Chapter

Phytochemicals and Their Antifungal Potential against Pathogenic Yeasts

Cristina de Andrade Monteiro
and Julliana Ribeiro Alves dos Santos

Abstract

The rate of fungal infections is increasing rapidly, and pathogenesis of their species is poorly understood. Among fungi, *Candida* species are a major cause of morbidity and mortality worldwide and thus represent a serious threat to public health. In addition, *Cryptococcus* spp. are yeasts responsible for serious lung infections and meningitis. Polyenes, fluoropyrimidines, echinocandins, and azoles are used as commercial antifungal agents to treat fungal infections. However, the presence of intrinsic and developed resistance against azole antifungals has been extensively documented. The re-emergence of classical fungal diseases has occurred because of the increment of the antifungal resistance phenomenon. In this way, the development of new satisfactory therapy for fungal diseases persists as a major challenge of present-day medicine. The urgent need includes the development of alternative drugs that are more efficient and tolerant than those traditional already in use. The identification of new substances with potential antifungal effect at low concentrations or in combination is also a possibility. This chapter briefly examines the infections caused by *Candida* and *Cryptococcus* species and focuses on describing some of the promising alternative molecules and/or substances that could be used as antifungal agents, their mechanisms of action, and their use in combination with traditional drugs.

Keywords: medicinal plants, yeast infections, antifungal agents, antifungal activity, phytochemicals

1. Introduction

Fungal infections are considered a serious health problem, especially in people with weakened immune systems, and are a main cause of morbidity and mortality worldwide [1].

However, the impact of these "opportunistic" diseases on human health is not widely highlighted [2]. Due to this, research related to fungi occurs slowly compared to those caused by other pathogens.

Among the different mycotic infections, those caused by *Candida* and *Cryptococcus* are the most threatening due to severity of the disease and higher worldwide occurrence [3]. The pathogenicity of fungal infections proceeds in well-organized steps. For example, *Candida* cell surface adhesion factors first promote its

adherence to host surface, followed by releasing of various hydrolytic enzymes and other virulence factors for invasion and damage of the host tissues [4].

Candida species can cause a variety of infections from the mildest to the most severe being candidemia the most frequent hospital infection accounting for up to 15% of bloodstream infections. *Candida* species are the main causative agents in 50–70% of systemic fungal infections [5].

Cryptococcus species are other yeasts of medical importance, with more than 39 species, among which *Cryptococcus gattii* and *Cryptococcus neoformans* are the most clinically relevant [6–8]. However, other species such as *Cryptococcus albidus* and *Cryptococcus laurentii* are emerging pathogens involved in several types of infections [6, 9–11].

These yeasts are present in several environmental niches, such as woody sites (decomposing tree trunks, mainly eucalyptus, and soil), vegetable remains, domestic dust, and bird excrement, more precisely in *Columba livia* [12–14]. The source of the infection is exogenous and occurs primarily by inhalation or by direct inoculation into the tissue after trauma of desiccated spores or yeasts. It is believed that the only source of infection is environmental, since there are no reports of transmission between animals and humans or between humans [15].

The main virulence factors of *Cryptococcus* species are growth capacity at 37°C, polysaccharide capsule, melanin synthesis, and production of urease and antioxidant enzymes, causing primary or opportunistic cryptococcosis, such as pulmonary, cutaneous, and meningitis diseases [6, 8, 13, 16–19]. Cryptococcosis is the third opportunistic infection associated with AIDS [20].

In addition to delays in yeast diagnosis, there is currently a limited antifungal armamentarium in use against yeast diseases including only four chemical classes: polyenes, triazoles, echinocandins, and flucytosine. Antifungals act by binding specific components of fungal plasma membrane or its biosynthetic pathways or even cell wall components [21]. However, most of the antifungal agents used in the clinic is fungistatic and often led to the development of resistance by fungal species. Modern early antifungal treatment strategies, such as prophylaxis and empirical and preemptive therapy, result in long-term exposure to antifungal agents, which is a major driving force for the development of resistance.

Among the available antifungal agents, azoles are the preferred and most frequently used drugs for treatment of *Candida* and *Cryptococcus* infections. Fluconazole (FLZ), a type of azole, is often preferred in treatments of *Candida* infections because of its low cost and toxicity, in addition to availability in varied formulations [22]. However, there are many reports that described resistance development among *Candida* species, especially in relation to azoles.

Infectious Diseases Society of America recommends the treatment of cryptococcosis through FLZ and amphotericin B (AMB) with or without combination with 5-flucytosine (5-FC), followed by prolonged maintenance with fluconazole. Other azole compounds such as itraconazole (ITC), voriconazole, and posaconazole may be used as an alternative to FLZ in cases of contraindication or inefficacy of the latter [23, 24]. However, there has been a progressive increase in isolates of *Cryptococcus* spp. resistant to FLZ, which complicates the management of cryptococcal meningitis [25]. On the other hand, AMB and 5-FC are not available in all countries and are, respectively, nephrotoxic and hepatotoxic, limiting the anti-cryptococcal therapeutic [24].

Considering the limited availability of antifungals in use and the emergence of resistance, the control of *Candida* and *Cryptococcus* infections is a challenge in the modern clinic. In this way there is a continuous need for the search for new substances with new mechanisms of action with the aim of developing novel broad spectrum antifungal drugs with better efficacy.

In this way, plants stand out as the major producers of promising substances, the phytochemicals. Identification of new molecules with antifungal potential for the manufacture of new drugs, more effective and less toxic, is essential to facing the challenge. The use of phytochemicals alone or in combination with traditional drugs represents an important alternative to conventional therapy. The combination of drugs usually requires lower doses of antimicrobials. This reduction might lead to a toxicity decrease, which results in a higher tolerance to the antimicrobial by the patient.

2. Pathogenic yeast infections: a serious health problem

In the last two decades, fungal infections have shown a significant increment. In addition to the increase in the number of patients with compromised immune system, factors such as increasing number of patients using catheters, the use of broad-spectrum antibiotics, the rising number of patients requiring organ transplantations, as well as those with hematological malignancies and diabetes also contribute to this phenomenon [26, 27].

Even though fungal infections cause significant amount of human morbidity and mortality, the impact of these "opportunistic" diseases on human health is not widely highlighted [2]. Due to this, the research into the pathophysiology of human fungal infections is slow in comparison to other disease-causing pathogens. Recently, an editorial published in the journal *Nature Microbiology* [28] ratified the importance of not neglecting fungi. The call proposed a reflection on fungi and how these microorganisms have been neglected, even with studies already consolidated showing their medical relevance.

The most frequent fungal diseases affecting populations in the world are candidiasis [29–34] and cryptococcosis [8, 20, 25]. There are several types of candidiasis as mucosal candidiasis, cutaneous candidiasis, onychomycosis, systemic candidiasis [35, 36], and pulmonary candidiasis. An important fact is that candidiasis is an infection that can affect both immunocompromised and healthy people [37, 38]. Candidemia is the most relevant and prevalent nosocomial fungal infection associated with a high mortality rate (up to 49%) in patients with a compromised immune system [39, 40]. The association of *Candida* with bloodstream infections depends on patient's condition, age, and geographic region. Candidemia is such an important infection that in 10–40% of cases, it is associated with sepsis or septic shock [41].

Candida albicans continues to be the most prevalent species isolated from fungal infections [27, 42–44]. However, the prevalence of other *Candida* species has increase substantially. These species are *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. glabrata*, *C. guilliermondii*, *C. orthopsilosis*, *C. metapsilosis*, *C. famata*, and *C. lusitaniae* [44–46].

Candida species presents high degree of flexibility, being able to grow in extremely different environments regarding to the availability of nutrients, temperature variation, pH, osmolarity, and amount of available oxygen [47]. This fact associated with the high resistance capacity of species to antifungals, their virulent features, and capability of forming biofilms with other species [48, 49] makes the genus *Candida* a serious risk to human health [50]. Thus, *Candida* species are highly adaptable and possess numerous strategies to survive in conditions that can affect their overgrowth and alter their susceptibility profiles.

Cryptococcus spp. may remain latent in the lungs, leading to asymptomatic infection, or may cause multifocal lung disease. The latency period of *Cryptococcus* can range from 6 weeks to more than 1 year after inhalation [51]. The fungus

presents neurotrophism and can migrate to the central nervous system (CNS) through hematogenous dissemination and, when crossing the blood-brain barrier, can cause meningoencephalitis [13, 18]. Episodes of mental confusion in patients with cryptococcosis have been described [52, 53]. Neurocryptococcosis is the most severe form of the disease with high mortality rates in the absence of adequate treatment [18, 23]. The mortality due to cryptococcosis is higher than the mortality caused by tuberculosis and similar to that caused by malaria [54].

Another clinical manifestation is cutaneous cryptococcosis, which is rare and usually secondary to hematogenous dissemination. Cutaneous lesions are characterized by an infiltrative plaque of a solid tumor mass that can present ulcerative and necrotic lesion [17]. Pulmonary and cutaneous lesions due to nodular features may be misdiagnosed as tumor lesions [55]. In addition to the respiratory tract, CNS and skin, other sites may be affected: prostate, eyes, adrenal glands, lymph nodes, bone marrow, and liver [51].

Until now, there are three proposals to explain fungal neurotropism. The first is that neuronal substrates present in the basal ganglia promote cryptococcal growth and survival, and, thus, perivascular spaces may serve as a niche for *Cryptococcus*, as described by [56] in a healthy female patient who had evidence of *Cryptococcus* infection within the perivascular spaces of the parenchyma. The second proposal describes that it is possible that there are specific neuronal receptors that can attract *Cryptococcus* to the CNS [57]. The third hypothesis, one of the most widespread, is that the fungus uses neurotransmitters such as dopamine that aids in the synthesis of melanin [19, 57, 58].

Besides the clinical importance of fungal infections caused by theses pathogenic yeasts, interestingly, climatic abnormalities due to phenomena such as La Niña and El Niño have recently been described as important in the distribution and occurrence of mycoses in countries influenced by them [59].

3. Traditional antifungal agents against yeasts

In the last two decades, there has been an increasing, but limited, discovery of antifungal agents [47]. These include azoles, such as fluconazole, itraconazole, ketoconazole (KTC), miconazole, and clotrimazole, polyenes (amphotericin B [AMB] and nystatin), allylamines, thiocarbamates, morpholines, 5-fluorocytosine, and echinocandins (for instance, caspofungins) [21]. However, fungal cells and human cells are eukaryotic, so antifungal compounds target both cell types, resulting in considerable side effects in patients and fewer available targets for drug action. Antifungals target three cellular components of fungi (**Figure 1**). Azoles inhibit ergosterol biosynthesis by interfering with the enzyme lanosterol 14-α-demethylase in endoplasmic reticulum of the fungal cell. This enzyme is involved in the transformation of lanosterol into ergosterol, a component that is part of the plasma membrane structure of the fungus (**Figures 1** and **2**). Thus, as the concentration of ergosterol is reduced, the cell membrane structure is altered, thereby inhibiting fungal growth [60].

Azoles comprise a five-member azole ring containing two (imidazole) or three nitrogen atoms (triazole) attached to a complex side chain [61, 62]. Imidazoles include KTC, miconazole, econazole, and clotrimazole, and triazoles include FLZ, ITC, voriconazole (synthetic triazole derivative of FLZ of second generation), and posaconazole (hydroxylated analog of itraconazole) [63].

AMB and nystatin bind to ergosterol causing the disruption of the membrane structure and promoting extravasation of intracellular constituents such as ions and sugars and, consequently, cell death [21] (**Figure 1**).

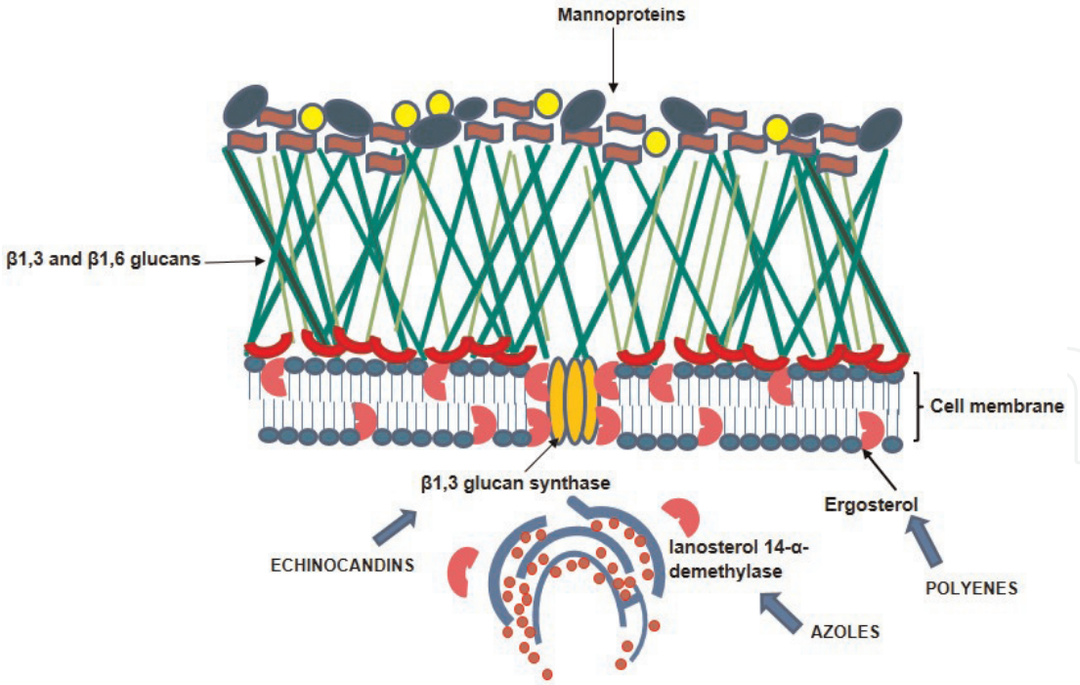

Figure 1.
Mechanisms of action of some traditional antifungal agents on cellular targets. Azoles inhibit the ergosterol synthesis in the endoplasmic reticulum of the fungal cell by interfering with the enzyme lanosterol 14-α-demethylase. Polyenes act by binding to ergosterol present at the cell membrane. Echinocandins inhibit (1,3) β-D-glucan synthase, thereby preventing glucan synthesis.

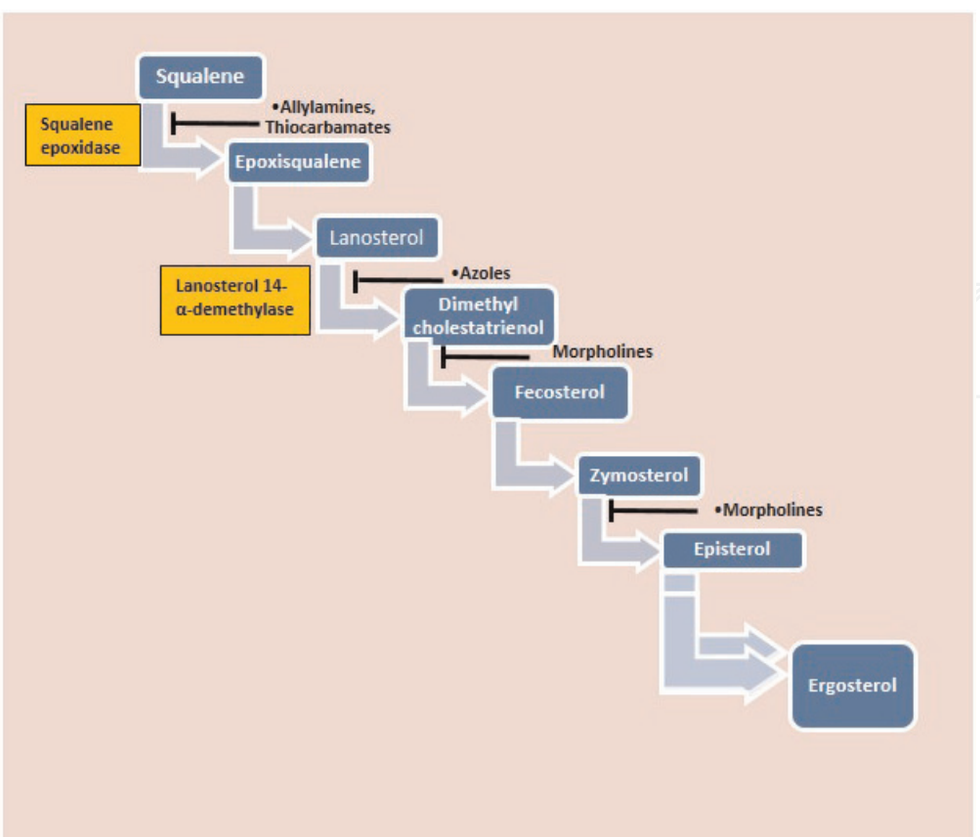

Figure 2.
Specific point of action of antifungal drugs in the ergosterol biosynthesis pathway.

Pyrimidine analogs include 5-fluorocytosine and 5-fluorouracil (5FU). The first has fungistatic properties and enters the fungal cell through cytosine permease, inhibiting the thymidylate-synthetase enzyme and interfering with DNA. 5-fluorouracil, which in turn can be phosphorylated to 5-fluorodeoxyuridine monophosphate, can be incorporated into RNA molecules [63]. Due to toxicity [64]; stronger side effects, such as hepatic impairment; interference with bone marrow function; and rapid occurrence of resistance especially among *Candida* species, the clinical use of 5-FC is preferred in association with AMB [65, 66]. In addition, the nephrotoxicity and hepatotoxicity of AMB and 5-FC, respectively, and the unavailability of these antifungals in many countries have limited their use in cryptococcal therapeutic [24].

Host's immunity, type of infection, site of origin of the samples, toxicity, bioavailability of the drug, and the sensitivity/resistance profile of the isolates interfere in the choice of the type of agent to be used [22]. AMB is considered the gold standard drug for most mycoses that affect patients at risk [67], although it has high toxicity. Azoles have fungistatic properties that affect cell growth and proliferation [65]. Among azoles, KTC was one of the firsts to emerge and was the first alternative to AMB [68]. Currently, FLZ is the drug of choice for most *Candida* and *Cryptococcus* infections [64] and is the most recommended antifungal agent for use in invasive candidiasis [47, 49].

For cryptococcosis, the choice of treatment depends on the patient's immunological status and mainly on the clinical of the disease, if it is just a pulmonary manifestation or if the infection is systemic. Fluconazole is recommended in cases of lung disease with mild to moderate symptoms. Amphotericin B with or without combination with 5-flucytosine is the recommended therapy for more serious infections such as meningoencephalitis, followed by prolonged maintenance with fluconazole [23, 24].

Although azoles are generally well-tolerated, they have limitations such as hepatotoxicity and the emergence of resistance among fungal isolates [69] which provide motivation for improving this class of antifungal agents [68]. For instance, alterations in triazole molecule gave rise to voriconazole (structurally related to FLZ) and posaconazole (related to ITC), both available for systemic therapy [66].

Echinocandins, which include caspofungin, micafungin, and anidulafungin, are a new class of antifungals and have fungicidal effects in all *Candida* species [66]. They inhibit (1,3) β-d-glucan synthase, thereby preventing glucan synthesis, which is present in the cell membrane of fungi (**Figure 1**). As this drug acts on the wall structure of the fungus, it has the advantage of a lower side effect in animal cells [47].

Allylamines (terbinafine and naftifine) and thiocarbamates inhibit the enzyme squalene epoxidase, which participates in the synthesis of ergosterol and is encoded by the *ERG1* gene (**Figure 2**). This activity leads to membrane rupture and accumulation of squalene. Allylamine effects can also prevent the production of other sterol derivatives.

To minimize toxicity and resistance, some pharmacological strategies were developed. The preparation and use of new antifungal formulas (liposomal AMB (Ambisome®), AMB lipid complexes (Abelcet®), AMB colloidal dispersions (Amphocil®/Amphotech®), and AMB lipid nanosphere formulations and β-cyclodextrin itraconazole) are one strategy [68]. Others include combination therapies of antifungal compounds (e.g., AMB + 5-FC, FLZ + 5-FC, AMB + FLZ, caspofungin + liposomal AMB, and caspofungin + FLZ) and nanostructuring of conventional antifungal agents [70–73].

However, all traditional antimycotic drugs have at least one restriction related to their use. Some do not have a broad spectrum of action or are fungistatic. Others have high toxicity and low bioavailability with significant side effects [74].

Therefore, limitations of treatment and drug resistance associated with pathogenicity of the clinical isolates support the urgent need to identify substances that are more effective, with new mechanisms of action in the fight against *Candida* and *Cryptococcus* infections.

4. Resistance in pathogenic yeasts: a significant problem

Most antifungals target sterols or the enzymes that synthesize them. However, the fungistatic nature of many of these antifungals and emergence of clinical drug resistance limits their success. Increased drug resistance in fungi is a problem that cannot be avoided, particularly for FLZ, which is the preferred antifungal for treating yeast infections [75].

The number of people at risk for fungal infections has been increasing, resulting in an increased use of antifungal agents, even as prophylaxis. Thus, besides the existence of some non-*albicans Candida* (NAC) species presenting inherent resistance to azoles, higher minimum inhibitory concentrations (MICs) for antifungals against *C. albicans* strains have been observed [76]. The World Health Organization (2014) categorizes antimicrobial resistance as that developed by the microorganism to an antimicrobial drug, which was initially effective in treatment of such infections. Low-dose prophylactic administration of azole derivatives, such as FLZ, for prolonged periods to prevent the occurrence of opportunistic infections in immunosuppressed patients also results in resistant phenotypes [27, 75]. Therapeutic failures and empiric treatment are facts which are likely to collaborate to the increased incidence of fungal infections.

In the last decade, a number of new clinical problems have arisen, requiring new guidelines regarding the treatment of cryptococcosis, mainly because clinical data have suggested that cryptococcal strains have become more resistant to drugs [23, 25]. Some relates say that clinical *Cryptococcus* isolates are frequently less susceptible to fluconazole than environmental isolates. However, Chowdhary et al. [77] evaluated the susceptibility profile of environmental and clinical strains of *C. gattii* and observed that environmental samples were less susceptible to fluconazole, itraconazole, and voriconazole in comparison to clinical isolates.

Heteroresistance is also a worrying phenomenon. It consists of the ability of a subpopulation of microorganism to adapt to high concentrations of the drug, resulting in resistant homogenous populations. However, heteroresistant strains return to the initial phenotype when the stimulus with the drug is withdrawn [78].

Some mechanisms for cellular and molecular resistance to FLZ in yeasts are described. In *Candida* and *Cryptococcus*, the first is related to the induction of multidrug pumps, which decrease the concentration of drug available in the intracellular compartment of yeast cells. Various genes belonging to the ATP-binding cassette superfamily or to the major facilitator superfamily encode efflux pumps were identified in *C. albicans*. Overexpression of some transporter genes or of their regulated genes can confer cross-resistance to various azoles [21]. In *C. gattii* and *C. neoformans*, *AFR*1, *MDR*1, and *AFR*2 genes encode ABC transporters that expel the azole out of the fungal cell, thereby causing resistance to these drugs [79].

A second mechanism of resistance involves modification of the target enzyme encoded by the *ERG11* gene, also known as cytochrome P_{450} lanosterol 14-α-demethylase (Cyp51). Mutations in this gene prevent azoles from binding to enzyme sites. Another mechanism of resistance is related to mutations in the *ERG3* gene which does not convert 14-α-methylfecosterol into 14-α-methyl-3,6-diol in the ergosterol synthesis pathway. This substitution causes azoles to have no fungistatic effects on the fungal cell membrane [21].

Transcriptional regulation is also important for the development of resistance mechanisms. YAP1, a protein, is important for the mechanism of *C. neoformans* heteroresistance to fluconazole and oxidative stress. Mutant strains of *C. neoformans* that lost protein YAP1 became hypersensitive to a variety of oxidizing agents and mainly to fluconazole [80].

Resistance to polyenes (AMB) in fungus is less common and in *C. albicans* is associated with the substitution of ergosterol with a precursor molecule or a general reduction of sterols in the plasma membrane [81]. Reduction of membrane ergosterol renders *Cryptococcus neoformans* and *Aspergillus* spp. less susceptible to amphotericin B [82]. Enzymes encoded by *ERG3* and *ERG2* genes participate in ergosterol biosynthesis and have the main alterations related to AMB resistance because mutations in their genes modify ergosterol content required for the action of polyenes [83].

The main resistance mechanism to echinocandins is related with point mutations in gene that encodes the major subunit of the glucan synthase enzyme (Fks subunit) (**Figure 1**) and can provide resistance to all echinocandin [84]. Other *Candida* species also present this resistance mechanism such as *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, *C. guilliermondii*, and *C. dubliniensis* [85, 86].

Resistance to 5-FC can be of two types: primary, occurring via cytosine permease (encoded by the *FCY*2 gene) whose mutation decreases drug uptake [87], and secondary, related to alterations in cytosine deaminase (encoded by *FCY1*) or uracil phosphoribosyltransferase (encoded by *FUR1*) activities. Cytosine permease is responsible by conversion of 5-FC to 5-fluorouridine or to 5-fluorouridine monophosphate (5-FUMP) [88]. Resistance is easily developed in fungal isolates from patients who are receiving the drug. However, other molecular mechanisms related to resistance to 5-FC must exist because most of them have not been observed in *C. albicans* [89].

The increase in the drug-resistant *Candida* and *Cryptococcus* strains to commercial antifungals has caught the attention of clinicians and researchers to medicinal plant products (commonly referred as phytochemicals). The use of phytochemicals with greater antifungal potential and different mechanisms of action may be useful in reducing the phenomenon of resistance. Lately, they have become a significant alternative for discovery of commercially viable, economically cheaper, and safe phytomedicines.

5. Medicinal plants as a source of antifungal agents

Global Action Fund for Fungal Infections (GAFFI), an international organization working to reduce infections and deaths associated with fungi, has reported that approximately 300 million people in the world suffer from a serious fungal infection every year and that among them over 1.35 million deaths are registered [90].

Despite the introduction of new and novel antifungal drugs, their production and impact are slow, and the development of antifungal resistance has forced the attention of researchers toward herbal products, mainly phytochemicals, in search of development of safe and economically viable antifungals.

Populations around the world have used folk medicine as an alternative therapy for various disorders. Currently, many species have been extensively studied in an attempt to discover new biologically active compounds with novel structures and mechanism of action for the development of new drugs.

Medicinal plants are commonly preferred because of their wide level of functional chemical groups with comparatively poor toxic substances, low-cost extracts,

fewer side effects, and easy accessibility to people. Various bioactive compounds have been abundantly found such as phytochemicals.

Leaves, as well as the seeds and fruits of plants, have higher levels of phenolic compounds. The concentration of these compounds also depends on the nature of the chemical used as solvent in the extraction process as well as on the growth and storage conditions [91].

The biological activity of plant products has been evaluated against fungi. The ethanol extract, *Lonicera japonica* aerial parts, a medicinal plant of folk medicine of China that used to treat some diseases, showed a very strong antimicrobial activity against *Candida* species and potent wound healing capacity [92]. Methanolic extract of *Lannea welwitschii* leaves was antimicrobial against clinical yeasts. A preliminary phytochemical screening of extracts revealed tannins, flavonoids, alkaloids, and glycosides as compounds [93]. *Pyrostegia venusta* crude flower extracts, fractions, and pure compounds showed an effective broad spectrum antifungal activity [94].

An extract of *Piper betle* leaves inhibited the growth of *Candida* species [95], and four different extracts of *Strychnos spinosa* showed anti-*Candida* activity [96]. Hydro-methanolic extracts of leaves from *Juglans regia* and *Eucalyptus globulus* and methanol extract of *Cynomorium coccineum* demonstrated excellent antimycotic property against *Candida* strains [91, 97]. Akroum [98] showed antifungal activity in an acetylic extract of *Vicia faba* against *C. albicans* in vitro and reduced mortality rates in *Candida*-infected mice that were treated with the extract.

Berberine, a protoberberine-type isoquinoline alkaloid isolated from the roots, rhizomes, and stem bark of natural herbs, such as *Berberis aquifolium*, *Berberis vulgaris, Berberis aristata*, *Hydrastis canadensis*, *Phellodendron amurense, Coptis chinensis,* and *Tinospora cordifolia*, was described as powerful reducer of the viability of in vitro biofilms formed by fluconazole-resistant *Candida tropicalis* cells [99].

Ethanolic and aqueous extracts from different plants from Brazilian Cerrado commonly used in folk medicine such as *Eugenia dysenterica* and *Pouteria ramiflora* were promising against *C. tropicalis*, *C. famata*, *C. krusei*, *C. guilliermondii*, and *C. parapsilosis*. A phytochemical screening of active extracts from these plants disclosed as main components flavonoids and catechins [100]. Crude extract and fractions (n-butanolic and ethyl acetate ones) from *Terminalia catappa* leaves showed antifungal properties against *Candida* spp.; hydrolysable tannins (punicalin, punicalagin), gallic acid (GA), and flavonoid C-glycosides were the active components found in butanolic fraction [101].

Bottari et al. [102] determined the antimicrobial activity of the aqueous and ethanolic leaf extracts of *Carya illinoensis*. Both extracts had MIC values against seven *Candida* reference strains between 25 and 6.25 mg/mL. Phenolic acids (gallic acid and ellagic acid), flavonoids (rutin), and tannins (catechins and epicatechins) were likely responsible, in part, for the activity against *Candida* strains. Further, the extracts inhibited the production of *C. albicans* germ tubes.

5.1 Phytochemicals: polyphenols as substances most found in plants

Several woody plant produce medicinal phytochemicals such as polyphenols that are low molecular weight naturally occurring organic compounds containing one or more phenolic groups [103]. Further, polyphenols perform various substantial functions in plant physiology and, therefore, can be found, in lesser or greater quantity, in all of them.

Phenolic acids, flavonoids, tannins, and coumarins are some examples of phenolic compounds found in and extracted from medicinal plants [104] (**Table 1**). Research has shown that polyphenols have potentially healthy effects in

Phytochemicals	Bioactive compounds	Properties	Plant sources
Flavonoids	Flavan-3-ol	Against *Candida*	*Syzygium cordatum*
	Baicalein, gallotannin	Against *Candida*	*Scutellaria baicalensis*
Coumarins	Ulopterol	Against *M. canis*	*Skimmia laureola*
	Prenyletin; prenyletin-methyl-ether	Against *T. rubrum*; *T mentagrophytes*	—
	Osthenol	*C. albicans*, *Fusarium solani*, *A. fumigatus*	—
	5,8-Dihydroxyumbelliprenin	*T. interdigitale*, *M. gypseum*	*Ferula foetida*
Saponins	Colchiside	Phytopathogenic fungi	*Dipsacus asper* roots
Terpenes or terpenoids	Triterpenes	Against dermatophytes	Ethyl acetate leaf extract of *Satureja khuzestanica*
Lectins	Lectins	*Fusarium oxysporum*	Seed from native Amazon species
Tannins	Punicalagin Punicalin	Against *Candida* spp.	*Terminalia catappa*
	Punicalagin	*T. mentagrophytes*; *T. rubrum*; *M. canis*; *M. gypseum*	*Punica granatum*
	Ellagic acid, gallagic acid, punicalins, punicalagin	*C. albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*	*Punica granatum*
	Lambertianin C, sanguiin H-6	*Geotrichum candidum*	*Rubus idaeus*

Table 1.
Phytochemicals with antifungal compounds derived from plants.

humans, working primarily as anticancer, antihypertensive, anti-allergen, anti-inflammatory, antioxidant, and antimicrobial agents. The antimicrobial activity of polyphenols has been extensively investigated mainly against bacteria [104]. Nevertheless, the antifungal activity of most of the phenolic compounds remains unknown. There are few studies on the mechanism of action of the substance, cytotoxicity, the synergism with traditional antifungals drugs, and their anti-virulence activities.

Those with the most promising antifungal activity isolated from natural sources include flavonoids, tannins, coumarins, quinones, lignans, and neolignans [105] (**Table 1**).

Flavan-3-ols, flavonols, and tannins have received the most attention among the known polyphenols, attributable to their large spectrum of efficacy and high antimicrobial property. Structurally, flavonoids are aromatic compounds with 15 carbon atoms (C15) on their basic skeleton; they consist in tricyclic phenolic compounds with two aromatic rings on their structure (C6–C3–C6) [105]. Flavonoids are a class of natural compounds with several known protective activities, including antifungal activity. The flavonoids include subclasses such as chalcones, flavones, isoflavones, flavonols, flavanols (flavan-3-ol), and anthocyanidins [106].

The activity of flavonols such as quercetin, myricetin, and kaempferol has been described in *C. albicans*. For instance, quercetin, myricetin, and kaempferol from propolis have showed activity against *Candida* species [107]. The flavanol subclass (flavan-3-ol) and gallotannin, extracted from *Syzygium cordatum*, also

showed inhibitory properties on the growth of *C. albicans* [108]. Serpa et al. [109] isolated baicalein, belonging to a subclass of flavones, from *Scutellaria baicalensis*, and induced apoptosis in *C. albicans* (**Table 1**), and apigenin, a flavone isolated from propolis, showed antifungal potential. Flavonoids as much as coumarins and lignans have shown an antifungal potential against several species of dermatophytes [105].

Other important groups of polyphenolic compounds present in various plant parts, such as the roots, flowers, leaves, fruits, and seeds, are tannins. They are divided into hydrolyzable (ellagitannins) and condensed tannins (proanthocyanidins) and gallotannins [110]. They have the ability to precipitate macromolecules such as proteins [111] as well as have antimicrobial properties. However, the mechanisms underlying the antimicrobial action of tannins in different microorganisms are still under investigation [111].

Ellagitannins constitute a complex class of polyphenols characterized by one or more hexahydroxydiphenoyl (HHDP) which can be linked in various ways to the glucose molecule [112]. Ellagic acid, gallagic acid, punicalins, and punicalagins isolated from ethyl acetate and butanolic fractions of *Punica granatum* revealed antifungal activity against *C. albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* [113] (**Table 1**).

Ellagitannins isolated from *Ocotea odorifera*, a plant commonly used in Brazil in folk medicine, have a potential against *C. parapsilosis* [114]. Two ellagitannins isolated from raspberry (*Rubus idaeus* L.) fruit, lambertianin C and sanguiin H-6, showed fungistatic activity both in vitro and in situ against *Geotrichum candidum* [115]. Dos Santos et al. [111] verified that encapsulated tannins from *Acacia mearnsii* have moderate activity against *Aspergillus niger* (ATCC 9642) and *C. albicans* (ATCC 34147).

Coumarins have a C6-C3 skeleton, possessing an oxygen heterocycle as part of the C3 unit [105]. These compounds are known to play a role in disease and pest resistance, as well as UV tolerance. The antifungal activity of 40 coumarins was tested against reference strains of *Candida albicans*, *Aspergillus fumigatus*, and *Fusarium solani*, but among them only osthenol showed the most effective antifungal activity (Table 1). The authors argue that the action of osthenol can be related to the presence of an alkyl group at C-8 position [116].

Another coumarin derivative, 4-acetetatecoumarin, was effective in inhibiting *Aspergillus* spp., acting on the factors of virulence and affecting the structure of the fungal wall. Diversinin, a coumarin isolated from the petroleum ether extract of *Baccharis darwinii*, demonstrated antifungal activity against *T. rubrum*, *T. mentagrophytes*, and *M. gypseum*, being fungicidal. Another coumarin derivative, 5,8-dihydroxyumbelliprenin, isolated from *Ferula foetida*, was active against *M. gypseum* and *Trichophyton interdigitale* [105] (**Table 1**).

Phenylpropanoids are other naturally occurring compounds categorized as coumarins, phenylpropanoic acid, and lignans frequently studied for their anti-*Candida* properties [117]. Navarro-Garcia et al. [118] and Raut et al. [119] found that a coumarin (scopoletin) and two phenylpropanoic acids (salicylaldehyde and anisyl alcohol) have antifungal property against *C. albicans*, with MICs of 25, 31, and 31 μg/mL, respectively.

Shahzad et al. [103] observed the effectiveness of pyrogallol and curcumin (CUR) against various *C. albicans* clinical isolates. In addition, curcumin inhibited the adhesion capability of cells and demonstrated anti-biofilm activity. Curcumin is a flavonoid found in turmeric (Curcuma longa L.). Pure curcumin had potential activity against *Cryptococcus gattii* both in vitro and in vivo [120]. According to Ferreira et al. [121], the essential oil from *Curcuma longa* L. can reduce the colony diameter, germination, and sporulation of *Aspergillus flavus*.

Alalwan et al. [122] undertook a series of adsorption experiments with varying concentrations of curcumin and showed that 50 μg/mL could prevent adhesion of *C. albicans* SC5314 to denture materials. Curcumin-silver nanoparticles also showed potential anticandidal activity against fluconazole-resistant *Candida* species isolated from HIV patients with MIC range of 31.2–250 μg/mL [123].

Gallic acid is a polyphenol natural compound found in many medicinal plant species that has been shown to have anti-inflammatory and antibacterial properties. GA was found to have a broad spectrum of antifungal activity against dermatophyte and *Candida* strains. Authors verified that GA reduced the activity of sterol 14-α-demethylase P450 (CYP51) and squalene epoxidase in the *T. rubrum* membrane.

Teodoro et al. [124] demonstrated that acetone fraction from *Buchenavia tomentosa* aqueous extract and its major compound gallic acid had the ability to inhibit reference strains *C. albicans* ATCC 18804 and *Candida albicans* SC 5314 adherence and to disrupt 48 h-biofilm.

5.2 Essential oils as potential antifungal

In the eagerness to research and develop new substances to suppress the development of pathogenic fungi from natural plant substances, knowledge about the biological activities of essential oils has been growing. Essential oils' pharmacological activities, mainly related to their complex chemical composition and high concentrations of phenols, make these compounds particularly interesting for both the treatment and the prevention of fungal infections. Natural phenolic substances are among the most antifungal active substances present in essential oils, generally showing low toxic effects in animals [125]. They consist in a complex mixture of monoterpene and sesquiterpene hydrocarbons and oxygenated derivatives such as alcohols, aldehydes, ketones, and phenylpropanoids.

Essential oils are also called volatile oils or ethereal oils, as they have a high degree of evaporation when exposed to air. The presence of terpenes contributes to the complex constitution with the action against microorganisms being directly related to this characteristic [126]. Since ancient times, Mondello et al. [127] proposed that tea tree oil could be used in antifungal therapy, because it showed efficacy against multidrug-resistant *Candida* species in vitro and against mucosal candidiasis in vivo; they have also showed that terpinen-4-ol was the main substance presented in the oil which contribute to the anticandidal activity.

Several oils have demonstrated activity against *Candida* species. Sharifzadeh et al. [128] observed that essential oils from *Trachyspermum ammi* have anticandidal effects against isolates resistant to FLZ. Herbal essences from *Foeniculum vulgare*, *Satureja hortensis*, *C. cyminum*, and *Zataria multiflora* were tested against *C. albicans*. Essential oils from *Z. multiflora* showed the best anticandidal activity [129].

Carica papaya essential oils have inhibitory effects against *Candida* species, detected by agar diffusion and microdilution assays [130]. Minooeianhaghighi et al. [131] verified that a combination of essential oils from *Cuminum cyminum* and *Lavandula binaludensis* showed growth inhibition of *C. albicans* isolates, at very low concentrations (between 3.90 and 11.71 μg/mL). Essential oils from *Cymbopogon nardus* have also shown antimicrobial potential against *Candida* species, with inhibition of hyphal growth in *C. albicans* at concentrations between 15.8 and 1000 μg/mL. This oil also inhibited growth of filamentous fungus from the environment. Main compounds of *C. nardus* essential oil were the oxygen-containing monoterpenes: citronellal, geranial, geraniol, citronellol, and neral [126]. In addition to inhibiting biofilm formation [132], essential oils from *Artemisia judaica* have been shown to inhibit the formation of germination tubes in *C. albicans* and have shown

that at a very low concentration (0.16 μL/mL), it inhibited 80% of *Candida* filamentation. Kose et al. [133] demonstrated the fungicidal potential of essential oils from *Centaurea baseri* against *Candida* species, with an MIC of 60 μg/mL.

Among the monoterpenes there is thymol (2-isopropyl-5-methylphenol) [134]. It is the most abundant constituent in essential oils from *Thymus vulgaris* (thyme) [135] and the major component of essential oils from *Origanum vulgare* (oregano) [136]. Thymol showed antifungal activity, fungistatic and fungicidal one, against *Candida* strains. Authors verified an MIC of 39 μg/mL against *C. albicans* and *C. krusei* and MIC of 78 μg/mL against *C. tropicalis*. Probably thymol acts by binding to ergosterol in the plasma membrane, thereby increasing ion permeability and resulting in cell death because an eightfold increase (from 39.0 to 312.5 μg/mL) in thymol MIC values against *C. albicans* was seen in the presence of exogenous ergosterol. A combination of thymol and nystatin resulted in synergy [137].

Terpenoids have shown synergistic effects with FLZ, so it may be useful as a candidate antifungal chemotherapeutic agent. In addition, terpenoids exhibit a very good antimycotic activity of filamentous-form growth of *C. albicans* at nontoxic concentrations [138]. Further, in experiments realized by [139], rubiarbonol G, a triterpenoid from *Rubia yunnanensis*, showed potent antimicrobial activity against *C. albicans*, with an MIC of 10.5 μg/mL.

The antifungal potential of terpenes, geraniol, and citronellol has been investigated previously, with effective inhibitory activity against *C. albicans* [138] and filamentous fungi of the *Aspergillus* species [140]. In addition, Mesa-Arango et al. [67] showed that oxygenated monoterpenes in the citral chemotype, such as geraniol, citral, and citronellal, have antifungal activity against *C. parapsilosis*, *C. krusei*, *Aspergillus flavus*, and *Aspergillus fumigatus*.

Terpenes' anti-biofilm activity and the efficacy of thymol, geraniol, and carvacrol in the treatment of *Candida* infections associated with the use of hospital devices have been related [141]. Effects of carvacrol on *Candida* cells can be associated with alterations in the cytoplasmic membrane and induction of apoptosis [108].

Although the process of discovering bioactive molecules is complex and time-consuming, involving isolation, identification, and optimization of pharmacokinetic and pharmacodynamic properties, as well as the selection of lead compounds for further drug development, data related here showed that plants are a promising source of active molecules with antifungal properties. Biological assays have shown that plant extracts or essential oils and their bioactivity molecules inhibit ATCC and clinical strains of fungi species, including those with resistance to drugs employed in medical practice. In addition, some are able to inhibit and control the main virulence factors of fungi species, such as the formation and proliferation of hyphae and filamentation and, more importantly, the eradication of mature biofilms.

Eugenol (4-allyl-2-methoxyphenol) is a phenolic compound and the main constituent of the essential oil isolated from the *Eugenia caryophyllata*. There are reports of some pharmacological effects of eugenol, such as antifungal and antibacterial agent, and its anti-*Candida* action seems to be related to the generation of oxidative stress concomitantly with lipid peroxidation of the cell membrane of *Candida albicans* yeast and the generation of reactive oxygen species [142]. Eugenol also showed antifungal effects against both *Cryptococcus gattii* and *C. neoformans* cells by causing morphological alterations, changes of cellular superficial charges, and oxidative stress. Thymol and carvacrol can represent alternative, efficient, and cost effective drugs for anti-biofilm therapy for *Cryptococcus* species.

Eugenol showed activity against *Alternaria* spp. and *P. chrysogenum*, by agar diffusion method [143] and, along with other monoterpenes such as carvacrol and isoeugenol, exhibited strong antifungal activity against *Rhizopus stolonifer* and *Absidia coerulea* [144].

5.3 Synergistic action between phytochemicals and antifungals

Resistance mechanisms are developed by fungi to the treatment with conventional drugs in addition to toxic side effects to human cells showed by these drugs; researchers' efforts in developing new strategies to improve treatment effectiveness of fungal infection are growing, with an interest in plants and folklore medicine.

The knowledge about synergistic effects of plant extracts or their compounds with traditional agents is nowadays a type of study that has aroused interest. Some in vitro screening assays have evidenced that plant extracts are less toxic than existing antifungal agents and, in combination with them, could reduce toxicity and increase antifungal potential [21, 145].

Accordingly, combination antifungal therapy offers the possibility of broadening the spectrum of drug activity, reducing toxicity, and decreasing fungal resistance [146].

Although combination of medications requires a careful evaluation of the synergistic, antagonistic, and agonist properties of the drugs involved [147], the use of drug combinations in treatment of infections by fungi is a common preferred strategy clinically. In many cases of fungal infection, combination therapy has been used successfully [21]. For some examples, see **Table 2**.

There are two main hypotheses about the type of interaction resulting from the combination of fluconazole and amphotericin B, based on the mechanisms of action of these drugs. In the theory of depletion, the interaction between fluconazole and amphotericin B would result in antagonism due to pre-exposure to fluconazole, which would lead to depletion of the membrane ergosterol, and thus there would be a decrease in the available sites for amphotericin B. In the second theory, the synergism, amphotericin B would lead to the formation of pores, which would facilitate the greater access of azole to the intracellular space, which by inhibiting the enzymes involved in ergosterol biosynthesis would increase the antimicrobial

Combination of antifungals	Target	References
AMP B + posaconazole	*Candida* biofilms	[148]
AMP B + caspofungin	*Candida* biofilms	[54]
AMP B + fluconazole	Cryptococcosis in murine model	[149]
Micafungin + fluconazole Micafungin + voriconazole Micafungin + AMP B Micafungin + isavuconazole	*Candida* infections	[150] [151] [152]
Flucytosine + voriconazole	*Candida* infections	[148]
Minocycline + fluconazole	*Candida albicans* biofilms	[148]
Posaconazole + caspofungin	*Candida* infections	[153] [154]
Terbinafine + azole	*Candida* growth	[155] [156]
Echinocandin + azole	Invasive candidiasis	[157]
AMP B + flucytosine	Invasive candidiasis	[158]
Natamycin + 5-fluorouracil	*Fusarium* species ocular isolates	[159]

AMP B: amphotericin B.

Table 2.
Various regimes of combinatorial antifungal therapy showing better efficacy in combination than that of independent drugs (adapted from [21]).

efficacy. According to these theories, the combination of fluconazole and amphotericin B could involve different interactions [160–162].

Considering the difficulties regarding to the treatment of candidiasis and cryptococcosis, the combination of antifungals represents an important alternative to conventional therapy. The synergistic effects of drugs are primarily attributable to cell wall damage by one antifungal. Thus, this component potentiates the activity of other drugs exactly against some constituent of plasma membrane. Alternatively, compromised cell wall with an increased permeability could facilitate movement of drugs across the cell membrane to their targets. Or, the synergistic action of different drugs occurs because they act on different targets of the same pathway, which can happen, for example, with the combination of azoles and allylamines.

The objective of this strategy is to maximize the antifungal effects. Tangarife-Castaño et al. [163] reported synergy between essential oils or plant extracts associated with antifungal drugs when used as anti-*C. albicans* agents. The best synergistic effects were obtained from the combination between itraconazole and *P. bredemeyeri* extract against *C. albicans*.

Synergistic potential was observed when methanolic extract of *T. catappa* leaves was combined with nystatin or AMB against reference strains of *C. albicans*, *Candida neoformans*, *C. glabrata*, *Candida apicola*, and *Trichosporon beigelii* [164]. The combination showed maximum synergy against *C. apicola*.

Santos et al. [165] related synergistic antifungal activity of an ethanol extract of *Hyptis martiusii* in combination with metronidazole against *C. albicans*, *C. krusei*, and *C. tropicalis*. Avijgan et al. [166] reported a potent synergistic effect between an *Echinophora platyloba* ethanolic extract and itraconazole or FLZ against isolates of *C. albicans* from vaginal secretions of patients with recurrent vulvovaginitis, significantly lowering the concentrations of both substances.

A combination between thymol and nystatin was found to have synergistic effects against *Candida* species [137], reducing the MICs of both products by 87.4%. Synergism was observed between a water insoluble fraction from *U. tomentosa* bark and terbinafine, as well as between it and FLZ against seven resistant isolates of *C. glabrata* and *C. krusei* [167]. Synergistic effects led to cell damage, and authors demonstrated, through differential scanning calorimetry and infrared analysis, that intermolecular interactions between the extract components and either terbinafine or FLZ occurring outside the cell wall are likely responsible for synergistic effects observed between substances.

Subfraction combinations of *Terminalia catappa*, *Terminalia mantaly*, and *Monodora tenuifolia* showed synergistic interactions against *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. neoformans* isolates. Synergistic combination between *M. tenuifolia* and *T. mantaly* subfractions also showed fungicidal effects against most tested strains [168].

The combination therapy with curcumin and fluconazole was the most effective among the treatments tested against *Cryptococcus gattii*. The association was able to reduce the fungal burden and damage on lung tissues of infected mice and to eliminate the fungal burden in the brain, enhancing the survival of mice with *C. gattii*-induced cryptococcosis [120].

Methanolic extract of *Buchenavia tetraphylla* is a great source of antimicrobial compounds and enhanced the action of FLZ against different *C. albicans* isolates from vaginal secretions as well as azole-resistant isolates. The extract increased the action of FLZ in most strains through additive (20% of strains) or synergistic (60% of strains) effects [169].

Kumari et al. [170] investigated the effect of six essential oil compounds sourced from oregano oil (carvacrol), cinnamon oil (cinnamaldehyde), lemongrass oil (citral), clove oil (eugenol), peppermint oil (menthol), and thyme oil (thymol)

against three infectious forms: planktonic cells, biofilm formation, and preformed biofilm of *C. neoformans* and *C. laurentii*. The anti-biofilm activity of the tested compounds was in the order thymol > carvacrol > citral > eugenol = cinnamaldehyde > menthol. The three most potent compounds thymol, carvacrol, and citral showed best anti-biofilm activity at a much lower concentration against *C. laurentii*. In the presence of these potent compounds, assays revealed the absence of extracellular polymeric matrix, reduction in cellular density, and alteration in the surface morphology of biofilm cells. In addition they were the most efficient in terms of human safety in keratinocyte-*Cryptococcus* spp. co-culture infection model suggesting that thymol, carvacrol, and citral can be further exploited as cost-effective and nontoxic anti-cryptococcal drugs.

The lectin pCramoll from *Cratylia mollis*, a native forage plant endemic to the semiarid region of Brazil (caatinga biome), showed an immunomodulatory effect and a synergism in combination with fluconazole, increasing the survival of animals with cryptococcosis caused by *C. gattii* and improving aspects of morbidity present in the progression of cryptococcosis [171].

Thymol exhibited synergistic effects when combined with fluconazole against clinical species of *Candida*, enhancing the antifungal potential of the drug and decreasing the concentration required for the effect [172]. Zaidi et al. [173] found that methanolic extract of leaves of *Ocimum sanctum* in combination with fluconazole showed higher antifungal potential and synergistic activity against resistant *Candida* spp. than methanolic extract or fluconazole when used alone.

Essential oils were also recently proposed to increase drug effectiveness. *Lavandula* and *Rosmarinus* essential oils were selected as antiproliferative agents to compound lipid nanoparticles for clotrimazole delivery in treatment of *Candida* skin infections. Authors confirmed the potential anti-*Candida* activity of the selected oils due to their interaction with membrane permeabilization. In addition, in vitro studies against *Candida albicans*, *Candida krusei*, and *Candida parapsilosis* showed an increase of the antifungal activity of clotrimazole-loaded nanoparticles prepared with *Lavandula* or *Rosmarinus*, thus confirming that nanostructured lipid carriers (NLC) containing these essential oils represent a promising strategy to improve drug effectiveness against topical candidiasis [174].

A novel therapeutic strategy that has been adopted is photodynamic therapy (PDT). It is based on the interaction between a nontoxic photosensitizer and a safe source of visible light at a low intensity; the combination of these two factors in the presence of oxygen leads to the development of reactive oxygen species (ROS) which are toxic and cause oxidative damage to microorganism cells [175]. Curcumin associated with LED light was an efficient strategy against biofilms of *C. dubliniensis* isolates [176]. The uptake of CUR by yeast cells and its penetration through the biofilm were accompanied by confocal laser scanning microscopy. Daliri et al. [177] have assessed the effect of curcumin- and methyl blue-mediated PDT in combination with different laser exposure parameters on *C. albicans* colonies. They verified that the 460-nm laser in combination with CUR has the maximum antifungal efficiency against *C. albicans*.

Although we have described herein many in vitro studies examining synergistic effects among potential antifungal biomolecules and traditional antifungal agents, the mechanisms underlying these synergistic effects are poorly understood. Randomized and controlled analyses have been performed with the objective of verifying the efficacy and risks of using traditional antifungal combinations; however, the results are poor and contradictory. High cost to conduct these strategies, reduced number of clinical cases, and the existence of confusing variables are factors that contribute to the obtaining of vague and non-reproducible results.

Therefore, it is extremely relevant to examine carefully possible synergism between new phytocompounds and conventional antimycotic drugs in order to obtain more insight. Understanding the cellular action of each substance in the combination process is also a key step in inferring ways to employ strategy in the clinic. A lack of consensus in the medical clinic emphasizes the need to conduct further clinical trials using combinations of antifungals. The experiments and results addressed herein support further investigation of new plant constituents with antifungal properties and the efficacy of combination therapies involving phytocomponents and traditional antifungal agents as an important start for the development of unusual and original antifungal therapies.

6. Conclusions

The increase in *Candida* and *Cryptococcus* infections is alarming leading to high rates of morbidity and mortality worldwide. Concomitantly with the increase in fungal infections, species emerged, and the resistance phenomenon increased so that the available antifungal arsenal becomes irrelevant in the face of the problem. In addition, there are limitations manifested by some antifungal agents such as fungistatic character, severe toxicity, and renal dysfunction. Therefore, it is crucial to develop new drugs as alternative therapies that are potentially active against *Cryptococcus* and *Candida*. Plants are considered abundant and safe sources of phytochemicals endowed with many biological activities. Several polyphenols have been isolated and studied in relation to their anti-yeast and anti-virulence activities and may be useful in obtaining promising, efficient, and cost-effective drugs for the inhibition of *Candida* and *Cryptococcus* infections. Many phytosubstances are extremely effective in combination therapy with traditional or other phytochemicals, which can be further exploited to lead to novel drug therapies against recalcitrant infections.

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Conflict of interest

The authors declare no competing interests.

Author details

Cristina de Andrade Monteiro* and Julliana Ribeiro Alves dos Santos
Universidade Ceuma, Brazil

*Address all correspondence to: cristina.monteiro@ceuma.br

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