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RECENT REVIEW ON HERBAL APPROACHES TO REGULATE CANDIDA INFECTIONS

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ABSTRACT: Herbal plants have long been known to have antifungal properties. The medicinal plants are prospective in aquaculture as an alternative to antibiotics and other anti-candida drugs. This article aims to review the reported herbal medicines with their research findings that have an enormous future prospective for the effective treatment of *Candida* infections. Various species of *Candida* were classified and their pathogenesis and mechanism of action were highlighted. Mechanisms of action of commonly used synthetic anti-candida drugs were compared to that of the herbal plants. Recent plant-based antifungal activity studies were analyzed. Ten species of candida, namely *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, *Candida dubliniensis*, *Candida lusitanae*, *Candida guilliermondii*, *Candida rugosa*, *Candida zeylanoides* and *Candida tropicalis* were found to be responsible for infection in human. Plant-based natural products were found to produce anti-candida actions based on germination inhibition and formation of biofilm, cell metabolism, cell wall integrity, cell membrane plasticity, and induction of apoptosis. Around 20 research works were analyzed, and it was found that the majority of the active constituents that produced anti-candida action belonged to the alkaloid, flavonoid, saponin, triterpenoid and anthraquinone class of compounds.

INTRODUCTION: Approximately 8.7 million eukaryotic species have been found on earth, out of which, 7% are fungi (611,000 species). However, only around 600 species of this number are regarded as human pathogens¹. Some of the species have mild skin infections, *i.e.*, dermatophytes and *Malassezia* species, whereas some other have critical cutaneous infections, *i.e.*, *S. schenkii* and the rest cause congenital infections, *i.e.*, *Candida albicans*, *Histoplasma capsulatum*, *C. neoformans* and *A. fumigatus*².

In USA, *Candida* species cause hospital non-hereditary infections with a fatality rate of 50%³. *Candida* is a serious life-threatening pathogen with a major reason of mortality and morbidity, particularly in patients with impaired immune responsiveness⁴. The major two types of superficial infections in humans caused by *C. albicans* are mucocutaneous candidiasis, vulvovaginal candidiasis and dangerous systemic infections (*e.g.*, GIT and genital system)⁵.

In the case of buccal cavity infection, around 75% of the community is infected by *Candida species*. The oral *Candida* infections are known as "oral candidiasis"⁶. *C. albicans* may be responsible for such infections and may impact the pharynx & the digestive tract of persons with malfunctions of the innate immune system. The disease which is mostly responsible for Oral Candidiasis is HIV⁷.

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Approximately 74% of females suffer once in their life from fungal infection of the vagina⁸. Major synthetic drugs like 5-flucytosin, amphotericin B and azoles are routinely used to treat *Candida* infection⁹. However, these medicines become resistant over time and suffer from serious side effects. Plants are medicines sources for decades. From the earliest, plants have been a prominent source of efficient and safe medicines. Most Countries use plants as remedies, particularly in Asia and Africa. Medicinal plants originating from the desert play a vital role in the modern health service¹⁰.

Due to their safe, effective, and inexpensive cost, indigenous remedies are renowned amongst the masses of India's urban and rural areas. Several plants have been reported for their important antifungal activities¹¹. This review exclusively highlights the plants that have been assessed for anti-*Candida* activities with a suggestion for Promoting the use of these plants and the requirements of their extensive analysis and *in-vivo* testing.

1. *Candida*: *Candida* is a pathogenic fungus. This is generally recognized to cause fungal infection to human^{12,13}. *This fungus* is identified to cause deep tissue and mucosal infections. *Candida* also affects the oesophagus, vagina, and GIT, apart from mucosal tissues with mouth. Fungal infection of vagina persists to be a world health hassle to females. Hospitalized patients are commonly having Candidal infections and are not easy to prevent^{14,15}. Regarding 50% of juveniles have *Candida* yeasts in their oral mucosa. *Candida* infections can widen through the body and become dangerous, particular in patients with impaired immune responsiveness^{16,17}. *Candida* can be divided into two forms, hyphae and yeast forms. The major source of infectious agent *i.e.* *Candida* is hyphae³. *Candida* species produce biofilms on artificial substances, which aid attachment of the entity to devices and make the organism comparatively resistant to antifungal treatment¹⁸. *Candida* biofilms associated with catheter paves the way to infections of bloodstream¹⁹. *Candida*-infected catheters, particularly those associated with microbial biofilms, can account for up to 90% of infections among hospitalized patients, making them a leading cause of mortality²⁰. *Candida* has

different species, and each communicates with the body in different route²¹. Ten species are described below to highlight their pathogenesis and their mechanism of action.

1.1. *Candida albicans*: It is called an “expedient” fungus. *C. albicans* may cause the most common fungal infections in humans²². Even though *Candida albicans* is typically not dangerous unchecked it can damage physiological processes²³.

1.2. *Candida glabrata*: It is present in the mucous membrane. *C. glabrata* may cause systemic & mucosal infections²⁴.

1.3. *Candida parapsilosis*: It is recognized for the reason of infection amongst newborns and in patients with impaired immune responsiveness^{25,26}.

1.4. *Candida krusei*: It is a threat for persons who get received organ transplants²⁷.

1.5 *Candida dubliniensis*: It has been recognized in patients with HIV²⁸.

1.6. *Candida lusitanae*: It is also known as opportunistic yeast; this fungus is found in patients with blood cancer^{29,30}. Moreover, this fungus is resistant to the *Amphotericin* an antifungal drug³¹.

1.7. *Candida guilliermondii*: This is a less recognized species. *Candida guilliermondii* can be hit to persons with low immunity³².

1.8. *Candida rugosa*: It is a fungal pathogen³³. It has been found to be resistant to anti-fungicide drugs³⁴.

1.9. *Candida zeylanoides*: The sample of skin, blood and nails are the source of this fungus^{35,36}. It has been possibly treated with intravenous (iv) amphotericin therapy³⁷.

1.10 *Candida tropicalis*: It is a common class of *Candida* which is resistant to fluconazole^{38,39}.

2. Pathogenesis with *Candida* species: Three things are concerned for an infection to arise with *Candida* species: sources, the target of population, and transmission mode. Sources like surfaces and human skin are measured as the most vital sources

for Candida infection⁴⁰. Immuno-compromised patients forever remain at high risk for Candida infection. *C. albicans* is normally transmitted from mother to newborn baby during childbirth. The unwarranted growth of *C. albicans* leads to disease symptoms and it arises due to the imbalances – Such as, alter vaginal acidity. The normal human microflora is the classic reservoir of *C. albicans*^{41, 42}. Candida contaminations are linked with the formation of biofilm. In fungal infections, biofilms can develop on an assortment of surfaces as well as host tissues and implanted biomaterials, including vascular catheters. Additionally, the systemic infection can be increased by biofilms. The biofilm-forming capability can be encouraged by various factors by *C. albicans*⁴³.

3. Complications with Candida Infection:

According to earlier research, one-quarter of females who have had one yeast infection will have another within a year. Frequent yeast infections can

jeopardize a person's health. Infections can also cause problems in relationships by interfering with normal sexual activity⁴⁴. Yeast infections are an unpleasant but minor health problem for most people. There aren't many proofs that vaginal yeast infections might cause pregnancy complications. Pregnant women with yeast infections are more likely to have premature labour and preterm membrane rupture⁴⁵.

4. Antifungal Agents and Their Mechanism of

Actions: There are numerous antifungal agents which are commonly used for Candida infection treatment. The list of conventional used antifungal agents, available dosage forms in the market, and the commonly observed side effects are listed in **Table 1**. The disruption of the cell membrane, cell division inhibition, and cell wall formation inhibition are common mechanisms of antifungal agents.

TABLE 1: LIST OF COMMONLY USED ANTIFUNGAL AGENTS AND THEIR COMMERCIAL PREPARATIONS

S. no.	Name of Preparation	Active Ingredient	Dosage Form	Name of Manufacturer	Side Effects	Reference
1	Ketzol®	Ketoconazole	Cream	Anhui NHU Pharmaceutical	Burning, or irritation, severe itching	(www.everydayhealth.com)
2	Tebfin®	Terbinafine	Cream	Adams Pharmaceutical	Tingling dryness, redness Itching, Peeling, burning rash, stinging	(www.mayoclinic.org)
3	Canesten®	Clotrimazole	Cream	Bayer Healthcare	Severe dizziness, Swelling, rash, itching	(www.webmd.com)
4	Antifungal®	Tolnaftate	Lotion	Home Health	Dryness, itching, or peeling of treated skin.	(www.drugs.com)
5	FungaZoil®	Clotrimazole	Solution	PediFix	Vaginal/urethral itching, burning pain	(www.webmd.com)
6	Niosalic-6®	Clobetasol Propionate & Salicylic acid	Ointment	KLM Laboratories Pvt. Ltd.	Cracking, dry skin, changes in color of treated skin, blisters, pimples, acne	(www.rxlist.com)
7	Karpin®	Sodium thiosulphate, Sodium benzoate, Tartaric acid;	Lotion	DEYS Medicals	Dizziness, drowsiness, hypotension or a headache	(www.tabletwise.com)
8	Loprox®	Ciclopiroxolamine	Cream	Medicis Pharmaceutical Corp.	Redness, burning or itching at the application site	(www.webmd.com)
9	Mentax®	ButenafineHCl 1%	Cream	Mylan Pharmaceutical, Inc	Itching, burning, stinging	(www.rxlist.com)

4.1. Cell Membrane Disruption: The membrane of cell interruption by attacking ergosterol occurs by antifungal agents. Ergosterol is same to mammal cholesterol⁴⁶.

4.2. Inhibition of Cell Division: Division of cell is influenced by nucleoside antifungal agents⁴⁷.

4.3. Inhibition of Cell Wall Formation: Interference of fungal cell layer synthesis has not been as better and efficient as penicillin's and beta-lactam antibiotics oppose the bacteria⁴⁸.

5. Herbal Medicine as a Boom for Treatment of *Candida* Infections: Herbal medicine has developed to be a thing of global impact, both therapeutic and economical. Although the tradition of these herbal drugs has amplified, their worth, safety and effectiveness are serious concerns in industrialized and developing countries. Herbal preparation is receiving growing patient conformity as they are devoid of typical adverse effects of

allopathic medicines^{49, 50}. Plants have been well-acknowledged for decades as a foremost basis of medicines since age. Several countries still utilize them as main preparations, mostly in Africa and Asia⁵¹.

Herbal plants have been a rich resource of effective and harmless medicines from the earliest times. Due to their safe, effective, and inexpensive nature, indigenous remedies are admired among the people of both urban and rural areas in India⁵².

5.1 Mechanism of Action of Anti-candida natural Products: The anti-*Candida* mechanisms of action began by plant-based natural products can involve germination, inhibition, and formation of biofilm, metabolism of the cell, the integrity of cell wall, the plasticity of the cell membrane, or may engage induction of programmed cell death given in **Fig. 1**. They are further elaborated on in the following section:

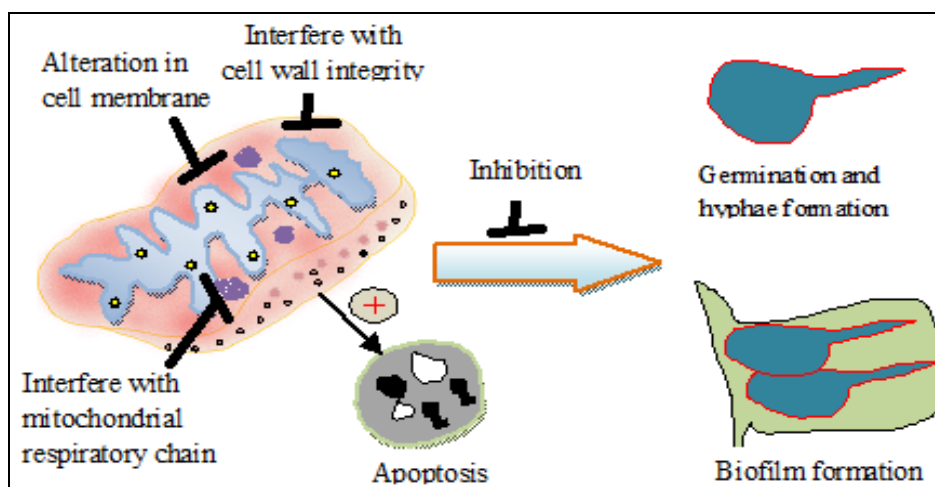


FIG. 1: MECHANISM OF ANTI-CANDIDA NATURAL PRODUCTS

Inhibition of Formation of *Candida* Biofilm and Transition to Hypha form: The switch of *Candida* from yeast to hyphae is mainly followed by the resistant formation of biofilm. *Candida* biofilms are hard to remove and are linked with resistance against many existing antifungals. Thyme oil is a chief element of Thymol, which can interfere with the metabolic activity of biofilm and the formation of biofilm grown-up⁵³.

Inhibition of *Candida* Germ Tube Formation: Among yeast and hyphal cells, GTF is a transitional stage which is an essential stage

for *Candida* malignancy activity. GTF promotes fungal adhesion to inflamed tissues as well as penetration. C is inhibited by oregano essential oil. When compared to other essential oils, albicans are the most potent. The lipophilicity of essential oils and their interaction with the *Candida* cell wall cause alterations and damage to fungal cell structural and enzymatic elements, including adenosine triphosphate (ATP)⁵⁴.

***Candida* Cell Membrane Alteration:** Terpenes can alter *Candida* cell permeability by getting entrapped between the fatty acyl chains of

membrane lipid bilayers, altering lipid packing and, as a result, membrane shape and function⁵⁵.

Candida Mitochondrial Respiratory Chain Interference: The respiration process in mitochondria is accompanied by the production of a large amount of ROS. ROS can injure proteins of cells, lipids, and DNA. HsAFP1 shows apoptic action against *C. albicans*⁵⁶.

Inhibition of Candida Adherence: The anti-adherent activity of *C. albicans* illustrated by the oil of *R. officinalis*. The bioactivity of *R. officinalis* is connected with its main chemical constituents, inclusive of limonene, cineole, and cymene⁵⁷.

Induction of Candida Apoptosis: Baicalein flavonoid shows potent activity as opposed to fluconazole-resistant *C. albicans*. *C. albicans* mainly inhibits by Baicalein by apoptosis Silibinin, extracted can cause *Candida* apoptosis through mitochondrial Ca²⁺ signaling interference. Ca²⁺ signaling plays a vital role in physiological processes and is associated with stress responses in fungi⁵⁸.

Interference with Candida Cell Metabolism: Allicin has a high anti-Candida effect, mostly through inhibiting thiol-containing amino acids and proteins, interfering with cell metabolism⁵⁹.

Interference with Candida Cell wall Integrity: During *Candida* cell growth and morphogenesis and in the face of extrinsic stresses that generate cell wall stress, cell wall integrity is critical. Several natural compounds have been demonstrated to interfere with the integrity of *Candida* cell walls⁶⁰.

6. Reported Research Works on Plant-Based Antifungal Activity: A glimpse of recent plant-based antifungal activity studies is presented in **Table 2**. Some of them are highlighted below. Plants *Cassia occidentalis* and *Oxalis corniculata* were indexed for skin disease treatment caused by fungi⁶¹. *Wrightiatintoriaw* was indexed as externally use in the treatment of vaginal candidiasis⁶². The stem bark of *Bauhinia variegata* Linn. was reported as antibacterial and antifungal⁶³.

TABLE 2: LIST OF INVESTIGATED PLANTS FOR ANTI-CANDIDA ACTIVITY

S. no.	Name of Plant & Family	Part Used	Chemical Class	Compound	Reference
1.	<i>Ajania fruticulosa</i> (Asteraceae)	Fruit	Xantholides	Seven different xantholides	64
2.	<i>A. macrophylla</i> (Rubiaceae)	Leaf	Non-glycosidic iridoid	1 z- and Ijl-Hydroxydihydrocornin aglycon	65
3.	<i>A. panurensis</i> (Lau raceae)	Whole plant	Alkaloid	6,8-didec-(1Z)-enyl-5,7-dimethyl-2,3-dihydro-1Hindolizinium	66
4.	<i>A. vulgaris</i> (Ranunculaceae)	Leaves and stems	Flavonoid	4 ¹ -methoxy-5,7-dihydroxyflavone 6-C-glucoside	67
5.	<i>Avena sativam</i> (Poaceae)	Root	Triterpenoid saponin	Avenacin	68
6.	<i>Blumea balsamifera</i> (Asteraceae)	Leaf	Flavonoid	Luteoli	69
7.	<i>C. Japonica</i> (Theaceae)	Leaf	Saponin	Camellidins I and II	65
8.	<i>Camptotheca acuminata</i> (Cornaceae)	Leaf	Flavonoid	Trifolin and hyperoside	70
9.	<i>Cassia occidentalis</i> (Fabaceae)	Leaf, Seed & Pod	Anthraquinone	Derivative of anthraquinone	71
10.	<i>Cassia tora</i> (Leguminoceae)	Seeds	Anthraquinone	Emodin	72
11.	<i>Celastrus hypoleucus</i> (Celastraceae)	Root	Triterpenoid	Pristimerin, celastrol	67
12.	<i>Detarium microcarpum</i> (Leguminaceae)	Pulp	Diterpene	Clerodane diterpene	73
13.	<i>Dolichos lablab</i> (Fabaceae)	Fruits	Protien	Dolichi	74
14.	<i>Ecballium elaterium</i> (Cucurbitaceae)	Fruit	Cucurbitacin	Cucurbitacin I	75
15.	<i>Eupatorium riparium</i> (Asteraceae)	Roots	Chromene	Methylripariochromene	76

16.	<i>Glycosmis cyanocarpa</i> (Rutaceae)	Leaf	Sulfur- containing amide	Sinharine, Methylsinharine	77
17.	<i>Oxalis corniculata</i> (Oxalidaceae)	Leaf	Flavonoid	Trifoli	78
18.	<i>P. regnellii</i> (Piperaceae)	Leaf	Neolignan	Eupamatenoid-3, Eupamatenoid-5	79
19.	<i>Rubia tinctorum</i> (Rubiaceae)	Roots	Anthra-quinone	Alizarin, Aglycone and Emodin	80
20.	<i>Wrightia tinctoria</i> (Apocyanaceae)	Leaf	Flovonoids	Terpenes	81

A variety of medicinal belongings have been accredited to this plant in the traditional system of Indian medicine⁸². Numerous anthraquinones have been secluded from the seeds of *C. tora*. Sennosides have been well recognized for their medicinal significance. *C. tora* extract has been used as a treatment for a variety of skin diseases, rheumatic disease and as laxatives. *C. tora* leaves extract has been originated from acquiring major anti-inflammatory and hepatoprotective activity. The seeds of *C. tora* have been used in Chinese

medicine as diuretic agents, antiasthma, aperient, and better visual activity^{83, 84}. *Ajania* is a genus of flowering plants from the daisy family. The genus is resident in temperate Asia, primarily in Russia and China. *Ajania fruticulosa* (Ledeb.) Poljak (Asteraceae), circulated primarily in the northwestern part of China, has long been used as traditional Chinese medicine to treat appendicitis, emphysema, tuberculosis, and skin disease^{85, 86}. Traditionally used herbals for treatment of *Candida* in various parts of the world are shown in **Table 3**.

TABLE 3: TRADITIONALLY USED HERBAL PLANTS FOR THE MANAGEMENT OF CANDIDA INFECTION

S. no.	Plant / Active constituents	Dosage form	Effect	References
1.	<i>Rhus coriaria</i> , <i>Punica granatum</i> , <i>Eugenia caryophyllata</i> , <i>Cichorium intybus</i>	Extract	These extracts are capable of being clinically useful in candida infections	87
2.	<i>Mentha longifolia</i>	Extract	Menthalongifolia extracts confirmed the antifungal activity against fluconazole-resistant strains	88
3.	Terpenoids, Carvacrol, Cuminaldehyde	Extract	The combined extracts showed safe prevention of biofilm formation in <i>C. albicans</i>	89
4.	<i>Elaeocarpus spp</i>	Extract	Elaeocarpus spp. showed more powerful anti-infective agents in <i>C. albicans</i>	90
5.	<i>Punica granatum</i>	Extract	Pomegranate revealed antimicrobial efficacy in Gram-positive bacteria and anti-candida activity	91
6.	<i>Anadenanthera colubrina</i>	Extract	Anti-Candida potential was evaluated mixture confirmed to be potential against Candida	93
7.	<i>Litcubeba</i>	Extract	Mixture confirmed to be potential against Candida	52
8.	<i>Fraxinus angustifolia</i> , <i>Clematis flammula</i>	Extract	Mixture shown efficacy against mucocutaneous infections caused by <i>C. albicans</i> biofilm	92
9.	<i>Zuccagnia punctate</i> , <i>Larrea nitida</i>	Extract	The mixture of <i>Zuccagniapunctate</i> and <i>Larreenitida</i> showed remarkable results in <i>C. albicans</i>	93
10.	<i>Aster yomena</i>	Extract	<i>A. yomena</i> showed promising activity against <i>C. albicans</i>	94
11.	<i>Hibiscus sabdariffa</i>	Extract	<i>Hibiscus sabdariffa</i> was found to have potential activity for inhibiting the growth of <i>C. Albicans</i>	95
12.	<i>Solidago virgaurea</i>	Extract	Studies confirmed the effectiveness of SV extract in reducing the growth of <i>C. albicans</i>	96
13.	<i>Ocimum americanum</i>	Extract	Ocimumamericanum showed efficacy against the <i>C. albicans</i>	97
14.	<i>Lippia junelliana</i> , <i>Laurus nobilis</i> ,	Essential oils	The essential oils of these mixtures showed to	48

	<i>Cymbopogon citrates, Menthe piperita, Thymu vulgaris</i>		a fungal infection caused by a few Candida species	
15.	<i>Larrea cuneifolia, Larrea divaricata</i>	Extract	The mixture of herbals weight their efficiency for candidiasis treatment	98
16.	<i>Cinnamomum zeylanicum, Thymus vulgaris, Caryophyllium aromaticus, Allium cepa, Echinophora platyloba</i>	Extract	These extracts of various herbs show effectiveness in controlling Candida albicans	99
17.	<i>Azadirachta Indica, Syzygium aromaticum</i>	Extract	The study's findings indicated that both plant extracts have antibacterial and antifungal action against Candida albicans	100
18.	<i>Taraxacum officinale</i>	Extract	The extract of Dandelion has a positive effect on Candida albicans	101
19.	<i>Amukkara choornam</i>	Extract	AmukkaraChoornam extracts have the potential to treat C. albicans biofilm-mediated infections as an alternative medication	102

7. Future Aspects: The effects of the herbals can be synergizing by combining with probiotics, probiotics are well known for their beneficial effect to host when used in adequate amount. Probiotics work by their antifungal property, which is essential for anti-candida activity. Various researchers have already done research work by combining the probiotic stain with herbal drugs, but at present, no marketed formulation is available in probiotic with herbal drugs for the treatment of candida infections. There are many active moieties in herbals that have potent effects that can be used for different research purposes. The potential effects of these herbals in combination with probiotics should be assessed at an *in-vivo* level for maximum assurance about the plant's effect

CONCLUSION: As concluding remarks, several natural products obtained from plant sources have been tested for anti-Candida activities. These herbal products can target actual cause of the biological activities of Candida, including cell membrane plasticity, the integrity of cell wall, induction of programmed cell death, metabolism of the cell, host cell and respiratory chain adherence, germination, and formation of biofilm. Natural items' anti-Candida activities have been compared to controls, but only a handful have been studied in vivo, and none have ever been used therapeutically as anti-Candida. On the other hand, while some of these ingredients, such as ginger, garlic, probiotics, cinnamon, and peppermint, are available in pharmacies for different medical purposes, they have never been used as antifungals. Because Candida is a serious resistant fungus, there is an urgent need for new anti-Candida drugs; therefore,

promoting some of the selected herbal medicines for clinical testing will be advantageous.

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