Possible plant-based solutions for skin yeast infections

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Abstract

Skin, hair, and nail fungal infections affect almost a billion people globally and their incidence is rising. *Candida* spp. and *Malassezia* spp., two yeasts that are part of the skin microbiota, normally do not cause disease. But, when dysbiosis occurs and the skin microbiome is disturbed, they can become pathogenic. There are conventional antifungals that treat candidiasis and *Malassezia* infections, such as azoles and allylamines, among others. However, the limitations of these treatments (resistance, side effects) lead to the search for new, alternative, and natural drugs, such as plant extracts (PEs) and essential oils (EOs). But these substances present some limitations (poor bioavailability and poor target capacity), which limits their efficiency. Their incorporation in formulations such as films and hydrogels (HGs) can help overcome these issues and may be a potential alternative to the current treatments. The main objective of this work is to provide a state-of-the-art review on *Candida* spp., *Malassezia* spp., mucocutaneous candidiasis and *Malassezia* infections, the conventional existing treatments and the incorporation of PEs and EOs in films and hydrogels as possible new alternative treatments for these diseases.

Keywords: *Candida* spp.; *Malassezia* spp.; films; hydrogels; essential oils; plant extracts[1]

[1] Abbreviations:

PEs - plant extracts

EOs - essential oils

HG - hydrogel

1. Introduction

Skin is the largest organ in the human body representing approximately 15% of the total body mass (Tchemtchoua et al., 2011) and is composed by three main layers. The outer layer (epidermis) is a cellular stratified structure responsible for the barrier function of the skin, mainly composed by keratinocytes. Between the epidermis and the dermis there is a membrane made of collagen, elastin, hyaluronan and proteoglycans responsible for skin's elasticity and mechanical resistance. The dermis, the second layer of the skin, is composed of fibroblasts that synthesize extracellular matrix components and endothelial cells that form blood vessels. The deepest layer of the skin, the hypodermis, possesses adipose tissue and is well vascularized, playing a role in the skin thermoregulatory and mechanical properties (Tchemtchoua et al., 2011).

The main function of the skin is to serve as barrier between our internal physiological environment and the exterior, preventing our body to be invaded by pathogenic microorganisms and protecting it from UV rays' exposure. It also plays a role in limiting the evaporation of water from the body, thus contributing to control our internal temperature (Gupta et al., 2012; Kozlowska et al., 2020).

Skin also has its own microbiota comprised by millions of bacteria, fungi and viruses that also covers its appendages and glands. The bacterial communities found on the skin are usually formed by bacteria belonging to the phyla Actinobacteria, Firmicutes, Bacteroidetes and Proteobacteria (Grice and Segre, 2011). Although some inter-variability and intra-variability exists, the dominant genera of skin bacteria are *Staphylococcus*, *Propionibacterium* and *Corynebacterium* and, less frequently, *Streptococcus* and *Pseudomonas* (Byrd et al., 2018; Grice and Segre, 2011). Regarding the fungal skin microbiome, yeasts belonging to the genus *Malassezia* are the main component of this community. Nevertheless, species belonging to genera *Cryptococcus* spp. *Rhodotorula* spp. and *Candida* spp. can also be present (Boxberger et al., 2021).

Mites from genus *Demodex* are also part of the eukaryotic organisms living on the skin (Boxberger et al., 2021). Viruses are also found on the skin and bacteriophages are the predominant ones. Other common viruses are Densovirus, Alphapapillomavirus, Human papillomavirus, Merkel cell polyomavirus, Molluscum contagiosum virus, Polyomavirus HPyV7, Polyomavirus, HpyV6 RD114 retrovirus and Simian virus. Papillomaviruses (Hannigan and Grice, 2013).

The skin microbiome varies with the body site. In oily sites bacteria from genera *Staphylococcus* and *Corynebacterium* dominate, whereas on dry sites *Corynebacteria, Flavobacteriales*, or β-*Proteobacteria* are the most abundant genera. Regarding the fungal microbiome, *Malassezia* spp. are usually found at the core body and arm sites. In the feet, more fungal species can be found, including *Aspergillus* spp., *Rhodotorula* spp., *Epicoccum* spp., *Malassezia* spp., and others (Fernandes et al., 2023).

Skin microbial communities play an important role in the protection from pathogens invasion, regulation of local pH and rapid response to sudden environmental changes (Pereira et al., 2017). However, when the skin barrier is broken or when the delicate equilibrium between commensals and pathogens is disturbed (dysbiosis), it can result in a skin disease (Byrd et al., 2018). In fact, this condition is associated with several diseases, some pathological (acne with the loss of phylotype diversity of *Cutibacterium acnes* (*C. acnes*) and atopic dermatitis with the increase in pathogenic *Staphylococcus aureus* and commensal *S. epidermidis*; others non-pathogenic, (sensitive and dry skin) or intensifying other skin disorders (psoriasis) (Byrd et al., 2018; Fournière et al., 2020).

Nowadays, skin diseases are an emerging concern affecting millions of people every day. They are mainly caused by infectious agents or inflammatory situations and can range in severity from benign to life threating. The severity of the dermatological condition depends on the type of pathogens involved, the integrity of the skin layers and structures and the underlying medical condition of the patient (Gupta et al., 2012). Several factors can be pointed out for the emergence of skin diseases, such as, environmental reasons, lifestyle changes, urbanization, widespread use of cosmetics, globalization and travel, antibiotic resistance, stress and mental health, changes in hygiene practices and aging population (English et al., 2003; Singh and Schikowski, 2023). Despite the great scientific progress in the treatment of dermatological conditions, many skin-related diseases are still difficult to solve. The effective treatment of skin disorders demands timely identification and management of the causative agent, choosing the most efficient treatment and the optimal administration route with an optimized dosing schedule (Gupta et al., 2012).

Conventional treatments for skin diseases, usually administered in the form of ointments and creams, need to be applied in high concentrations due to the low efficiency of the common delivery systems. This may result in toxic reactions such as skin irritation and allergies. Furthermore, they present other disadvantages such as greasiness and

stickiness, as well as an uncontrolled evaporation of the active ingredient that causes an unpleasant smell (Gupta et al., 2012).

This review will focus on essential oils (EOs) and plant extracts (PEs) for the treatment of fungal infections by *Candida* spp. and *Malassezia* spp. It will also provide a state-of-the-art review on films and hydrogels as biodegradable formulations for the delivery of EOs and PEs to the skin.

2. Skin yeast infections

Skin, hair, and nail fungal infections affect almost a billion people globally. Of these, more than 150 million people are affected with serious fungal infections that if left untreated, can evolve into systemic diseases, thus impacting their lives significantly or becoming fatal (Bongomin et al., 2017). The incidence and prevalence of each fungal infection depends on the socio-economic conditions, geographic region and cultural habits (Brown et al., 2012). The increasing number of people with HIV/AIDS, tuberculosis, chronic obstructive pulmonary disease, asthma, and cancer is responsible for the rise in the incidence and prevalence of fungal diseases across the world. The severity of fungal infections ranges from asymptomatic-mild mucocutaneous infections to potentially life-threatening systemic diseases, resulting in a mortality rate similar to that of tuberculosis and 3-fold more than malaria (Bongomin et al., 2017).

Candida spp. is a group of commensal yeasts usually found on the skin and mucous membranes of humans and animals (Bona et al., 2016). The genus *Candida* comprises more than 200 species, some of which are found in several body sites and secretions, (de Abreu et al., 2016), as part of the commensal microbiota. However, some species are pathogenic, being responsible for many diseases that represent a risk for human health (Bonifácio et al., 2015). Normally, the proliferation of these microorganisms is controlled by the host immune system, and they do not cause disease in healthy individuals. But, in immunocompromised patients or when microbial dysbiosis is present, they can become pathogenic (Bona et al., 2016; de Abreu et al., 2016; Höfling, José Francisco Puppin et al., 2019; Rai et al., 2017). Diabetes, immunosuppression, damage of the stratum corneum, wet conditions, occlusion, obesity, Cushing's syndrome and hormonal diseases are predisposing factors for candidiasis. Infants, pregnant women and elderly people are more likely to suffer from this disease (Rai et al., 2017).

Candida spp. is responsible for most of the invasive fungal infections all over the world. Mucocutaneous candidiasis is a very common fungal infection (M et al., 2020); it normally involves the skin folds in axillae, inguinal, genital and perigenital areas, hands, fingernails, skin beneath the breasts in women and mucous membranes (Rai et al., 2017). The most common etiological agent is *Candida albicans* (*C. albicans*), accounting for 80-90% of the cases (Talapko et al., 2021). However, *Candida tropicalis* (*C. tropicalis*), *Candida glabrata* (*C. glabrata*), *Candida parapsilosis* (*C. parapsilosis*), *Candida krusei* (*C. krusei*) and *Candida guilliermondii* (*C. guilliermondii*) can also be responsible (Rai et al., 2017). The main symptoms are erythema, erosions and cheesy white plates that are mostly frequent on mucosal tissues. In the intertriginous zones, such as submammary, inguinal folds, intergluteal creases, and pannus folds in overweight patients, the disease manifests as erythematous patches, sometimes erosive with light scaling on the surface and papules and pustules on the periphery (Talapko et al., 2021). *C. albicans* and *C. tropicalis* can also be responsible for onychomycosis or tinea unguium, infections that affect the nails or cause nails' dysfunction (Kumar et al., 2014).

Yeasts belonging to the genus *Malassezia* are the dominant eukaryotic colonizers of the skin, being more abundant on the sebaceous sites, such as scalp, face, chest and upper back, and less abundant on the trunk, arms and feet (Chandra et al., 2021). Usually, they grow and do not cause any disease due to a strict balance between the immune system and the skin microbiome. However, when this equilibrium is disturbed, due to dysfunctional skin barrier, genetic background or environmental factors, they can become pathogenic (Pedrosa et al., 2014; Saunders et al., 2012).

Malassezia-caused diseases are usually not life threating but constitute one of the most common diseases of the humankind (White et al., 2014). These skin conditions are either caused by these microorganisms or exacerbated by them in a changing skin environment (Chandra et al., 2021). Table 1 lists the diseases caused by *Malassezia*, the area(s) of the body affected, some characteristics/ symptoms of these conditions, and the responsible species.

2.1. *Candida* spp. and *Malassezia* spp. virulence factors

Both *Candida* spp. and *Malassezia* spp. are commensal colonizers of the skin that only cause disease when the host immunity is compromised. For these microorganisms

to become pathogenic and invade the skin, they need to produce several virulence factors (Figure 1).

The ability of *Candida* spp. to invade human tissues and cause disease depends on the 1) expression of adhesion proteins and hydrolytic enzymes; 2) characteristics of the cell wall; 3) morphological modification from yeast to pseudohyphal and hyphal forms; and 4) biofilm formation capability (Bona et al., 2016; Höfling, José Francisco Puppin et al., 2019) while for *Malassezia* spp., the principal characteristics that contribute for their pathogenicity are their lipolytic activity, special cell wall construction, hyphae formation/ biofilm formation and pigment production (Hort and Mayser, 2010)

2.2. Available conventional treatments

Cutaneous candidiasis is usually treated with topical antifungal drugs in the form of creams, gels, and solutions. The regular application of the antifungal for at least a few weeks is necessary for the complete cure of the infection. In immunosuppressed patients and in the case of widespread lesions and deep infections of the scalp, it is necessary to use systemic antifungals in combination with the topical ones (Rai et al., 2017). Azole drugs, such as econazole, clotrimazole, ketoconazole, and miconazole and polyene antifungals, such as nystatin, amphotericin B, and natamycin are usually used (Hay, 2018). *Candida* infections of the groins and inframammary folds are treated topically with azole or polyenes creams for at least 2 weeks. It is also important to dry the infected area because the skin moisture can cause discomfort (Hay, 2018). Onychomycosis by *Candida* can be treated with antifungals, such as itraconazole, fluconazole or ketoconazole, or by chemical removal, i.e., removal of the diseased and damaged part of nail alone, followed by local antifungal therapy. If these treatments do not work, avulsion (i.e., chemical destruction of the nail plate) and antifungal therapy must be used. Chronic mucocutaneous candidiasis must be treated with itraconazole and the daily dose can be increased to 200 mg. The treatment should be stopped when the remission is achieved. *Candida paronychia* is frequently aggravated by bacterial infections of the nail fold and irritant agents or contact dermatitis. In this case, the treatment consists of oral or topical antifungals and topical corticosteroids. But this condition often relapses since the swollen nail fold is a way for microbes and irritant substances to penetrate the skin. This situation

193 can be fixed through surgery that removes the fibrotic tissue that is found in chronic nail
194 swelling (Hay, 2018).
195 There are several studies on the antifungal activity of commonly used drugs upon
196 *Candida* species *in vitro*. Table 2 lists the minimum inhibitory concentrations (MICs) of
197 six of these antifungal agents.
198 Because *Malassezia* spp. can cause a series of diseases, the antifungal treatment to be
199 used will depend on the infection type. Several studies did an *in vitro* determination of
200 the antifungal activity of the most common drugs used against *Malassezia* species. In
201 Table 3, a list of MICs of seven antifungal agents commonly used upon 5 *Malassezia*
202 species is presented.
203 There are several antifungal therapies to treat *Malassezia* caused diseases (see
204 Supplementary table 1). Usually, topical antifungal drugs are used for the management
205 of localized skin diseases, while extensive disorders require administration of systemic
206 antifungals (Velegraki et al., 2015).
207

208 2.3. Problems with the current treatments for skin yeast infections: side 209 effects and antifungal resistance

210

211 The current treatments for mucocutaneous candidiasis and *Malassezia* infections
212 present a series of undesirable side effects. Azole antifungals, such as miconazole, present
213 increased burning, itching and irritation of the skin. Econazole can cause burning, itching
214 and redness too, while ketoconazole presents adverse effects such as itching, stinging, dry
215 skin and dry or oily scalp. The polyene antifungal nystatin has side effects that include
216 burning, itching and skin rash. It can also cause eye irritation, redness and generalized
217 pustular eruption (Rai et al., 2017).
218 Systemic antifungals have more severe adverse side effects. Fluconazole and
219 itraconazole can cause headache, dizziness, diarrhea, stomach pain, heartburn, changes in
220 the ability to taste food, excessive tiredness, loss of appetite, upset stomach, vomiting,
221 tingling or numbness in the extremities, fever, chills, exanthema, urticaria, angioedema
222 and difficulty swallowing. Terbinafine has similar adverse effects to those of triazoles.
223 These antifungal drugs cannot be used by pregnant and breastfeeding women and must
224 be used with caution in patients with severe hepatic and renal insufficiency and in children
225 (Rai et al., 2017).

Resistance to antifungal drugs is also a problem that has been arising in yeast infections (Rai et al., 2017). The main cause for the appearance of resistant yeast strains is the irregular use of antifungal drugs by patients, that often shorten the duration of the treatment which does not allow the complete elimination of the pathogenic agent. As such, the reinfection by fungal strains that became resistant to the antifungal drugs may occur, as well as the subsequent reinfection with different infectious strains that were not present in the first infection (Rai et al., 2017). Fungi developed a variety of mechanisms to overcome the fungistatic or fungicidal effects of all known antifungal classes (See Supplementary materials - Table 2) (Kaur et al., 2021; Vandeputte et al., 2012). Although they are diverse, they fit in the following generic classes: (i) reduction of the accumulation of the drug within the fungal cell; (ii) decreasing in the affinity of the drug for its target, and (iii) modifications of metabolism to counterbalance the drug effect (Vandeputte et al., 2012).

The direct consequence of the arising of resistant strains is the failure of conventional antifungal treatments and the difficulty in achieving the total cure of the disease (Rai et al., 2017). As such, the necessity for new antifungal agents is a reality.

3. Plant extracts and essential oils as antifungal agents

Humanity has been using plants for centuries as food source, raw materials for cloth production, shelter, decoration and remedies (Veiga et al., 2020). The use of medicinal plants is one of the oldest forms of healthcare known to man being a part of traditional and modern medicines (Massiha and Muradov, 2015; Veiga et al., 2020). Currently, in some countries of Africa, Asia and Latin America, traditional plant-based medicine is still used in primary healthcare needs (Massiha and Muradov, 2015). Recently, the interest of scientific community in PEs and EOs has increased because of their multiple properties, including antimicrobial and antioxidant activities (Freitas and Cattelan, 2018).

PEs are obtained by natural plants and have antioxidant activity, antimicrobial and immune response mediator activities, thus being of paramount importance for human health (Bashir et al., 2018; Liu et al., 2021). Besides, PEs can be effective at low concentrations, are cost-effective and easy to apply and present low toxicity levels and high stability during processing (Liu et al., 2021). The antifungal activity of some PEs

against some *Candida* and *Malassezia* species has already been determined by some authors (Table 4).

In yeast cells, PEs provoke changes in the cell morphology, such as elongation of the conidia, deposition of flocculated material in the fungal colonies and depressions on the cell surface (Cavalcanti Filho et al., 2017). They are also able to disrupt the plasma membrane by binding to ergosterol (Butassi et al., 2019), thus causing loss of membrane integrity, leakage of cellular materials (Alyousef, 2021) and cytolysis (Okla et al., 2021). Other mechanism of action of PEs is the rupture and shrinkage of fungal hyphae (Okla et al., 2021). In yeasts cells, PEs exert effects on the morphogenetic transition, leading to a predominance of isolated cells over budding cells and pseudohyphae (Cavalcanti Filho et al., 2017). They also have an inhibitory effect on biofilm formation (Chevalier et al., 2012; Ourabah et al., 2020; Soliman et al., 2017).

EOs are natural complex compounds composed of terpenes, aromatics and terpenoid molecules (Zuzarte et al., 2011). Usually, they are characterized by two or three major components, comprising 20-70% of their constitution that are responsible for most of their biological activities (Donato et al., 2020). EOs are liquid at room temperature, volatile, limpid, rarely colored, soluble in lipids and organic solvents, present a strong odor and are usually less dense than water (Bakkali et al., 2008). More than 17500 plant species are able to produce EOs that can be synthesized by all organs, and stocked in different structures, like secretory cells, cavities, canals, epidermic cells, and glandular trichomes (Bakkali et al., 2008; Baptista-Silva et al., 2020). EOs composition presents high variability among plant species and within the same species is frequent to find EOs with different chemo-types (Baptista-Silva et al., 2020). Inside the plant, EOs present a protective function because they act as antimicrobials, insecticides and protect them against herbivores by reducing the appetite of these animals for them. Additionally, they may also attract some pollinizing insects and repel the undesirable ones (Bakkali et al., 2008). They present antimicrobial activity against several microorganisms including antifungal activity against *Candida* spp. and *Malassezia* spp. (Table 4).

Some mechanisms of action of EOs include the reduction in ergosterol content by impairment of its biosynthesis (Pinto et al., 2006), damage of the cell membrane and cell wall as well as lysis of the mycelia (Inouye et al., 2007), destruction of the inner mitochondrial membranes and cell wall as well as expansion of endoplasmic reticulum near cell membranes (Park et al., 2007), inhibition of the ion transport process (Rivera-Yañez et al., 2017), intercalation between the fatty acids of lipid bilayer of the membrane

thus disrupting its fluidity and permeability (Rhimi et al., 2021), inhibition of the respiration process (Rivera-Yañez et al., 2017) and inhibitory action on spores germination (Bajpai et al., 2009). The antimicrobial activity of EOs is not attributable to one specific mechanism since they are constituted by different groups of chemical compounds and depends on their chemical composition. Instead, EOs act on several targets and provoke a cascade of reactions that involve the entire microbial cell (Burt, 2004; Nazzaro et al., 2013). Overall, studies on EOs and PEs seem to indicate that the antimicrobial activity of these compounds result from the effect of different substances on several cell targets (Zuzarte et al., 2011). Thus, the occurrence of resistant microbes to these substances seems unlikely because it would be necessary the occurrence of several mutations simultaneously to overcome all the distinct mechanisms of action at once (Zuzarte et al., 2011). Both EOs and PEs have a pleasant aroma which can be an advantage of these compounds when compared to traditional antifungal agents.

4. Films and hydrogels incorporated with PEs/EOs for the treatment of skin yeast infections

EOs and PEs have antifungal activity against yeasts of the genera *Candida* and *Malassezia* and other important bioactive properties, such as antioxidant activity, anti-inflammatory, anti-hemolytic, thrombolytic activity, anti-tumoral activity, etc. (Howard et al., 2015; Kar et al., 2018; Nascimento et al., 2020; UdDen and Shahid, 2017; Xavier et al., 2021). However, EOs and PEs activities can be altered due to environmental stress, high temperatures that can cause epimerization, and oxygen exposure (Dai and Mumper, 2010; Kaur et al., 2021). Additionally, some fungal species produce enzymes that can oxidize and inactivate EOs (Kaur et al., 2021). PEs and EOs also lack in targeting capacity and have poor bioavailability, which limits their therapeutic efficiency (Yang et al., 2018). Their incorporation in formulations such as films and hydrogels increase their physical stability and may modulate their bioactivity and antimicrobial potential. It also reduces the volatility and toxicity of EOs and controls their release (Bal-Öztürk et al., 2021).

4.1. Films

Films are thin and flexible structures with a continuous matrix that can be made of proteins, polysaccharides and/or lipids (Avila-Sosa et al., 2016; Karki et al., 2016). The three main components of a film are polymer(s), solvent, and plasticizer, which can be or not present (Avila-Sosa et al., 2016; Karki et al., 2016).

Polymers are the major film components; they are usually biocompatible and non-toxic. Also, their mechanical and barrier properties to water, oxygen, CO_2 transference and solute movements make them suitable for biomedical applications (Augusto et al., 2018; Karki et al., 2016). Proteins and polysaccharides are the most common used polymers in film production (Avila-Sosa et al., 2016). Water is the most used solvent to obtain solutions, but in some cases, ethanol or acidic solutions can be used to dissolve the polymer (Avila-Sosa et al., 2016). Solvents used in film formation need to be safe and suitable for biomedical applications.

Plasticizing agents are used in film formation to emulsify phases that are not miscible, affecting the film flexibility and resistance. Additionally, these substances make the film structure smoother by increasing the mobility of the polymer chains, reducing the intermolecular forces and improving mechanical properties such as elongation. The most used plasticizing agents are sorbitol, glycerol, mannitol, sucrose and polyethylene glycol (Avila-Sosa et al., 2016).

Usually, films are produced by solvent casting technique because it is feasible and cost-effective (Castro, 2018). However, hot melt extrusion and printing techniques can also be used (Karki et al., 2016).

When a film is completely formed, it needs to be characterized to understand their mechanical and permeability properties but also potential functional properties. There are several tests that can be performed to assess the quality parameters of a film and a summary of these attributes and the methods used for its evaluation can be found on Supplementary Table 3.

The use of films for bioactives delivery offers some advantages when compared to other formulations, such as: a) non-invasive way for administration; b) easy to manufacture and transport; c) cheap formulations; d) their ability to cover large body areas; e) high bio-adhesion; f) uniform surface and g) transparency that permits the control of skin healing without frequent changes (Karki et al., 2016; Leyva-Gómez et al., 2021). An ideal film must have good drug loading capacity, fast dissolution rate or long

residence time at the administration site and good stability. Additionally, it should be non-toxic, biocompatible and biodegradable (Karki et al., 2016).

EOs and PEs can be incorporated in the film matrix either by emulsification or homogenization techniques, thus changing its functionality (Atarés and Chiralt, 2016; Augusto et al., 2018).

4.1.1. Antifungal activity of films incorporated with EOs against skin yeasts

Nowadays, the available treatments for the management of skin infections caused by yeasts are largely based on small molecule antifungal drugs. But, these substances present poor solubility and bioavailability, limiting their efficiency, as well as undesirable side effects, and a rise in the number of resistant yeast strains that contribute for the search of new substitutes (Ntow-Boahene et al., 2021). Because of their antioxidant and antifungal properties, EOs and PEs can potentially be an alternative to common antifungal drugs. Additionally, their biocompatibility facilitates their incorporation into polymeric materials (Ntow-Boahene et al., 2021). In fact, several studies suggest that polymeric films incorporated with EOs and PEs, due to their antifungal activity, can be applied to food packaging for the control of food spoilage fungi (Nguyen Van Long et al., 2016). The use of films with EOs and PEs for the control of skin yeast infections is still not fully understood. However, there are some studies that suggest that these formulations can play a role in the control of skin candidiasis (Table 5). Usually, the antimicrobial activity of the films is determined by disc diffusion assay, in which the film is placed on the top of the solid culture medium on Petri dishes, inoculated with the bacteria; after incubation, the inhibition halo around the film is measured.

The incorporation of EOs and PEs on films is advantageous because the polymer(s) that compose the film have the ability to improve the interactions between the EOs/ PEs and the fungal cell since they are electrostatically attracted to the fungal membranes; polymeric films also allow a slow release of EOs over time by creating a diffusion matrix and therefore increase the stability of EOs and PEs (Ntow-Boahene et al., 2021). Up to date, to best of our knowledge, there are no studies, either *in vivo* or *in vitro* (in skin cells) reporting the effect of films with PEs and EOs for the treatment of *Candida* infections and, as such, additional studies in this area are needed for these formulations to constitute a real alternative to the current treatments.

Regarding the use of polymeric films with EOs and PEs for the treatment of infections caused by *Malassezia* spp. so far, to best of our knowledge, there are no studies addressing the use so this review intents to tackle this hypothesis, since they have been used to control *Candida* spp. infections.

4.2. Hydrogels

Hydrogels (HGs) are three dimension cross-linked polymeric networks, that are able to absorb and retain large amounts of water by swelling up (without dissolving) (Kaur et al., 2021; Micale et al., 2020). These characteristics are due to capillary, osmotic and hydration forces that account for the collaboration between the polymeric chain and organic liquids, contributing for the chain´s network balance and expansion (Kaur et al., 2021). These formulations have an excellent biocompatibility and, because of their rubber-like appearance, they closely resemble living tissues, which makes them very effective drug delivery systems (Das et al., 2016; Kaur et al., 2021). Because they are highly porous matrices, they can be loaded and assure the prolonged release of highly active compounds (Kaur et al., 2021). To boost their bio-stability and mechanical strength, these scaffolds must be optimized because they do not exhibit great stability and must be replaced frequently (Das et al., 2016).

HGs are formed by cross-linking techniques that can be physical, chemical, enzymatic or irradiated, and are classified according to their synthesis method (Supplementary Figure 1). The cross-linking method used in the production of a HG determines its physicochemical and mechanical properties (Pan et al., 2021) with different advantages and disadvantages (Supplementary Table 4). The type of polymer, the cell encapsulation strategy, the drug release kinetics and the target tissue are determinant for the choice of the cross-linking method to be used (Ermis et al., 2018).

The parameters that are used to characterize HGs are the same as those used to characterize films (Supplementary Table 3).

Some HGs are sensitive to stimuli and respond by changing their form or volume. They can respond to physical (light, pressure, temperature, electric field, magnetic field and ultrasound), chemical (pH, redox, ionic strength, CO_2 and glucose) and biological factors (enzymes, antigens, glutathione and DNA) (Kaur et al., 2021).

4.2.1. Antifungal activity of HGs incorporated with EOs and PEs against skin yeasts

HGs are very effective drug delivery systems. Their properties allow them to penetrate all the three layers of the skin and reach the dermis (Kaur et al., 2021), where they facilitate the controlled and sustained release of the antifungal medication, thereby diminishing the risk of local toxicity and excessive systemic drug levels (Zagórska-Dziok and Sobczak, 2020). Furthermore, HGs have the capacity to enhance the bioavailability, solubility, chemical stability, and skin penetration of drugs, ensuring the delivery of an effective therapeutic dose of the antifungal agent and its retention in specific skin layers. (Zagórska-Dziok and Sobczak, 2020).

The mechanism of action of a HG with antifungal activity involves several steps: 1) the swollen HG contacts with the infected skin and releases the antifungal agent, mainly due to changes in pH caused by fungal growth; 2) the antifungal agent acts on the fungal cell and inhibits the respiration of the cell leading to its death; or 3) the antifungal inhibits the synthesis of ergosterol, causing cell death (Kaur et al., 2021). Antifungal drugs in HGs are released through three different mechanisms: (a) diffusion-controlled mechanism in which the gel contacts with the skin with a higher temperature than normal, which leads to an increase in its hydrophobicity resulting in a slow and controlled release of the antifungal substance across the concentration gradient; (b) a chemical-controlled mechanism that involves reactions within the HG matrix that may be enzymatic, hydrolytic, reversible, or irreversible; and (c) a swelling-controlled mechanism. The specific mechanism at play depends on the type, concentration, and water-attracting properties of the polymer used in the HG (Kaur et al., 2021).

There are some studies that demonstrate the antifungal activity of HGs with EOs in the management of *Candida* sp. infections (Table 6). Usually, the antifungal activity of HGs is determined by diffusion method, and the yeast that is commonly tested is *C. albicans* due to its clinical importance. The use of HGs incorporated with PEs for the treatment of skin candidiasis is also mentioned in the literature. Although less studied than HGs incorporated with EOs, these formulations also have the potential to eradicate *Candida* spp. In fact, (Iraqui et al., 2019) describe the preparation of a HG incorporated with an extract from the plant *Cassia alata*. The formulation made of carbapol 934 and propylene glycol was incorporated with the extract and showed antifungal activity against *C. albicans,* both *in vitro* (in an agar diffusion test that showed the existence of an

inhibition halo in a *C. albicans* culture treated with the HG; the HG presented a larger inhibition halo when compared to commercial formulations against the same microorganism) and *in vivo* (in rat model in which the HG with PE displayed better and faster healing activity than commercial formulations).

Regarding the treatment of infections caused by *Malassezia* spp., Mirzaii et al. (2021) developed HGs incorporated with EOs of black cumin, cinnamon and orange and assessed their antifungal activities against the species *M. furfur*. The antifungal activity against this yeast was also tested by Dhamane et al. (2015) for a gel with tea tree oil, with both authors concluding that their formulations presented antifungal activity against *M. furfur*. Dhamane et al. (2015) also tested their hydrogel on a rat model to evaluate if was irritant to the skin and concluded that it was not. Kulkarni et al. (2020) produced a sodium alginate gel incorporated with the fenugreek leaves extract to test against the yeast *M. furfur* and concluded that it had antifungal activity against this microorganism.

To the best of our knowledge, only these studies point to the use of HGs incorporated with EOs and PEs for the treatment of *Malassezia* infections, emphasizing the need of more studies in this area. Nevertheless, these formulations show promising results and can potentially constitute an alternative to traditional treatments for *Malassezia* sp. infections.

5. Conclusions and future perspectives

Skin yeast infections caused by *Candida* sp. and *Malassezia* sp., are an emerging concern affecting millions of people every day. The current conventional treatments for these diseases normally consist in the application of gels, ointments and creams that have several undesirable side effects.

In this paper, the use of films and HGs for the delivery of EOs and PEs to the skin aiming the treatment of mucocutaneous candidiasis and *Malassezia* caused diseases was discussed.

The antimicrobial activity of EOs and PEs against *Candida* spp. and *Malassezia* spp. is documented by several works and some studies also show that EOs and PEs incorporated into films and HGs have antifungal activity against *Candida* sp., thus being a possible treatment for mucocutaneous candidiasis. But more *in vivo* studies are needed to assess the potential of these formulations.

Regarding the incorporation of these compounds in films and HGs for the treatment of *Malassezia* caused diseases, the number of studies is scant. Nevertheless, the authors believe that these formulations can constitute a possible treatment for these skin conditions and be deeper explored in future.

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998 **Tables**

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1000 Table 1 – Diseases caused by *Malassezia* sp.

Disease	Affected body area(s)	Characteristics/ symptoms/ epidemiology	*Malassezia* species	References
Pityriasis versicolor or tinea versicolor	Trunk Shoulders	Hyper- or hypo-pigmented (discolored patches) round to oval, flaking lesions. In some cases, can be pruritic. Commonly found in adolescents and young adults. Affects both genders equally. Prevalence: higher in tropical climates than in temperate ones. Often occurs in the summer.	*M. furfur* *M. sympodialis* *M. globosa*	Chandra et al., 2021; Pedrosa et al., 2014; Saunte et al., 2020; Sugita et al., 2010
Folliculitis	Torso Neck Arms	Erythematous, asymptomatic or pruritic papules and pustules. Prevalence: more frequent in tropical and hotter climates; often occurs in association with pregnancy, leukemia, and Hodgkin's disease.	*M. furfur* *M. sympodialis*	Chandra et al., 2021; Pedrosa et al., 2014; Saunte et al., 2020; Sugita et al., 2010
Dandruff	Scalp	Common chronic relapsing skin disease. Loosely adherent oily flakes, generally not associated with overt inflammation. Extremely common disease; practically all people are affected at some point in their life.	*M. furfur* *M. obtusa* *M. sympodialis* *M. restricta* *M. globosa* *M. arunalokei*	Chandra et al., 2021; Pedrosa et al., 2014; Saunte et al., 2020
Seborrheic dermatitis	Scalp, Nasolabial folds Ears Eyebrows Chest	Common chronic relapsing skin disease. Inflammation is present with superimposed greasy and yellowish flakes Prevalence: occurs in 1-3% of the general population; 3 times more common in men than in women; increases with age and in the winter.	*M. furfur* *M. obtusa* *M. yamatoensis* *M. sympodialis* *M. restricta* *M. globosa* *M. arunalokei* *M. slooffiae*	Chandra et al., 2021; Pedrosa et al., 2014; Saunte et al., 2020; Sugita et al., 2010
Atopic dermatitis	Head Neck	Chronic dermatitis with frequent exacerbations. Prevalence: 1-3% in adults; 10-20% in children. It is more severe in adults than in children.	*M. furfur* *M. obtusa* *M. japonica* *M. yamatoensis* *M. sympodialis* *M. dermatis* *M. restricta* *M. globosa*	Chandra et al., 2021; Pedrosa et al., 2014; Saunte et al., 2020; Sugita et al., 2010
Psoriasis	Skin Nails Joints	Chronic skin inflammation. *Malassezia* sp. does not cause psoriasis but can exacerbate its symptoms. T cell mediated autoimmune disease that results of a combination of genetic and environmental factors. Characterized by epidermal hyperproliferation and hyperkeratinisation. Some *Malassezia* species are associated with some subtypes of psoriasis.	*M. restricta* *M. globosa* *M. furfur* *M.japonica*	Chandra et al., 2021
Systemic infections	Blood Urine	Occurs mainly in premature neonates and immunocompromised patients. Clinic signs and symptoms are non-specific. Fever of unknown origin is common.	*M. furfur* *M. packydermatis* (in animals)	Chandra et al., 2021; Pedrosa et al., 2018

1001

1002 Table 2 – Minimum inhibitory concentrations of six conventional antifungals against some *Candida*
1003 species.

	Minimum inhibitory concentration (mM)						References
	Amphotericin B	**Fluconazole**	**Flucytosine 5C**	**Clotrimazole**	**Nystatin**	**Ketoconazole**	
C. albicans	0.00108	0.00163	0.00775	----------	----------	0.24086	a), b)
C. tropicalis	0.00108	0.00653	0.00093	----------	0.00054	0.24086	a), c)
C. glabrata	0.00027	0.01306	----------	----------	----------	0.12043	a), b), d)
C. parapilosis	0.00108	0.00653	0.00194	----------	0.00054	0.06021	a), b), c)
C. krusei	0.00108	0.10448	0.06197	0.00009	0.00108	0.24086	a), b), c), e)

1004 References: a) Pfaller et al., 1994; b) Turecka et al., 2018; c) Arikan et al., 2002; d) Chen et al., 2015; e)
1005 Pelletier et al., 2000
1006
1007 Table 3 – Minimum inhibitory concentrations of seven conventional antifungals against 5 species of
1008 *Malassezia*

	Minimum inhibitory concentration (mM)							References
	Amphotericin B	**Terbinafine**	**Ketoconazole**	**Fluconazole**	**Itraconazole**	**Posaconazole**	**Voriconazole**	
M. furfur	0.00128	0.03157	0.00098	0.13713	0.00035	0.00036	0.00143	a), b)
M. sympodialis	0.00137	0.00395	0.00188	0.02286	0.00071	0.00051	0.00109	b)
M. slooffiae	0.00308	0.00515	0.00013	0.00637	0.00006	0.00004	0.00006	b)
M. pachydermatis	< 0.00006	0.00686	0.00011	0.10448	0.00004	0.00004	0.00017	a), b)
M. dermatis	0.00054	0.00086	<0.00006	0.00163	0.00004	0.00002	0.000009	b)

1009 References: a) Cafarchia et al., 2015; b) Leong et al., 2017

Table 4 – Antimicrobial activity of some essential oils and plant extracts against some *Candida* and *Malassezia* species. The minimum inhibitory concentration (% (w/v)) for each EO/ PE is indicated.

		Yeasts										References
		C. albicans	***C. glabrata***	***C. parapsilosis***	***C. krusei***	***C. tropicalis***	***M. furfur***	***M. sloffiae***	***M. sympodialis***	***M. pachydermatis***	***M. globosa***	
Essential oils	**Arborvitae**	0.05		0.05								Kozics et al., 2019
	Cassia	0.125		0.125								Kozics et al., 2019
	Clove	0.5		0.5	0.00025	0.0005						Kozics et al., 2019; Trajano et al., 2010
	Eucalyptus	2.5	> 0.2	2.5	> 0.2	> 0.2						(Kozics et al., 2019; Pedroso et al., 2019)
	Lavandula	0.5		0.5	0.5							Carbone et al., 2019
	Lemon	> 0.2	> 0.2	> 0.2	> 0.2	> 0.2	0.09					Pedroso et al., 2019; Sharma et al., 2012
	Lemongrass	0.125		0.125								Kozics et al., 2019
	Tea tree	0.125	> 0.2	0.125	0.2	> 0.2	0.0032		0.25			Hammer et al., 2000; Kozics et al., 2019; Pedroso et al., 2019; Siva Sai and Mathur, 2021
	Myrtle						0.003125	0.003125	0.00625		0.003125	Barac et al., 2018
	Orange	> 0.2	> 0.2	> 0.2	> 0.2	> 0.2	0.22					Pedroso et al., 2019; Sharma et al., 2012
	Oregano	0.05	0.05	0.05	0.1	0.05	0.078			0.06		Kozics et al., 2019; Pedroso et al., 2019; Sim et al., 2019; Vinciguerra et al., 2019
	Rosemary	2.0	> 0.2	0.5	2.0	> 0.2	0.026		0.025	0.036	0.041	Carbone et al., 2019; Khosravi et al., 2016; Pedroso et al., 2019
	Spearmint						0.0125	0.01	0.01	0.015	0.025	Khosravi et al., 2016; Siva Sai and Mathur, 2021
	Thyme	0.05		0.05			0.092			0.125		Kozics et al., 2019; Sim et al., 2019; Vinciguerra et al., 2019
Plant extracts	***Allium cepa (cebola)***	0.125	0.25	0.25		0.125	8					Shams-Ghahfarokhi et al., 2006
	Allium sativum (alho)	0.0312	0.0312	0.0312		0.0312	0.125					Shams-Ghahfarokhi et al., 2006
	Anacardium occidentale	> 0.2	> 0.2	> 0.2	> 0.2	> 0.2						Pedroso et al., 2019
	Artemisia abrotanum	0.2					0.2	0.2	0.2	0.2	0.2	Brodin et al., 2007
	Asphodelus tenuifolius	0.005										Soliman et al., 2017
	Curcuma longa	> 0.2	> 0.2	> 0.2	> 0.2	> 0.2						Pedroso et al., 2019

	Dittrichia viscosa	0.5		0.5	0.5		0.5			0.5		Rhimi et al., 2018
	Illicium verum						2.5					Lalitha et al., 2008
	Lawsania inermis	0.001										Soliman et al., 2017
	Nyctanthes arbor-tristis						2.5					Lalitha et al., 2008
	Portulaca oleracea	0.001										Soliman et al., 2017
	Punica granatum						2.5					Lalitha et al., 2008
	Salvadora persica	0.0025										Soliman et al., 2017
	Salvia officinalis	0.1	1.0		0.1	0.1						Almeida et al., 2019
	Vochysia divergens	> 0.2	> 0.2	> 0.2	> 0.2							Pedroso et al., 2019

Table 5 – Films with antifungal activity against *Candida* spp.

A) Films incorporated with EOs

	Film characteristics				Antifungal activity			
Essential oil	**Polymer**	**Plasticizer**	**Incorporation in nanosystems?**	**Preparation method**	**Experimental method**	**Studied species**	**Antifungal activity values***	**References**
Eucalyptus	Chitosan	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans* *C. parapsilosis*	98.86 mm^2 65.94 mm^2	Hafsa et al., 2016
Elicriso	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	0.5 mm	Liakos et al., 2014
Cinnamon	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	18 mm	Liakos et al., 2014
Lavender	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	2 mm	Liakos et al., 2014
Tea tree	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	2 mm	Liakos et al., 2014
Peppermint	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	6 mm	Liakos et al., 2014
Eucalyptus	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	1 mm	Liakos et al., 2014
Lemongrass	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	All zone	Liakos et al., 2014
Lemon	Alginate	Glycerol	No	Solvent casting	Disc diffusion assay	*C. albicans*	1 mm	Liakos et al., 2014
Clove	Chitosan	----------	No	Solvent casting	Disc diffusion assay	*C. albicans*	7 mm	Santos et al., 2019
Tea tree	Chitosan	----------	No	Solvent casting	Disc diffusion assay	*C. albicans*	9 mm	Santos et al., 2019

B) Films incorporated with PEs

	Film characteristics				Antifungal activity			
Plant extract	**Polymer**	**Plasticizer**	**Incorporation in nanosystems?**	**Preparation method**	**Experimental method**	**Studied species**	**Antifungal activity values**	**References**
Salix alba	Chitosan Poly (vinyl pyrolidone) Poly (N-isopropyl acrylamide)	----------	No	Solvent casting	Disc diffusion assay	*C. albicans* *C. parapsilosis* *C. tropicalis* *C. glabrata* *C. guilliermondii*	*4 mm *4 mm *4 mm *5 mm *6 mm	Qureshi et al., 2015
Glycyrrhiza glabra	Starch (Lycocat®)	Glycerol	Yes. Polylactic acid nanoparticles	Solvent casting	Microdilution method	*C. albicans*	**125.0 µg/mL	Roque et al., 2018
Punica granatum	Starch Poly (vinyl alcohol) Poly (acrylic acid)	Glycerin	No	Solvent casting	Disc diffusion assay	*C. albicans* *C. glabrata* *C. krusei* *C. tropicalis*	*14.67 ± 0.53 mm *15.50 ± 0.57 mm *20.25 ± 1.70 mm *12.50 ± 1.20	de Paula et al., 2022

Antifungal activity values refer to the values reported on the articles cited on the table. *Results based on the inhibition halo diameter; **Results based on Minimum Inhibitory Concentration (MIC)

Table 6: HGs incorporated with antifungal activity against *Candida* sp.

	Hydrogel characteristics			Antifungal activity			
Essential oil	**Polymer**	**Plasticizer/ Emulsifier**	**Incorporation in nanosystems?**	**Experimental method**	**Studied species**	**Antifungal activity values**	**References**
Bidens tripartita	Alginate	Glycerol	No	Well diffusion method	*C. glabrata* *C. krusei* *C. albicans* *C. tropicalis* *C. parapsilosis*	8.0 mm 9.7 mm 7.7 mm 9.7 mm 10.3 mm	Tomczykowa et al., 2018
Melaleuca alternifolia	Chitosan	Poly-vinyl alcohol/ Na-P	No	Well diffusion method	*C. albicans*	> 25 mm	Low et al., 2016
Thymus vulgaris	Chitosan/ dextrin	Glycerol/ Tween 80	No	Disc diffusion method	*C. albicans* *C. parapsilosis*	38 mm > 40 mm	Dinu et al., 2021
Melissa officinalis	Methylcellulose	Tween 80	No	Disc diffusion method	*C. albicans*	17.5 mm	Serra et al., 2020
Thymbra capitata	Chitosan	Tween 80	No	Microdilution method	*C. glabrata* *C. krusei* *C. albicans* *C. tropicalis* *C. parapsilosis*	125 mg/mL < 15.7 mg/mL 125 mg/mL 31.3 mg/mL < 15.7 mg/mL	De-Oliveira et al., 2013
Nigella sativa *Cinnamomun verum* *Citrus sinensis*	Mucilage		No	Microdilution method	*C. albicans*	3.125 mg/mL	Mirzaii et al., 2021
Syzygium aromaticum	Chitosan	Tween 80	No	Percentage of inhibition	*C. albicans*	60%	Stoleru et al., 2022
Cymbopogon citratus	Carbopol 940		Yes. Nanosponges of ethyl cellulose	In vivo test with rats	*C. albicans*	Decrease in fungal cells concentration	Aldawsari et al., 2015
Thymus vulgaris	Alginate/ Layered double hydroxides		No	Disc diffusion method	*C. albicans*	12.5 mm	Boccalon et al., 2020

Figure captions

Figure 1: Virulence factors of *Candida* spp. and *Malassezia* spp. Sources: (Angiolella et al., 2017b; Figueredo et al., 2013; Hort and Mayser, 2010; Pedrosa et al., 2014; Ro and Dawson, 2006; Williams et al., 2011)

Supplementary figure 1: Classification of hydrogels