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Chapter 2

Antifungal Activity of Brazilian Medicinal Plants against *Candida* Species

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Additional information is available at the end of the chapter

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Abstract

Due to the resistance of *Candida* sp. to the usual antifungal, the demand for active principles found in the plants has been the target of diverse studies around the world. There are few *in vivo* and human studies on the antifungal activity of medicinal plants in the mouth. Native and imported medicinal plants, used by the Brazilian population for traditional medicine use, are the subject of study in this chapter. Thirty-eight Brazilian plants were related to information on species, family, name, used part, and medical indication of popular use. All the species mentioned had their extracts tested *in vitro* against *C. albicans*, *C. tropicalis*, *C. krusei*, *C. parapsilosis*, among other species that occur more frequently in the mouth. In the articles consulted, there is a great variation in *Candida* species tested and in minimum inhibitory concentration. The *in vitro* studies serve as information for the continuity of studies on the best performing plants, validate the popular belief about the use, and provide subsidies for the development of new products that are effective in the control of oral and systemic candidiasis and that are cheap and accessible for the population.

Keywords: Brazilian medicinal plants, *Candida* sp., oral candidiasis, minimum inhibitory concentration

1. Oral candidiasis—by Elizete Maria Rita Pereira/Vagner Rodrigues Santos

The most common fungal pathogens detected from the oral cavity are *Candida* sp. and their transition of harmless commensals to pathogenic microorganisms is often related to decrease immunity. Often, candidiasis occurs in a localized and superficial manner in the oral cavity,

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but it can be systemic or invasive and even lead to death in immunocompromised individuals [1, 2]. Like other pathogenic fungi, *Candida* spp. present dimorphism in the yeast and pseudohyphatic forms. The hyphal form is associated with epithelial cell invasion and thus causing tissue damage [3]. *Candida* spp. has other virulence factors such as adherence, production of tissue-damaging hydrolytic enzymes such as proteases, and the biofilm formation in host tissue and in medical devices [4]. Several predisposing factors, local and systemic, may result in the transition from yeast Candida to the hyphal form (pathogenic). Local factors include the use of prostheses, corticosteroid inhalers, and xerostomia, while systemic factors include immunosuppressed states as human immunodeficiency virus—HIV for example. Psoriasis, recently, was described as a predisposing factor for oral candidiasis [5].

The type of *Candida* spp. most commonly isolated from the oral cavity is *C. albicans*, which occurs in both healthy and diseased individuals [1, 6, 7]. Nonalbicans species were also isolated from the oral cavity of immunocompromised patients, such as *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. guilliermondii*, and *C. dubliniensis* [8]. Protective immune response can be induced by Candida in the host that allows its own survival. Immunocompetent adults, usually, present acquired immunity underlying the fungus that prevents the progression of oral colonization to symptomatic infection. Integrity of the mucosa is important for oral health because normally it prevents the invasion of microorganisms, as well as macromolecules, which may be antigenic [9].

1.1. Main types, diagnosis, and treatment of oral candidiasis

Candidiasis is an acute or chronic infection produced by *Candida* sp., often, limited to the skin and mucous membranes, but can produce a severe systemic disease in immunocompromised patients [3]. It may exhibit various clinical patterns such as the four primary oral forms: pseudomembranous candidiasis (thrush), acute erythematous oral candidiasis, chronic erythematous oral candidiasis, and chronic hyperplastic candidiasis (**Table 1**). These primary forms of candidiasis are also associated with lesions called secondary forms of candidiasis, such as angular cheilitis, median rhomboid glossitis, and *Candida* sp.-associated prosthesis stomatitis [10].

Diagnosis of oral candidiasis is established by identification of clinical signs and symptoms in conjunction with the presence of Candida organisms in the examination of an injury smear, biopsy examination containing hyphal form in the epithelium (Schiff's Periodic Acid), or positive culture and serological tests [11–13].

Generally, the drugs of choice for localized, uncomplicated candidiasis in patients with normal immune function are topical antifungal agents (**Figure 1**). These agents can achieve elevated levels of concentration in the oral epithelium [14]. Azoles act inhibiting the lanosterol 14-*α*-demethylase (enzyme involved in ergosterol biosynthesis) activity 14-α-demethylase (enzyme involved in ergosterol biosynthesis) and disrupt the cell membrane. The resistance to azole, generally, can be observed in HIV/AIDS patients receiving treatment for pre-HAART oral or esophageal candidiasis, for example. The resistance mechanisms of *C. albicans* include mutations that result in increased expression of efflux pumps (CDR1P, CDR2P, and MDR1P) and mutations in the target ERG11 drug [15].

Polyenes act by direct binding to ergosterol within the membranes of fungal cells, therefore, inducing the leakage of cytoplasmic content and leading to the death of microorganism.

Primary forms of oral candidiasis	Characteristics
Pseudomembranous candidiasis (oral thrush)	Confluent white plaques with epithelial desquamation and accumulation of keratin, fibrin, necrotic tissue, and fungal hyphae [5, 11]
	• Ability to easily remove white plaques with gauze [5]
	• Most commonly found in immunosuppressed individuals [5]
Acute erythematous oral candidiasis	• Known as "sore mouth antibiotic," due to its association with prolonged use of broad-spectrum antibiotics [11]
	• It presents as erythematous patches, commonly on the palate, but may also present on the buccal mucosa or on the back of the tongue [5]
Chronic erythematous oral candidiasis	• These are atopic lesions associated with angular cheilitis and prosthetic stomatitis [5]
	• Prevalence in HIV-positive and AIDS patients [11]
Chronic hyperplastic candidiasis (candida leukoplakia)	• Homogeneous type of adherent white or erythematous nodular/speckled type that cannot be easily erased [5, 11]
	• It is present bilaterally in the commissure regions of the buccal mucosa [11]

Table 1. Primary forms of oral candidiasis [10].

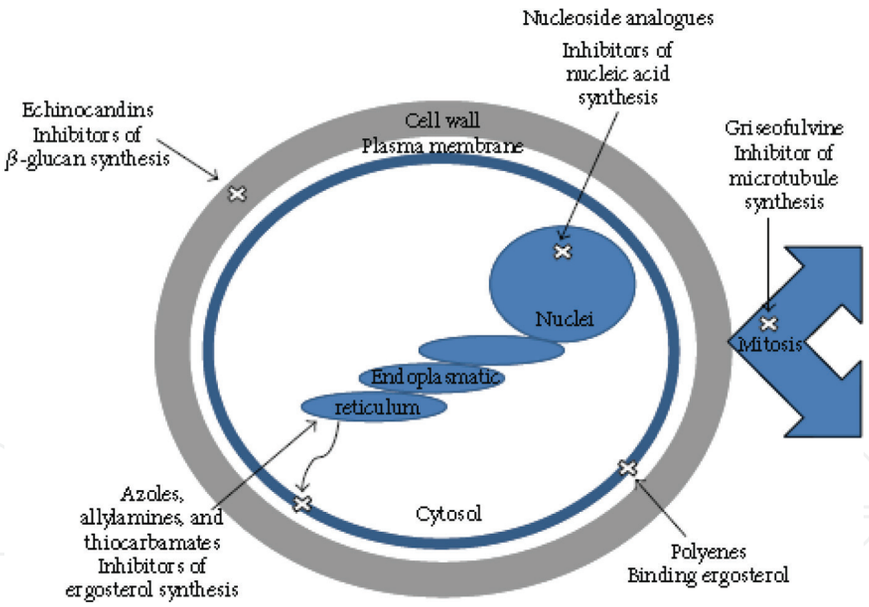


Figure 1. Primary targets of several antifungal agents by Garcia-Cuesta et al. [14].

Formulations of nystatin or amphotericin B are used for 4 weeks [11, 14]. Resistance was observed in case reports of cancer patients on chemotherapy and those who have received long-term prophylactic therapy. The mechanism of Candida resistence to the polyenes are not yet known, but seem to involve changes in the cell membrane composition [15].

Echinocandins are noncompetitive inhibitors of the β-1,3 glucan synthase encoded by the FKS1 gene of *C. albicans*, which leads to the formation of fungal cell walls with impaired structural integrity, leading to osmotic lysis. Resistance is associated with acquired or intrinsic

FKS1 point mutations [15]. Flucidosycin is a pyrimidine analogue, which is transported to fungal cells by cytosine permeases. After this, 5-fluorouracil and phosphorylation of 5-fluorodeoxyuridine monophosphate are deaminated. This nucleotide acts by inhibiting thymidylate synthase and interferes with DNA synthesis [14]. Mutations in the cytosine-permease FCY2 gene or the cytosine-deaminase gene FCY1 are the most common causes of drug resistance. To avoid this increased resistance, flucytosine is almost always administered to patients in conjunction with amphotericin B [15]. Griseofulvin, first isolated from griseofulvin, first isolated from *Penicillium griseofulvum,* inhibits the fungal mitosis to act by disrupting the production of microtubules in the spindle and cytoplasm [14].

Antifungal systemic agents are indicated in fungemia when found in low immunity or immunodeficiency, high agranulocytosis, cancer patients or patients with intravenous catheters [11]. Worldwide, an increase in the number of antifungal resistant yeasts is recognized. An important factor in contribution to human candidiasis is the ability of *Candida* species to form drug-resistant biofilms [4]. The antifungal resistance can occur by different mechanisms, such as the reduction of the intracellular accumulation of the drug, decreased affinity of the target by the drug, and neutralizing the effect of the drug. Depending on the mode of action of the antifungal compounds, the mechanism of resistance will be different [14].

The search for new antifungal agents and the characterization of new targets that are more appropriate and efficient have been proposed [4]. Potential alternative therapies include the use of new active principles obtained from different general sources, such as natural products, in particular, the plants that contain several components that are important sources of biologically active molecules [14].

2. Brazilian medicinal plants tested against *Candida* spp.—by Vagner Rodrigues Santos

2.1. Introduction

The search for therapeutic applications of medicinal plants and their derivatives has grown in the past years throughout the world. Several studies have been carried out in order to evaluate new biological properties from the biodiversity. The discovery of new antimicrobial components is of great relevance, particularly for dentistry, since bacterial and fungal infections of the oral cavity are a relatively common problem: *Candida albicans* is an opportunistic yeast commonly identified in denture stomatitis and other oral candidosis clinical forms [12].

These are examples of infectious conditions of the mouth, and the resistance to antimicrobials in clinical cases has stimulated the search for natural agents as alternative treatments for the mouth infectious conditions. In Brazil, local communities use plants and their extracts for different medicinal purposes and take advantage of the availability of these plants and the low cost for product preparation. Plants have been used as antimicrobial, anti-inflammatory, wounds scarring, and antihemorrhagic agents, just to mention a few [16].

Medicinal plants continue to be widely used in rural and urban areas of Brazil. However, the intense miscegenation of crops over the last few centuries has more popularized the use of

exotic native Brazilian plants and plants imported from other countries in popular medicine, especially in the southcentral part of the country. Most of these species were introduced by the Europeans and Africans, and are usually used according to the traditions of their places of origin [15, 16]. The growth of the pharmaceutical industry during the second half of the last century also distanced the Brazilian population from traditional medicine based on native plants. In the mid-1970s, for example, commercial pharmacies had lost their importance as the pharmaceutical industry completely dominated the drug market. This period was also marked by intense repression of mysticism, including the traditional use of medicinal plants. These facts are aggravated also by the continuous destruction of the rich Brazilian ecosystems, a process initiated with the exploration of Brazilwood by the Portuguese. As a consequence, remedies prepared with native plants, especially those of Amerindian origin, are now little known or used [16].

The Brazilian territory has about 20% of the world's biodiversity, including plants, which serve as raw materials for the production of herbal medicines and other products. The great cultural and ethnic diversity of Brazil is responsible for the knowledge transmitted over generations on the management and use of medicinal plants [17]. The high frequency of infections by the *Candida* species, as well as the occurrence of resistance to the usual antifungal, either in the hospital environment or in domestic use, as well as the increasing number of immunocompromised patients puts us in check and leads us to search for new active principles originated from medicinal plants that are effective in the control of microorganisms [18].

Several plants have been studied in Brazil based on popular use, mainly by rural communities [16].

The antifungal activity observed in some plants may be related to the presence of flavonoid glycosides and tannins, components that have antimicrobial and anti-inflammatory properties [19]. There is a growing interest in the use of tannins as antimicrobial agents. The activity of tannins against bacteria and yeasts can be measured by their action on the membranes, since they can cross the cell wall, composed of polysaccharides and proteins, and bind to its surface [20].

Studies with natural products generate difficulties regarding the comparison of results. This situation is due to the different presentations of the products used as tincture, ethanolic extract, aqueous extract, essential oil, among others, as well as the various methodological criteria employed [21] and also the different forms of phytotherapic presentation, among them, oral solutions, gel, and tea by decoction. The greater or lesser biological activity of the essential oils has been shown to be dependent on the composition of their chemical constituents, such as citral, pinene, cineole, caryophyllene, elemeno, furanodiene, limonene, eugenol, eucalyptol, and carvacrol. These constituents are responsible for the antiseptic, antibacterial, antifungal, and antiparasitic properties [22].

The mode of extraction of the active principles can influence significantly the antimicrobial activity. Biosynthesis of the constituents of a plant is strongly affected by the environment, harvest and postharvest, rainfall, temperature, luminosity, and humidity [23].

The mechanisms of action of medical plant extents on *Candida* spp. are still poorly studied. Several mechanisms of action have been proposed from the rupture of the cellular membranes, which several mechanisms of action have been proposed from the rupture of the cellular membranes, which seems to interrupt the cell cycle through the synthesis of proteins and alteration of the yeast DNA [24].

The most common microbiological methods for testing plant-derived products such as extracts, resins, and essential oils are agar diffusion tests and liquid-liquid tests such as macrodilution and microdilution [25]. The techniques of application of the plant antimicrobial substance in the diffusion method are by means of disc, stainless steel, or glass cylinders and agar perforation. The agar diffusion test, also called plaque diffusion, is a physical method in which a microorganism is challenged against a biologically active substance in solid culture medium and relates the size of the growth inhibition zone of the challenged microorganism [25, 26]. The application of the diffusion method is limited to fast-growing microorganisms, which are aerobic or anaerobic. The evaluation is comparative against a reference biological standard (positive control), and the zone or halo of inhibition of growth is measured starting from the circumference of the disc or well, to the margin where there is growth of microorganisms [27]. According to the size of the halo, the microorganisms can be classified as: sensitive, when the diameter of the zone of inhibition is greater or no more than 3 mm less than the positive control; moderately sensitive, halo greater than 2 mm, but smaller than the positive control of more than 3 mm; and resistant, diameter equal to or less than 2 mm. As a positive control, a standard antimicrobial is used, and as a negative control, the solvent is used for the dissolution of the extracts [28–32]. The recommended incubation conditions are 35–37°C for bacteria for 24 to 48 hours and for fungi from 25 to 27°C for 48 to 72 hours [33–39]. These tests serve to define the minimum inhibitory concentration that quantifies the lowest concentration of the product capable of inhibiting the growth of microorganisms [40–46] (**Table 3**).

Table 2 shows the species, families, popular names, and used parts of plants for the various applications in traditional medicine.

Herbs	Family	Local popular name	Used source	Medical use	Ref.
Allium sativum L.	Liliaceae	Garlic	Bulb	Antimicrobial, healing, antioxidant, antitumor	[47, 48]
Anacardium humile L.	Anacardiaceae	Cajuzinho-do-cerrado, little cuckoo	Shells, sheets, pulp	Antifungal, anti-inflammatory, hypoglycemic antioxidant, antimicrobial antiparasitic	[49, 50]
Anadenanthera colubrina (Vell) Brenan	Fabaceae	Angico branco, white Angico	Shells, resin	Healing, anti-inflammatory, antimicrobial	[51, 52]
Annona crassiflora Mart.	Annonaceae	Araticum	Shells, sheets, fruits	Antimicrobial cytotoxicity	[53, 54]

Herbs	Family	Local popular name	Used source	Medical use	Ref.
Arrabidaea chica (Hum. & Bonpl.) B. Verlot	Bignoniaceae	Crajiru	Sheets, shells	Anti-inflammatory, Antimicrobial Antihypertensive, antitumoral	[55, 56]
Azadirachta indica A. Juss	Meliaceae	Neem, nim	Oil, flowers, leaves, seeds, bark	Antimicrobial, insecticide, antimalarial	[57, 59]
Baccharis dracunculifolia DC	Asteraceae	Rosemary, broom	Sheets, flowers, stalk	Antimicrobial antioxidant, antitumoral, healing	[38, 60, 61]
Baccharis trimera (Less.) DC	Asteraceae	Carqueja	Flowers sheets oil	Antioxidant, antihepatotoxic, anti-inflammatory	[62, 63]
Calendula officinalis L.	Asteraceae	Calendula	Flowers	Anti-inflammatory, healing, antimicrobial	[64, 65]
Ceiba speciosa (A.St-Hil) Ravena	Malvaceae	Paineira	Shells, sheets	Antiematism, antihypertensive, antimicrobial	[66, 67]
Centaurium erythraea Rafn	Gentianaceae	Centaurea	Shells, sheets	Digestive, emetic, febrifuge, hepatic, antioxidant, anti-inflammatory	[49, 68]
Chrysobalanus icaco L.	Chrysobalanus	Ajiru	Sheets	Antimicrobial, anti-inflammatory, antitumoral	[71]
Coriandrum sativum L.	Apiaceae	Coriander, coentro	Sheets, seeds	Antibacterial, antioxidant, hepatoprotective, anticonvulsivant	[69, 70]
Croton campestris (A. St-Hill.)	Euphorbiaceae	Canopy, velame	Oil, barks, root	Anti-inflammatory, antimicrobial, antioxidant	[49, 72]
Curatella americana L.	Dilleniaceae	Sambaiba	Sheets	Antimicrobial, anti-inflammatory, antiulcerogenic, antihypertensive	[73, 74]

Herbs	Family	Local popular name	Used source	Medical use	Ref.
Dalbergia ecastophyllum (Linn.) Taub.	Leguminosae	Rabo-de-bugio	Resin, sheets	Antitumoral, antimicrobial, antioxidant, anti-inflammatory	[75, 76]
Drimys winteri (J.R.Forst & G. Forst)	Winteraceae	Casca d'anta	Bark	Antifungal, antibacterial, antioxidant	[77, 78]
Eugenia dysenterica ex DC Mart.	Myrtaceae	Cagaita	Leaves, barks	Antidiarrhoeic, antileukemic	[79, 80]
Eugenia uniflora L.	Myrtaceae	Pitanga	Leaves	Diarrhea, fever, diabetes, inflammation, headache	[81, 82]
Equisetum arvense L.	Equisetaceae	horsetail	Sheets, bark	Antioxidant, anti-inflammatory, antimicrobial, antitumoral	[83, 84]
Glycyrrhiza glabra L.	Fabaceae	Licorice Alcacuz	Root, rhizome	Antioxidant, anti-inflammatory, antiosteoporotic	[85, 86]
Hymenaea courbaril L.	Leguminosae	Jatobá	Sap, peel	Antimicrobial, anti-inflammatory, bronchitis, antidiarrheal	[87, 88]
Jacaranda cuspidifolia Mart.	Bignoniaceae	Rosewood Jacarandá	Barks, leaves, resin	Antimicrobial anti-inflammatory, antitumor	[89, 90]
Lafoensia pacari (A.St-Hill).	Lythraceae	Mangava brava	Stem bark	Anti-inflammatory analgesic	[91, 49]
Lippia sidoides Cham.	Verbenaceae	Rosemary-pepper, Alecrim-pimenta	Leaves, barks	Antinociceptive, anti-inflammatory antimicrobial	[60, 92]
Malva sylvestris L.	Malvaceae	Mauve, malva	Sheets, flowers	Cough, anti-inflammatory healing	[93, 94]
Maytenus salicifolia Mart Ex Reissek	Celastraceae	Holy Thorn, Espinheira santa	Sheets	Antiseptic, dyspepsia, antiulcer	[95, 96]
Melaleuca alternifolia Cheel	Myrtaceae	Melaleuca	Essential oil	Antiseptic anti-inflammatory, antifungal	[87, 97, 98]

Herbs	Family	Local popular name	Used source	Medical use	Ref.
Mentha piperita L.	Lamiaceae	Peppermint, H ortelã--pimenta	Sheets	Expectorant, carminative, anti-inflammatory antimicrobial	[55, 92]
Myroxylon peruiferum L.f.	Fabaceae	Cabreúva	Bark, fruits	Anti-inflammatory, anti-headache, antifungal	[87, 99]
Psidium guajava L.	Myrtaceae	Guava tree goiabeira	Leaves, fruits	Antioxidant, antimicrobial, anti-inflammatory	[81, 100]
Punica granatum L.	Punicaceae	Pomegranate Romã	Bark, peel, pericarp, leaves, juice	Antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic	[20, 101, 102]
Ricinus communis L.	Euphorbiaceae	Castor mamona	Aerial parts	Antidiabetic, antifertility, anti-inflammatory, antimicrobial, antioxidant	[103, 104]
Sapindus saponaria var. drummondii (Hook. & Arn.) L. Benson	Sapindaceae	Soapberry	Leaves, fruits, barks	Diuretics, expectorants antifungal, antioxidant	[105, 106]
Schinus terebinthifolius Raddi	Anacardiaceae	Aroeira	Fruits, leaves, stem bark, essential oil	Antioxidant, anti-inflammation antimicrobial, antifungal, antiulcer	[69, 107]
Stryphnodendron adstringens (Mart) Coville, 1910	Fabaceae	Barbatimão	Bark leaves	Anti-inflammatory, cicatrizant, antimicrobial	[108–110]
Vismia guianensis (Aubl.) Pers.	Clusiaceae	Sealing wax Pau-de-lacre,	Resin, sheets, stalk	Anti-inflammatory, antifungal	[87, 111, 112]
Ziziphus joazeiro Mart.	Rhamnaceae	Juazeiro	Leaves, fruits, bark, root.	Anti-inflammation, antimicrobial, healing	[87, 113]

The table lists the native species and those imported or brought to Brazil.
*Ref.—References.

Table 2. Relation of Brazilian medicinal plants tested *in vitro* against *Candida* species.

Herbs	Active compounds	Microorganism	MIC: µg//mL	Ref.
Allium sativum L.	Quercetin, cyanidin, allistatin, allicin, ajoene	*C. albicans* *C. glabrata* *C. tropicalis* *C. parapsilosis*	0.125 0.312 1.56 12.5	[47, 48]
Anacardium humile	Tannins, saponins, flavonoids amentoflavone	*C. albicans*	1.50	[114, 49, 50]
Anadenanthera colubrina (Vell)	Tannins, flavonoids	*C. albicans*	0.031	[115, 51, 52]
Annona crassiflora(Mart.)	Antioxidant, tannins	*C. albicans* *C. tropicalis* *C. krusei*	2.0 0.25 0.5	[54, 116]
Arrabidaea chica	Isoscutellarein, 6-hydroxyluteolin, hispidulin, scutellarein, luteolin, apigenin; anthocyanins, coumarins, flavonoids, saponins, tannins, triterpenes	*C. albicans,* *C. dubliniensis* *C. parapsilosis* *C. tropicalis* *C. krusei* *C. guilliermondii,* *C. utilis* *C. lusitaniae* *C. glabrata* *C. rugosa*	0.007/0.015	[55, 56, 102]
Azadirachta indica	Nimonol, mahmoodin, naheedin	*C. albicans*	1000/500	[58, 117, 118]
Baccharis dracunculifolia	Artepillin C, baccharin, kaempferide, drupanin, p-coumaric acid, culifolin, caffeic acid phenethyl ester, chlorogenic acid, kaempferol, pinocembrin, naringenin, chrysin	*C. albicans,* *C. glabrata.* *C. albicans,* *C. tropicalis,* *C. stellatoidea,* *C. krusei*	0.350 0.43 20–320	[24, 38, 92, 119]
Baccharis trimera	Flavonoids, phenolic acids, quercetin, luteolin, nepetin or eupafolin, apigenin, hispidulin, phytoalexin	*C. albicans*	2.0	[120, 121]
Calendula officinalis L.	Quercetin, hyperosides, α-cadinol, gamma-cadinene, 1,2,3-cadinatriene, α-muurolol	*C. albicans* *C. parapsilosis* *C. dubliniensis* *C. glabrata*	11.0 a 30	[64, 65]
Ceiba speciosa (A.St-Hil) Ravena	Quercetin, ruthin, kaferol, gallic acid, chlorogenic acid, elagenic acid, caffeic acid	*C. albicans*	0.2	[66, 67]

Herbs	Active compounds	Microorganism	MIC: μg//mL	Ref.
Centaurium erythraea Rafn	Erytaurin, gentiopicrin, erytro-centaurin	*C. albicans,*	10.5	[49, 68]
Coriandrum sativum L.	Decanal, trans-2-decenal, 2-decen-1-ol, cyclodecane, mono- and sesquiterpene hydrocarbons	*C. albicans* *C. tropicalis* *C. stellatoidea* *C. krusei*	0.007 20 32 20	[60, 92, 122]
Chrysobalanus icaco	Pomolic acid	*C. albicans,* *C. tropicalis*	1.56 6.25	[71]
Croton campestris L.	Spathulenol, borneol, B-caryophyllene, 1,8-cineole	*C. albicans*	5.25	[49, 123, 124]
Curatella americana L.	Tannins, 4-O-methyl—catechin; epicatechin-3-O-gallate; 4-O-methyl-catechin-3-O-gallate	*C. albicans* *C. tropicalis* *C. parapsilosis*	15.6 31.3 31.3	[73]
Dalbergia ecastaphyllum	Luteolin, quercetin, biochanin A, Dalbergin, liquiritigenin, rutin	*C. albicans,* *C. glabrata,* *C. tropicalis*	64	[125, 126]
Drimys winteri	Polygodial, caffeic acid, 3-caffeoylquinic acid	*C. albicans*	0.015	[92, 127]
Eugenia dysenterica ex DC Mart.	Caryophyllene, bicyclogermacrene, spathulenol, Caryophyllene oxide	*C. albicans,* *C. tropicalis,* *C. stellatoidea,* *C. krusei.* *C. albicans*	20 32 32 20 0.250	[69, 92]
Eugenia uniflora Linn	Castor oil, isoquercetin, quercetin	*C. krusei* *C. famata,* *C. guilliermondii* *C. tropicalis*	250 125 500 125	[79, 80, 128]
Equisetum arvense L.	Camptothin A, Eugiflorins D1 and D2, afzelin, myricitrin, quercetin, myricetin, betulinic acid, centelloside C	*C. albicans* *C. albicans* *C. tropicalis* *C. krusei* *C. parapsilosis*	0.250 1000 31.2 31.2 125	[129, 81, 82, 130]
Glycyrrhiza glabra L.	Flavonoids, phenolic acids, alkaloids, phytosterols, tannins, and triterpenoids	*C. albicans*	0.78–3.12	[131, 132]

Herbs	Active compounds	Microorganism	MIC: µg//mL	Ref.
Hymenaea courbaril L.	Triterpenic saponins, glycyrrhizin, glabridin	*C. glabrata*	8	[133]
Jacaranda cuspidifolia Mart.	Terpene, phenolic, salicylic acid	*C. albicans*	1.25	[87]
		C. glabrata	0.625	
		C. krusei	1.25	
		C. parapsilosis	1.25	
		C. tropicalis	0.625	
Lafoensia pacari St. Hil.	Saponins, coumarins, quinones, flavonoids, tannins, triterpenes, steroids, alkaloids	*C. albicans*	16	[90]
Lippia sidoides Cham.	Ellagic acid	*C. albicans,*	4.40	[60, 92]
Malva sylvestris L.	Isoborneol, bornyl acetate, α-humulene, α-fenchene	*C. albicans*	0.250	[92, 134]
Maytenus salicifolia Mart Ex Reiss	Mucopolysaccharides, mucilages, flavonoids	*C. albicans*	20	[69, 93, 94]
		C. tropicalis	32	
		C. stellatoidea	32	
		C. krusei	20	
Melaleuca alternifolia Cheel	Tannins, nepeticin, rigidenol, gliquidone, 11-Î ± –hydroxygliquidone, 16-b-hydroxypristymerin	*C. albicans*	50	[95, 96]
Mentha piperita L.	8-cineole, neomenthol, menthol, carvone, acetato de metila, trans-cariofileno e viridiflorol menthol, menthone	*C. albicans*	0.73	[87, 97, 98]
Myroxylon peruiferum	α-Copaene, safrole, δ-cadinene, cumarin, cabreuvina	*C. albicans*	0.500	[55, 92]
Psidium guajava	Phenolic, flavonoid, carotenoid, terpenoid triterpene	*C. albicans*	1.25	[87, 99, 135]
		C. glabrata	1.25 µg	
		C. krusei	0.625	
		C. parapsilosis	0.625	
		C. tropicalis	1.25	
Punica granatum	Tannins, piperidine alkaloids, polyphenols, oxalic acid, malic acid, ascorbic acid, estrone punicic acid, punicalagin	*C. albicans*	20	[136, 69, 81]
		C. tropicalis	32	
		C. stellatoidea	20	
		C. krusei	32	
		C. albicans	125	
		C. krusei	15,6	

Herbs	Active compounds	Microorganism	MIC: μg//mL	Ref.
Ricinus communis	Ricinoleic acid,	*C. albicans,*	125	[137–139]
	ricin, ricinin	*C. dubliniensis,*	15.6	
		C. parapsilosis	125	
		C. tropicalis	12.5	
		C. krusei	125	
		C. guilliermondii	100	
		C. utilis,	100	
		C. lusitaniae,	30	
		C. glabrata,	100	
		C. rugosa	30	
Sapindus saponaria var. Drummondii (Hook. & Arn.) L. Benson	Terpene-acetylated saponins hederagenin	*C. albicans*	200/400	[140, 141]
Schinus terebinthifolius Raddi	α-Pinene, sabinene,	*C. albicans*	300/600	[105, 106, 142]
	z-salven, β- pinene,	*C. parapsilosis*	600	
	α-funebrene,	*C. glabrata*	300	
	limonene, myrcene,	*C. tropicalis*	300	
	alphaphellandrene			
Stryphnodendron adstringens (Mart) Coville, 1910	Gallic acid,	*C. albicans,*	4.25; 20	[49, 143, 144]
	procyanidin	*C. tropicalis,*	32	
	tannins,	*C. stellatoidea,*	32	
	delphinidin	*C. krusei*	20	
		C. albicans	7.8	
Vismia guianensis (Aubl.) Pers.	Vismiofuranoxantona, isojacareubina	*C. albicans*	4.25	[108, 110, 145]
	flavan-3-ol: epicatequina			
Zizyphus joazeiro Mart.	Betulinic acid, oleanolic acid, caffeine, amphibine D, jujubogenin	*C. albicans*	0.625	[87, 92, 112, 146]
		C. glabrata	1.25	
		C. krusei	0.625	
		C. parapsilosis	1.25	
		C. tropicalis	1.25	
		C. albicans	1.00	

* Ref—References.

Table 3. Minimum inhibitory concentration(MIC)—*in vitro* antimicrobial test of Brazilian medicinal plants against *Candida* species.

3. Oral candidiasis clinical trial studies

There are few clinical studies in humans on the efficacy of extracts from Brazilian plants in the treatment of oral candidiasis. More recently, human effectiveness of Brazilian green propolis derived from *B. dracunculifolia* on plaque control and gingivitis [49] has been shown

for the prevention and control of oral mucositis and candidiasis [147, 148] and compared green propolis gel with benzydamine hydrochloride in cancer patients and irradiated in the head and neck regions [149]. Also, the Brazilian red propolis, derived from *D. ecastaphyllum*, both extract and gel, inhibited *C. albicans* in vitro, periodontopathogenic bacteria in vitro and in vivo, besides controlling periodontitis in rats [150]. The antifungal activity of Brazilian green propolis, originated by *Baccharis dracunculifolia*, was proven when tested against *Candida albicans* collected from HIV-patients mouth. The authors also demonstrated the more effectivity of propolis compared with usual antifungal tested [29].

4. Conclusions

In this chapter, there is information about the most used Brazilian species of plants against *Candida* species. The highest antimicrobial activities were obtained with diverse plant extracts. Some tests were done with the wild-type microorganisms collected from patients' mouths; however, most tests were done using standardized American Type Culture Collection (ATCC) samples. There is a certain difficulty in doing clinical tests on humans, especially when it comes to natural products. On the other hand, tested are antibacterial and anticandidal agents and could be used in the treatment of various oral diseases caused by multiresistant microbial agents. It is also clear from this study that the antifungal activity of these 38 medicinal plants was found with ethanolic, methanol, n-butanol, and chloroformic fractions. Studies have also revealed that the plants tested are not toxic at therapeutic doses with good antimicrobial properties. However, this study is an important step toward clinical evaluation in order to produce improved phytomedicine in the treatment of oral candidiasis for multiresistant *Candida albicans*.

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A. Plant image glossary index

Photo Credits (alphabetical order of Latin names): 1 Allium sativum, alho; 2 *Anacardium humile*, cajuzinho do campo. https://www.dicaparasaude.com/beneficios-do-caju/; 3 *Anadenanthera colubrina* (Vell.) Brenan; Angico branco. https://sites.unicentro.br/wp/manejoflorestal/8598-2/; 4 *Annona sylvatica* (Araticum) http://independente.com.br/os-araticuns/; 5 *Arrabidea chica* (crajirú), https://manausalerta.com.br/pesquisa-analisa-acao-anti-inflamatoria-do-crajiru/, 6 *Azadirachta indica* (nem) -https://br.pinterest.com/pin/520095456944307200/, 7 *Baccharis dracunculifolia*, alecrim. http://www.ufrgs.br/fitoecologia/florars/open_sp.php?img=14749, 8 *Baccharis trimera* (carqueja) - http://plantaslujan-a.blogspot.com/2015/01/baccharis-trimera.html, 9 *Calendula officinalis*, calêndula. https://plantsam.com/calendula-officinalis/10 *Ceiba*



speciosa(https://www.ebay.co.uk/itm/50-seeds-of-Ceiba-speciosa-Chorisia-speciosa-bottle-of-fake-kapok-tree-R-/151774995083, 11 *Centaurium erythraea*, centaurea. http://naturalhealingroom.com/Centaury-Herb-Centaurium-Erythraea_p_1337.html, 12 https://en.wikipedia.org/wiki/Chrysobalanus_icaco; 13 *Coriandrum sativum*, coentro. https://commons.wikimedia.org/wiki/File:Starr_070906-8875_Coriandrum_sativum.jpg; 14 *Croton campestris*, https://www.flickr.com/photos/142712970@N03/38936756240; 15 *Curatella americana*, cajueiro-bravo-do-campo. https://pt.wikipedia.org/wiki/Cajueiro-bravo-do-campo; 16 Dalbergia ecastophyllum http://www.ufal.edu.br/unidadeacademica/ceca/pt-br/pos-graduacao/zootecnia/dissertacoes/talita-almeida-de-paula; 17 *Drimys winteri*, https://futureforests.ie/products/drimys-winteri; 18 *Equisetum arvense*, https://www.ebay.com/itm/Equisetum-Arvense-15-Fresh-Seeds-Herb-Medicinal-Plant-Field-Common-Horsetail-/132339802749; 19 *Eugenia dysenterica*, cagaita. http://www.viveiroipe.com.br/?mudas=cagaita; 20 *Eugenia uniflora*, pitangueira. https://www.fazfacil.com.br/jardim/pitangueira/; 21 Glycyrrhiza glabra https://www.indiamart.com/proddetail/glycyrrhiza-glabra-mulethi-extract-12502491912.html; 22 Hymenaea courbaril http://fredsonpaivareporter.blogspot.com/2017/01/hymenaea-courbaril-viveiro-da-patrulha.html; 23 Jacaranda cuspidifolia -https://br.pinterest.com/pin/247698666729355 94/?lp=true; 26 *Malva sylvestris*, malva. http://johnstarnesurbanfarm.blogspot.com/2011/11/malva-sylvestris.

html; 27 *Maytenus salicifolia*, espinheira santa. http://www.ervanariamarcosguiao.com/product-page/espinheira-santa; 28 Melaleuca alternifolia; 29 Mentha piperita, 30 Myroxylon peruiferum, 31 Psidium guajava, 32 Punica granatum, http://www.medicinanatural.com.br/; 34 Sapindus saponaria, https://www.flickr.com/photos/mercadanteweb/10829969066; 35 Schinus therebintifolia, https://en.wikipedia.org/wiki/Schinus_terebinthifolia; 36 *S. adstringens* https://www.tudosobreplantas.com.br;37Vismiaguianensis, lacre. http://tropical.theferns.info; 38 *Z. joazeiro* http://www.naturezabela.com.br/2011/04/juazeiro-ziziphus-joazeiro.html; 23 Photos of the author Vagner Rodrigues Santos: (1) *A. sativum*, (13) *Coriandrum sativum*, (24) *Lafoensia pacari*, (25) *Lippia sidoides*, (33) *Ricinus communis*.

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