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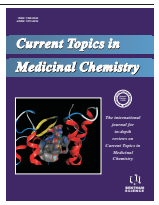
REVIEW ARTICLE

Exploration of Medicinal Plants as Sources of Novel Anticandidal Drugs



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ARTICLE HISTORY

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Abstract: ***Background*:** Human infections associated with skin and mucosal surfaces, mainly in tropical and sub-tropical parts of the world. During the last decade, there have been an increasing numbers of cases of fungal infections in immunocompromised patients, coupled with an increase in the number of incidences of drug resistance and toxicity to anti fungal agents. Hence, there is a dire need for safe, potent and affordable new antifungal drugs for the efficient management of candidal infections with minimum or no side effects.

***Introduction*:** Candidiasis represents a critical problem to human health and a serious concern worldwide. Due to the development of drug resistance, there is a need for new antifungal agents. Therefore, we reviewed the different medicinal plants as sources of novel anticandidal drugs.

***Methods*:** The comprehensive and detailed literature on medicinal plants was carried out using different databases, such as Google Scholar, PubMed, and Science Direct and all the relevant information from the articles were analyzed and included.

***Results*:** Relevant Publications up to the end of November 2018, reporting anticandidal activity of medicinal plants has been included in the present review. In the present study, we have reviewed in the light of SAR and mechanisms of action of those plants whose extracts or phytomolecules are active against *candida* strains.

***Conclusion*:** This article reviewed natural anticandidal drugs of plant origin and also summarized the potent antifungal bioactivity against fungal strains. Besides, mechanism of action of these potent active plant molecules was also explored for a comparative study. We concluded that the studied active plant molecules exhibit potential antifungal activity against resistant fungal strains.

Keywords: *Candida albicans*, Mode of actions, Natural products, Thymol, Antifungal resistance, VVC.

1. INTRODUCTION

Candidiasis is an opportunistic fungal infection in humans caused by *Candida* species. *Candida* is a genus of yeasts of which more than 20 species are reported to cause infection in humans. The most common pathogenic Candida species are *C. albicans, C. glabrata, C. guillermondii, C. krusei, C. parapsilosis, C. pseudotropicalis, and C. tropicalis* [1, 2]. Candida normally resides in the moist upper parts of the skin and membranes without causing infection. However, the overgrowth of these organisms can cause diseases [3]. Candidiasis most frequently occurs in immunocompromised HIV and cancer patients and overuse of antibiotics and the use of immunosuppressive agents is also the reason for the development of resistance [4]. Candidiasis of the mouth is called thrush the symptoms of which include white patches or plaques on the tongue and other moist membranes [5]. *Candida* species are opportunistic polymorphic fungi. A resident of the normal vaginal microbiota, *Candida*, is the leading causative agent of vulvo-vaginal candidiasis (VVC) and presents the major quality of life issues for women worldwide [6]. It is estimated that almost 75% of all females of childbearing age are afflicted by VVC at least once in their lifetime [7] and approximately 5–8% (approximately 150 million worldwide) suffer from recurrent VVC (RVVC) [8]. Candidemia refers to the presence of fungi in blood. Presence of fungi in blood stream (Invasive candidiasis) causes a major issue in patients. Once the fungi enter into the bloodstream, it can spread to other parts of the body and cause widespread infections. The symptoms of invasive candidiasis are not specific. If the infection spreads to parts of the body such as kidneys, liver, bones, muscles, joints, spleen, or eyes, additional symptoms may develop and may vary depending on the site of infection. Antifungal drugs such as Amphotericin B and Fluconazole introduced in the late 90s, have till date been were the only available antifungal agents for the treatment of severe fungal infections; Furthermore, the emergence of the AIDS, modern patient management technologies and therapies such as solid-organ

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transplants, bone marrow and the more aggressive use of chemotherapy have resulted in a rapidly expanding number of patients highly susceptible to mycotic infections with the increased incidence of fungal infections and development of resistance to antifungal drugs. The rates of resistance of pathogenic microorganisms to antifungal agents are increasing with alarming frequency. The emergence of fungal resistance to antifungal agents has consequently become a worldwide concern [9, 10].

In the past decade research on medicinal and aromatic plants has attracted global attention. There is strong evidence to suggest the promising potential of medicinal and aromatic plants used in various traditional, complementary and alternative systems of medicine for the welfare of mankind. Medicinal plants are rich in a wide variety of secondary metabolites such as tannins, terpenoids, alkaloids, flavonoids, *etc.,* which have great *in vitro* and *in vivo* promising activity against diverse pathogens including bacteria, fungi and viruses. The anticandidal activity in plants can be attributed to the presence of some components such as allicin, thymol, carvacrol, cymene, cinnamaldehyde, pinene, linalool *etc.* In the current review, we have included plants responsible for anticandidal activity and have collated different modes of action of active components.

2. MATERIALS AND METHODS

The comprehensive and detailed literature on medicinal plants was carried out using different databases, such as Google Scholar (http://scholar.google. com), PubMed (http://www.ncbi.nlm.nih.gov/ pubmed), and Science Direct (http://www. sciencedirect.com) which were used to find the literature on anticandidal activity. Suitable Publications up to the end of November 2018 reporting anticandidal activity have been included in the present review.

3. RESULTS

3.1. Antifungal Activity

Antifungal activity (MIC and MFC) of a compound is generally determined by *in vitro* Disc Diffusion and broth dilution assays. It is further evaluated by fungicidal kinetics, protein release, DNA/RNA release or ion leakage. More than 100 papers that reported the antifungal activity of plant extract and constituents based on the *in-vitro* methods have been reviewed. Several papers, considered the significant activity of phytochemicals if the MIC values lie below 100 mg/ml (this high concentration cannot be considered as significant) for crude extract and moderate when it lies between 100-625 mg/ml [11]. In the case of active constituent from plant sources, few authors reported MIC values in v/v [12] and remaining in w/v [13] and MIC ranges in between 0.016µg/ml to 32 mg/ml. List of plants which is reported to have anticandidal activity, their biological source, parts used and minimum inhibitory concentration (MIC) against candida strains are listed in Table **1**.

3.2. Active Constituent: Anticandidal Activity & Mode of Action

Plants produce a variety of components with anticandidal activity, of which some are produced in response to mechanical injury with infection or due to microbial invasion [62]. Identification of the most active constituent from essential oil or plant extract is a cumbersome process because both extract as well as essential oils are complex mixture of molecules [63] and the composition of active constituents may vary depending on the method of collection, harvesting, extraction procedure and processing method [64]. Most studies have focused on the mechanism of action carried out in bacteria, while a few studies have studied the mode of action of fungi and moulds. Thus, we are providing an individual list of components that are active against fungi, thereby revealing their mechanism of action against strains. Table **2** and Fig. (**1**) enlisted the active constituents and their mode of action.

3.2.1. Thymol

Thymol (2-isopropyl-5-methylphenol) is monoterpene phenol present abundantly in plants belonging to the family Lamiaceae [65] (*Monarda* genera, *Ocimum*, *Origanum*, *Satureja*, *Thymbra*, and *Thymus*), and other families Apiaceae, Ranuncolaceae, Scrophulariaceae, and Verbenaceae families [65, 66].

Thymol is closely similar to carvacrol having a different position of hydroxyl group in a phenolic ring. The antimicrobial activity of thymol is not fully known but is believed to work by structural changes in the cytoplasmic membrane and interact with the intracellular targets [67]. Previous studies reveal that thymol interacts with the cell membrane and affects the cellular permeability at a concentration of 0.1% and is documented by the uptake of ethidium bromide [68], leakage of carboxyfluorescein, cellular ions [69] (18 µl of essential oil for *S. aureus* and 36 µl for *P. aeruginosa* to a culture of approximately $1x10^9$ CFU/ml), and ATP and loss of membranous potential (IC50 value at 31.2) [65, 70]. Thymol interacts with the phospholipid by intercalating between the head group region of the bilipid layer [71]. The antimicrobial activity of thymol is ascribed to the presence of hydroxyl group, where lengthening of the chain by ester or ether increases the activity. Thymol interacts with the cell membrane, dissolves the phospholipid bilayer and lodges itself between the head group. Apart from interacting with the cell membrane phospholipid, thymol also interacts with the intracellular targets, which prevents cellular recovery after short term exposure [72]. Previous studies also reported that thymol disturbs the citrate pathway [73] and affects the enzymes involved in ATP production directly or indirectly and impairs the synthesis of ATP. Thymol's interacellular interaction affects the energy generating pathways and thus prevents the cellular recovery after short term exposure [73]. The action of thymol against fungi is not studied much, but few studies explain the interaction with the cell envelope and intracellular targets. Thymol disrupted the cell membrane and impaired the ergosterol biosynthesis in candida strains (400-500 mg/L), consequently affecting the membrane symmetry and fluidity [74]. Contrary to this, one of the authors proposed that thymol works on the TOR signalling pathway and activates the pathway in yeast [75].

3.2.2. Carvacrol

Carvacrol or 2-methyl-5-(1-methylethyl)-phenol is a monoterpenoid biosynthesized from γ-terpinene through p-

Table 1. List of plants reported to have anticandidal activity, their biological source, parts used and minimum inhibitory concentration (MIC) against *Candida* strains.

Plant	Biological Source	Part(s) Used	Used Strain(s)	Minimum Inhibitory Concentration (µg/ml)	References
Velvet leaf	*Abutilon theophrasti*	Leaf and stems	*C. albicans* 90028	5.0	[14]
Karrad	*Acacia nilotica*	Fruit, Leaves	*C. albicans* ATCC 10231	9.5-39	[15]
Yarrow	*Achillea millefolium L.*	Whole aerial part	*C. albicans* ATCC 14053 *C. albicans* (MTCC)	0.19 0.19	[16]
Chaff flower	*Achyranthes aspera*	Extract	*C. albicans* ATCC 10231	780	[17]
Aloe	*Aloe secundiflora*	Leaves	*C. albicans*	8.1	[18]
Aloe	*Aloe barbadensis*	Roots and leaves	*C. albicans* *C. glabrata* *C. tropicalis*	1000 1000 200	[19]
Onion	*Allium cepa*	Bulb	*C. albicans* (clicical iolates, n=18) *C. glabrata* (n=6) *C. tropicalis* (n=5) *C. parapsilosis* (n=1)	62.5–16000 62.5–32000 62.5–32000 62.5–32000 62.5–32000	[20]
Garlic	*Allium Sativum*	Cloves	*C. albicans* (n=18) *C. glabrata* (n=6) *C. tropicalis* (n=5) *C. parapsilosis* (n=1) *C. Albicans* (n=40)	15.6–2000 15.6–1000 15.6–1000 15.6–500 MIC50 (32-80) MIC90 (64-128)	[20] [21]
Oriental garlic	*Allium tuberosum*	Aerial part extract	*C. albicans* CBS-562	100-625	[22]
Lesser alpinia	*Alpinia conchigera*	Rhizomes and stems	*C. albicans* ATCC 10231	100-625	[23]
Galangal	*Alpinia galanga*	Roots	*C. albicans* LFO 1061 *C. utilis* OUT 6020	12.5 12.5	[24]
Wild garlic	*Allium ursinum*	Extract and Volatile oils	*C. albicans* (n=3) *C. fusarium* (n=3) *C. glabrata* (n=3) *C. krusei* (n=3)	500-2000 500-4000 1000-4000 500-4000	[25]
Monkey nut	*Anacardium humile*	Leaves	*C. albicans* 10231	400	[26]
Dill	*Anethum graveolens*	Seeds	*C. albicans* ATCC 64550 *C. albicans* 09 5304 *C. albicans* 09 1502	62.5 62.5 62.5	[27]
Axlewood	*Anogeissus latifolia*	Hydro-alcoholic after maceration with ether	*C. albicans* (MTCC183)	7.28	[28]
Desert date	*Balanites aegyptiaca*	Fruit	*C. albicans* ATCC 90028	1000	[29]
Paper mulberry	*Broussonetia papyrifera*	Bark and Root	*C. albicans* 10231	10-25	[30]
Buchenavia	*Buchenavia tomentosa*	Aqueous extract, Gallic Acid	*C. albicans* ATCC 18804 *C. tropicalis* ATCC 13803 *C. krusei* ATCC 6258 *C. glabrata* ATCC 90030 *C. parapsilosis* ATCC 22019 *C. dubliniensis* NCPF 3108	12.5 12.5 0.78 0.20 6.25 0.20	[31]
Rubber tree	*Calotropis procera*	Leaves	*C. albicans* ATCC 10231	320-1280	[32]

(Table 1) contd….

Plant	Biological Source	Part(s) Used	Used Strain(s)	Minimum Inhibitory Concentration (µg/ml)	References
Papaya	*Carica Papaya*	Leaves and seeds	*C. albicans* MTCC 227	15.62	[33]
Ceylon cinnamon	*Cinnamomum verum*	Bark	*C. albicans* MTCC 227	15.62	[33]
-	*Cirsium sp.*	Aqueous extract	*C. albicans* ATCC 10231	780-1560	[34]
Key lime	*Citrus aurantifolia*	Essential oil	*C. albicans* PTCC 5027	--	[35]
Coriander	*Coriandrum sativum*	Aerial part, leaves, Essential oil	*C. albicans* CBS 562	15-125	[22]
Lemon grass	*Cympopogon citratus*	Leaves, essential oil: Lemon Grass Mentha Eucalyptus	*C. albicans* ATCC 10231	288	[36]
Indian geranium	*Cympopogon Martini*	Aerial part extract Essential oil	*C. albicans* CBS 562	63-250	[22, 37]
Java citronella	*Cympogon winterlanus*	Aerial part, dried extract	*C. albicans* CBS 562	125-1000	[22]
Dorstenia	*Dorstenia manni*	Dried Extract twigs	*C. albicans* ATCC 9002	64	[38]
Longan	*Dimocarpus longan* Lour	Spray dried extract (Gallic Acid)	*C. krusei* ATCC 6258 *C. parapsilosis* ATCC 20019 *C. albicans* ATCC 90028	8000 4000 4000	[39]
Fish mint	*Houttuynia cordata*	Aerial part and un-derground stem	*C. albicans* ATCC 14053 *C. albicans* (clinical isolate) *C. kefyr* ATCC 204093	2080 4160 16660	[40]
Poison nut	*Jatropa Curcas*	Seeds	*C. albicans* NIPRD	12500	[41]
Apple mint	*Mentha suaveolens*	Leaves	*C. albicans*	390-780	[42]
Ligusticum	*Ligusticum mutellina L.*	Methanolic extract (Gallic, benzoic, caffeic, coumaric, and ferulic acids)	*C. albicans* ATCC 10231 *C. parapsilosis* ATCC 22019	1250 1250	[43]
-	*Limonium avei*	Methanolic extract	*C. albicans* ATCC 10231	4000	[44]
Radal	*Lomatia hirsuta*	Leaves	*C. albicans* IMI 349010	8	[45]
Great basil or Saint-Joseph's-wort	*Ocimum basilicum*	Whole aerial part	*C. albicans* ATCC *C. keyfer* *C. albicans* (Clinical isolate)	500 562 562	[12]
Camphor basil	*Ocimum kilimand-scharicum*	Whole plant essential oil	*C. albicans* ATCC 10231 *C. keyfer* *C. albicans* (Clinical isolate)	1330-33340 1560-16670 860-27780	[46]
Jamaican pepper	*Piper hispidum*	Leaves, fruit, root	*C. albicans* 10231	62.5	[47]
Phlomis	*Phlomis olivieri*	Whole Plant extract	*C. albicans* (Clinical isolates)	100 000	[47]
Cinquefoils	*Potentilla sp.*	Acetone and metha-nol extract (Caffeic acid and ferulic acid)	*C. albicans* ATCC 10231	780-1560	[48]
Psammosilene	*Psammosilene tunicoides*	Root	*C. albicans* SC 5314 *C. albicans* Y0109	4 16	[49]
African nutmeg	*Pycnanthus angolensis*	Bark extract	*C. albicans* (Clinical isolate, vulvo vaginal strain)	25000	[50]

(Table 1) contd….

Plant	Biological Source	Part(s) Used	Used Strain(s)	Minimum Inhibitory Concentration (µg/ml)	References
Beach rose	*Rosa rugosa*	Methanolic extract (Protocatechuic, gallic and p-coumaric acids)	*C. albicans* ATCC 10231 *C. parapsilosis* ATCC 22019	156 156	[51]
Rosemary	*Rosmarinus officinalis*	Extract, herbal tea	*C. albicans* (Clinical isolates)	250-2250	[52]
Wing leaf soap-berry	*Sapindus saponaria*	Fruits	*C. albicans* (Clinical isolate)	310	[53]
Satureja	*Satureja intermedia*	Leaves flower and stem	*C. albicans* ATCC 13803	3400	[54]
African tulip tree	*Spathodea campanulata*	Stem Bark	*C. albicans* ATCC 10231	45000-50000	[55]
Clove	*Syzygium aromaticum*	Leaves	*C. albicans* (Clinical isolate)	150	[15]
French tamarisk	*Tamarix gallica L.*	Methanolic extract	*C. kefyr,* *C. holmii,* *C. albicans* *C. sake* *C. glabrata*	2000	[56]
Indian-almond	*Terminalia catappa*	Aerial Part and Stem barks	*C. albicans* (Clinical isolates)	145-523	[57]
Ivory Coast almond	*Terminalia ivorensis*	Aerial Part and Stem barks	*C. albicans* (Clinical isolates)	35-54	[57]
Madagascar almond	*Terminalia mantaly*	Aerial Part and Stem barks	*C. albicans* (Clinical isolates)	36.04-42.30	[57]
African limba wood	*Terminalia superba*	Aerial Part and Stem barks	*C. albicans* (Clinical isolates)	30.08-57.46	[57]
Teucrium	*Teucrium arduini L.*	Ethanolic extract (Ferulic acid)	*C. albicans* ATCC 10231	4000	[58]
Breckland thyme	*Thymus serpyllum*	Aerial Part	*C. albicans*	1/1600	[59]
Himalayan Thyme	*Thymus linearis*	Aerial Part	*C. albicans*	1/3200	[59]
Caraway	*Trachyspermum ammi*	Fruits, essential oil	*C. albicans* ATCC 24433	500	[60]
Fenugreek	*Trigonella foenum-graecum*	Seeds	*C. albicans* MTCC 227	15.62	[33]
Cassumunar ginger	*Zingiber montanum*	Rhizomes	*C. albicans* ATCC 14053 *C. albicans* MTCC 1637	0.19 0.19	[61]

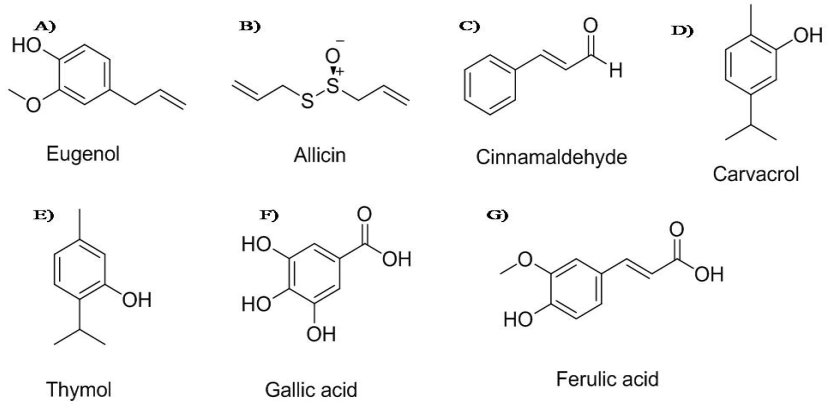

Fig. (1). List of active constituents from plant sources.

Table 2. List of active constituents against *candida* strains and their modes of action.

Plants	Constituents	Model Organism	Measured MIC	Mechanism
Ocimum gratissimum *Thymus vulgaris* *Trachyspermum ammi L.* *Satureja Montana*	Thymol	*C. albicans* ATCC 10231 *C. tropicalis* ATCC 201380 *C. albicans* *C. krusei* *C. tropicalis*	Thymol MIC values ranged from 0.125 to 1 µg/ml. MIC: 39 µg/ml for *C. albicans* and *C. krusei*; MIC: 78 µg/ml for *C. Tropicalis* [111].	Damage to the cell membrane [67], disrupted the cell envelope, increased the membrane permeability, leakage of ions like potassium, ATP [68], interaction with cell membrane and internal proteins, inhibited ergosterol biosynthesis and disturbed cell membrane integrity and fluidity [74].
		C. albicans SC 5314	MIC ranged from 64 µg/ml to 128 µg/ml [112]	
		C. albicans ATCC 11006	MIC: 350 µg/ml [113]	
		C. albicans	MIC: 125 µg/ml [114]	
		C. albicans	Treatment of 24-h-old *C. albicans* biofilms with thymol (0.06%) resulted in >80% inhibition [115].	
		C. albicans MTCC 227	MIC of thymol: 0.12 % (v/v)[116]	
		C. albicans	Thymol prevented biofilm formation at MIC 1 mg/ml and exhibited a MIC of 2 mg/ml against mature biofilm and was active at 0.5 mg/ml concentration on planktonic cells [117].	
Oreganum compactum *origanum vulgare*	Carvacrol	*C. albicans* ATCC 40042 *C. albicans* ATCC 13803 *C. albicans* ATCC 7648	256 µg/ml 256 µg/ml 256 µg/ml [79] [79, 118]	Disrupted the cytoplasmic membrane, loss of ions [67], increased the permeability [118] and fluidity of the membrane, changed the fatty acid composition and impaired the ergosterol biosynthesis [13]. Interaction with the membrane proteins and periplasmic enzymes [72].
Syzygium aromaticum *Myristica fragrans* *Cinnamomum verum* *Ocimum basilicum*	Eugenol	*C. albicans* (oropharyngeal strains) *C. albicans* (vaginal strains) *C albicans* (skin damaging strains)	7.9 mg/ml [119] 7.5 mg/ml 7.2 mg/ml	Increased the membrane permeability, increased the transport of ions, and ATP out of the cell [87]. Inhibited the activity of enzymes *i.e.* inhibition of ATPase, Histidine decarboxylase, amylase and protease [90], disruption of cell membrane and wall structure [89].
		C. albicans ATCC 10231 *C. krusei* ATCC 6258 *C. tropicalis* ATCC 13803 *C. parapsilosis* 9001 *C. parapsilosis*	0.64 mg/ml 0.64 mg/ml 0.64 mg/ml 0.32 mg/ml 0.32-0.64 mg/ml [109]	
		C. albicans isolates (n=38) *Candida* spp *C. albicans* (n=31) *C. albicans* FLC-S *C. albicans* FLC-R *C. albicans* ATCC 90028 *C. tropicalis* FLC-S *C. tropicalis* FLC-R *C. parapsilosis* FLC-S *C. parapsilosis* FLC-R	0.03–0.25% (v/v)[120] 3200 µg/ml [121] 625 µg/ml [122] 475–500 µg/ml [80] 490–500 µg/ml [80] 0.1 µl/ml [123] 475–500 µg /ml [80] 490–500 µg /ml [80] 490–500 µg /ml [80] 475–500 µg /ml [80]	

(Table 2) contd….

Plants	Constituents	Model Organism	Measured MIC	Mechanism
		C. glabrata FLC-S *C. glabrata* FLC-R *C. krusei* FLC-R *C. dubliniensis* FLC-R	485–500 µg /ml [80] 475–500 µg /ml [80] 495–500 µg /ml [124] 0.44-0.88 mg/ml [124]	
Cinnamomum cassia *Cinnamomum verum*	Cinnamaldehyde	*C. albicans* (n=32)	125 µg/ml [125]	Reacted with the proteins and interferes by a normal function, inhibited the cytokinesis and cell division [93], inhibited the activity of transmembrane ATPase and caused membrane disruption [92].
		C. albicans *C. tropicalis*	400 µg/ml 500 µg/ml [126]	
Allium sativum	Allicin	*C. albicans* 381 *C. albicans* Nakamura *C. albicans* ATCC 14053 *C. albicans* 3092 *C. tropicalis* ATCC 750 *C. tropicalis* 5483 *C. parapsilosis* ATCC 22019 *C. parapsilosis* 2707 *C. glabrata* ATCC 2001 *C. glabrata* 2737 *C. rugosa* ATCC 10571 *C. rugosa* 3114 *C. krusei* ATCC 6258 *C. krusei* 3109	6.25 µg/ml 3.13 µg/ml [127] MIC 50: 0.05 µg/ml, MIC 90: 0.1 µg/ml MIC 50: 0.39 µg/ml, MIC 90: 0.78µg/ml MIC 50: 0.1 µg/ml, MIC 90: 0.2 µg/ml MIC 50: 0.39 µg/ml, MIC 90: 0.78 µg/ml MIC 50: 0.1 µg/ml, MIC 90: 0.2 µg/ml MIC 50: 0.39 µg/ml, MIC 90: 1.56 µg /ml MIC 50: 0.1 µg/ml, MIC 90: 0.2 µg/ml MIC 50: 0.1 µg/ml, MIC 90: 0.2 µg/ml MIC 50: 0.1 µg/ml, MIC 90: 0.2 µg/ml MIC 50: 0.39 µg/ml, MIC 90: 3.13 µg /ml MIC 50: 0.1 µg/ml, MIC 90: 0.2 µg/ml MIC 50: 1.56 µg/ml, MIC 90: 3.13 µg/ml [128]	Readily transported into the cell, changed the cell morphology, interacted with the intracellular enzymes by binding with the free SH group [129]. Allicin inhibited the enzymes involved in acetyl-CoA synthesis, inhibited the DNA replication and protein synthesis, reducing the RNA synthesis [85].

cymene [76] and is abundantly present in the Labiatae family plants including *Corydothymus, Origanum, Satureja, Thymbra* and *Thymus* [77, 78]. Antimicrobial activity of carvacrol is similar to thymol (as both resemble in shapes and intercalate between the fatty acid chains) and causes structural changes in the membrane. It increases the fluidity and permeability of the membrane and changes the fatty acid composition, carvacrol interacts with the membrane, dissolves the phospholipid bilayer and occupies the space between the fatty acid chains, distortion of the physical structure cause destabilization and increases the permeability and fluidity of the membrane [79]. An increase in the permeability of the plasma membrane is confirmed by monitoring H^+, K^+, ATP and carboxyfluorescein efflux and the influx of nucleic acid dyes [68, 69]. The antifungal activity of carvacrol is similar to thymol, it shows an imbalance in Ca^{2+} and H^+ homeostasis. It affects the plasma membrane integrity and impaires the ergosterol biosynthesis in *candida* stains [80].

3.2.3. Allicin

Allicin (diallyl thiosulfinate) is an oxygenated sulphur compound, first identified and isolated in the year 1944 as a compound responsible for antimicrobial activity [81]. Allicin is found mainly in fresh cloves of *Allium sativum*. It is formed when the broken clove facilitates contact between the enzyme alliin alkyl-sulfonate-lyase or allinase and alliin leading to the formation of allicin [82]. Allicin readily transported through the cell membrane into the cytoplasm where it binds with the free –SH group containing moiety (glutathione, free cysteine, low molecular weight thiols and cysteine containing proteins) and inhibited the broad range of cellular targets. Allicin inhibited the thiol-protease papain, $NADP^+$-dependent alcohol dehydrogenase and a NAD+-

dependent alcohol dehydrogenase [83], all the enzymes can be reactivated by the dithiothreitol, glutathione and 2-mercaptoethanol, confirming that the inhibition is reversible [83, 84]. Allicin reversibly inhibited the enzymes involved in acetyl-CoA synthesis in prokaryotes and eukaryotes [85]. Allicin partially inhibited the DNA replication in *S. Typhimurium* and RNA synthesis was reduced to 90% indicating RNA synthesis as the primary target of allicin [85]. Allicin is generally used with other chemotherapeutic agents as it exhibits inhibitory effect on the RNA synthesis and makes the cell more prone to death. These studies collectively indicate that allicin is a non-specific inhibitor of enzymes, thereby reducing or hindering cell protection mechanisms induced by other antimicrobials.

3.2.4. Eugenol

Eugenol, a polyphenol (Hydroxyphenyl propene), is present abundantly in plants belonging to the family Lamiaceae, Lauraceae, Myristicaceae and Myrtaceae [86]. It is a major constituent of *Syzygium aromaticum*. Its antimicrobial activity is associated with its ability to cross the cell membrane and interact with the internal protein. Various studies discussed the role of eugenol in non specific membrane permeabilization as it increases the efflux of K^+ and ATP from the cell [87, 88]. Eugenol interferes with the fatty acid of cell membrane in *E. coli, S. enterica, P. fluorescens, B. thermosphacta* and *S. aureus* further it interferes with the cellular morphology and disruption of cell membrane in *C. albicans, S. typhi, S. agalactiae* and *S. cerevisiae* [86-89]. Eugenol increases the intracellular production of ROS in *C. albicans* and *S. aureus* and inhibits the enzyme in *E. aerogenes, B. subtilis, L. monocytogenes* and in *E. coli* [86]. Eugenol also inhibits the activity of amylase, ATPase, histidine decarboxylase and protease [90, 91], ATPase inhibition is the most important activity, as it impairs the cell sensitivity, leading to cell death [92]. Previous studies also explained that hydroxyl group of eugenol binds with the internal proteins and exhibits inhibitory effect at sub MIC. The anticandidal mode of action needs more investigation, but little study explains that eugenol disturbs the cell proliferation and promotes cell death by altering the cell wall structures and by releasing cellular content of the cell [89].

3.2.5. Cinnamaldehyde

Cinnamaldehyde is a bioactive component present in the genus *Cinnamomum.* It is also produced by *E. coli* from its biosynthetic precursor and served as another source for the production of cinnamaldehyde. Aldehydes are reactive groups and are capable of cross link covalently with the other molecules. Cinnamaldehyde covalently linked with the DNA and proteins and interferes with the normal function of a cell, as like thymol and carvacrol it does not interfere with the cell membrane in gram-negative bacteria while inhibiting the energy generation process [68]. Cinnamaldehyde also changes the fatty acid composition in the membrane, alters the fluidity accompanied by the leakage of micromolecules, inhibition of ATP synthesis and inhibition of ATPase activity. Histidine decarboxylase is also inhibited by cinnamaldeyde [91]. Cinnamaldehyde is reported to inhibit cytokinesis in *B. cereus* [93]. Cinnamaldehyde binds with the FtsZ protein and inhibits the GTP dependents polymerization and prevents cell division [94]. *In silico* study of cinnamaldehyde reveals multiple mechanisms including disruption of carbohydrate, amino acid and lipid metabolism resulting in the inhibition of defenses mechanism against oxidative stress [30, 95]. The cited literature indicates that antimicrobial action of cinnamaldehyde is governed by the various mechanisms. The specific mechanism might not be associated with other pathogens due to the differences in membrane susceptibilities. In fungi, cinnamaldehyde reported the inhibition of cell division followed by the inhibition of β -(1,3)-glucansynthase and chitin synthase isozymes [96].

3.2.6. Alkyl Glycosides

A series of alkyl glycosides and thio glycosides derived from mannose, glucose, galactose and cellobiose, which are the major component of *Candida* cell walls, were synthesized and evaluated for their anti-Candidal activity. Only the mannosides and glucosides exhibited inhibitory activity. The inhibitory potential was determined by the aglycone chain length, only compounds with C-10 and C-12 aglycone chains (decyl α -D-mannoside, dodecyl α -D-mannoside, dodecyl 1-thio-α-D-mannoside and dodecyl β -D-glucoside) found as efficient *Candida* inhibitors. The mode of action of the alkyl glycosides was not studied, but the author hypothesized that these are carbohydrate homologues of structural components of cell walls and can interfere with the structure and disruption of bilayer anticipated [97].

3.2.7. Phenolic Compounds

Phenolic compounds are abundantly present in plants, and foods (cereal grains, fruits, legumes, and vegetables, tea and coffee). The most common are phenolic acids (cinnamic and benzoic acids, gallic acid, ferulic acid, sinapic acid, vanillic acid *etc.*), coumarins flavonoids, lignans and lignins, proanthocyanidins, stilbenes, and Tannins [98]. The anti-*Candidal* properties of phenolic compounds believed to be the inactivation of enzyme production [99] and anti-biofilm effect [100]. These are derivatives of hydrocinnamic, hydrobenzoic, phenylacetic, and phenylpropionic acids [101] and exist as the salts of amides, esters or glycosides. With over 9000 natural antimicrobials identified [102], flavonoid family, is the largest group of phenolic compounds that are involved in the plant growth, reproduction and provide resistance to plant pathogens and protect crops and seed from diseases [103].

Phenolic acids such as gallic and ferulic acids are known to affect the cell membrane of bacteria and change the surface hydrophobicity and charge and cause cell leakage [104]. In fungi, gallic acid inhibits the ergosterol biosynthesis, reduce the activity of sterol 14α-demethylase P450 (CYP51) and squalene epoxidase [105], while caffeic acid and quinic acid is reported for cell leakage and to interfere with 1,3-β-glucansynthase [106]. Isoquercetin [107], curcumin [108] and lariciresinol [109] damage the cell membrane. Catechin (flavan-3-ols), luteolin (flavone) and quercetin (flavonol) were reported for their antimicrobial activity but strong evidence for their antifungal activity is not reported, one of the authors reported that flavonoid such as catechin, quercetin and epigallocatechin gallate did not possess antifungal activity of their own at concentration tested but they significantly increase the activity of fluconazole when tested against C. tropicalis [110].

4. ANTIFUNGAL RESISTANCE

Despite advances in the chemotherapeutic regimen, fungal infections cause severe morbidity and mortality in immunocompromised patients. The development of resistance in immunocompromised patients is a major concern. A better understanding of the mechanism of drug resistance is required for the development of a prompt and efficient regimen for the benefits of patients [129]. Widespread use of fluconazole and itraconazole in HIV infected patients with oral or esophageal candidiasis is thought to be responsible for azole resistance (infection with intrinsically resistant organisms and over expression of MDR and CDR genes encoding efflux pumps (but not ERG11) are the reason behind the development of resistance). Resistance to azoles was majorly seen with HIV immunocompromised patients, rarely with other types of candidiasis [130]. Several mechanisms of resistance to antifungal drug azoles have been identified and at least more than one mechanism of resistance can be functional at a given time in a candida strain. Differences in the structures of azoles develop the cross resistance patterns against candida strains [131]. Although complete cross resistance in triazoles was seen against *C. glabrata* only, but no such cross resistance pattern was observed with *C. krusei* [132]. Azoles work by inhibiting 14α demethylation of lanosterol thus interferes with the cell membrane. Resistance is mainly developed due to the activation of efflux pumps in candida species thus decreasing the drug concentration at the site of action. Upregulation of CDR1, CDR2, and MDR1 transporter in *C. albicans* [133], PDH1 and CgCDR1 in *C. glabrata* and CdMDR1 and CdCDR1 in *C. dubliniensis* [134] has been associated with the activation of efflux pump and development of cross resistance against candida species, while upregulation of CDR gene confers resistance to all azoles. Alteration in the target site is another mechanism that develops resistance. Mutations in ERG11 [135] gene or affinity to ERG11p [136] gene encoding the lanosterol C14α-demethylase enzyme also prevent the binding of the drug to the site.

Some *candida* isolates upregulate the concentration of intracellular target enzymes ERG11p as compared to susceptible strains with azoles and confer the development of resistance to azoles. Up-regulation of enzymes can be achieved by an increase in transcription or gene amplification rate. However, enzyme up regulation contributes to a little resistance in *candida* species [137]. Consistent exposure of *candida* to azoles results in the loss of ergosterol from the membrane and accumulation of 14α-methyl-3,6-diol, which leads to cell death. Mutations in the ERG3 gene by fungal strains inhibit the formation of 14α-methyl-3,6-diol and develops the resistance to azoles as well as polyenes [138].

The development of resistance to polyenes among *candida* species is rare [139], but recently increasing MICs to polyenes were noted specifically with amphotericin B against *C. glabrata* and *C. krusei* isolates [140]. Intrinsic resistance was also observed with *C. lusitaniae* [141] and *T. beigelii* [142]. Filamantous fungi develop more resistance than yeast to polyenes, while resistance to *Aspergillus* species is rare except *A. terreus* to amphotericin B [143] but susceptible to itraconazole and voriconazole. Low ergosterol content in the *A. terreus* is the reason behind the poor activity of amphotericin B. Changes in the ergosterol pathway due to mutation in the *ERG3* gene lead to the accumulation of sterols and confer resistance in *candida* species [144]. Resistance to polyene also mediated through catalase activity, due to less susceptibility towards oxidative damage [145]. Some yeasts also develop resistance to flucytosine due to the changes in cytosine permease, cytosine deaminase and alteration in cellular uptake machinery, because of the recent and rapid development of resistance, clinicians have become aware and started using flucytosine in combination therapy along with amphotericin B. The development of resistance was also noted with echinocandins, a new class of drug against *candida* species. Echinocandins work by inhibiting β-1,3-D glucan which is an integral part of cell wall that maintains the rigidity and fluidity of the cell. The inhibition of the β-1,3-D glucan forms the defective cell wall leading to cell disruption. Although the mechanism of resistance to echinocandins is not so much investigated. But few authors suggested that the resistance is due to the mutations in the Fks1 gene mainly in conserved region of Ser645 position in β-1,3-D-glucan synthase complex [146]. Recently, resistance to echinocandins was observed in patients with *candida* infections (due to *C. albicans, C. glabrata*, *C. krusei,* and *C. parapsilosis*) and resistance was developed during therapy and associated with treatment failure [147]. The mechanism of resistance reported in patients was other than Fks1 gene and hence it is clear that some other pathways are involved in the development of Resistance [148].

CONCLUSION

This article reviewed natural anticandidal drugs of plant origin. Plants reviewed potent activity against fungal strains and components responsible for potent anticandidal activity in plants are also discussed along with their various mechanisms of action. Few plant molecules showing mechanism of action believed that they can be active on resistant strains. Further studies and information are warranted to explore the mechanism of action of phytomolecules and confirm the safety, so as to reach the conclusion that plant components, individually or in combination can be used to combat drug resistance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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