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Mini-Reviews in Medicinal Chemistry, 2020, *20*, 000-000

SYSTEMATIC ARTICLE

Herbal Extracts with Antifungal Activity against *Candida albicans*: A Systematic Review

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ARTICLE HISTORY

Received: February 20, 2020
Revised: May 19, 2020
Accepted: May 21, 2020

DOI:
10.2174/1389557520666200628032116

Abstract: In the era of antimicrobial resistance, fungal pathogens are not an exception. Several strategies, including antimicrobial stewardship programs and high throughput screening of new drugs, are being implemented. Several recent studies have demonstrated the effectiveness of plant compounds with antifungal activity. In this systematic review, we examine the use of natural compounds as a possible avenue to fight fungal infections produced by *Candida albicans*, the most common human fungal pathogen. Electronic literature searches were conducted through PubMed/MEDLINE, Cochrane, and Science Direct limited to the 5 years. A total of 131 articles were included, with 186 plants extracts evaluated. Although the majority of the natural extracts exhibited antifungal activities against *C. albicans* (both *in vivo* and *in vitro*), the strongest antifungal activity was obtained from *Lawsonia inermis*, *Pelargonium graveolens*, *Camellia sinensis*, *Mentha piperita*, and *Citrus latifolia*. The main components with proven antifungal activities were phenolic compounds such as gallic acid, thymol, and flavonoids (especially catechin), polyphenols such as tannins, terpenoids and saponins. The incorporation of nanotechnology greatly enhances the antifungal properties of these natural compounds. Further research is needed to fully characterize the composition of all herbal extracts with antifungal activity as well as the mechanisms of action of the active compounds.

Keywords: Herbal extracts, antifungal properties, *Candida albicans,* gallic acid, thymol, catechin, nanotechnology.

1. INTRODUCTION

Candida species are commensal microorganisms in human oral mucosa, digestive and vaginal tracts. Normally, people with healthy immune systems can control the growth and spread of this opportunistic fungus. However, when the host becomes weak and immunocompromised, it can lead to serious infection. These infections can be superficial such as thrush, vaginitis, skin infections, or invade the bloodstream and spread to any site of the human host, which can cause many clinical complications such as brain abscess, endocarditis, meningitis, arthritis and pyelonephritis [1].

Approximately 150 *Candida* species have been identified, of which only about 20 species can cause infection in humans. Among these, *Candida albicans* is the most common pathogenic species responsible for most invasive infections in immunocompromised patients, followed by *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis,* and *Candida krusei,* which comprised up to 90% of *Candida* infections [2]. It is estimated that more than a quarter of a million patients are infected with invasive candidiasis, with the incidences rates up to 2-14 per 100000 populations globally [3]. In addition, *Candida* is ranked fourth of the most common pathogens of bloodstream infections after *Staphylococcus aureus* and *Enterococci* [4]. Furthermore, *C. albicans* is one of the most isolated species responsible for nosocomial infections due to the use of intravenous catheters, invasive procedures, transplantation, wide range use of broad-spectrum antibiotics and chemotherapies [2]. Particular characteristics of *C. albicans* are their morphological transition between yeast and hyphal forms, which allow adherence to oral mucosa; formation of biofilms; phenotypic switching and the secretion of virulence factors such as adhesins and hydrolytic enzymes [5].

Currently, there are only five major classes of antifungal agents available to treat *C. albicans* infections. These include polyenes, allylamines and azoles, which target ergosterol and nucleoside analogues, which inhibit DNA and/or RNA syn-

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1389-5575/20 $65.00+.00

thesis, and echinocandins, that inhibit the synthesis of β-1, 3-glucan [6]. Among these, azole antifungals such as fluconazole are often selected as the treatment choice because they are well tolerated, exhibit low toxicity, available for oral administration, and are inexpensive. However, in recent years, the resistance of *Candida* species to antifungal drugs has increased worldwide [7]. Generally, antifungal resistance is achieved through reduced intracellular drug accumulation, decreased target affinity for the drug and counteraction of the drug effect**.**

Due to the widespread and overuse of limited antifungal drugs, the search for alternatives against *C. albicans* is ongoing, especially in plants and natural herbs. It is estimated that there are 250,000-500,000 species of plants on earth and only 10% are used by humans [8], which provided 50% of commercially available modern drugs [9]. Plant extract therapies have been utilized and accepted all over the world due to their low side effects. The earliest record of plant medications can be traced back to 2600 BCE in Mesopotamia, Egypt, India, Greece and China, revealing about 300-1000 different drugs [9]. The most common species used by ancient people are algae, bryophytes, pteridophytes and angiosperms [9]. Different geographical locations also have a big impact on the development of herbal drug systems and the availability of plant resources. Kier and coworkers describe that the highest diversity of plants may be found in the Neotropic (central and south America) and the Asia-Pacific region (China, India, USA, Australia), and lower diversities in Africa and on oceanic islands [10]. Traditionally, the majority of medicinal plants are found in India and China, while Europe and the USA have developed fewer sources [9]. The diversity of plants provides a wide range of important sources of biologically active molecules with enormous potential antifungal properties, such as phenols, tannins, terpenoids and alkaloids [9]. Isolated and modified compounds such as dimethyl pyrrole, hydroxydihydrocornin-aglycones and indole derivatives have also shown antifungal activity *in vitro* [8]. Studies have reported that the extraction method of active substances has a great influence on the function of antimicrobial components and their antifungal effectiveness. Silver nanoparticles, antibodies, and photodynamic inactivation have increased the distribution and effectiveness of antifungal drugs [2]. For this reason, the antifungal activity of natural herbs and extracts have been assessed as an alternative antifungal drug against *C. albicans.* In this systematic review, we evaluate the antifungal activities of natural herbs and extracts and their synergistic effect with common antifungal agents.

2. MATERIALS AND METHODS

2.1. Search Strategy

This review was carried out in accordance with PRISMA guidelines. Comprehensive, structured literature searches were conducted *via* the databases PubMed/MEDLINE, Cochrane and Science Direct. The publication date was limited from Jan 1st, 2015 until Feb 23rd, 2019. The electronic search was performed using the phrases**:** *C. albicans* AND (extract OR herbal OR natural) AND (antifungal) for Science Direct and Cochrane Library; Search terms with Mesh terms: (*C. albicans)* AND extracts [MeSH Terms]) OR natural products [MeSH Terms]) OR herbal [MeSH Terms]) AND antifungal [MeSH Terms]) were searched in PubMed in the English language.

2.2. Inclusion Criteria

The fundamental inclusion factors were that the studies must involve the use of natural products, herbs, or extract against *C. albicans.* Studies could be either *in vitro*, *in vivo,* or both for the purpose of assessing the antifungal activity of natural products against *C. albicans.* Table **1** shows all the study inclusion and exclusion criteria.

2.3. Types of Study

All prospective or longitudinal studies, experimental studies, clinical trial/study, double-blinded, randomized, placebo-controlled trials examining nature were included.

2.4. Types of Preparation

Herbal preparations are described as naturally prepared from herbs or plants from their roots, flowers, leaves, fruits, bulbs or seeds through different extraction methods into essential oil or extracts. These were then applied to inactive placebo or active control such as common antifungal drugs (azoles, nystatin, amphotericin B). Studies combining herbal interventions and routine pharmacologic therapy (co-intervention) were also reviewed.

2.5 Selection Criteria

Studies omitted from this review include retrospective studies, editorials, letters, reviews, case reports, cohort studies and pilot studies. Studies not using *C. albicans* as a tested organism and not presenting minimum inhibitory concentration values (MIC) were also excluded. Essential oils and extracts originating from animals or insects were excluded from this study.

2.6. Study Selection

Firstly, primary literature research was conducted. Next, the abstracts and titles were evaluated in order to screen and eliminate articles unrelated to this research topic. Following this, the remaining studies were downloaded as full-text articles and were assessed for eligibility. Only studies meeting the inclusion and exclusion criteria were included in this systematic review.

2.7. Data Extraction

Tables **2** and **3** were used to organize the information gained from each study [11-19]. Table **2** displays data from combined *in vivo/in vitro* studies whilst Table **3** contains information from *in vitro* studies only [20-141]. The following data was collected from all eligible articles: the scientific and common names of the plants; country of collection; parts of the plants that were extracted; extraction methods*;* strains that were tested; MIC or colony-forming units (CFU) of the products and outcomes.

Table 1. List of inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Study type: prospective or longitudinal studies, experimental studies, Clinical Trial, Clinical study, RCT (Only articles with level of evidence of 1b are included)	Retrospective study, editorials, letters, review, case report, cohort, pilot study
C. albicans strains must be tested	Algae/Animal/Insects as interventions.
Results must include antifungal assessment/evaluation method using MIC *in vitro* and *in vivo*. CFU unit is also included in *in vivo* studies.	Studies in which *C. albicans* are not tested.
Full length article available	-
English-language only	-
Published between Jan 1,2015 to Feb 23rd, 2019	-
Studies combined natural products with common antifungal drugs are included (Nystatin and azoles)	-

Table 2. Data extraction table from combination *in vivo/in vitro* studies investigating the antifungal activity of plant extracts against *C. albicans.*

Refs.	Plant/Organism (Common Name)	Country of Origin	Plant Part(s)	Product (s)	*In vivo*: MIC /CFU (mg/mL, mg/mL)	*In vitro*: MIC (mg/mL, mg/mL)	Host Organism	Strains	Conclusion
[11]	*Lawsonia inermis*	Iran	Leaves	EE	5-10 mg/mL	-	Wistar rats	*C. albicans LC201976*	4% was more effective than 2% and was as effective as clotrimazole.
[12]	*Punica granatum L.*	Algeria	-	AC	80 mg/mL	0.090 mg/mL	Male mice	*C. albicans* *C. krusei* *C. guillier-mondii*	*Quercus suber L.* show the best and *Vicia faba* had the poor antifungal activity.
	Quercus suber L.				20 mg/mL	0.105 mg/mL			
	Vicia faba				>100 mg/mL	0.010mg/mL			
[13]	*Camellia sinensis* (L.) O Kuntze	Algeria	-	AC	40 mg/mL	5 µg /mL	C57BL6 mice	*C. albicans,* *C. glabrata,* *C. tropicalis,* *C. krusei*	AC was more active
				AQ	60 mg/mL	20 µg /mL			
[14]	*Morinda tomentosa*	Indonesia	Roots	ME	>32mg/mL	-	*Galleria mellonella*	*C. albicans* DSY2521 *C. albicans* CAF2-1	x
[15]	*Melaleuca alternifolia*	Brazil	-	Essential oil	5.33 Log_{10} CFU	1.95 mg/mL	Male mice	*C. albicans* strain ATCC 18804	• 12.5% extract concentration completely inhibited the biofilms • Protective effect against oral *C. albicans* infections in mice.
[16]	*Mitracarpus frigidus*	Brazil	Aerial	ME	400 and 4000mg kg^{-1} CFU: Log 4.68 (day one)	500 µg /mL	Female Wistar rats	*C. albicans ATCC 10231*	• Promising antifungal activity in vitro and in vivo. • In vitro results suggest its ability to act on the cellular envelope. • Better than fluconazole (MIC value = 10,000µg /mL)

(Table 2) Contd….

Refs.	Plant/Organism (Common Name)	Country of Origin	Plant Part(s)	Product (s)	*In vivo*: MIC /CFU (mg/mL, mg/mL)	*In vitro*: MIC (mg/mL, mg/mL)	Host Organism	Strains	Conclusion
[17]	*Syzygium cumini*	Brazil	Seeds	NaP	100mg/kg	-	Diabetic infected Wistar rats	-	• Nanotechnology improve antioxidant properties. • Contain high concentrations of phenols and flavonoids (gallic acid, chlorogenic acid, grutin, quercetin) • Hypoglycaemic activity in rat models of DM
[18]	*Astragalus membranaceus*	China	Roots	Low molecular weight polysaccharide (LMW-ASP)	CFU: 5.87 ± 0.03c -6.05 log10	-	Sera of mice infected with live *C. albicans* cells	-	Greatly improved against systemic candidiasis by strongly enhancing Th1 and Th2 responses in recombinant protein rP-HSP90C, but mechanism is unclear.
[19]	*Jatropha curcas L*	Mauritius	Barks, roots leaves, seeds	Crude extracts	350-3290 mg/L	17.80-83.30 mg/mL	*Bactrocera zonata* and *B. cucurbitae* (Diptera fruit flies)	*C. albicans ATCC 1023*	• Show antifungal activity *in vivo* and *in vitro*. • ME of mature leaves show the lowest activity and bark ME extract was highest *in vivo*. • Contains alkaloid, steroids, tannins, flavonoids, phenol and coumarins.

Abbreviations: *-: Not specified/Not available, *X: No antifungal effect; *ME: Methanolic extract, * AC: Acetone extract, *AQ: Aqueous extract, *AQE: Aqueous ethanolic extract; *EtOAc: Ethyl actetate extract, * EE: Ethanol extract, *Dichloromethane extract: DCM , *HE: Hexane extract; *CHL:Chloroform extract , *BA: butanol extract; *NaP: Nanoparticles/Nano formulations.

2.8. Antifungal Activity Measurement

Both *in vitro* and *in vivo* antifungal activities are measured by Minimum Inhibitory Concentration (MIC), which is defined as the lowest concentration of an antimicrobial drug that will inhibit the visible growth of a microorganism after overnight incubation. Antifungal activities are measured either by microdilution assay, tube diffusion method or serial microplate dilution methods. In addition, *in vivo* studies are also assessed by quantifying the CFU, which is a measure used to estimate the number of viable bacteria or fungal cells in a sample.

2.9. Data Quality Evaluation

The quality of studies was evaluated according to the Centre for Evidence-based Medicine Levels of Evidence and PRISMA guidelines [149,150].

3. RESULTS AND DISCUSSION

3.1. Description of Selected Reports

Fig. (**1**) depicts an overview of the study selection procedure. After the removal of duplicates, a total of 2666 articles were recovered from three databases, with publication dates ranging from January 1, 2015, to February 23rd, 2019. Following the screening of titles and abstracts, 2283 articles were excluded, leaving 379 full-text articles, which were assessed for eligibility. Finally, a total of 131 articles met the inclusion criteria and were considered suitable for this systematic review. In total, there were 186 natural products involved in this systematic review; please see Tables **2** and **3** for further details on each study, [11-19] [20-141]. Plants identified in the review originated in 42 countries, with the largest percentages in Brazil (20%), India (9%) and Iran (7%) (Fig. **2**). This geographical distribution and preference are supported by a study by Kier and coworkers [10].

Most herbal extracts show minimal to moderate antifungal effects against *C. albicans;* however, 27 tested plants were ineffective against it. In terms of herbal interventions, seven studies utilized nanotechnology with herbal extracts; ten articles assessed the synergistic effect of natural products with common antifungal drugs. Fourteen plants have been tested repeatedly in several studies and appear more than once in this review, which are *Salvadora persica, Camellia sinensis, Cinnamomum verum, Cuminum cyminum, Lawsonia inermis, Melaleuca alternifolia, Mentha piperita, Origanum vulgare, Paeonia lactiflora, Pelargonium graveolens, Psidium guajava*, *Syzygium aromaticum* and *Thymus vulgaris.*

Table 3. Overview of names, countries of origin, plant part(s), formulation, MIC, strains used and conclusions of the herbal interventions *in vitro.*

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[20]	*Olea europaea* (Olive)	Croatia	Leaves	Extract	46.875 mg/mL	*C. albicans* ATCC 10231 *C. dubliniensis* CBS 7987	• Cytotoxic effect on tested yeast strains • Concentration dependent. • Contains hydroxytyrosol, protocatechuic acid, tyrosol, oleuropein, pinoresinol and apigenin.
[21]	*Melaleuca alternifolia*	Australia	Leaves	Tea tree oil (TTO)	Average 0.19% Fluconazole +TTO: 38.46mg/mL	*C. albicans* ATCC 10231 *C. albicans strains resistant to fluconazole*	Show antifungal and synergistic effect with fluconazole
[22]	*Stryphnodendron adstringens (Mart.) Coville (Leguminosae)*	Brazil	Stem barks	Dried and pulverized	15.6 µg/mL	*C. albicans ATCC 10231*	Successfully inhibited planktonic growth and biofilm development.
[23]	*Metasequoia glyptostroboides*	Korea	Cone (abietane-type diterpenoid taxodone)	EtOAc	250-1000(mg/mL)	*C. albicans KBN06P00076 C. Albicans KBN06P00074*	Effective against *C. albicans*
24]	*Eugenia dysenterica DC. (Hexachlamys macedoi Legrand) Pouteria ramiflora (Mart.) Radlk, Pouteria torta (Mart.) Radlk, Bauhinia rufa (Bong.) Steud, Erythroxylum subrotundum A*	Brazil	Leaves	AQ	Cannot be detected	*C. guilliermondii ATCC 6260, C. tropicalis ATCC 28707 C. parapsilosis ATCC 22019 C. albicans ATCC 90028, C. Glabrata ATCC 2001, C. Famata ATCC 62894 C. krusei ATCC 34135*	• No inhibition detected against *C. Albicans and C. Glabatra*. • AQ show significant inhibitory activity against C. *Parapsilosis, C. Guilliermondii, C. Tropicalis, C. Krusei and C. Famat.*
[25]	*Piper guineense*	Nigeria	Fruits and leaves	AQ EE ME CHL HE	AQ: NA EE:78 µg/mL ME:39 µg/mL CHL:78 µg/mL HE:78 µg/mL	*C. albicans ATCC 10231 C. Glabrata ATCC 2001 C. Tropicalis ATCC 750 C. Parapsilosis ATCC 7330*	ME, EE, CHL and HE show antifungal efficacy, whereas AQ is not effective.
[26]	*Pelargonium graveolens*	USA	Purchased	Geranium oil (GO) Nanoemulsion geranium oil (NGE)	GO:1.82 µg/mL NGE:3.64 µg/mL	*C. albicans* ATCC 14053 *C. Tropicalis* ATCC 66029 *C. Glabrata* ATCC 66032 *C. Krusei* ATCC 6258	• NGE was twice higher □uv the GO and □uve□le to reduce the amount of biofilm in the catheter. • Eliminate biofilm formation.
[27]	*Swartzia simplex*	Panama	Root and bark	DCM	32 µg/mL	*C. albicans DSY2621* Parent wild-type CAF2-1	Show antifungal activity
[28]	*Bursera morelensis*	Mexico	Stems	Ramirez essential Oil	0.062 – 0.25 mg/mL	*C. albicans* ATCC 14065 *C. Albicans* ATCC 32354	Germ □uve inhibition and diminish the transcription of the gene *INT1*.

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[29]	*Aeollanthus cucullathus*	Cameroon		Hexane ethyl acetate extract	0.625 - 5 mg/mL	*C. albicans* *C. glabrata*.	Biofilm inhibition by blocking the filamentation process and by reducing the biofilm thickness.
[30]	*Leguminosae* family species	Brazil	Leaves	ME	-	*C. albicans* *C. krusei* *C. glabrata* *C. tropicalis* *C. parapsilosis,*	None of them show antifungal activity.
[31]	*Ricinus communis*	Ghana	leaves	AQ ME EE	3.13 - 25.0 mg/mL	*C. albicans*.	• All are effective against *C. albicans,* • ME show higher antifungal activity than other extract. may be due to the presence of high amount of tannins, flavonoids, and terpenoids.
[32]	*Cochlospermum regium*	Brazil	Pilger roots	EtOAc	250 mg/mL	*C. albicans* 10231 C. *krusei* 34135 C. *glabrata* 2001 C. *tropicalis* 28707	Effective due to the presence of tannins and gallic acid.
[33]	*Salvia adenophora Fernald (Lamiaceae)*	Italy	Aerial	Isolated compounds	-	*C. albicans* clinical strain.	X
[34]	*Olea africana*	South Africa	Leaves	HE CHL DCM, EtOAc EE ME BA AQ	Average 0.37 mg/mL	*C. albicans*	All are effective however *C. neoformans* and *E. faecalis* were the most sensitive test organisms.
35]	*Helichrysum* species: *H. armenium DC, H. arenarium L. (Moench)*	Turkey	-	EE	All are 8 µg /mL	*C. albicans* *C. parapsilosis*	*H. arenarium* is the most remarkable among other tested extracts.
[36]	*Antidesma madagascariense Lam. (Euphorbiaceae)*	Mauritius	Leaves	AQ AC	4.00 mg/mL	*C. albicans ATCC 10231*	Show antifungal activity and show antioxidant, anti-inflammatory activity and serve as AChE inhibitors.
[37]	*Lavandula binaludensis*	Iran	Aerial parts	Essential oils	7.91 mg/ mL	*C. albicans* isolates	• Effective against *C. albicans.* • Antifungal are attributed to g-terpinene and 1,8-cineole through destroying cell walls and proteins, interfering in the work of membrane enzymes and affecting DNA and RNA replication.
	Cuminum cyminum				8.00 mg/mL		
[38]	*Lawsonia inermis*	India	Leaves	ME EE	ME:2.8 mg/mL	*C. albicans*	*W. somnifera, C. longa, Euphorbia hirta, Echinophora platybola, Zingiber officinale, L. inermis, Adenocalymma alliacum, P. parviflorus and Swertia chirata* effective against *C. albicans* at MIC 5 mg/mL without any toxic effect.
	Withania somnifera				ME: 3.2 mg/mL EE: 3.1 mg/mL		
	onga				ME:5.0 mg/mL EE: 2.81 mg/mL		
	Euphorbia hirta				ME:1.5 mg/mL EE: 2.75 mg/mL		
	Pogostemon parviflorus				ME: 4.3 mg/mL EE: 4.25 mg/mL		
	Adenocalymma alliacum,				ME: 3.15 mg/mL EE: 3.85 mg/mL		

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
	Echinophora platybola				EE: 2.3 mg/mL		
	Zingiber officinale				ME: 2.10 mg/mL EE: 4.25 mg/mL		
39]	*Thymus capitatus*	Tunisia	Aerial parts	Essential oils	125 µg/mL	*C. albicans 328, C. albicans 247, C. albicans 311, C. albicans 249, C. riferii 648, C. tropicalis, C. glabrata 239, C. glabrata* 113	• *C. verum* exhibited the best activity; *S aromaticum* showed moderate. activity; *P. graveolens* EO was less active. • Affect ergosterol biosynthesis and disturb fatty acid homeostasis.
	Pelargonium graveolens				250-1000 µg/mL		
	Cinnamomum verum				31.25-62.5 µg/mL		
	Syzygium aromaticum				125-250 µg/mL		
[40]	*Sideroxylon obtusifolium*	Brazil	leaves	Hydro alcoholic extracts	62.5 mg/mL	*C. albicans ATCC 10231*	Show antifungal activity in the presence of flavonoid and saponins.
	Syzygium cumini				125 mg/mL		
[41]	*Polyscias fulva (Hiern)*	Cameroon	Stem bark	Crude DCM ME	12.5 µg/mL 50 µg/mL 100 µg/mL	*C. albicans ATCC 1663* *C. Krusei ATCC 6258* *C. Parapsilosis ATCC 22019* *C. Lucitaniae ATCC 200950* *C. Glabrata IP 35* *C. Guilliermondii clinical isolate*	Show antifungal activity due to the presence of terpernoid and saponins
[42]	*Ficus drupacea*	Egypt	Stem bark	7 isolated compounds and	7-7521µg/mL	*C. albicans ATCC 26555*	• Isolate compounds show better antifungal activity than extract. • Compounds 5-O-methyllatifolin) and 7 (epilupeol acetate) exhibited the highest antifungal ctivety.
				n-Hexane extract	4–15 µg/mL		
[43]	*Tamarix gallica*	Tunisia	Leaves and flowers	ME	0.292 mg/mL	*C. parapsilosis, ATCC 22019* *C. Albicans, ATCC 90026;* *C. Krusei ATCC 6258;* *C. Glabrata ATCC 90030*	• Show antifungal activity. • Flower presence flavonoids and leaves showed quercetin 3-O-glucuronide these suggest antifungal activity.
44]	*Carissa opaca*	Pakistan	Root	ME Ethyl Acetate (EA)	ME: 20 mg/mL EA: 7.8 mg/mL	*C. albicans ATCC 10231*	ME showed moderate to high antimicrobial activities and EA displayed especially notable efficacy.
[45]	*Helichrysum microphyllum subsp. Tyrrhenicum*	Italy	-	Essential oils (ESO)	750 µg/mL	*C. albicans ATCC 10231*	• Chitosan formulations increased antifungal activity against *C. albicans.* • Terpenes and alcohols such as c-curcumene and lina- examined is responsible for the antifungal effect
				ESO with Chitosan	94.5 µg/mL		
[46]	*Rhaphiodon echinus* (Nees and Mart)	Brazil	Leaves	Essential oils	>1024 µg/mL	*C. albicans,* *C. Krusei* *C. Tropicalis*	X

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[47]	*Carya illinoensis*	Brazil	Leaves	AE EE	AE: 0.78 - 25 mg/mL EE:1.56 - 25 mg/mL	*C. tropicalis ATCC 66029* *C. parapsilosis ATCC 22019* *C. albicans ATCC 14053*	• AE and EE were effective at all concentrations by inactivating germ tube production. • Presence of phenolics acids (gallic acid and ellagic acid), flavonoids (rutin) and condensed tannin (catechin and epicatechin).
[48]	*Buchenavia tetraphylla*	Brazil	Leaves	HE CHL EE ME	HE 156 - 2500 mg/mL CHL: 156-1250 mg/mL. ME: 625-1250 mg/mL EE :625-2500 mg/mL	*C. albicans strains F01, F02,F03,F08, F11,F14,F22,F23,F27,UFPEDA 1007*	ME showed the best activity which inhibit cell division and able enhance the action of fluconazole
[49]	*Corymbia intermedia*	Australia	Stem and leaves	AQE	500 µg/mL,	*C. albicans*	• 80% AQEt of *S. glomulifera* was the most active. • The leaves of *S. glomulifera* contain antibacterial components: α-pinene, aromadendrene and globulol, eucalyptin, and compounds betulinic acid, oleanolic acid-3-acetate and ursolic acid-3-acetate
	Lophostemon suaveolens				125 µg/mL		
	Syncarpia glomulifera				31 µg/mL		
[50]	*Ocimum basilicum*	Italy	-	Essential oils	0.09 - 4.58 mg/mL	*C. albicans* *C. famata*	• *T. vulgaris* and *O. vulgare* essential oils showed the best activity against all the tested pathogens. • Rich in monoterpenes, carvacrol and thymol, there together can completely block ergosterol synthesis and making porous the membrane • *S. sclarea* showed no antifungal effect
	Origanum vulgare				0.018 - 3.6 mg/mL		
	Salvia sclarea				No activity		
	Thymus vulgaris				0.09 – 1.87 mg/mL		
	Illicium verum				0.19 - >19.5 mg/mL		
[51]	*Plumbago rosea*	India	-	Plumbagin	5 µg/mL	*C. albicans ATCC2091,* *C. tropicalis clinical isolate* *C. parapsilosis clinical isolate*	Show antifungal activity by disrupting biofilm.
[52]	*Scabiosa arenaria*	Tunisia	Flowers, fruits, stems, leaves and roots	BA	0.02 mg/mL	*C. ATCC reference strains,* *C. albicans ATCC 90028,* *C. glabrata ATCC 90030,* *C. krusei ATCC 6258,* *C. parapsilosis ATCC 22019.*	• Show antifungal activity. • Present of oleanolic acid and luteolin-7-*O*-glucoside show good antimicrobial effect.
[53]	*Bersama abyssinica,* *Embelia schimperi,* *Ocimum lamiifolium,* *R. steudneri* *R. nepalensis* *Z. scabra*	Ethiopia	Leaves and roots	EE	512 mg/mL 512 mg/mL 512 mg/mL 512 mg/mL 512 mg/mL 512 mg/mL	*C. albicans*	• 74% of the medicinal plant extracts tested exhibited antimicrobial effect against more of the 12 different microbial strains. • *E. schimperi*, *O. lamiifolium*, and *R. steudneri* was found to be the most promising plants against microbes.

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[54]	*Euphorbia paralias L*	Tunisia	Stems and leaves	CHL	0.015 – 5 mg/mL	*C. albicans ATCC 90028*	Could be great potential as new antimicrobial agents.
[55]	*Eucalyptus globulus*	Brazil	Purchased	Essential oil (EO) Nanoemulsion (NE)	0.219 mg/mL 0.7 mg/mL	*C. albicans* *C. tropicalis* *C. glabrata*	• Nanoemulsion was more efficient for two of the three *C.* species when compared to free oil. • EO-NE protect the components through nanoencapsulation and increase of the contact area due to the reduced size of the nanoemulsion may favor antibiofilm activity.
[56]	*Cyclopia intermedia*	South Africa	Purchased	AQ ME fermented AQ	150 mg/mL 7.5 mg/mL 150 mg/mL	*C. albicans. ATCC 10231;*	ME show most effective against *C. albicans*
57]	*Erythrina stricta Roxb.*	India	Stem bark	DCM EtOAc n-Hexane	7.8 mg/mL 125 mg/mL 125 mg/mL	*C. albicans.*	Both show significant antifungal activity against *C. albicans.* Present flavonoids and phenolics
[58]	*Matricaria recutita*	Egypt	-	Pharmacopeia (PhEur) grade essential oil	160 to 320 µg/mL.	*C. albicans ATCC 90028*	• Combination of essential oil with fluconazole and nystatin showed synergic inhibitory effects. • Show the best when combining to tetracycline.
[59]	*Piper hispidum*	Brazil	Leaves	Crude extract	62.5 mg/mL	*C. albicans, C. parapsilosis C. tropicalis.*	Show antifungal activity against *C. albicans,* by inhibition biofilm formation. Presents antimicrobial properties of chalcones
[60]	*Justicia glauca*	USA	Leaves	Green synthesis of gold nanoparticals (AuNPs) extract	12.5 ± 0.3 (µg/mL ± SD)	*C. albicans*	NPs greatly increased *J. glauca* against *C. albicans* by interference with growth-signaling pathway inside the cell via modulating tyrosine phosphorylation of growth essential peptides substrate
[61]	*Funtumia africana*	South Africa	Leaves	Isolated methyl ursolate HE CHL	Methyl ursolate: 63-µg/mL HE:40 µg/mL CH:80 µg/mL	*C. albicans ATCC 10231*	• CHL show strongest synergistic activities with methyl ursolate low toxicity which may support the use of this plant. • Antimicrobial and anti-inflammatory activities of the crude extract provide some support for the traditional use of the plant.
[62]	*Pappea capensis*	South Africa.	Leaves	HE DCM EtOAc BA extracts	0.39 - 0.78 mg/mL	*C. albicans*	Show antifungal activity
[63]	*Equisetum hyemale*	Japan	Stems	Crude extract DCM EtOAc	6.5 - 52.4 mg/mL	*C. albicans* *C. kefyr* *C. geochares* *C. krusei*	Show antifungal activity and negligible cytotoxicity. It contains epicatechin and β-carotene-linoleic acid

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[64]	*Croton limae*	Brazil	Leaves	Essential oil	>1024 (mg/mL)	*C. albicans ATCC 40006 C. krusei ATCC 2538 C. tropicalis ATCC 40042*	• Show antifungal activity against *C. albicans,* however antagonist effect was seen when combine with benzoyl-metronidazole. • Cedrol, eucalyptol, a-pinene, b-pinene and linalool may be responsible for the antibacterial activity
[65]	*Citrus sinensis*	USA	Peels	Essential Oils	1.68 µg /mL	*C. albicans C. tropicalis C. glabrata C. guilliermondii, C. lusitaniae,*	• Moderate activity • Can be used in oral hygiene products • Less toxic alternative to amphotericin B.
	Citrus latifolia				0.4 µg /mL		
[66]	*Haplophyllum tuberculatum* (Forssk.) A. Juss.	Tunisia	Leaves, stems	Essential oils	0.30 mg/mL	*C. albicans ATCC 90028; C. glabrata ATCC 90030; C. parapsilosis ATCC 27853 C. krusei ATCC 6258.*	• Effective and has potential to prevent cancer development. • Significant correlation existed between the concentrations of the essential oils. • Antifungal activity may be attributed to R-(+)-limonene, S-(−)-limonene and octanol.
[67]	*Camellia sinensis (L.) O Kuntze*	Brazil	Leaves	Green tea	16-33 µg/mL	*C. albicans ATCC 14053 C. albicans ATCC 64548 C. krusei ATCC 6258*	• Antifungal activity was highest in black tea> green tea >white tea • Suggesting no direct relationship with the concentration of total phenols.
				While tea	16-135 µg/mL		
				Red tea	>270 µg/mL		
				Black tea	16-33 µg/mL		
[68]	*Leucaena leucocephala*	Malaysia	Leaves	ME	3.15 - 25.0 mg/mL	*C. albicans C. tropicalis*	• Significant antifungal activity through inhibition of cell proliferation and induced apoptosis in MCF-7. • Contained condensed tannins and phenols.
[69]	*Trametes hirsuta Trametes gibbosa Trametes versicolor*	Serbia	Dried mycelia and fruiting bodies	EE	32.0 mg/mL	*C. albicans BEOFB 811m C. krusei BEOFB 821m C. parapsilosis BEOFB 831m*	Showed low antifungal potential in comparison with ketoconazole.
[70]	*Artemisia herba-alba*	Jordan	Aerials	Essential oils	1.25 mg/mL	*C. albicans ATCC 10231 C. parapsilosis ATCC 90018 C. tropicalis ATCC 13803*	Show antifungal and anti-inflammatory activities and without detrimental effects. Revealed an important inhibitory effect on germ tube formation
[71]	*Avicennia marina*	U.A.E.	-	EE	-	*C. albicans SC5314*	*L. inermis* and *P. oleracea* showed significant anti-C. activity and against biofilm formation Lower cytotoxicity and higher selectivity indices, both plant extracts represent promising area of future research.
	Fagonia indica				-		
	Lawsania inermis				10 µg/mL		
	Portulaca oleracea				10 µg/mL		
	Salvadora persica				25 µg/mL		
	Asphodelus tenuifolius				-		
	Ziziphus spina-Christi				-		

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[72]	*Aster yomena*	Korea	Aerial	ME and Isolated compound apigenin (AP)	ME: - AP: 2.5 µg/mL	*C. albicans ATCC 90028*	ME show no antifungal effect. Only isolated apigenin has the antifungal activity.
[73]	*Artemisia vulgaris* *Biden pilosa* *Sphagneticola trilobata*	Brazil	Leaves	Essential oils	100 µg /mL 64 µg /mL 100 µg /mL	*C. albicans ATCC14057* *C. glabrata ATCC2301* *C. krusei ATCC6258* *C. parapsilosis ATCC22018*	All three are able to inhibit the growth of the C. genus yeasts. Differences in the contents of the chemical components in the essential oils significantly influence antifungal activity action.
[74]	*Muntingia calabura L.*	Philippines	Stem and dried leaf	EE	Leaf: 0.625 mg/mL Stem: 2.5 mg/mL	*C. albicans*	Show antifungal activity. Presence of sterols, flavonoids, alkaloids, saponins, glycosides and tannins
[75]	*Ixora megalophylla*	Thailand	Leaves stems	Petroleum ether (Pet), EtOAc EtOH	Leaf Pet:1250 mg/mL EtOAc:78 mg/mL EtOH:156 mg/mL Stems Pet:1250 mg/mL EtOAc:78 mg/mL EtOH:78 mg/mL	*C. albicans*	EtOAc extract from the leaves and the EtOAc and EE from the stems possessed antifungal activities.
[76]	*Siegesbeckia orientalis*	China	-	EE, petroleum ether fraction (PE-SO), EtOAc, BA and water fraction (WE-SO).	EE:2.50 µg/mL PE-SO:4.0 µg/mL EtOAc :1.25 µg/mL BA:2.50 µg/mL WE-SO:2.50 µg/mL	*C. albicans* ATCC 1023	EE showed the strongest antimicrobial, antioxidant and cytotoxic activities.
[77]	*Berberis lycium Royle*	India	Roots	Berbarine (BE), ME HE AQ	BE:41.6 ± 18.04 mg/mL ME: 187.5 ± 62.5 mg/mL HE: NA AQ: 8 mg/mL	*C. albicans* SKUAST- TAM-1	Pure berberine found more effective than crude extract, followed by methanolic and aqueous extracts.
[78]	*Calamus leptospadix Griff.*	India	Shoots	Saponin	80 mg/mL	*C. albicans* MTCC 3007	Significant amount of saponin possesses antimicrobial properties.
[79]	*Sapindus saponaria L.*	India	Trees	Hydro alcoholic extract	390-1560 µg/mL	*C. albicans* *C. glabrata* *C. tropicalis* *C. parapsilosis*	Show antifungal activity by acting on cell membrane causing cell lysis within 60min.
[80]	*Ziziphus nummularia*	India	Leaves	Zinc oxide nanoparticles (ZnO NPs) and leaf extract	>10mg/mL NP: 1.25mg/mL	*C. albicans* ATCC2091 *C. glabrata* NCIM3448	ZnO NPs exhibited very good antifungal activity, even better than standard antibiotic Amphotericin B attributed to the small size of synthesized ZnO NPs.
[81]	*Juniperus communis*	Portugal	Mature berries	Essential oils	0.039-0.16 %	*C. albicans* ESAB.	• Against all the tested organisms, support the use of traditional medication usage of this species. • Inhibited by morphological changes in the cell membrane. Also, antimicrobial activity may due to monoterpenes, such as terpinen-4-ol and 1,8-cineol.

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[82]	*Artemisia judaica L.*	Jordan	Aerial	Essential oil	1.25 µg/mL	*C. albicans* ATCC 10231 *C. parapsilosis* ATCC 90018 *C. tropicalis* ATCC 13803	• Significantly inhibited germ tube formation and disrupted preformed biofilms of *C. albicans.* • It contains piperitone, camphor and ethyl cinnamate
[83]	*Ipomoea procumbens*	Brazil	Leaves, stem and roots	Hydro-methanol extracts	>250 µg/ /mL	*C. krusei* *C. parapsilosis* *C. albicans*	X
[84]		Brazil	Leaves	Essential oil	4,096 µg/mL.	*C. albicans* *C. krusei* *C. tropicalis*	• The oil caused the inhibition of *C. albicans* and *C. tropicalis* by disrupting morphological transition. • Related to selena-1,3,7(11)-trien-8-one and selina-1,3, 7(11)-trien-8-one epoxide,
[85]	*Cinnamomum verum*	Iran	Leaves and bark	Essential oils	125 to 175 mg/mL	*C. albicans* *C. Tropicalis* *C. Krusei* *C. Glabrata* *C. Parapsilosis* *C. Famata.*	Could be applied as supplementary agents along with conventional antifungal drugs.
	Caryophillium aromaticus				700 to 1000 mg/mL		
	Artemisia dracunculus				1000 to 2000 mg/mL		
	Origanum vulgare				173 to 350 mg/mL		
	Cymbopogon citratus				125 to 175 mg/mL		
[86]	*Baccharis trinervis (Lam.)*	Brazil	Aerial	Essential oil	X	*C. albicans,* *C. Parapsilosis* *C. Tropicali*	X
[87]	*Sedum sediforme*	Turkey	-	Petroleum ether (PE), AC ME	PE:8 ± 0.4 µg/mL AC:1 ± 0.2 µg/mL ME:1±0.3 µg/mL	*C. albicans*	• ME most active one. • Contains 4 phenolic acids (protocatechuic acid, p-coumaric acid, caffeic acid, and chlorogenic acid and flavonoids(quercetin)
[88]	*Mentha piperita*	Saudi Arabia	Aerial	Essential oil	1.50 ± 0.16 mg/mL	*C. albicans ATCC 26790*	• Show significant antifungal activity and potential to perform better an amphotericin B. • Presence of high menthol and menthone components.
[89]	*Curcuma aeruginosa* Roxb	Thailand	-	Essential oils	250 mg/mL	*C. albicans ATCC 90028*	• Major components are oxygenated monoterpenes, 1,8- cineole and camphor
	Curcuma glans K. Larsen						
	Curcuma cf. xanthorrhiza Roxb						
[90]	*Thymus vulgaris*	Iran	-	ME	68 µg/mL	*C. albicans ATCC10231*	• *C. Zeylanicum* show better antifungal activity compared to other. • Antifungal activity may due to eugenol, cinnamic aldehyde, saponin, alkaloid and flavonoid.
	Caryophillim aromaticus				48 µg/mL		
	Echinophora platyloba				27 µg/mL		
	Allium cepa				75 µg/mL		
	Cinnamomum zeylanicum				18 µg/mL		

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[91]	*Cuminum cyminum* *Salvadora persica*	Iran	Seeds	Alcoholic extract	578 mg/L 4.9 mg/mL	*C. albicans ATCC 14053* *C. dubliniensis ATCC CD60, C. glabrata ATCC 90030* *C. krusei ATCC 6258* *C. parapsilosis ATCC 22019.*	• Both show strong to moderate activity. • *C. cyminum* characterized by high amounts of a-pinene, limonene and 1,8-cineole.
[92]	*Paeonia lactiflora*	USA	Roots	EE	49 mg/mL 196 mg/mL	*C. albicans SC5314* *C. albicans ATCC 18804*	Show antifungal activity associated with cell membrane integrity and permeability on (1.3)- β-D-glucan synthase.
[93]	*Isodon flavidus (Hand. -Mazz.)*	China	Twigs and leaves	Crude extract	62.5 mg/mL	*C. albicans.*	Show antifungal activity *Fladin A and lophanic acid* can breakdown the formed biofilm of *C. albicans*.
[94]	*Rubus idaeus*	France	Ripe and unripe fruits	n-hexane, EtOAc BA	> 1000 µg/mL	*C. albicans* *C. glabrata* *C. parapsilosis.*	• HE and EtOAc have significant anti-adhesion activity against *C. albicans* • Contains high condensed tannins.
[95]	*Pogostemon heyneanus* *Cinnamomum tamala* *Camphor*	India	Leaves	Patchouli essential oil	0.6-1 mg/mL 0.6 mg/mL 1 mg/mL	*C. albicans ATCC-90028* *C. Glabrata MTCC 6507* *C. Tropicalis MTCC 310*	Inhibited the key virulent property of *C. Albicans*, the transition from yeast cells towards hyphal formation of *C. Albicans.*
[96]	*Pluchea dioscoridis*	USA	Leaf	EE	30 mg/mL	*C. albicans strains*	Exhibited high antifungal activity which cause changes in phospholipase, hemolysin, and secreted aspartyl proteinase gene expression could completely collapse the yeast cell and inhibit the growth.
[97]	*Equisetum telmateia*	Iran	Aerial	Superfical fluid extraction (SFE), cold maceration (CM) and Fractionation extracts (F)	SFE:32 mg/mL MC&F: >128 mg/mL	*C. albicans*	• SFE method show more appropriate for extraction against *C. albicans*. • Antimicrobial attributed to the phenolic substances identified such as catechin, kaempferol derivatives and p-OH-benzoic acid.
[98]	*Pogostemon cablin*	India	Purchased	Patchouli essential oil (PC, PH and PP)	PC: NA PH:25 mg/mL PP:50 mg/mL	*C. albicans*	• PH exhibited better antifungal activities than the other two.
[99]	*Succisa pratensis*	Poland	Leaves or flowers	ME	0.11 mg/mL	*C. albicans* *T. mentagrophytes*	• Show antifungal activity. • The compounds 10-(acetylmethyl) -(+), 3-carene, methyl linolenate, hexadecanoic acid, pentacosane, hexacosane, heptacosane and thymol having strong antimicrobial activity.
[100]	*Tritomaria quinquedentata (Huds.)*	China	-	Crude extract	>128 mg/mL	*C. albicans wild strain SC5314 and four mutant strains DSY448, DSY653, DSY465, DSY654*	Show antifungal activity

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[101]	*Citrullus colocynthis*	Iran	Fruits	Hydroalcoholic extracts	1.56 -12.5 mg/mL	*C. albicans*	Show antifungal activity
[102]	*Salvia rhytidea Benth(Mint)*	Iran.	-	ME.	3.125 to > 100 mg/mL	*C. albicans* *C. glabrata* *C. tropicalis* *C. krusei* *C. parapsilosis* *C. Lusitania* *C. guilliermondii*	Show antifungal activity
[103]	*Allium hushidari, Allium sativum*	Iran	-	Essential oil	0.25- 2 mg/mL	*C. albicans*	• Show antifungal activity. • Antimicrobial activity is related to alkaloids, tannins, saponins, flavone and glycosides.
[104]	*Laserpitium spp.*	Macedonia	Roots and rhizomes	Extract	1.25 mg /mL	*C. krusei*	• Inhibition of biofilm. • Major components are isomontanolide, laserpitine and montanolide. All showed a more pronounced effect than fluconazole.
[105]	*Anthemis nobilis, Foeniculum vulgare, Simmondsia chinensis, Nigella sativa, Trigonella foenumgraecum, Gadus morhua, Mentha piperita, Syzygium aromatic, Zingiber officinale*	Egypt	Purchased	Essential oils	Fennel oil :0.78% Others: NA	*C. albicans ATCC 10231* *C. Glabrata* *C. tropicalis*	• Fennel essential oil had significantly higher antifungal activities compared with other tested. • Fennel essential oil alone or in combination with fluconazole could provide a promising approach in management of vulvovaginal candidiasis.
[106]	*Cocos nucifera*	Brazil	Purchased	NaP	6.25 µg/mL	*C. albicans* *C. glabrata,*	• Exhibited high antifungal activity against pathogenic *Candida* spp. • The nano-capsules formulations prolonged storage, and increased photostability of clotrimazole and prolonged drug release.
[107]	*Lycium barbarum*	Romania	Leaves	Phenolic oil	0.031-0.062 mg/mL	*C. albicans ATCC 10231,* *C. parapsilosis ATCC 22019*	• Show antifungal activity. • The leaves contain higher amounts of chlorogenic acids and flavonoid glycosides.
[108]	*Garcinia xanthochymus*	Brazil	Fruits	Xanthochymol and garcinol, isoprenylated benzophenones	1 to 3 µg/mL	*C. albicans*	• Show antifungal activity and can also potentiate the activity of fluconazole. • inhibited development of hyphae and subsequent biofilm maturation, inducing cell death
[109]	*Spondias tuberosa*	Brazil	Leaves	HE	2.0 mg/mL	*C. albicans URM 5901, from ungual scales*	• Show antifungal activity by disrupting cell membrane. • It contains flavonoids, hydrolysable tannins, saponins, terpenes and unsaturated fatty acids

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[110]	*Holothuria scabra, Holothuria parva, Holothuria leucospilota*	Iran	-	Crude extract	NA	*C. albicans ATCC 10231*	X
[111]	*Glycyrrhiza glabra*	Spain	Rhizomes and roots	Phenolic extract	>1.5 mg/mL	*C. glabrata, C. parapsilosis C. albicans.*	X
[112]	*Myracrodruon urundeuva*	Brazil	Bark	EE	4-512 µg/mL (topical)	*C. albicans C. krusei C. tropicalis*	Show antifungal activity which contains flavonoids and tannins.
[113]	*Ficus elastica* Roxb. ex Hornem.	Cameroon	Aerial roots	ME	4.9 µg/mL;	*C. albicans*	ME show antifungal activity. The most active antimicrobial components are elastiquinone and ficusosid
[114]	*Daucus virgatus (Poir.) Maire*	Tunisia	Aerial	EtOAc ME	625 µg /mL	*C. albicans*	Exhibited moderate activity
[115]	*Pistacia vera L., Bronte*	Italy	Hulls	Essential oil	2.5-5 mg/mL	*C. albicans ATCC 64550 4 clinical strains of C. albicans,*	Show antifungal activity.
[116]	*Anisophyllea laurina R. Br. ex*	Guinea	Pulp seed	ME EE	500-1000 µg/mL	*C. albicans*	Both ethanol and methanol are very effective to extract phenolics and show antifungal activity.
[117]	*Thymus vulgaris, Citrus limonum, Pelargonium graveolens, Cinnamomum cassia, Ocimum basilicum, Eugenia caryophyllus*	Poland	Purchased	Essential oils	Cinnamon oil:0.002–0.125% (*v*/*v*) Others: 0.005% or less to 2.5% (*v*/*v*).	*C. albicans and 76 isolates of C. glabrata*	• Cinnamon oil is the most active against *C. albicans.* • All of the tested oils demonstrated the ability to inhibit the transition of yeast to mycelium form. Thyme, lemon, and clove oils affected cell membranes by influencing potassium ion efflux, which was not seen in the lemon oil. • No synergistic interactions between antifungal drugs; possible synergism was between amphotericin B and geranium oil.
[118]	*Lippia sidoides Cham*	Brazil	Purchased	Essential oil	156 and 312 µg/mL	*C. albicans ATCC 64548*	• Show antifungal activity against *C. albicans*
[119]	*Mentha piperita*	Brazil	Purchased	Essential oil	1.875 µg/mL	*C. albicans* INCQS 40277 *C. tropicalis* ATCC 28707	Show antifungal activity and inactivate potentially spoilage yeasts in fruit juices through disturbance of different physiological functions in yeast cells.
[120]	*Hippophae rhamnoides L*	Poland	Twigs and leaves	Extract	250 mg/mL (twig), 31.5 mg/mL (leaf)	*C. albicans, ATCC 10231 fluconazole-sensitive* and *clinical, C. glabrata G1*	Significant antifungal activity by inhibited morphogenesis such as germ tube and hyphae formation.
[121]	*Paeonia lactiflora*	Korea	Root	EE	196 µg/mL	*C. albicans, ATCC 188040 C. albicans KCCM 50235*	EE show good inhibitory effects against biofilm formation by impeding cell adhesion and obstructing the morphological transition of hyphae. Also inhibited the cell wall synthesis and damages cell membrane functions which lead to cell swelling and lysis.

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[122]	*Psidium guajava*	Brazil	Leaves	AQ and Hydroethanolic extract	>8192 mg/mL	*C. albicans* *C. tropicalis*	X
[123]	*Kedrostis africana*	South Africa	Dried tubers	AcE AQ EE	Ac:0.312 mg/mL Aq: >5 mg/mL Eth:0.325 mg/mL	*C. albicans ATCC 10231*	• Show antifungal activity. • The flavonoid, proanthocyanidin and total phenolic concentrations were higher in AcE compared to the aqueous and EE.
[124]	*Eucalyptus microcorys*	Australia	Leaves	AQ	1250 µg/mL.	*C. albicans ATCC 10231*	• Show antifungal activity and was found to be a good source of TPC, TFC, proanthocyanidins and saponins.
[125]	*Psiadia punctulata (DC.)* Vatke	Saudi Arabia	Leaves	Extract	50 µg/mL	*C. albicans.*	• Show antifungal activity against *C. albicans.* • Isolated 3′,4′,5,7-tetramethoxyflavone, displayed the ability to reduce biofilm formation of *C. albicans* by 90%
[126]	*Camellia sinensis* (L.) O Kuntze	Korea	Seed	Green tea seed extract	938 µg/mL	*C. albicans ATCC 10231*	• Active compounds: theasaponin E1, assamsaponin A and assamsaponin B • GTS extract can be used as a safe and strong natural anti-yeast.
[127]	*Psidium guajava*, *Psidium browniannum* Mart. Ex DC	India	Leaves	Hydroethanolic extracts	8,192 µg/mL,	*C. albicans* *C. tropicalis strains*	• Show antifungal activity against *C. albicans* and are effective on potentiating the effect of fluconazole. • Presence of phenols, flavonoids and tannins.
[128]	*Murraya koenigii (L.) Spreng*	India	Leaves	Hydrodistillate essential oil	12.5-100 µg/mL	*C. albicans strain MTCC 3017*	Show antifungal activity against *C. albicans* inhibited by the compound mk309
[129]	*Melaleuca alternifolia*	-	-	Essential oils	0.25-2% v/v	*C. albicans ATCC 10231,* *C. glabrata,* *C. tropicalis,* *C. parapsilosis* *C. krusei,* *C. guilliermondii,* *C. lusitaniae,* *C. dubliniensis,*	• All strains show antifungal activity • Peppermint oil demonstrated the lowest antifungal activity.
	Mentha piperita				0.03-0.25% v/v		
	Thymus vulgaris				0.25-2% v/v		
	Syzygium aromaticum				0.06-0.25 % v/v		
[130]	*Combretum erythrophyllum*	South Africa	Leaves	AQ AcE DCM HE	1.25 mg/mL	*C. albicans*	• Antifungal activity followed by AQ > AcE >DCM> HE • Provide some indication for the traditional use of the plant.
[131]	*Strychnos spinosa Lam.*	Nigeria	Leaves	AcE ME DCM	1.25 or >1.25 mg/mL	*C. albicans ATCC 10231*	Show antifungal activity and support the traditional use of this plant as treatment of infectious.
[132]	*Aloe trigonantha L.C. Leach*	Ethiopia	leaf latex	Aloesin, 8-O-Methyl-7-hydroxyaloin	400 µg/mL.	*C. albicans ATCC 10231*	Show weak antifungal activity

(Table 3) Contd….

Refs.	Plant/Organism	Country of Origin	Plant Part(s)	Formulation	MIC (mg/mL, mg/mL)	Used Strains	Conclusion
[133]	*Nigella sativa* *Murraya koienigii* *Trachiyspirum ammi* *Piper betel*	India	Leaves	Hydro-steam distilled essential oils	15.62 µg/mL 250 µg/mL	*C. albicans MTCC-183, C. tropicalis MTCC-184, C. glabrata MTCC-3019*	Ajwain and Black Cumin leaf oils showed better antifungal activity by inhibition of cell membrane synthesis, specifically by extracting the sterols from the membrane or inhibiting steroid synthesis.
[134]	*Carpolobia lutea*	Nigeria	Leaves	EE ME AQ HE	25 mg/mL	*C. albicans*	• EE show significant antifungal effect. • Both AQ and HE show no inhibitory effect.
[135]	*Zuccagnia punctata Cav.* *Larrea nitida Cav.*	Argentina	Aerial parts	DCM	27.33-31µg/mL	*C. albicans* *C. glabrata*	• Show antifungal activity. *ZpE-Ln*E have synergistic effect, support the proper joint use of both antifungal herbs in traditional medicine.
[136]	*Tetraglochin cristatum (Britton) Roth*	Argentina	Leaves and aerial	Hydroalcoholic dry extract	12.5 and 25 µg/mL	*C. albicans 144783, 134333, 2089; C. glabrata 031646, 042030, 031982; C. tropicalis 1841;*	• Show antifungal activity and give support to their traditional use for treating infections. • It contains hydrolysable and condensed tannins
[137]	*Satureja Khuzistanica*	Iran	Aerial	EE	299.4 mg/mL	*C. albicans ATCC 10231* *C. albicans ATCC 66506 a*	Show synergistic effect with amphotericin B and ketoconazole, while this extract had no effect on clotrimazole activity.
[138]	*Alchemilla vulgaris L.*	Serbia	Root	ME	>20 µg/mL	*C. albicans ATCC 10259,*	X
[139]	*Ferula assa-foetida*	Iran	oleo-gum-resin	Essential oil	0.19 (0.12-0.25) µg/mL	*C. albicans CBS 5982, 1905 and 1949*	Show remarkable antifungal activities
[140]	*Thymus vulgaris*	Brazil	Leaves	Extracts	50 mg/mL	*C. albicans ATCC 18804, S. aureus ATCC 6538*	Show antifungal activity by acting on the biofilm formation. It contains thymol, carvacrol, linalool, geranoil, citral, tannins, organic acids, flavonoids, minerals.
[141]	*Eugenia leitonii, Eugenia brasiliensis, Eugenia myrcianthes Eugenia involucrate*	Brazil	Leaves pulps seeds barks	Dry extracts	Barks: 15.62 ->2000 µg/mL *E. leitonii* (seed) :15.62 µg/ mL) *E.brasiliensis*(leaf) :31.25 µg/ mL *E. brasiliensis* (seed) :5.62 µg/ mL	*C. albicans ATCC 90028*	The seeds of *E. leitonii* and the seeds and leaves of *E. brasiliensis* were found to have strong antifungal activity against *C. albicans* by acting on mature biofilms. However, Bark show no antifungal effect. Phenolic compounds epicatechin and gallic acid were the major constituents in the extracts.

Abbreviations: *-: Not specified/Not available, *X: No antifungal effect.; *ME: Methanolic extract, * AC: Acetone extract, *AQ: Aqueous extract, *AQE: Aqueous ethanolic extract; *EtOAc: Ethyl acetate extract, * EE: Ethanol extract, *Dichloromethane extract: DCM , *HE: Hexane extract, *CHL:Chloroform extract , *BA: butanol extract, *NaP: Nanoparticles/Nano formulation.

The most common source types investigated were the aerial parts of the plants. Methanolic and ethanolic extractions exhibited higher antifungal efficacy, amongst other extracts. A total of 30 articles investigated the mechanisms of the herbal extracts against *C. albicans,* which they exert antifungal effects through inhibiting biofilm formation, hyphal transformation, germ tube inhibition; alteration of membrane potential and permeability; disrupting transcription, cell division and inhibition of virulence factors.

Overall, the presented evidence shows that natural products may be employed effectively as an alternative therapy against *C. albicans*. Among the tested plants, common plants with a long history and well-known beneficial effects such as

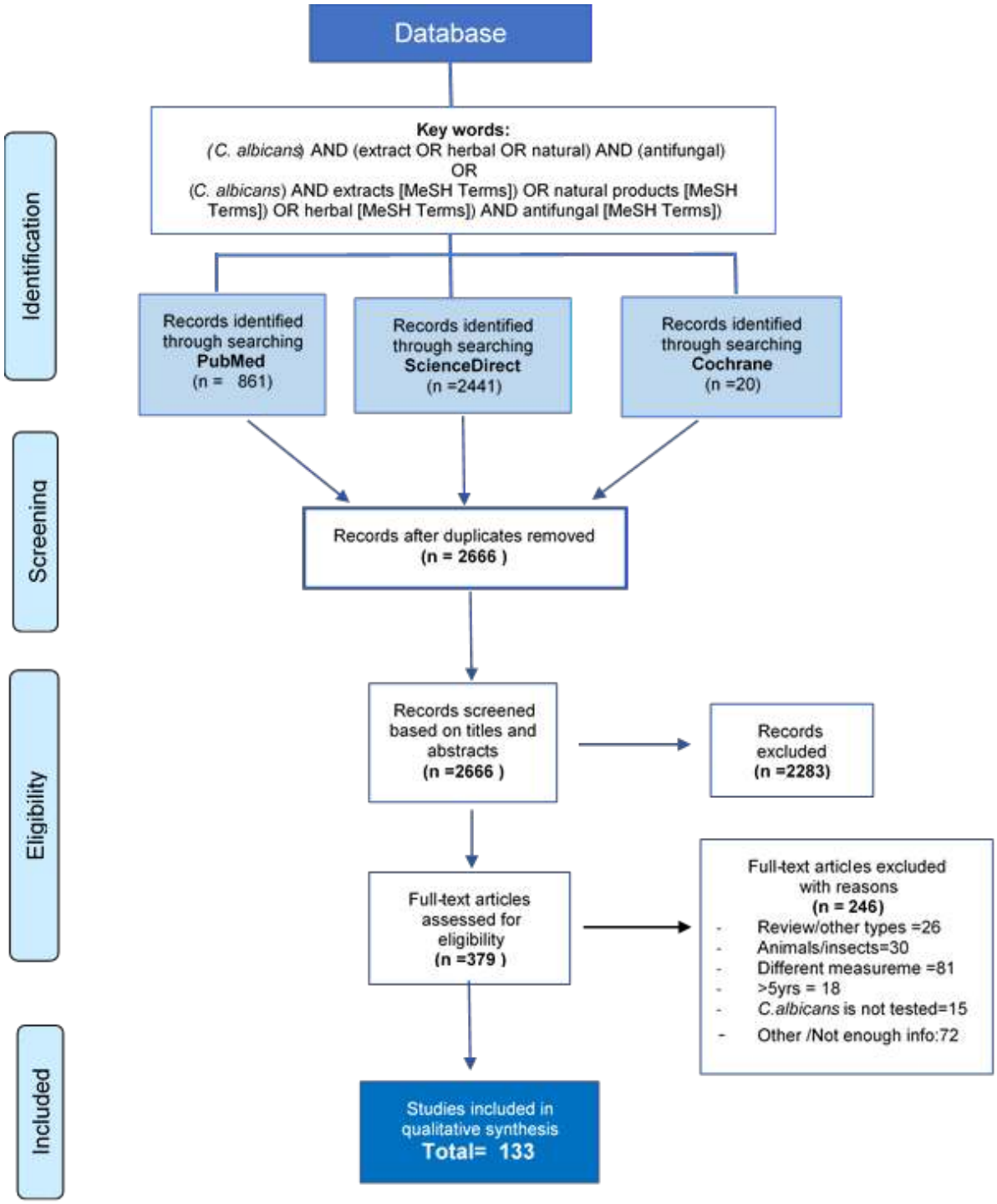

Fig. (1). Flowchart of search strategy and study selection procedure. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

tea (*C. sinensis*), tea tree oil (*M. alternifolia*), cinnamon (*C. verum*), cumin (*C. cyminum*), henna (*L. inermis*), mint (*M. piperita*), and thyme (*T. vulgaris*), whose antifungal activity was confirmed in several studies of this review, support the traditional use of these plants. Furthermore, several novel natural herbs have been discovered as potential adjunctive treatments against *C. albicans.*

3.2. Herbal Interventions *In Vivo*

When investigating the *in vivo* effects of herbal extracts on *C. albicans,* 9 articles that matched the search criteria with a total of 11 plants were examined (Table **2**). Most studies used rats as the host organism by infecting them with *C. albicans* in which, only *Vicia faba* and *Morinda tomentosa* show no antifungal activity against *C. albicans* [12, 14]. The

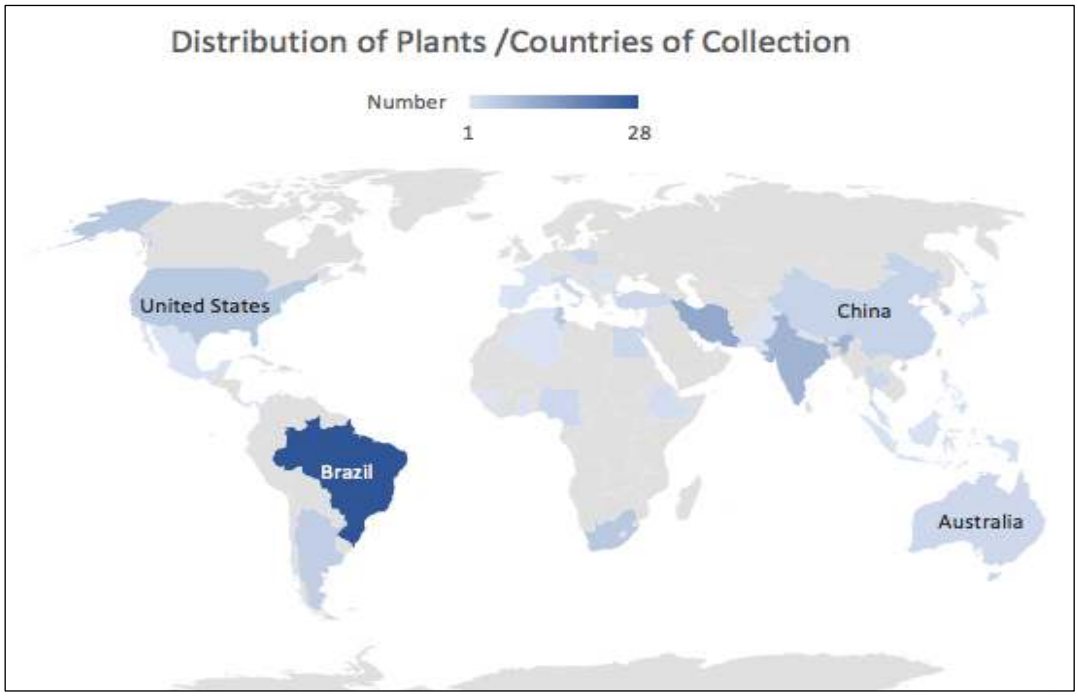

Fig. (2). Distribution of the geographical locations of the origins of plants cited in this review, per source country. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

most active plants were *C. sinensis* with MIC values of 40 µg/mL [13]. Topical applications of 4% *L. innermis* show similar or better effect than clotrimazole and *Mitracarpus frigidus* presents antifungal activities greater than fluconazole against candidiasis [11, 16]. *M. alternifolia* inhibited biofilm formation [15] *Syzygium cumini* and *Jatropha curcas,* which contained a high amount of phenols and flavonoids are responsible for the inhibitory effect against *C. albicans* [17, 19]. Nano-formulations of the seeds of *S. cumini* exhibited an improved antioxidant activity of the plant extract as compared to other formulations [17]. When comparing all the *in vivo* herbal interventions, *L. innermis* and *M. alternifolia* seem to have the most significant antifungal activity with the MIC values as low as 5-10 mg/mL *in vivo* and CFU value 5.33 Log_{10} [10, 15]. Nano formulations of all seven herbal extracts that were included in this review (*P. graveolens*, *Eucalyptus globulus, Justicia glauca*, *Ziziphus nummularia*, *Pogostemon cablin* and *Cocos nucifera*) demonstrated increasing plants properties and better antifungal effects than traditional extraction methods (Tables **2** and **3**).

3.3. Herbal Interventions *In Vitro*

Table **3** summarizes the herbal interventions *in vitro*, where 122 studies were included explaining the effects of 175 herbal interventions [20-141]. Most of the herbal extracts examined demonstrate activities against *C. albicans* in which, the most active were *C. sinensis*, *Citrus sinensis*, *Citrus latifolia, C. nucifera*, *Ficus elastica* Roxb. Ex Hornem, *M. piperita* , *Garcinia xanthochymus, M. alternifolia, P. graveolens, Siegesbeckia orientalis, Sedum sediforme* and *L. inermis* with MIC values ranging from 0.0945 µg/mL to 10 µg/mL. A total of 25 natural extracts were ineffective against *C. albicans*. Twelve articles assessed the synergistic effect of herbal extracts with antifungal drugs in which, *M. alternifolia*, *Buchenavia tetraphylla*, *Foeniculum vulgare*, *G. xanthochymus*, *P. guajava, Psidium brownianum* Mart. ex DC and *Satureja khuzistanica* showed a synergistic effect with fluconazole. *Matricaria recutita* showed an additive effect with nystatin and fluconazole. *P. graveolens* showed synergism with amphotericin B. *S. khuzistanica* potentiated the effect of amphotericin B and ketoconazole. However, five tested extracts, which are *T. vulgaris, Citrus limonum, Cinnamomum cassia*, *Ocimum basilicum* and *Eugenia caryophyllu* showed little or no enhancement. The antagonist effect of *Croton limae* with benzoyl metronidazole was observed.

Three herbal interventions demonstrated greater antifungal effect than common antifungal drugs in which, *Z. nummularia* presented better antifungal activities over Amphotericin B, due to the incorporations of synthesized zinc nanoparticles that help to enhance plant properties [80]. The presence of isomontanolide, leserpitine and montanolide in *Laserpitium* species exhibited a more pronounced effect than fluconazole by inhibiting the hyphae and subsequent biofilm maturation [104]. In a study of the aerial parts of *M. piperita,* the MIC value of the extracts (1.5 µg/mL) [88] was smaller than the Amphotericin B (MIC: 5 µg/mL), implying that it has the potential to perform better antifungal activities than the synthetic drugs.

3.4. Preparation of Herbal Extracts

Differences in parts of plants extracted and extraction methods on the same plant greatly influenced its antifungal activities. In the study of *Piper guineense,* the fruits and leaves were prepared in five different extracts. Among these, aqueous extraction shows no inhibitory effect, while methanolic

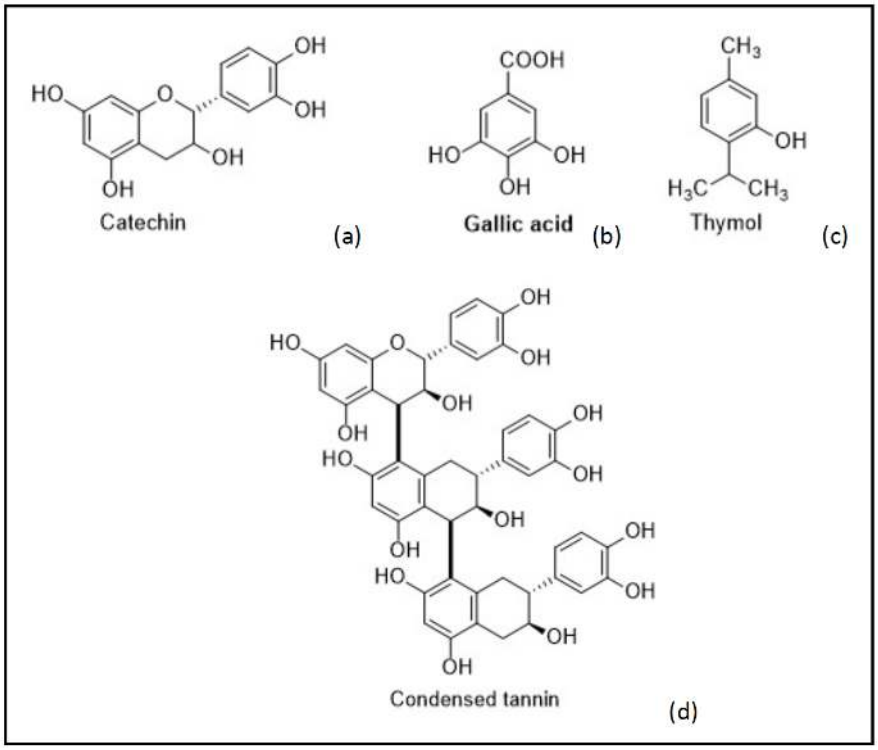

Fig. (3). Chemical structures of (**a**) Catechins, (**b**) Gallic acid, (**c**) Thymol, and (**d**) condensed Tannins, as described in the systematic review.

extracts present the most significant activity with MIC of 39 µg/mL and the rest with MIC of 78 µg/mL [24]. In another study investigating Leguminosae family species, the authors examined the leaves of 8 plants which were prepared in both methanolic and ethanolic extracts, showing that *Withania somnifera, Echinophora platybola* and *Zingiber officinale* demonstrated better effect in ethanolic extracts, while *Curcuma longa* and *Pogostemon parviflorus* present better effect in methanolic extracts [28]. Another study, using hexane and chloroform extracts of the leaves of *B. tetraphylla,* exhibited significantly greater inhibition as compared to ethanolic and methanolic extracts [48]. It appears that it is difficult to generalise and select an extraction method that preserves the greatest activity of the plant extract that is valid for all plants. It is equally difficult, given the range of plant types and parts used in the studies, to generalise about the specific part of a plant, which would give the highest concentration of the active substance. It can, therefore, be concluded that the extraction method and selection of the part of the plant to be used must be individualised on a plant-by-plant basis.

However, when comparing common extraction methods such as methanol and aqueous extracts with nano-formulated extracts, the use of nanotechnology greatly improves the plant's properties and the antifungal effects remain active for a longer period of time. The increase in antifungal activity may be attributed to its small size (200nm), which may activate the passive transport mechanism across the cell membrane. The study of *P. graveolens*, revealed that nano-formulations of geranium oil (MIC: 1.82 µg/mL) are twice as active as crude extracts (MIC: 3.64 µg/mL) and the former are sufficiently active to reduce the amount of biofilm on catheters [117]. The nanoparticles protect the components through nanoencapsulation and increase the contact area due to the reduced size of the formulations, which improves anti-biofilm activity. In the study of *J. glauca* against *C. albicans,* the nanoparticles greatly inhibited bacterial growth by interfering with the growth-signaling pathway inside the cell *via* modulating tyrosine phosphorylation of growth essential peptides substrate [60]. In addition, in the study of *C. nucifera*, the nano-capsule formulations exhibit favourable properties after 60 days of storage and in prolonged drug release [106].

Several studies have examined the significant antifungal effects of these herbs more than once, which are S. persica, C. sinensis, C. verum, E. uniflora, L. inermis, M. alternifolia, M. piperita, P. lactiflora, P. graveolens, S. cumini and T. vulgaris. Two studies [71, 91] revealed that S. persica (MIC: 25 µg/mL and 4.8mg/mL) had strong to moderate activity against different pathogenic Candida species. Both use the alcoholic extraction methods and the results are in accordance with each other.

Three studies demonstrated the activity of *C. sinensis* [13, 58, 118] in which, the leaf extracts (MICs ranging from 16-135 µg/mL) exhibited higher antifungal activities than the seeds (MIC: 938 µg/mL). Also, studies revealed that green and black leaves present better activities than white and red tea leaves, which may be due to different fermentation methods. What's more, a higher percentage of catechins are found in green tea leaves, which are well known for their antioxidant activity. Catechins are reducing agents or chelating metal ions, which are able to inhibit both DNA damage and lipid peroxidation, ultimately cause membrane integrity [142]. The final study showed that *C. sinensis* was effective

both *in vivo* and *in vitro* against *C. albicans* [13]. All three studies demonstrate a significant effect of tea tree against *C. albicans.*

When comparing two studies using cinnamon [37], the aerial parts of the plant with the MIC values of 31.25 to 62.5 μg/mL exhibited greater fungicidal effects than the leaves and bark (MIC: 127-175 μg/mL) [95]. Both studies revealed the importance of cinnamaldehyde and cinnamaldehyde dimethyl-acetate against microorganisms. In other studies, all five studies investigating *T. vulgaris* exhibited significant antifungal activities of this plant against *C. albicans* [50, 91, 118, 129, 140]. The results demonstrated the importance of thymol as an active agent inhibiting biofilm formation, promoting high cell viability, having anti-inflammatory effects and presenting no genotoxicity [140].

3.5. Active Compounds

Phenolic compounds have been studied extensively of their wide range of antioxidants and beneficial effects on the human body for decades. In this systematic review, numerous active compounds have been identified to be active against *C. albicans.* Compounds that stand out for their marked antifungal activity include phenols such as gallic acid, thymol, and flavonoids (especially catechin – Fig. **3a**), polyphenols such as tannins, terpenoids and saponins.

Gallic acid is a trihydroxybenzoic acid with antioxidant, anti-inflammatory, and antimicrobial properties (Fig. **3b**). In this review, four articles reveal the antifungal effectiveness of gallic acid [17, 31, 46, 141]. Particularly in the study of *Cochlospermum regium*, it has been demonstrated that the antifungal mechanism of gallic acid is either by binding to ergosterol on the cell membrane that leads to pore formation or by distrusting the enzymes responsible for the ergosterol synthesized, thereby causing membrane damage [32].

Thymol (2-isopropyl-5-methylphenol) isomeric with carvacrol (Fig. **3c**) is the main monoterpene phenol isolated from plants belonging to the *Lamiaceae*, *Verbenaceae, Scrophulariaceae, Ranunculaceae*, and *Apiaceae* families. It has been used for treatment due to its antioxidant, anti-inflammatory, local anaesthetic, antinociceptive, antiseptic, antibacterial, and antifungal effects as well as for their beneficial effects on the cardiovascular system [143]. The studies of *T. vulgaris* and *Succisa pratensi* revealed that thymol is able to block ergosterol synthesis and ultimately caused pore formation in the membrane [49,99].

Tannins (Fig. **3d**) are known for their potent antioxidant, cytotoxic and antimicrobial activities. The study of *Ricinus communis* suggests that the potential fungicidal activity occurs by the targeting of surface-exposed adhesins, cell wall polypeptides and membrane-bound enzymes of the fungal cell. The proposed mechanism involves complex formation between tannins and flavonoids with nucleophilic amino acids in proteins, leading to the inactivation of the proteins and loss of function. The methanolic extracts show greater antifungal effective over aqueous and ethanolic extracts, due to the higher preservation of the tannins, flavonoids and terpenoid compounds in the extracts. In this systematic review, tannins were found to be present and showed antifungal activity in 11 herbal extracts [18, 31, 47, 75, 95, 104, 109, 113, 128, 136, 140].

Saponins are phytochemicals, which can be found most in peas, soybeans and herbs. In this review, multiple studies reveal the potential antifungal activities against *C. albicans* in the presence of saponins [40, 41, 75, 79, 80, 91, 104, 110, 125, 127]. However, in this review, the detailed mechanisms of action of saponins have not been well investigated. Previous research demonstrated that saponin is able to interfere with sterols, leading to inhibition of yeast-hyphal transition and biofilm formations [144].

Flavonoids are metabolites widely present in most vegetables, particularly green and red vegetables. Traditional and local communities used these plants due to their anti-inflammatory, antioxidant, anti-depressant and anti-infective effects. The mechanism of action has not been elucidated completely, even though it is believed to interfere with the cell wall and/or the ergosterol synthesis [145]. In this present review, several articles exhibited the importance of flavonoids in against microorganisms [17, 19, 21, 31, 40, 43, 47, 58, 75, 88, 91, 108, 110, 113, 124, 128, 140]. In the study of *S. cumini,* stating that plants containing high flavonoids were found to have strong inhibitory effects on the formation and metabolic activity of *C. albicans* biofilms or planktonic cells [40]. Catechin is a flavan-3-ol type natural phenol commonly found in oolong and green tea. Its anti-oxidant, anti-hypertensive, anti-inflammatory, anti-proliferative, anti-thrombogenic, and anti-hyperlipidemic activities have been clearly illustrated through various *in vitro* and *in vivo* studies. It was found that catechin can induce the generation of reactive oxygen species (ROS). ROS are implicated in the disruption of molecular mechanisms such as angiogenesis, extracellular matrix degradation and have been shown to lead to cell apoptosis [146]. The antifungal effect of catechins is demonstrated across several of the articles included in this review, all supporting the role played by catechin as an antifungal against *C. albicans* [47,68,98,141]. In addition to catechin, green tea seeds extract contain theasaponin E1, assamsaponin A and assamsaponin B, all of which were active against *C. albicans* and may have applications in food preservation against yeast contamination [127].

Terpenoids**,** sometimes called isoprenoids, can be found in the leguminous plant, turmeric and mustard seed. In this review, a number of investigations report that plant extracts like *Helichrysum* and *Juniperus communis* containing terpenoids exhibited antifungal activity against *C. albicans* [22, 31, 45, 82, 90, 110]. The proposed mechanism of action is that terpenoids have a fungistatic effect on *Candida* by modulating specific signaling pathways (TOR pathway or calcium signalling), rather than by creating nonspecific membrane lesions. The result of this is the alteration of gene transcription and stasis [147].

Other similar active compounds have been identified, such as g-terpinene and 1,8-cineole in *Lavandula binaludensis and C. cyminum* [37,91]*;* 5-O-methyllatifolin; epilupeol acetate in *Ficus drupacea L.* [42]; α-pinene, aromadendrene, globulol, betulinic acid, oleanolic acid-3-acetate and ursolic acid-3-acetate present in *S. glomulifera, C. cyminum and S. persica* [49]*;* a-pinene, limonene and 1,8-cineole, oleanolic

acid and luteolin-7-*O*-glucoside in *Haplophyllum tuberculatum* (Forssk.) A. Juss. [66]; vepicatechin and β-carotene-linoleic acid in *Equisetum hyemale* [63]*;* and selena-1,3,7(11)-trien-8-one in *E. uniflora* [63]. Further studies are required in order to characterize their antifungal activity against *C. albicans,* since their mechanisms of action are not yet well established.

2.6. Strengths

Only clinical studies, clinical trials and RCTs are included in this systematic review in order to reduce experimental bias. Most trials used placebos or standard antifungal agents in the control group. Overall, the majority of herbal interventions reviewed indicate the antifungal effect and the major bioactive compounds responsible for the antifungal activity against *C. albicans.*

2.7. Limitations

This systematic review highlights the lack of consensus and standardization of MIC values defining the strength of antifungal activity specifically for *C. albicans*. Each investigator and study determine its own scale regarding what is significant inhibition and what is not. For example, the studies of *Glycyrrhiza glabra (*MIC:1500 µg/mL) and *Rhaphiodon echinus* (MIC:1024 µg/mL) are reported inactive [111, 46], on the contrary, in the case of *M. tomentosa* with MIC value as low as >32 µg/mL is considered ineffective by the investigator [14]. However, in general, most authors considered MIC values below 100 µg/mL as significant; between 100-1000 µg/mL as moderate; and above 1000 µg/mL as inactive.

The majority of studies utilized methanolic and ethanolic extracts, whereas other extraction methods such as aqueous, hexane, ethyl-acetate, acetone and dichloromethane. Other formulations studies used essential oils. Some drawbacks of essential oils have been identified, such as chemical complexity, high volatility, susceptibility to degradation and oxidation, insolubility in aqueous systems and low bioavailability [148]. These characteristics hinder their direct use of products, although all studies established the extraction process and methods thoroughly and in detail. Several factors, like temperature, pH, particle size and solvent, may affect the outcomes.

Furthermore, the difference in concentrations, quantities, incubation time and treatment duration are not equivalent, which will greatly influence the outcomes and make it difficult to compare. Most of the *in vitro* studies are incubated mostly for 24 hours; however, in some studies, it may extend to 48 to 72 hours, allowing the formation of the biofilm. The incubation temperatures range from 30-37ºC, and a variety of culture methods are used across the studies, for example, agar, microwell, and sabouraud dextrose agar plates. As for the treatment duration, *in vivo* studies using *C. sinensis* and *M. alternifolia,* the mice were treated for 5 days, whereas, in the study using *S. cumini,* the rats were treated for 21 days [13, 15]; and the treatment period was 2 weeks in the study of *Astragalus membranaceus* [18]. Several herbal and extraction solvent concentrations were used in which it can be postulated that a longer period of treatment and higher concentrations could lead to an overestimation of positive outcomes.

The parts of the plants collected are also different such as bark, roots, leaves, flowers, hulls and seeds. A difference in concentrations used between *in vivo* and *in vitro* studies could lead to variation in response mechanisms towards the extracts. One drawback relates to this review is that majority of the studies were the very first study of examining the activity of the extracts or in the early phase of trials. Several studies did not illustrate the antifungal mechanisms and active components. Another concern is that the safety measure of the studies and their potential interactions with other drugs were not investigated. Further studies are needed to ensure the effectiveness, determine the mechanisms of action as well as efficacy, safety and intrinsic toxicity of the active compounds *in vivo*. During the data collection process, only English studies are included; therefore, language bias could be another restriction of this study.

CONCLUSION

The results show that a wide range of plant extracts are able to inhibit C. albicans *in vitro*. The most active extracts were *M. alternifolia, Cit. sinensis, C. latifolia, C. nucifera, F. elastica Roxb. Ex Hornem, M. piperita, G. xanthochymus, P. graveolens, Sedum sediforme, L. inermis* and *S. orientalis*. The least active extracts were *R. echinus*, and *G. glabra*. The most active extract *in vivo* was *C. sinensis*.

The most common source types investigated were the aerial parts. Most plants with methanolic and ethanolic extraction exhibited high antifungal efficacy, amongst others. This could be due to the increased solubility of non-polar compounds in such solvents [151]. The most crucial components that have proved to have antifungal activities were the phenols such as gallic acid, thymol, and flavonoids (especially catechin), polyphenols such as tannins and terpenoids. The incorporation of nanotechnology shows promising results in the use of natural compounds against bacterial infections.

LIST OF ABBREVIATIONS

DNA	=	Deoxyribonucleic acid
RNA	=	Ribonucleic acid
BCE	=	Before Common Era
CFU	=	Colony Forming Units
MIC	=	Minimum Inhibitory Concentration
TTO	=	Tea Tree Oil
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

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