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 anticandidal 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].

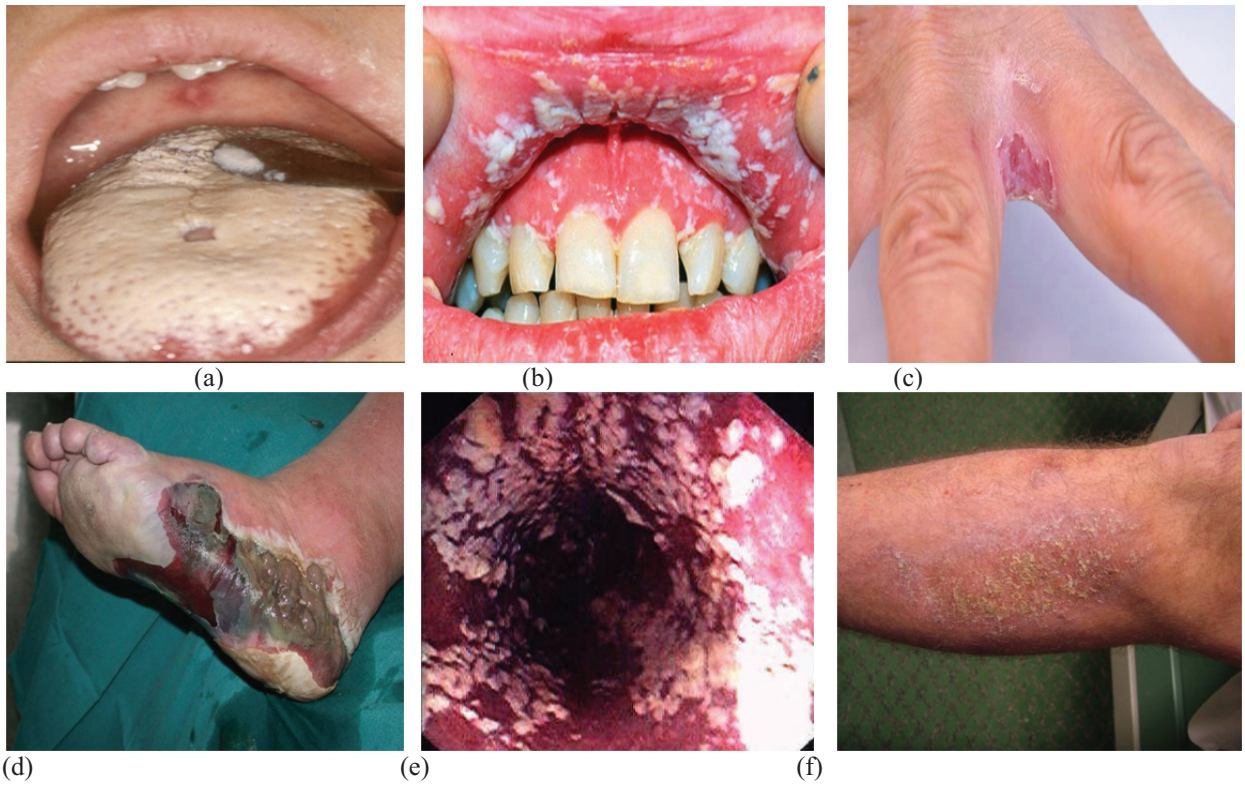

Fig. 1 Some infections caused by *Candida* spp. (a) (b) oral candidiasis, (c) (d) mucocutaneous candidiasis, (e) gastrointestinal tract candidiasis, (f) skin candidiasis.

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 polyene 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]. Itroconazole 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 existing azole 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 of azole drugs to get deposited inside the fungs 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 anticandidal 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 coccineum* 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. guilhermondii.* 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 *Ecballium 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. Gavanji *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 anticandidal effect of *Trachyspermum 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

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 epicola* NCIM3367. Avijgan *et al.,* (2014) reported synergistic anticandidal 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 anticandidal 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 candidaisis 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.

Acknowledgements The authors thank Prof. S. P. Singh, Head Department of Biosciences (UGC-CAS), Saurashtra University, Rajkot, Gujarat, India for providing excellent research facilities. The authors Mr. Tejas Rathod acknowledges the award of Senior Research Fellowship from UGC, New Delhi, India and Ms. Hemali Padalia is thankful to UGC, New Delhi, India for providing Junior Research Fellowship.

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

Plants Name	Part used	Solvent used	*Candida* spp.	Anti fungal drugs	Reference
Abutilon theophrasti	Aerial parts	ME	*C. albicans*	-	[75]
Achillea fragrantissima	Aerial parts	PE, ME	*C. albicans*	-	[76]
Allium sativum, Azadirachta indica, Murraya koenigii, Ocimum sanctum, Withania somnifera	Leaves	-	*C. albicans, C. dublinensis C. glabrata, C. krusei, C. tropicalis*	AMP, CC, FLC, VLC, IT,	[77]
Alstonia scholaris, Argemone maxicana, Datura alba	Roots, Aerial parts, Seeds	ME	*C. albicans*	-	[78]
Annona cornifolia	Seeds	HE, ME, ET	*C. albicans, C. parapsilosis C. tropicalis,*	AMP	[79]
Azadirachta indica, Aloe barbadensis, Melaleuca alternifolia, Cymbopogon citrates, Muntingia calabura	Leaves , Oil, Grass, Fruits	ET, AQ	*C. albicans*	FLC	[80]
Camellia sinensis	Leaves	AQ	*C. albicans*	-	[81]
Cassia alata Linn	Leaves	ET, AQ	*C. albicans*	-	[82]
Cinnamomun verum	Bark	HE, ME, AQ, ET	*C. albicans, C. glabrata*	-	[83]
Cassia roxburghii	Flower	AQ	*C. albicans, C. glabrata*	-	[84]
Citrullus colocynthis	Fruits	ET	*C. albicans, C.dubliniensis C. glabrata, C.guilliermondii, C. kreusei, C. parapsilosis, C.tropicalis,*	AMP	[85]
Cuminum cyminum, Salvadora persica	Stems	ET	*C. albicans, C. dubliniensis*	-	[86]
Curcuma longa L.	-	ME	*C. albicans*	-	[87]
Acalypha indica L.	Leaves	PE, CH, EA, AC, ME	*C. albicans, C. tropicalis*	-	[88]
Cynomorium coccineum	Aerial parts	ME	*C. guilliermondii, C. krusei, C. neoformans,*	-	[60]
Ecballium elaterium	Fruits	ET	*C. albicans*	-	[63]
Echinophora platyloba	Aerial parts	ET	*C. albicans*	CC, FLC, IT, MC	[72]
Eugenia uniflora	Leaves	AC, AQ	*C. albicans*	-	[89]
Heracleum persicum	Fruits	ME, ET	*C. albicans, C. glabrata,*	CC, NYS,	[90]
Lallemantia royleana	Aerial parts, Oil	-	*C. albicans*	KT	[91]
Lavandula stoechas, Lavandula pedunculata	Aerial parts	HE, EA, DCM, ME, AQ	*C. albicans, C. guillermondii*	-	[92]
Luehea paniculata	Leaves, Sapwood	ET	*C. albicans, C. krusei, C. tropicalis*	-	[93]
Manilkara zapota L.	Seeds	AQ	*C. albicans, C. guilliemondii, C. krusei,*	-	[68]

			C. lusitaniae, *C. tropicalis*		
Matricaria chamomilla L.	Flowers	ET	*C. albicans*	-	[94]
Melaleuca alternifolia	Oil	-	*C. albicans*	FLC	[95]
Melilotus albus, *Dorycnium herbaceum*	Aerial parts	EA, AC, ET	*C. albicans*	-	[96]
Metasequoia *glyptostroboides*	Cones	HE, EA, ME	*C. albicans,* *C. glabrata* *C. guilliermondi,* *C. parapsilosis* *C. tropicalis*	-	[37]
Moringa oleifera	Stems, Flowers, Leaves, Pods, Seeds	ET	*C. ciferrii,* *C. famata,* *C. guilliermondii,* *C. parapsilosis,* *C. tropicalis*	FLC, IT,	[97]
Myrtus communis	Oil	-	*C. albicans*	AMP	[98]
Nigella sativa, *Murraya koienigii,* *Trachiyspirum ammi,* *Piper betel*	Oil	-	*C. albicans,* *C. glabrata,* *C. parapsilosis* *C. tropicalis*	-	[99]
Origanum vulgare	Oil	-	*C. albicans,* *C. dubliniensis,* *C. krusei,* *C. lusitaniae,* *C. parapsilosis*	-	[100]
Pimenta pseudocaryophyllus	Leaves	HE, EA, DCM, ET, AQ	*C. albicans,* *C. parapsilosis*	-	[101]
Piper betle L.	Leaves	AQ	*C. albicans,* *C. dubliniensis,* *C. glabrata,* *C. krusei,* *C. lusitaniae,* *C. parapsilosis,* *C. tropicalis*	-	[66]
Piper longum, *Aloe vera,* *Withania somnifera*	Roots, Leaves, Fruits	ET	*C. albicans*	-	[102]
Psidium guajava L.	Leaves	ET, AQ	*C. albicans,* *C. glabrata* *C. krusei*		[103]
Pyrostegia venusta	Flowers	ME, ET	*C. albicans,* *C. guilhermondii,* *C. krusei,* *C. parapsilosis,* *C. tropicalis*	-	[61]
Quercus infectoria, *Punica granatum,* *Thymus kotschyana,* *Zingiber officinalis,* *Rhus angustifolia ,* *Cinnamomum spp.*	Aerial parts	ET, AQ	*C. albicanus,* *C. dublicans,* *C. glabrata* *C. krusei,* *C. tropicalis*	-	[104]
Salvia officinalis L.	Aerial parts	ME	*C. albicans,* *C. glabrata,* *C. parapsilosis* *C. tropicalis*	-	[65]
Sida tuberculata	Roots, Leaves	ET, AQ	*C. albicans,* *C. dubliniensis,* *C. glabrata,* *C. guilhermondii,* *C. krusei,* *C. parapsilosis,* *C. tropicalis*	-	[105]

Strychnos spinosa Lam	Leaves	HE , CH, AC, ME	*C. albicans*	-	[62]
Syzygium aromaticum, Punica granatum	Plant parts	ME	*C. albicans*	NYS	[106]
Tagates erecta	Flowers	AQ	*C. albicans, C. glabrata*	-	[107]
Thottea ponmudiana	Whole plant	PE, ME	*C. albicans*	-	[108]
Trachyspermum ammi	Oil	-	*C. albicans*	FLC	[69]
Tridax procumbens	Flowers, Aerial parts	ME	*C. albicans*	-	[109]
Uncaria tomentosa	Stems, barks	ET	*C. glabrata, C. krusei, C. parapsilosis*	-	[70]
Vitis vinifera	Seeds	ET	*C. albicans*	-	[110]
Xanthoria parietina	Whole parts	AC	*C. albicans*	KT	[111]
Xylaria curta	Fruiting bodies	EA	*C. albicans*	-	[112]
Zuccagnia punctata , *Larrea nitida*	Aerial parts	DCM	*C. albicans, C. glabrata*	-	[113]

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

Antibiotics: Amphotericin B (AMP), Clotrimazole (CC), Fluconazole (FLC), Itroconazole (IT), Ketoconazole (KT), Nystatin (NYS), Miconazole (MC), Voriconazole (VLC)

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