cell morphology, and EPS production, especially given that these are in many cases species-specific or even stems. . In addition, external factors, including the surface where the biofilm forms, which can be a layer of epithelial cells or highly diversified plastic polymers, the cocktail of nutrients and inhibitors that are present in the environment, or the presence of other synergistic or antagonistic microorganisms, have a tremendous effect on the final characteristics of the formed biofilm. All this variability poses challenges from a clinical point of view, leading to the successful persistence of Candida infections associated with high mortality rates. All tactics against Candida biofilms implemented so far can solve this problem only partially. Therefore, the treatment and prevention of Candida biofilms must undergo improvements so that an effective solution can be applied. As discussed, newer strategies have the potential to be improved, although ongoing research into new therapies or the best combination of available ones is also a possible approach. However, specific knowledge of all the mechanisms behind biofilm formation and antifungal resistance in each Candida species will be crucial for delineating a more effective strategic plan in the fight against Candida infections.[16]

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