The potential of plant extracts against multidrug resistant Candida species- A review

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Candida spp. are opportunistic pathogens and their pathogenesis is increasing rapidly and there is a dramatic increase in resistance to existing antifungal drugs. The pathogenesis of Candida spp. infections is poorly understood. Candida albicans are the major species responsible for causing candidiasis in immunocompromised and immunocompetent patients. Candidemia accounts for 8 to 15% of nosocomial bloodstream infections and Candida spp. is the causative agent in 50 to 70% of the disseminated Candida infections. Therefore, it is important to control C. albicans infections through early diagnosis and prevention of candidiasis, especially for hospitalized patients. Earlier antibiotics and antifungals were effective in treating fungal infections, but resistance to these drugs has led to the emergence of new and the re-emergence of old infectious fungal diseases. Also, majority of clinically used antifungals suffer from many drawbacks in terms of toxicity, drug-drug interactions, lack of fungicidal efficacy, cost and emergence of resistant strains caused by frequent use of some of them. Development of effective and safe therapeutic treatment of fungal infections remains one of the major challenges of modern medicine. Design of novel drugs from traditional medicine offers new prospects in modern healthcare. The need of the hour is new drugs that are more effective and less toxic than those already in use. The present review describes some of the promising plant extracts that have been used as antifungal agents and are effective phytopharmaceuticals to treat fungal infections.

Keywords: Candidaemia; Candida species; Antifungal drugs; Synergistic effects; Herbal therapy

1. Introduction

1.1 Overview of Candida infection

Fungal diseases represent a critical problem to health and they are one of the main causes of morbidity and mortality worldwide [1] and a steady increase in the occurrence of fungal infections has been observed globally. Fungal infections have increased worldwide largely because of the increasing size of people at risk, including immune compromised patients receiving parenteral hyper alimentation and/or broad-spectrum antibiotics and intravascular catheter users [2] Other reasons are increase in immunosuppressive conditions like AIDS and other factors such as organ transplantation, leukemia, broad spectrum antibiotics, indwelling catheters, diabetes and intravenous drug misuse, etc [3]. Candidiasis is the most prevalent fungal infection affecting human and animals all over the world. The most common mucosal infections are thrush, vaginal candidiasis, cutaneous candidiasis, onychomycosis and chronic mucocutaneous candidiasis. The major concern with candidiasis is that it is associated with a mortality rate of 10-49% in immune compromised patients [4] and these infections are found around the hospital and even in the rest of the population [5,6] Candida is the most important causative agent of opportunistic fungal infections and a rising problem worldwide. The genus Candida includes hundreds of species of which over 40 have been recovered from human samples [7] and implicated in life-threatening infections, particularly in immune compromised hosts. They are one of the most common causes of bloodstream infection and one of the most frequent isolates from infected patients in intensive care units (ICUs) in many countries [8] Candida albicans is responsible for the majority of infections but several other emerging Candida species like C. tropicalis, C. glabrata, C. dubliniensis, C. parapsilosis, C. orthopsilosis, C. metapsilosis, C. krusei, C. famata, C. guilliermondii and C. lusitaniae [9, 10, 11, 12,13] have also been associated with disease. They represent a serious risk to human health, because they are highly resistant to the existing antifungal agents [14].

The polymorphic fungus C. albicans can live both as a harmless commensal on the human skin and mucosal surfaces and as an aggressive pathogen that causes candidiasis. It can cause even life-threatening systemic infections at a broad range of body sites[15]. It can colonize because of its high adaptability to different host niches by the activation of appropriate sets of genes in response to complex environmental signals [16]. C. albicans is the most wide-spread opportunistic pathogenic fungus, has a high degree of flexibility and thus, can exist and proliferate in environments that are extremely variable in oxygen and carbon dioxide levels, pH, osmolarity, availability of nutrients, and temperature [17, 18].
1.2 Parts of the body affected by Candidal infections

Candidiasis can be classified into two forms based on the degree of fungal invasion: superficial/mucosal candidiasis and deep-seated/systemic candidiasis. However, superficial candidiasis can affect the skin and mucous membrane and cutaneous candidiasis can affect virtually any part of the human body (e.g., finger nails, external ear, in between fingers and toes) [19]. Some of the most common candidal infection occurs in the human body parts are urinary track infection, skin, mouth and throat, gastrointestinal tract, kidney, etc. Candida infections cause a wide range of symptoms (Fig. 1).

**Urinary Tract:** Candida is most commonly found in the lower female urogenital tract in asymptomatic women. It accounts for approximately one-third of all infections in the vagina. Vulvovaginal candidiasis is most frequently caused by *C. albicans* [20, 21]. A typical symptom includes itching, discharge and sometimes a burning sensation of the vulvar skin. Approximately 75% of all women experience at least one yeast infection in their lifetime. Vulvovaginal candidiasis may be treated with local or oral antifungals [22].

**Skin:** Candida is one of a variety of fungi commonly found on human skin. Superficial infections of the skin and mucosa are the most common diseases associated with this fungus. However, the rate of skin candidal infection is high in immunocompromised patients. Even though availability of several treatment possibilities, the mortality rates associated with these infections remain high, reaching 50% [23, 24].

**Mouth and Throat:** Mucocutaneous oropharyngeal candidiasis are widespread among humans and predominately caused by *C. albicans* [25]. The most common symptoms of oral candidiasis (thrush) is characterized by whitish patches or velvety sores appearing on the mucous membranes inside of the mouth as well as the throat and tongue [26]. The occurrence of oral candidiasis in young adults has increased with the spread of HIV/AIDS [27].

**Gastrointestinal tract:** The polymorphic fungus *C. albicans* is a human commensal which grows in both yeast and filamentous forms particularly within the gastrointestinal tract [28]. However, in susceptible patients, *C. albicans* predominate at sites of primary epithelial infection, can enter the bloodstream by translocation and subsequent systemic spread [29]. Further, Candida colonizes in gut, can also promote inflammation of gastrointestinal tract [30].

**Candidal arthritis:** The adherence properties of *C. albicans* have the major role in the pathogenesis of the fungus. These most likely determine which host tissues the fungus will infect as a consequence of candidiasis [31]; this may result in candidal arthritis [32]. The occurrence of candidal arthritis is more in immunocompromised patients due to hematological malignancies [33].

![Fig. 1 Some infections caused by *Candida* spp. (a) (b) oral candidiasis, (c) (d) mucocutaneous candidiasis, (e) gastrointestinal tract candidiasis, (f) skin candidiasis.](image-url)
2. Traditional treatment of Candida Infection

Nowadays, the increased prevalence of antibiotic therapy, human immunodeficiency virus (HIV) infection and immunosuppressive disease have led humans to become more susceptible to Candida infection, with chief fungal pathogen Candida albicans [34]. The traditional antifungal agents used in the treatment of Candidal infections are azoles (fluconazole and voriconazole), polyenes (amphotericin B and nystatin), allylamines (naftifine and terbinafine) and echinocandins (anidulafungin and micafungin). Azole drugs and their derivatives continue to dominate as antifungal agents of choice against Candida related infections due to their broad spectrum of activity and high therapeutic values [35].

Amphotericin B a hydrophobic polyene antibiotic is generally used for the treatment of systemic fungal infections. However, Amphotericin B develops side effects such as hypokalemia, fever, renal dysfunction, and shivering when it is given intravenously to the patients [36]. Biofilm-associated infections and oral mycotic infections are difficult to treat because of their high resistance to a wide spectrum of antifungal drugs, including amphotericin B and azoles, such as clotrimazole or miconazole [37].

Fluconazole is most widely used antifungal agent based on its general efficiency, favourable safety profile and relatively low cost compound as compared to other antifungals. Fluconazole is a triazole, effective and used in the treatment of mucosal as well as invasive candidiasis in cancer patients [38]. Fluconazole inhibits the fungal pathogen by inhibiting the fungal cytochrome P-450-dependent enzyme and its inhibition disrupts the membrane synthesis [39].

Nystatin is a polycene antifungal antibiotic and active substance for treatment of susceptible cutaneous and mucocutaneous fungal infections caused by the Candida species [40]. Nystatin exerts both a fungistatic and fungicidal action against Candida albicans [41]. Itraconazole is a broad spectrum triazole, effective against a broad range of fungal pathogens.

These all azole drugs are well effective for the treatment of candidal infections; but drug resistance among fungal pathogens is a global problem. There are several reports that Candida become resistant to available conventional antifungal agents [42, 43]. Resistance of Candida species to existingazole and polyene antifungals is the most worldwide concern and treatment failures of some of candidiasis are because of the resistance of Candida pathogens to the antifungals drugs used. Resistance to antifungal agents can be caused by a modification of the target enzyme, the cytochrome P-450 or the failure ofazole drugs to get deposited inside the fungi which is mediated by MDR genes and CDR genes [44, 45].

Limitations in the treatment of fungal diseases such as few available antifungal agents, side effects, high cost and drug resistance have led to the search for novel antifungal drugs. So, there is need to develop some novel antifungal agents with high efficacy, low resistance and less side effects mainly from plant extracts, with the goal of discovering new chemical structures without the above disadvantages.

3. Alternative approach to treat candidal infection

Medical treatment for the candidal infections is generally carried out with chemotherapeutic drugs such as amphotericin B and the azole drugs, but toxicity and resistance to these drugs are a major problem [46, 47]. Therefore other methods are tried to control C. albicans infections like vaccine development [48], activation of innate immunity [49, 50], and immune modulation of immune responses as well [51, 52]. There may be fewer chances of resistance by these approaches. However, a search for new antifungal drugs is very necessary [53]. Interest in the search for innovative and effective drugs against resistant strains is still increasing. It is essential to search for antifungals belonging to a wide range of structural classes selectively acting on different targets with less lateral effects. The best opportunity is natural plant extracts which can be tried individually or in combination. The concept of using monodrugs to treat infections and diseases with multicausal etiology or complex pathophysiology is changing [54].

Use of combinations of available antifungal agents with different mode of action could increase the effectiveness of therapeutic potential. Synergistic interactions among the drugs present in a phytocomplex may enhance antimicrobial efficiency as compared with the efficacy exhibited by the pure substances. Synergistic effects may be due to certain complex formations that become more effective in the inhibition fungal pathogen by inhibiting the cell wall synthesis, interfering with enzymes, or causing cell death [55]. Multidrug therapy is considered advantageous because interactions between the substances accelerate the immunostimulatory, protective and repair mechanisms [56], expands the antimicrobial spectrum, prevents the emergence of resistant mutants, etc. [57].

Herbal medicines have been used to treat many diseases that are obstinate and incurable in other systems of medicine and they are gaining popularity because of many advantages such as fewer side effects, better patient tolerance, relatively lower expense and more ready acceptance due to a long history of use [58]. Plants have been used all over the world as unique sources of medicines and constitute the most common human use of biodiversity [59]. The natural medicinal plant extracts or essential oils can potentially be applicable as natural anticandidal agents. There are many reports in the literature where plant extracts have been shown to have antifungal activity. The natural medicinal plant extracts or essential oils can potentially be applicable as natural anticandidal agents in the pharmaceutical industries. The present review describes some of the most promising plants used against candidiasis. They are listed along with
their botanical name, part used, solvent used, Candida spp. used and antifungal drugs used in the treatment of candidiasis (Table 1).

4. Anticandidal activity

4.1 Anticandidal activity of plant extracts

Goncalves et al., [60] reported anticandidal activity of Cynomorium coccinum methanolic extract. The results suggested that methanolic extract was very active against C. neoformans, C. guilliermondii and C. krusei, with minimal inhibitory concentrations (MIC) values of 0.025 mg/mL. Pereira et al., [61] reported anticandidal activity of Pyrostegia venusta (Ker Gawl.) Miers phenolic compounds and crude flower extracts against clinical isolates of Candida sp. C. albicans, C. krusei, C. tropicalis, C. parapsilosis, and C. guilliermondii. All the fractions and pure compounds isolated from P. venusta showed broad spectrum effective antifungal activity against the different Candida spp. Isa et al., [62] observed anticandidal activity of Strychnos spinosa of four solvent extracts and their five fractions against C. albicans ATCC strains and C. albicans isolate (MICS 0.16 and 0.63 mg/ml).

Adwan et al., [63] reported anticandidal activity of bifonazole and Echallium elaterium fruit extracts against 3 clinical isolates of C. albicans by microdilution method. The results showed that E. elaterium fruit extracts showed good anticandidal activity, the MIC values of E. elaterium ethanolic fruits extract against C. albicans strains ranged from 0.048 to 6.250 mg/mL. Gavani et al., [64] observed the comparative efficacy of herbal essences of F. vulgare, S. hortensis, C. cyminum, and Z. multiflora essential oil on Candida albicans. The results showed that Z. multiflora essential oil had best anticandidal activity than other essential oils. The MIC values and MFC values of Z. multiflora essential oil was 34 μg/ml and 64 μg/ml respectively.

Martins et al., [65] reported the antifungal activity of extracts from ten different plants, commonly used in folk medicine, was evaluated against nineteen Candida strains. The hydro methanolic extracts of leaves of Juglans regia and Eucalyptus globulus showed promising antifungal activity against all the tested Candida strains. The antifungal activity of Piper betle L. leaf extract against seven Candida spp. was reported by Nordin et al., [66]. P. betle leaf extract effectively suppressed the growth of Candida spp. Hofling et al., [67] evaluated the potential antifungal activity of extracts from six selected plants against ten Candida species. Punica granatum and Syzygium cumini methanolic extracts showed strong antifungal activity against Candida spp.

Otari et al., [68] reported anticandidal activity of silver nanoparticles synthesized from Manilkara zapota (L.) seed extracts. The silver nanoparticles showed good anti-candidal activity against five Candida species. Sharifzadeh et al., [69] observed the antifungal activity of TC. ammi essential oil against clinically isolated susceptible and fluconazole resistant strains of Candida albicans. The results showed that all clinical C. albicans isolates were susceptible to T. ammi essential oil. Moraes et al., [70] investigated the anti-Candida activity of the hydroethanolic extract of U. tomentosa, fractions of quinovic acid glycosides, oxindole alkaloids, and fractions of polyphenols against resistant non-albican Candida isolates. The U. tomentosa water-insoluble fraction showed significant antifungal activity against several Candida spp.

4.2 Synergistic anticandidal activity of plant extracts

Chanda et al., (2013) reported the synergistic antifungal activity of methanolic extract of Terminalia catappa leaves with nystatin and amphotericin-B against five fungi. The results showed that maximum antifungal activity was found against Candida epilica NCIM3367. Avijgan et al., (2014) reported synergistic antifungal activity of Echinophora platyloba DC ethanolic extract and azole drugs against 27 clinical isolates of Candida albicans from women suffering chronic recurrent vaginitis. The results showed that MIC and MFC values were 3.1-6.25 mg/mL and 6.2-12.5 mg/mL, respectively and it also showed a potent synergistic effect of E. platyloba ethanolic extract and itraconazole and fluconazole.

Santos et al., (2013) reported synergistic antifungal activity of ethanol extract of Hyptis martiusii against three Candida spp. viz. C. albicans, C. Krusei and C. tropicalis. The results demonstrated by the ethanol extract of Hyptis martiusii (EEHM) showed synergistic antifungal activity against C. tropicalis when metronidazole was combined with EEHM. Castano et al., (2011) reported synergistic anti-Candida albicans activity of essential oils and extracts from aromatic and medicinal plants combination with antifungal drugs. The results showed that a best synergistic effect was obtained for the combination of itraconazole and P. bredemeyeri Jacq (FICI range 0.09-0.13) against C. albicans.

5. Conclusion

The present review finding corroborate the use of plant extracts/oils as alternative drugs to treat candidiasis and also endorses the use of phytocomplexes in the formulation of innovative and effective phytopharmaceuticals for preventive treatment of serious fungal infections caused by pathogenic Candida species. But there is still need for isolation and
identification of active phytoconstituent from active plant extracts and understanding the functional and structural properties of plants which may be used for herbal formulation against candidal infection.

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Table 1 List of plants, part used, solvent used, Candida spp. used and antifungal drugs used in the treatment of candidiasis.

<table>
<thead>
<tr>
<th>Plants Name</th>
<th>Part used</th>
<th>Solvent used</th>
<th>Candida spp.</th>
<th>Anti fungal drugs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abutilon theophrasti</td>
<td>Aerial parts</td>
<td>ME</td>
<td>C. albicans</td>
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<td>[75]</td>
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<td>Achillea fragrantissima</td>
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<td>PE, ME</td>
<td>C. albicans</td>
<td>-</td>
<td>[76]</td>
</tr>
<tr>
<td>Allium sativum, Azadirachta indica,</td>
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<td>-</td>
<td>C. albicans, C. dublinensis</td>
<td>AMP, CC, FLC, VLC, IT,</td>
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<tr>
<td>Murraya koenigii, Ocimum sanctum,</td>
<td></td>
<td></td>
<td>C. glabrata, C. krusei, C.</td>
<td></td>
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<tr>
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<td></td>
<td>tropicalis</td>
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<td>ME</td>
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<td>Seeds</td>
<td>HE, ME, ET</td>
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<td>AMP</td>
<td>[79]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>C. tropicalis</td>
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<tr>
<td>Azadirachta indica, Aloe barbadensis,</td>
<td>Leaves, Oil, Grass</td>
<td>ET, AQ</td>
<td>C. albicans</td>
<td>FLC</td>
<td>[80]</td>
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<td>Melaleuca alternifolia, Cymbopogon</td>
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<td>citrates, Muntingia calabura</td>
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<td>AQ</td>
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<td>Cassia roxburghii</td>
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<td></td>
<td></td>
<td></td>
<td>C. krusei, C. parapsilosis,</td>
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<td></td>
<td>C. tropicalis</td>
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<td>Cuminum cyminum, Salvadora persica</td>
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<td></td>
<td></td>
<td>AC, ME</td>
<td>C. tropicalis</td>
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<td>ME</td>
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<td></td>
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<td>C. neoformans</td>
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<td>C. albicans</td>
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<td>C. albicans</td>
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<td>HE, EA, DCM,</td>
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<td></td>
<td></td>
<td>ME, AQ</td>
<td>C. tropicalis</td>
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<td></td>
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<td>C. krusei</td>
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<td>Part(s)</td>
<td>Extract(s)</td>
<td>Effect on Yeast species</td>
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<td><em>Matricaria chamomilla</em> L.</td>
<td>Flowers</td>
<td>ET</td>
<td><em>C. lusitaniae</em>, <em>C. tropicalis</em></td>
<td>[94]</td>
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<td><em>Melaleuca alternifolia</em></td>
<td>Oil</td>
<td>-</td>
<td><em>C. albicans</em>, <em>C. glabrata</em></td>
<td>[95]</td>
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<td><em>Melilotus albus,</em> Dorycnium herbaceum*</td>
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<td>EA, AC, ET</td>
<td><em>C. albicans</em></td>
<td>[96]</td>
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<td><em>C. albicans</em>, <em>C. glabrata</em>, <em>C. guilliermondii</em>, <em>C. parapsilosis</em>, <em>C. tropicalis</em></td>
<td>[37]</td>
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<td><em>Moringa oleifera</em></td>
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<td><em>Myrtus communis</em></td>
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<td>-</td>
<td><em>C. albicans</em></td>
<td>[98]</td>
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<td><em>Nigella sativa,</em> Murraya koenigii,* Trachyspermum ammi,* Piper betel*</td>
<td>Oil</td>
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<td><em>C. albicans</em>, <em>C. dubiniensis</em>, <em>C. dubliniensis</em>, <em>C. dubiliniensis</em>, <em>C. lusitanae</em>, <em>C. parapsilosis</em>, <em>C. tropicalis</em></td>
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<td>Oil</td>
<td>-</td>
<td><em>C. albicans</em>, <em>C. dubliniensis</em>, <em>C. dubliniensis</em>, <em>C. dubiliniensis</em>, <em>C. lusitanae</em>, <em>C. parapsilosis</em>, <em>C. tropicalis</em></td>
<td>[100]</td>
<td></td>
</tr>
<tr>
<td><em>Pimenta pseudocaryophyllus</em></td>
<td>Leaves</td>
<td>HE, EA, DCM, ET, AQ</td>
<td><em>C. albicans</em>, <em>C. parapsilosis</em></td>
<td>[101]</td>
<td></td>
</tr>
<tr>
<td><em>Piper betle L.</em></td>
<td>Leaves</td>
<td>AQ</td>
<td><em>C. albicans</em>, <em>C. dubliniensis</em>, <em>C. glabrata</em>, <em>C. lusitanae</em>, <em>C. tropicalis</em></td>
<td>[66]</td>
<td></td>
</tr>
<tr>
<td><em>Piper longum,</em> Aloe vera,* Withania somnifera*</td>
<td>Roots, Leaves, Fruits</td>
<td>ET</td>
<td><em>C. albicans</em></td>
<td>[102]</td>
<td></td>
</tr>
<tr>
<td><em>Psidium guajava L.</em></td>
<td>Leaves</td>
<td>ET, AQ</td>
<td><em>C. albicans</em>, <em>C. glabrata</em>, <em>C. krusei</em></td>
<td>[103]</td>
<td></td>
</tr>
<tr>
<td><em>Pyrostegia venusta</em></td>
<td>Flowers</td>
<td>ME, ET</td>
<td><em>C. albicans</em>, <em>C. guilliermondii</em>, <em>C. lusitanae</em>, <em>C. parapsilosis</em>, <em>C. tropicalis</em></td>
<td>[61]</td>
<td></td>
</tr>
<tr>
<td><em>Quercus infectoria,</em> Punica granatum,* Thymus kotschyanu,* Zingiber officinalis,* Rhus angustifolia,* Cinnamomum spp.*</td>
<td>Aerial parts</td>
<td>ET, AQ</td>
<td><em>C. albicans</em>, <em>C. glabrata</em>, <em>C. lusitanae</em>, <em>C. parapsilosis</em>, <em>C. tropicalis</em></td>
<td>[104]</td>
<td></td>
</tr>
<tr>
<td><em>Salvia officinalis L.</em></td>
<td>Aerial parts</td>
<td>ME</td>
<td><em>C. albicans</em>, <em>C. glabrata</em>, <em>C. parapsilosis</em>, <em>C. tropicalis</em></td>
<td>[65]</td>
<td></td>
</tr>
<tr>
<td><em>Sida tuberculata</em></td>
<td>Roots, Leaves</td>
<td>ET, AQ</td>
<td><em>C. albicans</em>, <em>C. dubliniensis</em>, <em>C. glabrata</em>, <em>C. guilliermondii</em>, <em>C. lusitanae</em>, <em>C. krusei</em>, <em>C. parapsilosis</em>, <em>C. tropicalis</em></td>
<td>[105]</td>
<td></td>
</tr>
</tbody>
</table>

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**Strychnos spinosa Lam**  
Leaves  
Solvent: Acetone (AC), Aqueous (AQ), Chloroform (CH), Dichloromethane (DCM), Ethyl acetate (EA), Ethanol (ET), Hexane (HE), Methanol (ME), Petroleum ether (PE)

**Syzygium aromaticum, Punica granatum**  
Plant parts  
Antibiotics: Amphotericin B (AMP), Clotrimazole (CC), Fluconazole (FLC), Itroconazole (IT), Ketoconazole (KT), Nystatin (NYS), Miconazole (MC), Voriconazole (VLC)

**Tagetes erecta**  
Flowers  
**Thottea pomumdata**  
Whole plant  
**Trachyspermum ammi**  
Oil  
**Tridax procumbens**  
Flowers, Aerial parts  
**Uncaria tomentosa**  
Stems, barks  
**Vitis vinifera**  
Seeds  
**Xanthoria parietina**  
Whole parts  
**Syraxia curta**  
Fruiting bodies  
**Zuccagnia punctata, Lareea nitida**  
Aerial parts

**References**


Candida albicans


Stefanovic OD, Tesic JD, Comi LR. *Mellotus albus* and *Dorcymium herbaceum* extracts as source of phenolic compounds and their antimicrobial, antioxidant, and antimycotic activities. *Journal of Food and Drug Analysis*. 2015 (In press).


Fernandes MRV, Dias ALT, Carvalho RR, Souza CRF, Oliveira WP. Antioxidant and antimicrobial activities of *Psidium guajava* L. *Phytomedicine*. 2010; 17: 771–774.


