Plants’ Natural Products as Alternative Promising Anti-Candida Drugs

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ABSTRACT

Candida is a serious life-threatening pathogen, particularly with immunocompromised patients. Candida infections are considered as a major cause of morbidity and mortality in a broad range of immunocompromised patients. Candida infections are common in hospitalized patients and elderly people. The difficulty to eradicate Candida infections is owing to its unique switch between yeast and hyphae forms and more likely to biofilm formations that render resistance to antifungal therapy. Plants are known sources of natural medicines. Several plants show significant anti-Candida activities and some of them have lower minimum inhibitory concentration, making them promising candidates for anti-Candida therapy. However, none of these plant products is marketed for anti-Candida therapy because of lack of sufficient information about their efficacy, toxicity, and kinetics. This review revises major plants that have been tested for anti-Candida activities with recommendations for further use of some of these plants for more investigation and in vivo testing including the use of nanostructure lipid system.

Key words: Anti-Candida, biofilm, Candida, natural products, plants

INTRODUCTION

Candida is a fungal pathogen1 which is mostly known to cause high rate of mycotic infection to human worldwide.2 Candida is known to cause mucosal and deep tissue infections. Candida infects mucosal tissues including mouth, esophagus, gut, and vagina.3 Vaginal candidiasis continues to be a world health problem to women.4 Candidal infections are common in hospitalized patients and elderly people, and are difficult to control.5 About 50% of adults have Candida yeasts in their mouth and it is responsible for superficial easily treated infections. However, candidal infections can spread through the body and become life threatening, in particular with immunocompromised patients.6,7 Candidiasis represents a major cause of death.8 Candida can switch between two major forms, yeast and hyphae forms. The switch from yeast to hyphae is considered a major infectious agent of Candida.9 In addition, Candida spp. produces biofilms on synthetic materials, which facilitates adhesion of the organisms to devices and renders the organism relatively resistant to antifungal therapy.10 Catheter-associated Candida biofilms can lead to bloodstream infections.11 Candida-infected catheters, in particular those associated with microbial biofilms, can represent 90% of infections among hospital-admitted patients and hence considered as a major cause of death.11 Several synthetic drugs are established in the treatment regimens of candidal infections as indicated in Table 1, however drug resistance is developed.

MECHANISMS OF CANDIDAL RESISTANCE TO SYNTHETIC DRUGS

The formation of biofilms in Candida and the transition from planktonic to sessile form are mainly associated with highly resistant phenotype. Other mechanisms of resistance include the expression of resistance genes, particularly those encoding efflux pumps, and the presence of persister cells.12 Major synthetic drugs that develop candidal resistance include 5-flucytosin, amphothericin B, azoles, and echinocandins [Table 1].

PLANTS AS NATURAL SOURCES OF ANTI-CANDIDAL DRUGS

Plants are known for decades as the only source of medicines by traditional people.18 Moreover, plants are still used as major remedies by several countries, particularly in Africa and Asia.19 Several plant species showed effective anti-candidal activities [Table 2]. However, promoting a medicinal plant as an antimicrobial agent is challenging and requires more assessment including safety and efficacy prior to clinical study. Table 2 summarizes most of the reported plants tested for anti-candidal activities. Several of these plants showed promising minimum inhibitory concentration (MIC) such as peppermint (0.08 μg/mL).

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MECHANISM OF ACTION OF ANTI-CANDIDA NATURAL PRODUCTS

The anti-Candida mechanisms of action initiated by plant natural products can involve inhibition of germination and biofilm formation, cell metabolism, cell wall integrity, cell membrane plasticity, or can involve induction of apoptosis [Figure 1].

Inhibition of Candida biofilm formation and transition to hyphal form

The switch of Candida from yeast to hyphae is mainly accompanied by resistant biofilm formation. Candida biofilms are difficult to eradicate and are associated with resistance against many existing antifungals. Thymol which is a major constituent of thyme oil can interfere with biofilm metabolic activity and thus inhibits early and mature biofilm formation. Anthraquinones isolated from Heterophyllaeca pustulata showed significant activity against Candida tropicalis biofilm formation by interfering with the pro-oxidant–antioxidant balance leading to biofilm injury. They also showed synergistic activity with amphotericin B. Geraniol oil and its nanoemulsion showed antibiofilm activity against Candida albicans, C. tropicalis, and Candida glabrata. The smaller particle size of geraniol nanoemulsion efficiently penetrates biofilms and hence damages the organism’s cell membrane. Similarly, cinnamic acid derivatives showed great antibiofilm activity against C. albicans at lower MIC compared to fluconazole. The most active cinnamic acid derivative is a hybrid of cinnamic acid with miconazole that leads to inhibition of biofilm at 2 μg/mL and reduction in metabolic activity of preformed biofilm at 8 μg/mL. Furthermore, lemongrass oil and its major constituents exhibit strong inhibitory activity on Candida biofilm formation, germ tube formation (GTF), adherence, and candidal colonization. Many terpenes including carvacrol, geraniol, and thymol showed strong activity in reducing the development of C. albicans biofilms. Carvacrol was able to inhibit Candida biofilm regardless of the tested species and of the biofilm maturation state.

Inhibition of Candida germ tube formation

GTF is a transitional stage between yeast and hyphal cells which is an essential stage for Candida virulence activity. GTF increases fungal adherence and penetration to infected tissues. It has been shown that essential oil of oregano inhibits C. albicans GTF to a higher extent compared to other essential oils. The inhibition of GTF is mainly related to the lipophilicity of the essential oils and their interaction with the Candida cell membrane, leading to changes and loss of the structural and enzymatic constituents of fungal cells including 1,3-β-D-glucan synthases, adenosine triphosphatase (ATPase), mannan, and chitin that are required in GTF.

Alteration in Candida cell membrane

It has been reported that terpenes can cause alteration in Candida cell permeability by getting embedded between the fatty acyl chain in the membrane lipid bilayers and hence interrupting the lipid packing and consequently disturbing membrane structure and functions. Geraniol increases the membrane fluidity by affecting the central part of the lipid bilayers. Tea tree oil increases cell permeability and inhibits medium permeability and inhibits medium acidification. Salvia sclarea oil and its major constituents, linalyl acetate and linalool, induce a significant increase in plasma membrane fluidity, which in turn induces cell apoptosis. Thymol affects cell membrane electrophysics and can create deviated membrane tension. Coriander oil showed an increase in cell membrane permeability, loss of membrane potential, leakage of intracellular DNA, and damage of cytoplasmic membrane, thus causing impaired cellular functions. Raphanus sativus antifungal peptide 2 (RaAFP2) is a plant defensin that can interact with the sphingolipid glucosylceramide (GlcCer) of susceptible fungal membranes but not with the human GlcCer, and hence can exhibit

**Table 1: Candida resistance to synthetic drugs**

| Drug            | Mechanism of action                                                                 | Mechanism of resistance                                                                 | Reference |
|-----------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------|
| 5-flucytosine   | An antimetabolite that interferes with the fungal thymidylate synthetase               | Mutations in the permease enzyme encoded by FCy2 gene which results in impaired uptake of the drug | [12,13]  |
| Amphotericin B  | It binds to the fungal ergosterol, and causes pore formation in the cell membrane     | A total lack of ergosterol in the fungal membrane or a different ergosterol structure that prevents binding | [12,13]  |
| Azoles          | Inhibitors of the cytochrome P450 14a-sterol demethylase (CYP51), thus inhibiting biosynthesis of ergosterol | Overexpression of ERG11 and/or mutations in the gene. ERG11 encodes the azole target enzyme, and upregulation can result in resistance due to a nonoptimal enzyme–drug ratio, whereas sequence mutations can cause a decrease in affinity of the enzyme (Erg11p) toward the drug | [14,15]  |
| Echinocandins   | It is noncompetitive inhibitor of 1,3-β-D-glucan synthase which is responsible for the synthesis of fungal cell wall | Mutations in the FKS genes (FKS1, FKS2, and FKS3) which are related to amino acid substitutions in the 1,3-β-D-glucan synthase (the echinocandins target) | [16]     |

ATP=Adenosine triphosphate, ABC=ATP-binding cassette, MFS=Major facilitator superfamily
Table 2: Natural anti-Candida products, their botanical sources, and minimum inhibitory concentration

| Plant family       | Plant common name | Botanical name | Natural habitat                                      | Main active constituents                                                                 | Candida species          | MIC (µg/mL) | Reference |
|--------------------|-------------------|----------------|-----------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------|-------------|-----------|
| Anacardiaceae      | Marula            | *S. birrea*    | South Africa and Madagascar                       | Oleic acid                                                                               | *C. parapsilosis*        | 210         | [20]      |
|                    | Sicilian sumac    | *R. coriaria*  | Southern parts of Europe                           | Phenols                                                                                   | *C. albicans*            | 15,000      | [21]      |
| Annonaceae         | Bushveld bitterwood | *X. parviflora* | Sudan, Uganda, southern region of Kenya, Malawi, Mozambique, Zimbabwe, and Limpopo | β-pinene                                                                                   | *C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae*, *C. albicans*, *C. krusei* | 6250, 3120, 1560 | [22]      |
|                    | False nutmeg or calabash nutmeg | *M. myristica* | Evergreen forests of Liberia to Nigeria and Cameroon, Ghana, Angola, and Uganda | Linear alphatic primary alcohols, n-hexacosanol, diunsaturated linear 1,2-diol α-phellandrene and α-pinene | *C. albicans*, *C. krusei* | 1.6         | [22]      |
|                    | Sugar apple or custard apple | *A. squamosa* | Native to the tropical Americas and West Indies | Diterpenoid compound kaur-16-en-18-oic acid, α-pinene, sabiune, and limonene | *C. albicans* | Methanol and chloroform extracts: 600 and aqueous extract: 800 | [23,24] |
|                    | Ethiopian pepper  | *X. aethiopica* | Senegal, Sudan, Angola, Congo, Zambia, and Mozambique | β-pinene and β-phellandrene + 1,8-cineole | *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. albicans* | 3120         | [22]      |
| Anisophylleaceae   | Monkey apple      | *A. laurina*   | Africa, India, Sri Lanka, mainland Southeast Asia, Sumatra and Borneo | Seeds and pulps are rich in flavonoids, phenolics, citric acid, malic acid, tartaric acid, fumaric acids, oxalates, phylic acid, and tannins. The seeds and pulp oils were also found to be rich in unsaturated fatty acids | *C. albicans* | Methanol extract: 500 Ethanol extract: 1000 | [25,26] |
| Acanthaceae        | Firecracker flower | *C. infundibuliformis* | India and Sri Lanka | Ethyl acetate | *C. krusei* | 125,000      | [27]      |
|                    | False waterwillow | *A. paniculata* | Native to India and Sri Lanka | 14-deoxy-11,12-didehydroandrographolide | *C. krusei*, *C. albicans*, *C. tropicalis*, *C. albicans* | 250, 100     | [28]      |
| Acoraceae          | Sweet flag or calamus | *A. calamus* | North temperate hemisphere and Tropical Asia | Tripton and tetraployd | *C. krusei*, *C. lusitaniae*, *C. parapsilosis*, *C. albicans* | 12,500       | [29]      |
| Amaryllidaceae     | Garlic            | *A. sativum*   | Native to Asia | Flavonoids and lectins | *C. albicans*, *C. albiicans* | 28,800, 200-500 | [30]      |
|                    | Onion             | *A. cepa*      | Native to China | Allicin | *C. albicans* | 10,000 | [31,32] |
| Apiaceae           | Coriander         | *C. sativum*   | Native to the Mediterranean region | Linalool, 1-decanol, 2E-deceno1, 2 Z-dodecenol, aldehydes, 3-hexenol | *C. albicans* | ATCC 90028 | [33,34] |
|                    | Cumin             | *C. cyminum*   | Native to Asia | Pinene, cineole, linalool | *C. albicans* | 280         | [35]      |
|                    | Fennel            | *E. vulgare*   | Native to the Mediterranean region | Trans-anethole, limonene, fenchene | *C. albicans* | 300         | [36]      |
|                    | Persian hogweed   | *H. persicum*  | Native to Iran | Anethole, terpinolene | *C. albicans* | 1100 | [37]      |
|                    | Anise             | *P. anisum*    | Native to the Mediterranean region | Anethole, coumarins | *C. albicans* | 300 | [38]      |

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### Table 2: Contd...

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|-------------------|----------------|----------------|-------------------------|----------------|------------|-----------|
| Apocynaceae  | White's ginger    | M. whitei      | Tropical Africa | Alkaloids, anthocyanins, Anthraquinones, flavonoids, Phenols, saponins | C. guilliermondii | 6250       | [39]      |
|              |                   |                |                |                         | C. albicans     | 3120       |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
|              | Silk rubber       | Funtumia elastica | Senegal and Tanzania (Melanesia), But cultivated through the tropics | Tannins and flavonoids | C. guilliermondii | 100,000 | [40]      |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
| Areaceae     | Coconut           | C. nucifera    | Native to Pacific Islands (Melanesia), But cultivated through the tropics | Lauric acid, caprylic acid, and capric acid | C. guilliermondii | 25% (1:4 dilution) | [41]      |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              | Dhangri bet or    | C. leptospadix | Himalayas, Nepal, and Bengal | Ursolic acid (triterpenoid saponin) | C. guilliermondii | 60        | [42]      |
|              | Rab bet           |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
| Asteraceae   | Wormwood          | A. sieberi     | Central and Southwestern Asia | β-thujone, camphore α-thujone | C. guilliermondii | 37.4-4781.3 | [43]      |
|              |                   |                |                |                         | C. albicans     |            |           |
|              | Wild rhubarb or   | A. minus       | Native to Europe, but has become an invasive weed in Australia, North and South America | Major flavonoids (isouqueretirin and rutin), and five minor flavonoids (astragalin, kaemperol 3-O-rhamnoglucoside, quercetin 7-O-glucoside, an isomer of quercitrin, and quercetin 3-O-arabinoside), and arctiin | C. guilliermondii | 12,500   | [44,45]  |
|              | lesser burdock    |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              | Field wormwood    | A. campestris  | North America | Luteolin-7-O-rutinoside in MCE | C. guilliermondii | 25,000    | [29]      |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
| Betulaceae   | Green alder       | A. viridis     | Distributed widely across the cooler parts of the Northern Hemisphere | 5-ethyltetrahydro-5-methyl-2-furanyl moiety | C. guilliermondii | 25,000    | [29]      |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
| Yellow birch | B. alleghaniensis |                | North America | Oleanolic acid and kaempferol | C. guilliermondii | 25,000    | [29]      |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |
|              |                   |                |                |                         | C. albicans     |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. parapsilosis  |            |           |
|              |                   |                |                |                         | C. krusei       |            |           |
|              |                   |                |                |                         | C. lusitaniae   |            |           |
|              |                   |                |                |                         | C. tropicalis   |            |           |

Contd...
### Table 2: Contd...

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|-------------------|----------------|-----------------|--------------------------|-----------------|-------------|-----------|
| Bignoniaceae | Golden bell-bean  | *M. obtusifolia* | From Angola and Namibia eastwards and from the DRC and Kenya southwards to South Africa, including Malawi, Mozambique, and Zambia southwards to South Africa, including Malawi, Mozambique, and Zambia | Ursolic acid, pomolic acid and 2-epi-tormentic acid | *C. albicans* | Pomolic acid: 12.5-25  Plant extract: 160-320  Ursolic acid: 50-100  2-epi-tormentic acid: 50-100 | [47] |
|              | Flame vine        | *P. venusta*    | Native to Brazil and Paraguay | Isoverbascoside, verbascoside, quercetin-3-O-α-L-rhamnopyranosyl-(1-6)-b-D-galactopyranoside | *C. krusei ATCC 6258*  *C. krusei USP 2223*  *C. albicans ATCC 10231*  *C. albicans USP*  *C. albicans of *C. parapsilosis USP 1933*  *C. tropicalis USP*  *C. guillermondii USP 2234* | Crude extract: 3-24  Isoverbasco-side: 0.7-6  Verbasco-side: 0.7-1.5  Quercetin: 6 | [48] |
|              | Cricket vine      | *A. chica*      | Cerrado, Atlantic Forest, and the Amazon Region | Phenolics, flavonoids, anthocyanins, β-carotenes, and lycopenes | Naphthoquinones | *C. glabrata*  *C. rugosa*  *C. albicans*  *C. albicans* | Dichloromethane extract: 7-30  Methanol extract: 1-15 | [49] |
|              | Pink trumpet tree | *T. avellanedae* | America, Mexico, and Argentina | | | | |
|              | lavender trumpet tree |              | | | | |
| Caesalpinaceae | Divida  | *S. zenkeri*    | Africa and Madagasgar-Gabon | 2,4,5,7-tetrahydrooctane | *C. guillermondii*  *C. parapsilosis*  *C. tropicalis*  *C. glabrata*  *C. krusei*  *C. huxtianiae*  *C. albicans* | 6250  4680  3900  2340 | [51] |
| Caricaceae   | Papaya            | *C. papaya*     | Tropical America | Enzymes like α-D-mannosidase and glucosaminidase | | | |
| Combretaceae | Tanbuca           | *B. tormentosa*  | South America Brazil, Bolivia, and Peru | Gallic acid | *C. albicans*  *C. tropicalis*  *C. krusei*  *C. glabrata*  *C. parapsilosis*  *C. dubliniensis*  *C. albicans* | 200-12,500 | [54] |
|              | Bushwillow        | *C. albopunctatum* | Southern Africa | Terpenoids, flavonoids, phenanthrenes, and stilbenoids | | | |
|              | *C. imberbe*      | | Tropical Africa southward to Namibia and Botswana | Pentacyclic triterpenes, hydroxyemberbic acid | | | |
|              | *C. nelsonii*     | | | Asatic acid and arjunolic acid | | | |
|              | Myrobalan or      | *T. bellirica*   | Indian subcontinent and Thailand | Termilignan, thanmilignan, 7-hydroxy-3,4-(methylenedioxy) flavan, anolignan B | | | |
|              | beach almond      | | | | | |

*Contd...*
### Table 2: Contd...

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|-------------------|----------------|----------------|--------------------------|----------------|-------------|-----------|
| Curtisiaceae | Assegai tree      | C. dentata     | Zimbabwe, Mozambique, South Africa, and Swaziland | Phenols, flavonoids, tannic acid, saponins, steroids, and alkaloids | C. albicans | Leaf extract: 111 Stem bark extract: 610 | [60,61] |
| Cucurbitaceae| Bitter apple or bitter cucumber | C. colocynthis | Tropical and Subtropical North Africa and Asia | Glucosides and resins | C. albicans | 3125-12,500 | [16] |
| Ebenaceae    | Gabon ebony       | D. crassiflora | Endemic to Western Africa | Isoarborin methyl ether (cylindrin) | C. albicans | 25,000 | [62] |
|              | Evergreen tree    | D. canaliculata| Plumbagin and two known pentacyclic triterpenes (lupeol and lupenone) | Plant extract | C. albicans | 12.5 | [63] |
| Ephedraceae  | Joint-pine or Brigham tea | E. pachyclada, E. procera, E. strobilacea | Native to southwestern North America, southern region of Europe, and northern regions of Africa | - | C. albicans | 0.5 | [64] |
| Eriocaulaceae| Leiothrix         | L. spiralis    | South America | 8-carboxy-methyl-1,3,5,6-tetrahydroxyxanthone | C. albicans | 62.5 | [65] |
| Euphorbiaceae| Pillpod sandmat   | E. hirta       | Native to India | β-amyrin, and 24-methyleneoxyartenol Linool | C. albicans | 15.7 | [66] |
|              | Red sacaca        | C. cajucara    | Brazil | | C. albicans | 15.7 | [67] |
|              | Prostrate spurge or blue weed | E. prostrata | Native to the Caribbean and certain parts of South America | Flavonoids likesuch as apigenin-7-glycoside, luteolin-7-glycoside, and quercetin Phenolic compounds such asl like ellagic acid, gallic acid, and tannins | C. albicans (ATCC 51501) | 31.25 | [66,68] |
|              | Hydroalcoholic extract: 63 Ethyl acetate extract: 16 | | | | | |
| Fabaceae     | Prekese           | T. tetraperta  | Native to Western Africa | Oleanolic glycosides and cinnamic acids | C. glabrata | 6250 | [69] |
|              | | | | | C. krusei | 3120 |
|              | | | | | C. tropicalis | |
|              | | | | | C. albicans | |
|              | | | | | C. guilliermondii | |
|              | | | | | C. lusitaniae | |
|              | | | | | C. parapsilosis | |
|              | | | | | C. albicans ATCC 76645 | |
|              | | | | | C. albicans LMP-20 | |
|              | | | | | C. tropicalis | 25 | [70] |

Contd...
Table 2: Contd...

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|-------------------|----------------|----------------|----------------------------|-----------------|-------------|-----------|
| Albizia      | A. myriophylla    | Asia, Africa, Madagascar, America, and Australia | Flavan-3,4-diol, lupinofolin, dihydroxy derivatives, and lignan glycosides | C. albicans | 100–400 | [71] |
| Naranjito    | S. simplex        | Savannas       | Diterpenes     | C. albicans                | 32              | Seed extract: 300–350 |
| Golden shower tree | C. fistula     | Native to the Indian subcontinent | C. albicans, C. glabrata, C. tropicalis | [72] |
|  |                  |                |                |                            |                 | Fruit extract: 100–250 |
| Licorice     | G. glabra         | Native to southern region of Europe and India | Formononetin, liquiritigenin, and apigenin | C. albicans | 187.5 | [75] |
| Senna        | C. alata          | Native to South America | Chrysoeriol and stearic acid | C. albicans | 1500 | [76] |
| Salt-tree    | H. halodendron    | Native to Russia and Southern Asia | Salicylic acid, p-hydroxybenzoic acid (ferulic acid) and 4-hydroxy-3-methoxy cinnamic acid | C. albicans | 26900 | Salicylic acid: 150 |
| Senna        |                  |                |                |                            |                 | Benzonic acid: 100 |
| Gentianaceae | Common centaury   | C. erythraea    | Europe and Africa | Ferulic and sinapic acids | C. albicans | 100 | [78] |
| Lesser centaury | C. pulchellum     | Europe and Mediterranean region | Xanthone demethyleustomin | C. albicans | 400 | |
| Spiked centaury | C. spicatum      | Mediterranean region and Europe | Sweroside | C. albicans | 200 | |
| Senna        |                  |                |                |                            |                 | |
| Geraniaceae  | Rose geranium     | P. graveolens   | Zimbabwe and South Africa | Geraniol and linalool | C. tropicalis | 125 | [79] |
| Grosulariaceae | European gooseberry | R. uva-crispa | Europe and Africa | Citric acid | C. lipolytica | 4630 | [80] |
| Black currant | R. nigrum         | Native to temperate parts of central and northern regions of Europe | Gamma-linolenic acid and alpha-linolenic acid | C. tropicalis | 7160 | [80] |
| Juglandaceae | Persian walnut    | J. regia       | Central Asia | Juglone | C. albicans | 6 | [81] |
| Lamiaceae    | Texas sage        | S. texana      | Native to the US states of Texas and New Mexico and in northern part of Mexico | Polyphenolic flavonoids and phenolic acids. Flavones, flavonols, and their glycosides constitute the majority of flavonoids. Malonylated anthocyanins are abundant in red-to-blue salvia flowers | C. albicans, C. albicans | 125 | [82,83] |
| Peppermint   | M. piperita       | Europe and Middle East | Menthol, menthyl acetate, and menthofuran | C. albicans ATCC 10231 | 0.08 | [21] |
| Thyme        | T. maroccannus    | Native to temperate regions in Europe, North Africa, and Asia | Thymol, carvacrol | C. albicans | 125 | [84,85] |
|              | T. broussonetii   |                |                |                            |                 | |
|              | T. villosus       |                | Geranyl acetate, terpinen-4-ol, linalool, and geraniol | C. albicans ATCC 10231 | 0.64 | [86] |

Contd...
### Table 2: Contd...

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|------------------|----------------|-----------------|--------------------------|-----------------|------------|-----------|
| Oregano      | O. vulgare       | Eurasia and Mediterranean region | Carvacrol, β-fenchyl alcohol, thymol, and γ-terpinene | C. albicans | 50-100 | [43,87,88] |
| Mediterranean thyme | T. capitata | Mediterranean region | Carvacrol | C. albicans | 0.32 | [89] |
| Holy basil   | O. sanctum       | Native to Indian subcontinent and cultivated throughout tropical Asia | Methyl chavicol and linalool | C. albicans | 0.015%-0.045%v/v | [90] |
| Rosemary     | R. officinalis   | Native to the Mediterranean region | P-cymene, linalool, gamma-terpinene, thymol, beta-pinene, alpha-pinene, and eucalyptol | Methanol extract: 1-7 Dichloro- methane extract: 7-30 | [91,92] |
| Ginger bush  | T. riparia       | Native of South Africa | 14-hydroxy-9-epi-caryophyllene, calyculone, cis-muurolo:5-en-4-α-ol, fenchone, and α-trans-bergamotene | C. albicans | 250 | [93] |
| Hyssop       | H. officinalis   | Native to Southern region of Europe, the Middle East, and the region surrounding the Caspian Sea | B-pinene, 1,8-cineole, isopinocamphone | C. albicans | 3.13-30 | [94] |
| Patchouli    | P. cablin        | Native to tropical regions of Asia | Pogostone | C. albicans | 3.13-30 | [95] |
| Basil        | O. basilicum     | Native to Mediterranean Region and India | Linalool, 1,8-cineole, camphor, eugenol, (Z)-caryophyllene, limonene, b-pinene, camphene, α-pinene | C. albicans | 800-1600 | [90] |
| Sage         | S. officinalis   | Native to the Mediterranean region | Cis-tujhonethujone, trans- thujonetujhone, camphor, borneol, 1,8-cineole, α-pinene, camphene, b-pinene | C. albicans | 800-3200 | [82] |
| Avisan       | Z. multiflora    | Iran and Afghanistan | Thymol, carvacrol | C. albicans | 150 | [85] |
|              |                  |                |                 |                          |                 |            |           |

Contd...
| Plant family          | Plant common name | Botanical name | Natural habitat                                                                 | Main active constituents                                      | Candida species | MIC (µg/mL) | Reference |
|----------------------|-------------------|----------------|--------------------------------------------------------------------------------|----------------------------------------------------------------|----------------|-------------|-----------|
| Lippiaceae           | Baikal Skullcap   | S. baicalensis | Native to North America                                                        | Scutellarin                                                    | C. albicans    | 5000        | [97]      |
|                      | Ornamental oregano | M. laevigatum  | Caribbean Sea and Mexico                                                        | -                                                              | C. albicans    | 100         | [98]      |
|                      | Spiked thyme      | T. spicata     | Native to the Mediterranean region of Europe, North Africa, and the Middle East | Carvacrol                                                      | C. albicans    | 40          | [96]      |
|                      |                   |                |                                                                                  |                                                                | C. clus        | 10          |           |
|                      |                   |                |                                                                                  |                                                                | C. glabrata    | 10          |           |
|                      |                   |                |                                                                                  |                                                                | C. krusei      | 10          |           |
|                      |                   |                |                                                                                  |                                                                | C. parapsilosis | 10          |           |
|                      |                   |                |                                                                                  |                                                                | C. tropicalis  | 10          |           |
| Lauraceae            | Stenoloma         | S. chusanum    | China                                                                           | Syringic acid, vanillic acid, and gentisic acid                | C. albicans    | 50          | [99]      |
|                      | Cinnamon          | C. zeylanicum   | South-West India and Sri Lanka                                                  | Cinnamaldehyde, benzaldehyde, cinnamyl acetate                | C. albicans    | 0.01        | [100,101]|
|                      |                   |                |                                                                                  |                                                                | C. albicans    | 10.45       |           |
|                      |                   |                |                                                                                  |                                                                | C. glabrata    | 10          |           |
|                      |                   |                |                                                                                  |                                                                | C. glabrata    | 130         |           |
|                      |                   |                |                                                                                  |                                                                | C. glabrata    | 125         |           |
|                      |                   |                |                                                                                  |                                                                | C. glabrata    | 250         |           |
|                      |                   |                |                                                                                  |                                                                | C. albicans    | 3.9         |           |
|                      |                   |                |                                                                                  |                                                                | C. parapsilosis | 1.9         |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  | 780         |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  | 40          |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  | 700         |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  | 1           |           |
| Lythraceae           | S. nobilis        | L. nobilis     | Native to the Mediterranean region                                              | 1,8-cineole                                                    | C. albicans    | 160         | [96]      |
|                      | Pomegranate       | P. granatum    | Native to Iran and northeast regions of Turkey                                 | Anthocyanins, and hydrolysable tannins                        | C. albicans    | 40          | [102,103]|
|                      |                   |                |                                                                                  | Triacylglycerols                                              | C. glabrata    | 125         |           |
|                      |                   |                |                                                                                  | Punicalagin                                                    | C. glabrata    | 250         |           |
|                      |                   |                |                                                                                  |                                                                | C. albicans    | 3.9         |           |
|                      |                   |                |                                                                                  |                                                                | C. parapsilosis | 1.9         |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  | 250         | [104]     |
| Malvaceae            | Mangrove apple    | S. alba        | Seychelles and Madagascar                                                       | Lupeol and oleanic acid                                       | C. albicans    | 0.5-2       | [105]     |
|                      | Sorrel or roselle | H. sabdariffa  | Native to Tropical Africa                                                        | Flavonoids and cyaniding proanthocyanidin                     | C. albicans    | 0.125-16    | [106]     |
|                      | Han Fang Ji Dorstenia | S. tetrandra | China                                                                           | Tetrandrine                                                    | C. albicans    | 39          | [107]     |
|                      | D. turbinata      | D. turbinata   | Upper and Lower Guinea                                                           | (2'S, 3'R)-3'-hydroxymarmesin                                | C. albicans    | 9.8         | [52,108] |
|                      | Bubu Fig          | F. bubu Warb   | Coastal Tanzania                                                                | Trans-resveratrol 4a and picoed 7a                            | C. albicans    | 9.8         | [52,108] |
|                      | Brown-woolly fig  | F. drupacea    | Mediterranean region                                                             | 5-O-methylflavonol, epifriedelanol, friedelin                 | C. albicans    | Hexane extract: 13 | [109] |
|                      | Banjo fig or fiddle-leaf fig | F. lyrata | Mediterranean region                                                             | Alkaloids, flavonoids, coumarins, saponins, and terpenes       | C. albicans    | 50-2500     | [110]     |
|                      | Common dorstenia  | D. psilurus    | Native to tropical Africa                                                        | Dorsilurin F                                                  | C. glabrata    | 3120        | [107]     |
|                      |                   |                |                                                                                  |                                                                | C. krusei      |             |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  |             |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  |             |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  |             |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  |             |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  |             |           |
|                      |                   |                |                                                                                  |                                                                | C. lusitaniae  |             |           |

Contd...
### Table 2: Contd...

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|-------------------|----------------|----------------|--------------------------|-----------------|------------|-----------|
| Myrtaceae    | Gum coolibah     | *E. intertexta* | Native to Australia | 1,8-cineole | *C. albicans* | 62.5 | [111] |
|              | Eucalyptus        | *E. globulus*   | Native to Australia | 1,8-cineole, limonene, p-cymene, γ-terpinene, α-pinene, and α-phellandrene | *C. albicans* | 0.05 | [112] |
|              | Clove             | *S. aromaticum* | Native to Indonesia | Eugenol, thymol | *C. albicans* | 500 | [113] |
|              | Australian tea tree | *M. alternifolia* | Native to Australia | Terpinen-4-ol, γ-terpinene, α-terpinene, 1,8-cineole | *C. albicans* | 20.03 | [114,115] |
|              | Jambolan tree    | *S. cumini*     | Native to Bangladesh, India, Nepal, Pakistan, Sri Lanka, Malaysia, the Philippines, and Indonesia | Gallic, ellagic acid polyphenol derivatives, acylated flavonol glycosides, kaempferol, myricetin, and other polyphenols | *C. albicans* | Methanol extract: 1 | [113,117] |
|              | Red ironbark     | *E. sideroxylon* | Native to Australia | Leucocyanidin and 1,8-cineole | *C. albicans* | 400,000 | [118] |
|              | Coral Gum         | *E. torquata*   | Australia | 1,8-cineole | *C. albicans* | 400,000 | [118] |
|              | Flooded Gum       | *E. largiflorens* | Native to Australia | 1,8-cineole | *C. albicans* | 31.2 | [111] |
| Nitrariaceae | Syrian rue or Wild Rue | *P. harmala* | Asian origin and grows in the Middle East and in part of South Asia mainly in India and Pakistan | Alkaloids such as harmalin, harmalol, harmine, and harmane | *C. albicans*, *C. dubliniensis*, *C. parapsilosis*, *C. tropicalis*, *C. guilliermondii*, *C. utilis*, *C. krusei*, *C. lusitaniae*, *C. glabrata*, *C. rugosa* | Plant extract: 312-1250 Harmane: 583 Harmine: 500 Harmaline: 600 Harmalol: 750 | [119,120] |
| Olacaceae    | Upper Vvolta     | *O. subscorpioidea* | Mostly in forests, but extending far into the Savannah regions | - | *C. albicans*, *C. parapsilosis*, *C. kefyr*, *C. glabrata*, *C. tropicalis*, *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. guilliermondii*, *C. parapsilosis*, *C. lusitaniae*, *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei* | 1560 | [121] |
| Onagraceae   | Willow herb      | *E. angustifolium* | Native to the temperate Northern Hemisphere and forests | Oenothein B | *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. lusitaniae*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. lusitaniae*, *C. glabrata*, *C. albicans* | 200-400 | [29] |
| Paonaceae    | Rock’s peony     | *P. rockii*     | Gansu and China | Taxifolin, Gallic acid | *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. lusitaniae*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. lusitaniae*, *C. glabrata*, *C. albicans* | 100 | [122] |
| Plantaginaceae | Ribwort Plantain | *P. lanceolata* | Native to Eurasia and South America | Acteoside (verbascoside) and cistanoside F | *C. albicans* | 200,000 | [123] |
| Plumbaginaceae | Doctorbush or wild leadwort | *P. scandens* | | Plumbagin (naphthoquinon) | *C. albicans* | 0.78 | [124] |

Contd...
Table 2: Contd...

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|-------------------|----------------|----------------|--------------------------|-----------------|-------------|-----------|
| **Piperaceae** | Pepper | *P. bredemeyeri* | Native to Columbia and Venezuela | Trans-β-caryophyllene, caryophyllene oxide, β-pinene and α-pinene Monoterpenoid hydrocarbons | *C. albicans* (Clinical isolate) | 157.5-222.7 | [125,126] |
| | Wild pepper | *P. capense* | Guinea east to Ethiopia and south to Angola | | | | |
| | Black pepper | *P. nigroides* | India | BHA | *C. albicans* | 1560 | [126] |
| | Lacquered pepper | *P. regnellii* | Brazil | Ethyl acetate | *C. albicans* | 12,500 | [126] |
| | West African pepper | *P. guineense* | West Africa | Beta-caryophyllene | *C. albicans* | 6250 | [126,128] |
| **Poaceae** | Ginger grass oil | *C. martini* | India and Pakistan | Geraniol, (E)-β-ocimene and geranyl acetate Geranial, neral, and myrcene | *C. albicans* | 0.15 | [129] |
| | Lemongrass oil | *C. citratus* | Southeast Asia | | | 0.06 | [130,131] |
| | Cogongrass | *I. cylindrica* | Native to South America, North America, and Central America, and South America | Arundoin and 1-(3,4,5-trimethoxyphenyl)-1,2,3-propanetriol | *C. parapsilosis* | 6250 | [132] |
| **Pteridaceae** | Venus hairfern | *A. capillus-veneris* | Native to southern half of the US through Mexico | Flavonoids, sulphate esters of hydroxycinnamic acid-sugars, different classes of triterpenoids, steroids, quinic and shikimic acids | *C. albicans* | 1560 | [133,134] |
| **Ranunculaceae** | Common fennel flower | *N. sativa* | Native to Asia | P-cymene, thymol | *C. albicans* | 2300 | [135] |
| **Rhamnaceae** | Sierra nakedwood | *C. greggii* | Native to the lower Rio Grande Valley of Texas and Mexico | Chrysophanol | *C. albicans* | | [136] |
| **Rosaceae** | Virginia strawberry | *F. virginiana* | North America, in the United States (including Alaska) and Canada | Hydroxybenzoic acid and flavonols | *C. albicans* | 800 | [29] |
| | Morinda | *M. citrifolia* | Asia and Australia | 6a-hydroxyadonoside and americanin A Kämpferol 3- rhamnoside and chrysoeriol 7- neohesperidoside | *C. albicans* | 40,000 | [137] |
| | Morinda | *M. morindoides* | All tropical regions of the world | | *C. albicans* | 62,500 | [138] |
| **Salicaceae** | Quaking aspen | *P. tremuloides* | North America | Salicortin | *C. albicans* | 1600 | [29] |
| | | | | | | | |

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| Plant family        | Plant common name    | Botanical name | Natural habitat                                                                 | Main active constituents                                      | Candida species                  | MIC (µg/mL) | Reference |
|---------------------|----------------------|----------------|--------------------------------------------------------------------------------|----------------------------------------------------------------|----------------------------------|-------------|-----------|
| Salvadoraceae       | Toothbrush tree      | S. persica     | Native to Middle East                                                           | Camphor and cineole                                           | C. albicans C. dubliniensis      | 4900        | [35]      |
| Sapindaceae         | Western soapberry    | S. saponaria    | Native to the Americas                                                          | Carbohydrates and triterpenes                                | C. parapsilosis                  | 160         | [139]     |
|                     | Guarana              | P. capana      | Amazon and Brazil                                                               | (+)-catechin and (-)-epicatechin                             | C. albicans                      | 500         | [140]     |
| Sargassaceae        | Brown algae          | S. wightii     | Distributed throughout the temperate and tropical oceans of the world           | Sulfur                                                       | C. albicans C. glabrata C. guilliermondii C. krusei C. parapsilosis C. tropicalis | 100,000     | [113]     |
| Simaroubaceae       | Brucea fruit or Java | B. javanica    | Naturally from Sri Lanka and India to China, Malesia, New Guinea, and Australia | Triterpenoid                                                 | C. albicans C. krusei C. tropicalis | 50,000      | [141]     |
|                     | Brucea               | B. javanica    |                                                                                   |                                                                | C. tropicalis C. glabrata        | 25,000      |           |
| Solanaceae          | Black nightshade     | S. nigrum      | Native to Tropical Africa                                                        | Glycoprotein (glycine and proline)                           | C. albicans C. tropicalis        | 200         |           |
|                     | Eggplant             | S. melongena   | Savannahs, Asia, and Africa                                                      | 4α-methylsterols and vanillin                                | C. guilliermondii C. tropicalis  | 6250        |           |
|                     | Chinese boxthorn or  | L. chinense    | Native to China                                                                  | Dihydro-N-cafeoyltyramine, cis-N caffeoyltyramine, trans-N-feruloylctopamine, trans-N-cafeoyltyramine | C. albicans C. tropicalis        | 3120        |           |
|                     | wolfberry            | L. chinense    |                                                                                   |                                                                | C. glabrata C. tropicalis        | 40          |           |
| Theaceae            | White tea            | C. sinensis    | East and South Asia                                                              | Catechins and caffeine                                       | C. albicans                      | 10,000      | [144]     |
| Verbenaceae         | Mexican oregano       | L. graveolens  | The United States and Mexico                                                      | Carvacrol, thymol, and p-cymene                              | C. albicans                      | 100-200     | [145]     |
|                     | Brazilian Oregano    | L. origanoides | Brazil                                                                          | Oxygenated monoterpenes, carvacrol, and thymol              | C. albicans                      | 157.5-198.4 |           |
| Xanthorrhoeaceae    | A. vera              | A. barbadensis | Mediterranean region of Europe and Africa                                       | Amino acids and acemannan                                    | C. albicans                      | 1000        | [31]      |
| Zingiberaceae       | Turmeric             | C. longa       | Native to Southwest India                                                        | Curcumin                                                     | C. albicans C. glabrata C. tropicalis | 200         |           |
|                     | Ginger               | Z. officinale  | Native origin unknown, but widely cultivated in the tropics and subtropics       | α-curcumene, zingiberene, α-farnesene, β-bisabolene sesquiphellandrene, neral, and geranial | C. albicans C. tropicalis        | 400-800     |           |
|                     | Alligator pepper     | A. citratum    | Widespread across tropical Africa as well as on some islands of the Indian Ocean | Oxygenated components belonging to the acyclic terpene class, such as geranial | C. tropicalis C. parapsilosis C. glabrata C. guilliermondii C. albicans C. lusitaniae C. krusei | 6250        |           |
|                     |                      |                |                                                                                   |                                                                |                                  | 4680        |           |
|                     |                      |                |                                                                                   |                                                                |                                  | 3120        |           |
|                     |                      |                |                                                                                   |                                                                |                                  | 780         |           |
|                     |                      |                |                                                                                   |                                                                |                                  | 390         |           |

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selective antifungal activity.\textsuperscript{118, 119} The RsAFP2–GlcCer interaction can lead to increase in the permeability, Ca\textsuperscript{2+} influx, and growth arrest.\textsuperscript{116} Permeabilization due to RsAFP2 is mainly due to induction of many genes, which cause loss of cell membrane integrity, and increases cell permeability, thus causing cell survival.\textsuperscript{114} The essential oil derived from palmarosa oil, neenide oil, rose oil, and citronella oil can disturb the uniformity of cell membrane by interrupting sterol biosynthesis and inhibition of plasma membrane ATPase which is crucial for cell survival.\textsuperscript{112} Taxodone is a diterpenoid compound isolated from Metasequoia glyptostroboides and Taxodium distichum, which can cause loss of cell membrane integrity, and increases cell permeability, thus causing rapid loss of nucleic acid, ions, and some essential metabolites.\textsuperscript{113}

**Table 2: Contd...**

| Plant family | Plant common name | Botanical name | Natural habitat | Main active constituents | Candida species | MIC (µg/mL) | Reference |
|--------------|-------------------|----------------|----------------|--------------------------|-----------------|------------|----------|
| Melegueta pepper | A. melogetta | α- and β-caryophyllene | C. albicans | 6250 | [38] |
| C. krusei | 3120 |
| C. parapsilosis | 1560 |
| C. tropicalis | 1560 |
| C. guilliermondii | 1560 |

MIC=Minimum inhibitory concentration, C. infundibuliformis=Crossandra infundibuliformis, A. paniculata=Andrographis paniculata, A. calamus=Acrocalamus calamus, A. sativum=Allium sativum, A. cepa=Allium cepa, C. sativum=Coriandrum sativum, C. cinnimon=Cinnamon cinnomin, F. vulgare=Fnvicium vulgar, H. persicum=Heracleum persicum, P. anisum=Pimpinella anisum, M. white=Monda white, F. elastic=Funtoria elastic, C. nucifera=Cocos nucifera, C. leptoapadus=Calamus leptoapadus, A. sieber=Artemisia sieber, A. minus=Artemisia minus, A. campestris=Artemisia campestris, A. frigida=Artemisia frigida, S. giganteum=Solodgo giganteo, A. bierbeutelii=Achillia bierbeutelii, MCE=Menathonic crude extract, A. viridis=Arlos viridis, B. alleghaniensis=Betula alleghaniensis, M. obtusifolia=Markhamia obtusifolia, DRC=Democratic Republic of the Congo, P. venosa=Pyrostegia venusa, A. chica=Arribidua chica, T. avellaneae=Tabebia avellaneae, S. zenkeri=Scordophleus zenkeri, C. papaya=Cara papaya, B. tomentosa=Buchanania tomentosa, C. alpifaculatum=Chrombium alpifaculatum, C. interber=Chrombium interber, C. nelsonii=Chrombium nelsonii, T. bellirica=Terminida bellirica, C. dentate=Cortisia dentate, C. corynthis=Citrus corynthis, D. croscifera=Dispyros croscifera, D. canaliculata=Dispyros canaliculata, E. pachydula=Ephedra pachydula, E. procera=Ephedra procera, E. strobilacea=Ephedra strobilacea, L. spiralis=Leioforix spiralis, E. hirta=Euphorbia hirta, C. caucana=Coron ccaucana, P. prostrate=Euphorbia prostrate, T. tetraptera=Tetraplera tetraptera, D. caesalphyllum=Dalbergia caesalphyllum, A. myriophylla=Altizia myriophylla, C. simplex=Swartzia simplex, C. fistula=Cassia fistula, G. globa=Glycyrrhiza globa, C. alata=Cassia alata, H. heterodendron=Heterodendron heterodendron, LMP=Lyosomal membrane permeabilization, C. erythraea=Centaurium erythraea, C. pulchellum=Centaurium pulchellum, C. spicatum=Centaurium spicatum, C. tenuiflorum=Centaurium tenuiflorum, P. graevenis=Pelargonium graevenis, R. uva‑crispa=Ribes uva‑crispa, R. nigrum=Ribes nigrum, S. texana=Salvia texana, M. piperita=Menha piperita, T. maroccains=Thymus maroccains, T. broussonetii=Thymus broussonetii, T. villosus=Thymus villosus, O. vulgare=Oriignum Vulgar, T. captata=Thymba captata, J. regia=Juglans regia, O. sanctum=Ocimum sanctum, R. officinalis=Rosmarinus officinalis, T. riparia=Tetradenia riparia, H. officinalis=Hyssopus officinalis, P. capitatum=Pogostemon capitatum, B. officinalis=Ocimum basilicum, S. officinalis=Salvia officinalis, M. alternifolia=Melaleuca alternifolia, S. cumini=Syzygium cumini, E. sideroxylon=Eucalyptus sideroxylon, E. tenuifolia=Eucalyptus tenuifolia, E. langatensis=Eucalyptus langatensis, P. harma=Phormium harma, O. subcordata=Othax subcordata, E. angustifolium=Eupatorium angustifolium, Z. multiflora=Zataria multiflora, S. baicalensis=Scutellaria baicalensis, M. laevigatum=Mintum laevigatum, T. spicata=Thymus spicata, S. chusana=Stenodera chusana, C. zeleanicum=Cinnamomum zeleanicum, L. nobilis=Laurus nobilis, P. granatum=Punica granatum, S. albula=Sorrelaria albula, H. salsaffis=Hibiscus sabdariffa, S. tetrandra=Stephania tetrandra, D. turbinata=Dorstenia turbinata, F. drupacea=Ficus drupacea, F. lyrate=Ficus lyrate, D. pilaris=Dorstenia pilaris, F. buxus=Ficus buxus, E. interctica=Eucalyptus interctica, E. globulus=Eucalyptus globulus, S. aromanticum=Syzygium aromaticum, P. rokkii=Paonia rokkii, P. lanceolata=Plantago lanceolata, P. scandens=Plumbago scandens, P. bredeleyeri=Piper bredeleyeri, P. capense=Piper capense, P. nigrum=Piper nigrum, P. regnellii=Piper regnellii, P. guineense=Piper guineense, C. martini=Cymbopogon martini, C. citriodora=Cymbopogon citriodora, I. cymbifolium=Imperata cymbifolia, A. diffusus=Aremium diffusus, N. sativa=Nigella sativa, C. greggi=Cymbopogon greggi, V. virginiana=Vragaria virginiana, M. citrifolia=Morinda Citrifolia, M. morindoides=Morinda morindoides, P. tropicoides=Pumposa tropicoides, S. persica=Salvadora persica, S. saponaria=Seepeda saponaria, P. cupana=Paullinia cupana, S. wightii=Sargassum wightii, B. javanica=Brucia javanica, S. nigrum=Salomon nigrum, S. melongena=Solamun melongena, L. chinensis=Lycium chinensis, C. sinensis=Canella sinensis, L. graevenis=Lippia graevenis, L. angustifolia=Lippia angustifolia, A. barbadensis=Aloe barbadensis, A. vera=Aloe vera, C. longa=Cucumera longa, Z. officinalis=Zingiber officinalis, A. citratus=Africanum citratus, A. melogesta=Aframomum melogesta, S. mayrl=Morinda citrifolia, R. coriaria=Rhus coriaria, X. parviflora=Xylopia parviflora, M. myristica=Monodora myristica, A. squamosa=Arumus squamosa, X. aethiopica=Xylopia aethiopica, A. laurea=Anisophylla laurea, C. parapsilosis=Candida parapsilosis, C. albicans=Candida albicans, C. glabrata=Candida glabrata, C. guilliermondii=Candida guilliermondii, C. krusei=Candida krusei, C. tropicalis=Candida tropicalis, C. lusitaniae=Candida lusitaniae, C. stellatoidea=Candida stellatoidea, C. dubliniensis=Candida dubliniensis, C. rugosa=Coprosma rugosa, C. kofy=Candida kofy, C. inconspicua=Conspicua inconspicua, C. utilis=Canapa utilis, C. famata=Candida famata, C. holmii=Candida holmii, BHA=Butylated hydroxyanisole

**Inhibition of Candida adherence**

Essential oil of Rosmarinus officinalis showed anti-adherent activity of C. albicans. The biological activity of R. officinalis is mainly associated with its main chemical components, including cineole, limonene, and cymene.\textsuperscript{111} Schinus terebinthifolius and Croton urucurana have also

**Interference with Candida mitochondrial respiratory chain**

Respiration takes place in mitochondria that produce ATP required by all cells. The process is accompanied with the production of large amount of ROS such as hydrogen peroxide and hydroxyl radicals as by-products. ROS can cause damage to cell proteins, lipids, and DNA.\textsuperscript{114} HaAFP1 is a plant defense derived from *Heuchera sanguinea* that shows apoptotic action against *C. albicans* mainly due to accumulation of ROS leading to the induction of mitochondrion-dependent apoptosis.\textsuperscript{115} Dill seed essential oil (DSEO) can inhibit mitochondrial dehydrogenases mainly due to the disruption of the citric acid cycle and thus the inhibition of ATP synthesis.\textsuperscript{116} Furthermore, DSEO causes intracellular accumulation of ROS in *C. albicans* and hence has an antifungal activity.\textsuperscript{116} In addition, amitreflavone derived from Selaginella tamariscina has been associated with the induction of mitochondrial-dependent apoptosis in *C. albicans*.\textsuperscript{117} Lycopen is a carotenoid pigment mainly found in tomato that can cause accumulation of intracellular Ca\textsuperscript{2+} and interference with mitochondrial functions, such as cytochrome C release and mitochondrial depolarization, leading to caspase activation and ROS production and hence leads to mitochondrial dysfunction and apoptosis.\textsuperscript{118}

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showed strong anti-adherent activity of *C. albicans* that is associated with the presence of agpinigen. Apigenin can modulate gene expression and reduce the formation of glucan, leading to biofilm inhibition activity.[160]

**Induction of Candida apoptosis**

Baicalein is a flavonoid isolated from the roots of *Scutellaria baicalensis* Georgi and shows potent activity against fluconazole-resistant *C. albicans*. Baicalein mainly inhibits *C. albicans* by inducing programmed cell death (apoptosis) and reduction of drug extrusion out of the yeast cells.[170] Silibinin, a natural product extracted from *Silibum marianum* (milk thistle), can cause *Candida* apoptosis through interference with mitochondrial Ca²⁺ signaling. Ca²⁺ signaling plays an important role in physiological processes and it is associated with stress responses in fungi.[171]

**Interference with Candida cell metabolism**

Allicin isolated from *Allium sativum* (garlic) shows a strong anti-*Candida* activity mainly by inhibition of thiol-containing amino acids and proteins, therefore interfering with cell metabolism.[172,173] Human cells contain glutathione which can bind to allicin preventing cell damage whereas glutathione is lacking in *Candida* that makes allicin as selective and effective candidate in anti-*Candida* therapy.[174]

**Interference with Candida cell wall integrity**

Cell wall integrity is very important during growth and morphogenesis of *Candida* cells and in the face of external challenges that cause cell wall stress. Several natural products have showed interference effects with *Candida* cell wall integrity. For example, RsAFP2 defensin interacts with *Candida* cell wall GlcCers and hence damages cell wall integrity. Furthermore, it can disrupt the localization of septins and blocks the switch from yeast to hypha. The black tea polyphenols including catechins and theaflavins can cause *Candida* cell wall damage.[147] Similarly, casurinin isolated from *Plinia cauliflora* can target *C. albicans* cell wall, leading to significant changes in the cell wall architecture including the outer glycoprotein layer and cell wall porosity.[174]

**RESISTANCE OF Candida TO PLANT NATURAL PRODUCTS**

*Candida* strains lacking GlcCer in their membranes, either because of nonfunctional synthase enzyme or its complete absence (as in *Saccharomyces cerevisiae* or *C. glabrata*), are resistant to RsAFP2 and hence protected from cell permeabilization.[160] *C. tropicalis* shows resistance against *Uncaria tomentosa*, mainly due to the enhanced ability of *Candida* to form biofilms.[175]

**TOXICITY OF NATURAL ANTI-CANDIDA PRODUCTS**

The cytotoxic activities of anti-*Candida* natural products are rarely investigated and only few products have been tested. For example, the toxicity of geraniol oil was measured by hemolytic assay on human erythrocytes. Geraniol oil caused only 1% cell lysis at 5 µg/mL MIC compared to 10% lysis by amphotericin B or fluconazole at same tested concentrations, suggesting the safety of geraniol.[162] The cytotoxicity of *Morinda royoc* L extract was also investigated on vero cells (African green monkey kidney cells). *M. royoc* L extract showed no toxic activities according to criteria established by the American National Cancer Institute (IC₅₀ ≥200 mcg/mL).[176] Furthermore, oral administration of *M. royoc* in rats showed no toxic effects, suggesting that *M. royoc* is a good anti-*Candida* product.[177]

**IN VIVO INVESTIGATION OF NATURAL ANTI-CANDIDA AGENTS**

The anti-candidal activities of suppositories made from saponins derived from *Solanum chrysotrichum* were investigated in vulvovaginal candidiasis mice model. *S. chrysotrichum* treatment showed no significant difference in clinical effectiveness compared to ketoconazole.[179] On the other hand, garlic tablets (Garcin) showed similar activity to fluconazole on *Candida* vaginitis in women admitted to a health-care center in Iran, suggesting that garlic could be an alternative to fluconazole in the treatment of *Candida* infection.[179]

**FUTURE PROSPECTIVE AND BIOTECHNOLOGY ADVANCES IN THE PRODUCTION OF ANTI-CANDIDA-ACTIVE PLANTS**

The need for new anti-*Candida* agents is increasing, especially with the emergence of resistant *Candida* strains. The effectiveness of natural agents against different strains of fungi, particularly *Candida*, is confirmed in several publications. It has been reported that many patencies are using natural products as anti-*Candida*. For example, *Indigo naturalis* or indigo-producing plant extract has been used in the topical treatment of candidiasis.[180] A patent made from oral herbal preparation developed by Piramal Life Sciences showed efficient activity against oral candidiasis.[182] Pharmal developed an anti-candidal formula derived from *Epilobium parviflorum* for the use in the prevention and/or treatment of *Candida* infection.[181]

The screening for anti-*Candida* natural active products increased significantly during the past two decades. Several investigations have assessed the anti-*Candida* activities of natural products of plants from different geographical regions in the world. For example, Duarte *et al.* examined the anti-*Candida* activities of extracts of 258 Brazilian medicinal plant species.[184] However, other regions are still in the preliminary investigation stages such as the Arabian deserts. Desert plants of the arid/hyperarid climates of the Arab Gulf region are exposed to several environmental stresses, such as heat, drought, and salinity.
Such stresses may provide new active compounds which might have effective and unique anti-
*Candida* activities.

On the other hand, modern biotechnology techniques can improve the activity of plant extracts including anti-*Candida*; for example, the development of nanostructure lipid system. Nanostructure lipid system can improve the antimicrobial activity of plant extract, reduce the required doses, and reduce side effects. Nanostructure lipid system improves the anti-*Candida* activity of aqueous ethanol extract of stems and leaves of *Astronium sp.* The nanostructure lipid system can reduce the MIC of the plant extract ~ 9 times. Nanostructure lipid system can efficiently compartmentalize specific active components and modify their properties and behavior of plant extracts in a biological environment. Moreover, recent advances in metabolomics and engineering of target pathways may provide an optimized commercial production of the natural compounds and enhancement of their activity. Usually, metabolomics using various bioanalytical tools such as nuclear magnetic resonance, liquid chromatography-mass spectrometry (MS), and gas chromatography-MS can be done to identify the potential anti-*Candida* compounds. Once these compounds are identified and their biosynthetic pathways are assigned, candidate genes can be identified in *silico* [Figure 2]. Consequently, target pathways can be engineered with overexpression of the desired transcription factors and genes or silencing of the undesired competitive genes and pathways to enhance their production levels [Figure 2].

**CONCLUSION**

As concluding remarks, several plant natural products have been tested for anti-*Candida* activities. Several of these plant products can target critical processes in *Candida* biological activities including cell wall integrity, cell membrane plasticity, cell metabolism, respiratory chain, adherence to host cell, germination and biofilm formation, or induction of apoptosis. Despite these great anti-*Candida* activities of plant products compared to controls, only few have been tested in *vivo* and none of them have ever been clinically used as anti-*Candida*. On the other hand, although some of these products including garlic, probiotics, peppermint, cinnamon, ginger, and propolis are present in the pharmaceutical market for other medical purposes, they have never been used as anti-*Candida*. The need for new anti-*Candida* is urgent since *Candida* is known as a serious resistant microbe, and hence promotion of some of the selected plant products for clinical testing will be beneficial.

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There are no conflicts of interest.

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