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A Recent Report on 'Plants with Anti-*Candida* Properties'

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ABSTRACT

Fungal infections are drawing attention because of the high mortality and morbidity rate associated with them. *Candida, Cryptococcus, Pneumocystis*, and *Aspergillus* are the main members of fungal genera responsible for life-threatening fungal infections all over the world. *Candida* exists as commensal opportunistic pathogens in the natural flora of human beings. Members of this genus have specialized virulence attributes which include adhesion, biofilm formation, yeast to hyphal transition, cell surface hydrophobicity, and secretion of hydrolytic enzymes. *C. albicans*, *C. parapsilosis*, *C. glabrata*, and *C. tropicalis* are key species, mainly responsible for 95% of candidiasis worldwide. Azoles, amphotericin B, echinocandins and terbinafine are the main synthetic drugs against the pathogens. Rising resistance to antifungals demands the development of alternative drugs, especially of plant origin. In this review, we have included the selected plants having significant anti-*Candida* potential, based upon recent studies.

Key Words: *Candida*, Candidiasis, Biofilm, Anti-*Candida*, Phytoactive, Synthetic drugs, MIC, *Camellia sinensis*, *Hypericum havvae.*

INTRODUCTION

Fungi are considered to be one of the potential health hazards to animals including humans. Annually, fungal diseases are responsible for over 1.5 million deaths and infecting over a billion people worldwide. *Candida*, *Cryptococcus*, *Pneumocystis*and *Aspergillus* are the main fungal genera responsible for such infections[1]. The occurrence of life-threatening fungal infections has increased in immune-compromised AIDS patients, blood cancer, neonates, and organ transplants[2,3]. Fungal infections present a possible danger to health worldwide owing to their elevated mortality and morbidity rate [4]. Mortality associated with the fungal disease is similar to that of tuberculosis (more than 1.6 million) and above 3-fold more than malaria [1].

Candida is a well-known group of fungi containing around 20 pathogenic species. It is a member of the *Saccharomycetes* class, the *Saccharomycetales* order, and the *Saccharomycetaceae* family. Ubiquitous, opportunistic, dimorphic, and commensal fungi are representatives of this group. The natural flora of the gastrointestinal tract, the mucosal oral cavity, and the human reproductive organs comprises of various species of *Candida*[5].

Candidiasis is a condition of *Candida* infection which causes shallow mucocutaneous infections, invasive tissue, and bloodstream infections[6,7]. *C. albicans,* the most common pathogenic species, is followed by *C. tropicalis*, *C. glabrata*, and *C. parapsilosis*[8]. Clinical isolates have been reported to be resistant to existing antifungals, particularly azoles, echinocandins, and polyene[9]. Hydrophobicity of the cell surface, hyphal transformation hydrolytic enzyme secretion and development of biofilm over abiotic and biotic surfaces are well established primary virulence features of the *Candida*[10,11]. Most important features of *Candida* spp. are the ability to form a biofilm, a three-dimensional multicellular structure mainly composed of proteins, carbohydrates, phosphorus, hexosamine, and, uronic acid. Biofilm facilitates adhesion and maturation on the biotic and abiotic surfaces, ranging from the mineral surface and mammalian tissues to synthetic polymers and indwelling medical gadgets, resulting in drug

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resistance[12,13,14].

For decades plants have been known as the primary source of medicinal products among common citizens. Additionally, several countries still used plants as major remedies, particularly in Africa and Asia. Several plants had exhibited successful anti-*Candida* activities which are required to be tested for efficacy and safety[15].

Global burden of candidiasis

Candidiasis is due to the *Candida albicans* and non-albicans *Candida* (NAC) infection, which is mostly known to cause high rates of mucosal infection to humans worldwide.[1] *Candida* infects mucosal tissues, including mouth, oesophagus, gastrointestinal, vagina, and deep tissue infection[16]. Vulvovaginal candidiasis (thrush or yeast infection) continues to be a worldwide health problem for women[17,18]. *Candida* infection is common in hospitalized patients having a weak immune system or immunocompromised patients and elderly people [19]. More than 30 species of *Candida* have been recognized as the causative agent of candidiasis and approximately 95% of the contaminations are caused by its four species: *C. albicans*, *C. parapsilosis, C.* glabrata, and *C. tropicalis*[20, 21].

Nearly 50% of individuals have *Candida* yeast in the oral cavity which is responsible for the superficial infection. However, *Candida* infection can spread through the body and can end-up in life-threatening incidences, specifically in immunocompromised patients [22, 23].

The global burden of candidiasis is given in **Table-1**.

Table 1: Global burden of candidiasis

Candida spp. related disease.	Annual Incidence	Global Burden	Reference
1. Mucosal			
A. Oral candidiasis	~2,000,000	~2,500,000	1
B. Oesophageal candidiasis	~ 1,300,000		1
C. Vulvovaginalcandidiasis/Recurrent vulvovaginal candidiasis	~138,000,000	**~372,000,000**	17
2. Acute invasive			
A. Invasive candidiasis	~750,000		3
3. *Candida balanitis*		3-4% of uncircumcised males	24

Drug resistance

Azoles and its derivatives (fluconazole, voriconazole, Itraconazole, ketoconazole) are primarily used antifungals [24-25]. Isolates of *Candida* have been reported to develop resistance to the existing antifungals (fluconazole, anidulafungin, caspofungin, micafungin, etc). According to the Centers for Disease Control and Prevention (CDC, NIH, USA), about 7% of all *Candida* bloodstream isolates tested at CDC were resistant to fluconazole and about 1.5% were resistant to Echinocandin (Figure 1).

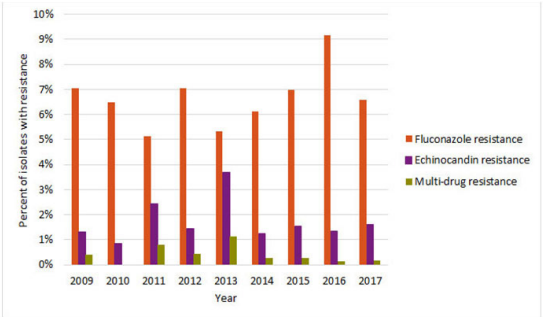

Figure 1: Drug Resistance in *Candida sp.* isolates during years, 2009–2017.

(*Photo Source*: CDC Report)

Increasing resistance to selected drugs encouraged the clinical practice of other drugs also e.g. amphotericin B, echinocandins, terbinafine, etc. as shown in **Table-2** along with its mode of action.

Plants with anti-candida properties

Plants and their extracts have been used in traditional medicine since prehistoric times due to its availability and efficacy without toxicity[33]. Plants produce numbers of natural active compounds for defence against fungi, insects, and herbivorous mammals. And many more phytoactive compounds have biological activities[34]. The use of herbal medicines has been widely accepted in many developed and developing countries. Herbal remedies are widely used in Asia, mainly India and China, and are now getting popularity in the UK and Europe, as well as in North America and Australia[33,35]. WHO estimated that around 80% population of the developing countries (like Latin America, Asia, Africa, etc.) depends on traditional therapy based on herbal medicines for their primary health care needs. In the year 2000, the global trade of medicinal plants and their products was reported to be US$ 60 billion, with a projected forecast to touch US$ 5 trillion by 2050[35]. India and China are the top global exporters

Table 2: Synthetic anti-*Candida* drugs

S. No.	Drug	Mechanism of action	Reference
1	Amphotericin B	Binds to the fungal ergosterol and causes pores in the cell membrane.	26, 27
2	Azoles	Inhibits the cytochrome P450 14a-sterol demethylase (CYP51), thus the inhibitor of biosynthesis of ergosterol.	28,29
3	Echinocandins	Inhibits the 1,3-β-D-glucan, a cell wall component.	27, 30
4	Terbinafine	Inhibits ergosterol biosynthesis by inhibiting squalene epoxidase (catalyses the conversion ofsqualene to lanosterol)	31, 32

of herbal drugs due to its systematic traditional knowledge of plant-based medicines and culture.

In the modern era, natural products are the source of bioactive substances with possible medical uses in pharmacy and dentistry. Natural ingredients include essential oils and their elements and can form part of several classes of compounds, most commonly phenylpropenes and terpenes with antioxidant, anti-inflammatory, antiseptic, and curative properties [36]. Looking at the rising demand for plant-based drugs, we tried to compile the details of plants showing anti-*Candida* properties (**Table-3**).

Table 3: Plants having anti-*Candida* properties

Table-3 is an effort to compile some recent studies in the subject matter in a tabulated form.

Biofilm is an important pathogenic implication of the *Candida* to survive the existing synthetic drug, which is responsible for drug resistance. Some of the plant extracts and their phytoactive compounds have exhibited remarkable anti-biofilm properties; e.g. *Berberis vulgaris*,[42] *Buchenaviatomentosa* Eichler,[44] *Cinnamomum zeylanicum*,[47] *Curcuma longa* L.,[48,49] *Matricaria chamomilla,*[55] *Peganum harmala* L.[58] and *Sanguinaria Canadensis* [61]. Berberine, Sanguinarine, Har-

Table 3: Plants having anti-Candida properties

Sr. No.	Botanical Name	Natural habitat	Phytoactive constituents	MIC (µg/ml)	Candida species	Ref.
1	*Acacia dealbata*	Native to south-eastern Australia in New South Wales, Victoria, Tasmania, and warm temperate, and highland tropical landscapes	Phenolic, Flavonoid, Tannins.	7920± 1520	*C.albicans* (ATCC 10231)	37
2	*Aframomum citratum*	Widespread across tropical Africa as well as on some islands of the Indian Ocean	Monoterpenes (Monoterpene hydrocarbons, β-Myrcene), Oxygen-containing monoterpenes (Geraniol)	256	*C. albicans* (ATCC 9002)	38
				1024	*C.albicans* (ATCC 1663)	
				256	*C.albicans* IS1	
				512	*C.parapsilosis*	
				1024	*C.parapsilosis* (ATCC 22019)	
				512	*C.krusei* (ATCC 750)	
				1024	*C.krusei*	
				1024	*C.tropicalis* (ATCC 750)	
				2048	*C.lipolithica*	
				256	*C.haemophilus*	

Table 3: *(Continued)*

Sr. No.	Botanical Name	Natural habitat	Phytoactive constituents	MIC (µg/ml)	Candida species	Ref.
3	*Aframomum daniellii*	West tropical Africa - Sierra Leone to Central African Republic, south to Angola.	Monoterpenes (monoterpene hydrocarbons, beta- pinene, limonene), oxygen-contan-ingmonoterpenes (eucalyptol, alpha-terpineol), sesquiterpe-nes (sesquiterpenes hydro-carbons, trans-beta-caryo-phyllene), oxygen-containing sesquiterpenes (caryophyl-lene oxide)	512	*C.albicans* (ATCC 9002)	
				1024	*C.albicans* (ATCC 1663)	
				512	*C.albicans* (IS1)	
				512	*C.parapsilosis*	
				1024	*C.parapsilosis* (ATCC 22019)	
				2048	*C.krusei*(ATCC 6258)	
				256	*C.krusei*	
				2048	*C.tropicalis* (ATCC 750)	
				4096	*C.lipolithica*	
				4096	*C.haemophilus*	
4	*Allium cepa.*	Worldwide	*NR*	1200-1500	*C. albicans* (ATCC 10231)	39
				1200-1500	*C. albicans* (clini-cal isolate)	
				1100-1500	*C. albicans* (clini-cal isolate)	
5	*Allium hirtifolium.*	Asian species of onion native to central and south-western Asia.	*NR*	500-800	*C. albicans* (ATCC 10231)	39
				500-900	*C. albicans* (clini-cal isolate)	
6	*Allium sativum*	Native to central Asia and north eastern Iran	*NR*	1100-1400	*C. albicans* (ATCC 10231)	39
				1100-1500	*C. albicans* (clini-cal isolate)	
7	*Alpinia galangal L.*	*NR*	*NR*	64	*C. tropicalis* (ATCC750)	40
				64	*C. glabrata* (ATCC2001)	
8	*Aloe barbadensis Miller*	Mediterranean region of Europe and Africa	Eicosyltrifluoroac-etate, Cyclopropanecarb-oxylic acid, 1-nonadecene, Cyclopropane, 1-methyl-1-(1-methyle, 1-undecanol.	25,000 -50,000	*C. albicans*	41
9	*Berberis vulgaris*	Native to central and south-ern Europe, northwest Africa and western Asia	Berberine	80	*C. albicans* (ATCC 10231)	42
				20	*C. glabrata* (ATCC 90030)	
				80	*C. albicans* (clinical isolate)	
				80	*C. glabrata* (clini-cal isolate)	

Table 3: *(Continued)*

Sr. No.	Botanical Name	Natural habitat	Phytoactive constituents	MIC (µg/ml)	Candida species	Ref.
10	*Boswellia carterii*	*NR*	Essential oils	1250	*C. albicans* (ATCC10231)	43
				1250-2500	*C. albicans* (clinical isolate)	
				1250	*C. tropicalis* (ATCC 750)	
				1250-2500	*C. glabrata* (clinical isolates)	
				1250	*C. krusei* (clinical isolate)	
				1250	*C. albicans* (ATCC10231)	
11	*Buchenavia tomentosa*, Eichler	*NR*	*NR*	625	*C. albicans* (SC5314)	44
12	*Calamus leptospadix* Grif	Native to tropical and subtropical Asia, Africa, & Australia	Saponin	60	*C. albicans* (ATCC3007)	45
13	*Camellia sinensis*	*NR*	*NR*	0.125	*C. albicans*	46
				0.125-0.250	*C. tropicalis*	
				0.125	*C. parapsilosis*	
				0.125-0.250	*C. glabrata*	
14	*Canarium luzonicum*	Native to the Philippines	Essential oils	2500	*C. albicans* (clinical isolate)	43
				2500	*C. albicans* ATCC10231	
				2500	*C. tropicalis* (ATCC750)	
				2500	*C. krusei* (clinical isolate)	
				2500	*C. glabrata* (clinical isolate)	
15	*Cinnamomum zeylanicum*	South – West India and Sirlanka	α –Pinene, Benzaldehyde, 1,8 –cineole, Limonene, Linalool, (E) –Cinnamaldehyde, Eugenol, (E)-Cinnamyl acetate.	70	*C. albicans* (ATCC 10231_	47
				1120	*C. albicans* (ATCC 90028)	
				<40	*C. parapsilosis* (ATCC 90018)	
				10.45± 1.00	*C. albicans* (clinical isolated)	
16	*Curcuma longa* L.	Native to the Indian subcontinent and Southeast Asia	Curcumin	250	*C. albicans* (ATCC 10261)	48,49
				500	*C. albicans* (ATCC 44829)	
				500	*C. tropicalis* (ATCC 750)	
				1000	*C. albicans* (clinical isolate)	
				250	*C. albicans* (clinical isolate)	
				500	*C. glabrata* (clinical isolate)	

Table 3: *(Continued)*

Sr. No.	Botanical Name	Natural habitat	Phytoactive constituents	MIC (µg/ml)	Candida species	Ref.
17	*Desmodium gangeticum*	*NR*	Flavonoids, Glycosides, Saponins ,Tanins	31.2	*C. albicans* (MTCC F7315)	50
18	*Euphorbia hirta* L.	Native to India	Free flavonoids, Bound flavonoids	39-156	*C. albicans* (MTCC183)	51
19	*Glycyrrhiza glabra* L.	native to the Western Asia and southern Europe	Glabridin	1250	*C.albicans* (MTCC 1637)	52
				1250	*C.albicans* (clinical isolates)	
				625	*C. pseudotropicalis* (clinical isolates)	
20	*Hypericum havvae*	worldwide distribution	Phenolic compounds (hypericin, hyperforin)	3120	*C. albicans* (ATCC 10231)	53
				6250	*C. tropicalis* (ATCC 13808)	
				6250	*C. guilliermondii* (ATCC 6260)	
				12500	*C. krusei*	
				25000	*C. glabrata*	
				25000	*C.parapsilosis*	
21	*Justicia adhatoda* L.	The plant's native range is the Indian subcontinent (Nepal , Sri Lanka).	Vasicine, a quinazoline alkaloid.	14.8±0.2	*C.albicans*	54
22	*Matricaria chamomilla*	*NR*	Essential oil	100	*C. albicans* (ATCC18804)	55
23	*Mentha piperita* L.	Europe and Middle East	Essential oil	1.50 ± 0.16	*C.albicans* (ATCC26790)	56
24	*Morus alba* L.	Native to northern China and India	Flavonoids, Tannins and Triterpenes	1024	*C. albicans* (ATCC-76645)	57
				256	*C. albicans* (LM-106)	
				512	*C.tropicalis* (ATCC-13083)	
				1024	*C.tropicalis* (LM-6)	
				512	*C.krusei*(LM-656)	
25	*Peganum harmala* L.	*NR*	Harmaline	62.5±2.04	*C. albicans* (ATCC 10231)	58

Table 3: *(Continued)*

Sr. No.	Botanical Name	Natural habitat	Phytoactive constituents	MIC (µg/ml)	Candida species	Ref.
26	*Retama raetam*	Native to northern Africa from the Western Sahara	Isoflavone (Derrone)	7.81	*C.albicans* (ATCC 90028)	59
				7.81	*C. glabrata* (ATCC 90030)	
				7.81	*C.parapsilosis* (ATCC 22019)	
				7.81	*C. kreusei* (ATCC 6258)	
				7.81	*C.albicans* (ATCC 90028)	
			Licoflavone C	15.62	*C. albicans* (ATCC 90028)	
				15.62	*C. glabrata*(ATCC 90030)	
				15.62	*C.parapsilosis* (ATCC 22019)	
				15.62	*C.kreusei* (ATCC 6258)	
27	*Rhizoma coptidis*	Native to China	*NR*	>1024	*C. albicans*(ATCC 14053)	40
				128	*C. tropicalis* (ATCC 750)	
				64	*C. glabrata* (ATCC 2001)	
				>1024	*C. krusei* (ATCC 6258)	
28	*Ruta graveolens* L.	It is native to the Balkan Peninsula	Volatile oils	35.10 ± 0.02	*C.albicans* (ATCC 26790)	60
29	*Sanguinaria canadensis*	Native to eastern North America	Sanguinarine	4	*C. albicans* (SC5314)	61
30	*Sapindus saponaria L.*	Native to the America and India	Carbohydrates and triterpenes	300-600	*C. albicans* (ATCC 90028)	62
				300-600	*C. albicans* (clinical isolate)	
				600	*C. glabrata* (clinical isolate)	
31	*Scutellaria baicalensis*	Nativeto China, Korea, Mongolia, and Russia	Baicalein	13	*C. albicans* (ATCC 64548)	63
				26	*C. albicans* (ATCC 64550)	
				104	*C. tropicalis* (186.06)	
				52	*C. tropicalis* (ATCC 200956)	
				13	*C. parapsilosis* (ATCC 22019)	
				13	*C. parapsilosis* (153.07)	

Table 3: ***(Continued)***

Sr. No.	Botanical Name	Natural habitat	Phytoactive constituents	MIC (µg/ml)	Candida species	Ref.
32	*NA*	*NA*	Eugenol	625	*C. albicans* (SC5314)	64
				625	*C. auris*	
33	*NA*	*NA*	Methyl Eugenol	1250	*C. albicans* (SC5314)	64
				1250	*C.auris*	
34	*NA*	*NA*	Thymol	625	*C. albicans* (SC5314)	64
				312	*C.auris*	
35	*NA*	*NA*	Carvacrol	250	*C.albicans* (SC5314)	64
				125	*C.auris*	
36	*Unonopsis duckei*	*NR*	Polycarpol	250	*C.albicans* (ATCC 10231)	65
				250	*C. albicans* (ATCC 1023)	
				250	*C.dubliniensis* (ATCC 778157)	

**NA: Not applicable; NR: Not reported*

maline, Curcumin, and many other phytoactive compounds have been reported to decrease the viability of *Candida* biofilm significantly[42,48,49,61].

CONCLUSION

Since the prehistoric period, plants have been the source of medicine in different countries like India and China. According to a WHO report, approximately 80% of the premier health issues in developing countries depend on traditional medicine. Currently, the scientific research community and government health agencies are focusing on the studies related to the bioactive compounds. Phytoactive compounds are generally safe and easily available for commercial-scale drug production. Therefore, it's encouraging to develop an effective and safe drug against microbial human pathogens from natural resources. Nature holds ample resources for the discovery of new and highly effective herbal drugs. It may be concluded from the table-3 that two plants *Camellia sinensis* and *Hypericum havvae* have remarkable anti-*Candida* properties and can be used to develop alternative anti-*Candida* drugs. *Camellia sinensis* have shown promising results against many pathogenic species of the *Candida* e.g. *C. albicans*, *C. parapsilosis*, C. *Tropicalis*, and *C. Glabrata*, and *Hypericum havvae* was effective against *C. glabrata*, *C. kreusei, C. parapsilosis, C. guilliermondii*, and *C. tropicalis.*

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