Plant-Derived Natural Antifungal Agents: Evaluation of *Candida species* Susceptibility in a Comprehensive Review

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Abstract
This comprehensive review examines the antifungal activity of natural plant extracts against *Candida species* (Candida spp.), especially with their increasing resistance to conventional drugs like azoles and echinocandins. The research includes an analysis of active plant compounds such as terpenoids, phenols, alkaloids, and flavonoids, and their mechanisms of action, including cell membrane disruption, inhibition of biofilm formation, and induction of oxidative stress. It also discusses the variation in sensitivity among different species, with a particular focus on *C. albicans*, *C. glabrata*, and *C. auris*, and the importance of standardized laboratory testing. The research addresses drug synthesis strategies, and toxicological and pharmacokinetic considerations, emphasizing the need for safety evaluation and standardization to promote the use of plant-based alternatives in the face of resistant fungal infections.

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1. Introduction

The genus Candida encompasses around 200 yeast species, with *Candida albicans* historically regarded as the most clinically significant due to its wide host distribution, pathogenicity, and the associated economic burden of candidemia (Martins *et al*., 2015) [39]. As member of the human microbiota, C. albicans is primarily a commensal organism, although it can colonies mucosal and integumentary surfaces or the gastrointestinal tract. In susceptible immunocompromised individuals, however, C. albicans becomes the leading cause of opportunistic fungal infections. The non-albicans species C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei also have considerable clinical relevance, particularly with the emergence of multi-drug-resistant Candida auris (Zubair Alam & Sajjad Ahmad Khan, 2021) [65]. *Candida glabrata* exhibits significant intrinsic tolerance to various antifungal agents, contributing to treatment failure when combined with echinocandins, and C. krusei has intrinsic resistance to fluconazole. C. auris infections rarely respond to conventional treatment modalities. Antifungal resistance mechanisms have been elucidated for C. albicans and C. glabrata both individually and collectively. Increasing isolation of the remaining species coupled with similar cross-species resistance mechanisms highlights a greater need to explore the activity of plant-derived antifungal compounds against clinically relevant Candida spp. and to synthesis whatever data is available. (Duggan & Usher, 2023; Chedraoui *et al*.2025) [17, 12]

The conventional antifungal armamentarium comprises polyenes (nystatin, amphotericin), azoles (fluconazole, voriconazole, itraconazole), echinocandins (caspofungin, anidulafungin, micafungin), pyrimidines (5-fluorocytosine), and allylamines (terbinafine), each targeting distinct cellular pathways and showing low cross-resistance. However, many antifungal agents can affect ergosterol biosynthesis but lead to organism resistance and therapy failure. Plant-derived antifungal agents are rarely detected; establishing the antifungal activity of selected phytochemicals may simultaneously address this oversight and guide future research aimed at broader-spectrum non-synthetic antifungals. (Vanreppelen *et al*., 2023; Adewole *et al*., 2026) [61, 2]

1.1. Rationale and scope

The prevalence of hospital-acquired candidiasis has alarmingly increased in the last two decades, making *Candida species* one of the principal pathogens responsible for mycoses in immunocompromised patients. The major *Candida species* associated with candidiasis include C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, and C. krusei, with resistance to the most widely used echinocandins, fluconazole, and voriconazole reported in all species but C. parapsilosis (Martins *et al*., 2015) [39]. *Candida species* can exploit multiple virulence strategies to adhere and form biofilms on health-care devices, which are periodic reservoirs for pathogens that can lead to systemic candidiasis. The markedly reduced susceptibility of different *Candida species* to several drugs has led to an increase in research on plant-derived antifungal agents, particularly chosen for emerging clinical glut of resistance (Hadano *et al*.2022) [24].To date, numerous plant-derived and synthetic compounds have been screened against *Candida species*. Extensive literature on propolis and others continues to surface covering this important area in the effort to curb an expected lethal Candidiasis epidemic (Felipe *et al*., 2017) [16].

1.2. Overview of *Candida species* and clinical relevance

Candida species are ubiquitous yeasts that play a dual role as commensals and pathogens in humans. Their commensal status is marked by a sustained presence on epithelial substrates in healthy individuals. Nevertheless, they can also have pathogenic attributes, leading to opportunistic infections that mainly affect immunocompromised patients. These infections range from mucosal forms to systemic forms considered among the most life-threatening healthcare-associated infections. Several species, including the traditionally neglected non-albicans *Candida species*, are now recognized as second to C. albicans among yeast pathogens. The distribution of opportunistic Candida closely mirrors the utilization of antifungal agents, with an increase in C. glabrata and a notable spread of azole-resistant C. parapsilosis in specific settings. Molecular epidemiology studies have revealed a low clonal diversity of C. albicans linked to the assessment of the global spread of candidemia. Despite significant advances in antifungal therapy, the mortality rate for candidemia remains unacceptably high because resistance can arise to all antifungal classes and pathogens become adept at evading host defenses. The high mortality rate linked to candidemia is also a major driver behind the search for alternative therapies (Rezazadeh *et al*., 2016) [50] ; (Gómez-Gaviria *et al*., 2022) [22].

1.3. Traditional and contemporary antifungal modalities

The antifungal arsenal includes various single compounds, plant extracts, and pharmaceutical drugs. Yet, increasing drug resistance highlights a need for novel approaches. Antifungal resistance is on the rise globally; *Candida species* are becoming increasingly resistant to first, second, and even third-line antifungal agents (Zubair Alam & Sajjad Ahmad Khan, 2021) [65]. The emergence of biofilm-forming species and their inherent or acquired resistance to antifungal drugs, notably Candida auris, constitutes a worldwide challenge (Herman & Przemysław Herman, 2021) [25]. Alternative solutions against Candida are actively pursued to fill the gaps caused by resistance, including phytocompounds and other sources. Increasing demand for natural plant-based antifungals, without significant side effects, opposes synthetic molecules (Chayachinda *et al*.2024) [11].

Potentially antifungal plant-derived compounds are abundant and include terpenoids, alkaloids, flavonoids, tannins, phenolics, and nitrogen-containing components. The present review critically evaluates the antifungal efficacy of plant-derived compounds against *Candida species*, reporting their minimum inhibitory concentrations, minimum effective concentrations, and cross-resistance considerations. (Kurhaluk *et al*., 2025; Babu and Banu2025) [31, 7]

2. Phytochemical Classes with Antifungal Activity Against Candida

Plant pathogenic fungi pose a threat to food production and security worldwide. Among the fungal genera, Candida accounts for several species that have since invaded various plant compartments including stems, leaves, and fruits of numerous plants worldwide. Even though there are numerous commercial broad-spectrum and narrow antifungal compounds, sensitivity has not only been realized in plants but also in human beings due to widespread and indiscriminate use. The fungal genus and species remain a significant threat to human health prompting the search for sensitive plant-derived antifungal agents. Plant-derived antifungal phytochemicals have been shown to have a broad-spectrum or multiple action antifungal activity against various human and plant-pathogenic fungi. The most abundant secondary metabolites in plants and a wide range of antifungal phytochemicals have been shown to be both sensitive and inhibit the growth of various *Candida species*. Plant essential oils receive considerable attention from the scientific community and even the pharmaceutical industry due to their large composition of bioactive phytochemicals that exhibit either fungicidal or fungistatic activity against mycelia and spores of various pathogenic fungi (Martins *et al*., 2015) [39]; (Yue *et al*.2024) [63]; (Dantas *et al*., 2025) [15]

2.1. Terpenoids and essential oil constituents

Plant-derived natural antifungal agents offer a promising alternative to conventional agents, as *Candida species* show variable sensitivity to plant-derived antifungal agents. The antifungal activity of over 40 plant-derived compounds from 12 distinct phytochemical classes against 13 *Candida species* was evaluated. (Esmaeili *et al*., 2025) [18] Terpenoids and essential oil constituents, the most widely studied class of plant-derived antifungals, exhibit activity against clinically relevant *Candida species* including C. auris, the most concerning emerging Candida pathogen. Comprehensive *in vitro* susceptibility data on *Candida species* were compiled from over 28 independent studies using standardized protocols, facilitating cross-species comparison. Seven *Candida species* (C. albicans, C. auris, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, and C. auris) were identified as conforming to the epidemiological cut-off criteria established for the application of a clinical break point (Zapata-Zapata *et al*., 2022) [64].

2.2. Phenolics and polyphenolic compounds

Phenolics and polyphenolic compounds are widespread secondary metabolites produced by plants. They are classified by the number of aromatic rings in their structure and the degree of hydroxylation of the rings. Monophenolic (e.g. phenolic acids) and diphenolic (e.g. flavonoids, tannins) groups are the simplest and most abundant. Other types include triphenolic compounds, stilbenes, and lignans. The

structure–activity relationship of phenolic compounds against *Candida species* generally indicates that the presence of a hydroxyl group and a phenolic ring is essential for antifungal activity (Martins *et al*., 2015) [39]. Natural extracts and derivatives such as gallic, caffeic, cinnamic, benzoic, protocatechuic, and phenylacetic acids have shown activity against *Candida species* and, depending on the type and quantity of phenolic acid in the extract and the extraction method employed, can impart stronger antifungal effects than other phenolic acids (Teodoro *et al*., 2015) [49]. Hydroxycinnamic acid derivatives exhibit lower minimum inhibitory concentrations against *Candida species* than hydroxybenzoic acid derivatives, with some exceptions. Notable examples include the extract of Alibizia myriophylla, isolonchocarpin, and albicanyl caffeate, which possess pronounced antifungal activity against C. albicans. Other virulence factors modulated by phenolic compounds include hyphal and germ tube formation and biofilm development. (Tahri *et al*.2022) [57]; (Mohamed & Hassabo, 2026) [42]

2.3. Alkaloids and nitrogen-containing phytochemicals

Many species of plants contain a variety of bioactive molecules known as secondary metabolites. Alkaloids and nitrogen-containing phytochemicals are groups of six or more classes of secondary metabolites containing nitrogen, which plays a major role in the growth and physiological activities of living organisms. These compounds are widely distributed in the plant kingdom (Martins *et al*., 2015) [39]. Interest in pharmacologically active alkaloids has been growing in recent decades, revealing their important phylogenetic and ecological roles in meso- and macroevolution (Rajput and Karuppayil, 2013) [5]. Phytochemicals with reported antifungal activity against *Candida species* are included. (Gizaw *et al*., 2022) [21]

Cinchona-derived alkaloids exhibit antifungal activity against *Candida species*. Quinine and quinidine have been studied for their anti-Candida effects. Quinine inhibited growth in a wide variety of *Candida species* and the MIC values ranged from 250 to 500 μg/ml. Quinine combined with conventional antifungals increases their activity against Candida infections. Although significantly less potent than quinine, quinidine is also an option to treat some Candida infections. A steroid alkaloid compound called pseudo-pregnane- androst-3,5-diene has been isolated from the leaves of the medicinal plant Lilium candidum, has antifungal activity and an MIC 0.01–0.05 mg/ml against *Candida albicans* (Sung & Lee, 2026) [56]

2.4. Flavonoids, tannins, and lignans

Flavonoids, tannins, and lignans represent yet another group of important plant-derived antifungal agents against *Candida species*. The strong antifungal activity of flavonoids can be attributed to their aromatic ring and hydroxyl substituents, which seem to play major roles in their activity (Alves *et al*., 2014) [58]. Many flavonoids, such as apigenin, daidzein, epicatechin, hesperetin, hesperidin, naringenin, and quercetin, have been shown to possess antifungal activity. Tannins, such as the gallic acid derivative prepared from the bark of Quercus infectoria and the catechin oligomer from Vaccinium angustifolium, and lignans, such as pinoresinol and red cedar oil, also exhibit good antifungal activity (Al Aboody and Mickymaray, 2020) [52].

3. Mechanisms of Action Against *Candida species*

Candida species represent a diverse group of fungi, some of which have become significant pathogens with diverse virulence traits. Various naturally occurring substances, ranging from essential oils to plant extracts, exhibit antifungal activity against these species. An analysis of these plant-derived antifungal agents points toward a number of species of Candida that are increasingly problematic. These same analyses further reveal patterns of susceptibility to widely used plant-derived antifungal agents such as thymoquinone, carvacrol, and eugenol (Martins *et al*., 2015) [39]. Among the mechanisms of action implicated in the activity of plant-derived antifungal agents against Candida spp., several appear particularly prominent. The first involves the disruption of cell membrane integrity through interference with ergosterol biosynthesis or direct interaction with the membrane lipid bilayer; these actions impair membrane integrity, as indicated by the leakage of intracellular constituents. A second mechanism entails inhibition of biofilm formation and maturation, with agents affecting either the initial adherence of yeast to the surface or subsequent maturation stages. Biofilm formation is a major factor in the persistence of Candida infections. Agents further induce oxidative stress by elevating the intracellular levels of reactive oxygen species; these compounds also trigger the expression of apoptosis-like markers, leading to cell death. Finally, the modulation of virulence factors may play a role; plant-derived antifungal agents can impair properties such as adherence, dimorphic transition to hyphae, and the production of hydrolytic enzymes (Santos *et al*., 2018) [10]

3.1. Cell membrane disruption and ergosterol interference

Many of the described plant-derived antifungal agents enhance cell membrane permeability, allowing the leakage of intracellular material such as ATP, casein, and cytoplasmic ions (Rajput and Karuppayil, 2013) [5]. Since the cell membrane is vital for the survival of C. albicans, agents disrupting membrane integrity or interfering with ergosterol biosynthesis are expected to exhibit antifungal activity. Compounds that interfere with ergosterol include eugenol, anisaldehyde, methyl eugenol, and flavonoids such as epigallocatechin-3-gallate. The primary sterol in both mammalian and plant cells is cholesterol, whereas the ergosterol pathway is unique to fungi (Martins *et al*., 2015) [39]. Ergosterol synthesis resistance mechanisms include the alteration of the target site involved in the sterol biosynthetic pathway; however, structural modifications of the target site have been reported. Various agents with high scarcity have shown effects on the ergosterol biosynthetic pathway in fungal and mycelial systems and are being considered for renewed investigation. (Li *et al*., 2023) [32]

3.2. Inhibition of biofilm formation and maturation

Suppression of Candida biofilm formation and subsequent maturation is observed for plant-derived agents that interact with ethanol-Cinnamaldehyde, Eugenol, Fennel, Oregano, and Thyme oils, Alpha-terpineol, Menthol, and Thymol. All act either in the initial phase or throughout the whole biofilm lifecycle, thus preventing or mitigating microbial persistence. Any biofilm intervention during development is clinically relevant because quiescent organisms within biofilms escape killing by antifungal therapies and host defence (Butassi *et al*., 2021) [9].

3.3. Induction of oxidative stress and apoptosis-like pathways

The antifungal activity of plant-derived agents contributing to *Candida species* susceptibility is often linked to the induction of oxidative stress and the triggering of apoptosis-like pathways (Kaloriti *et al*., 2014) [27]. Elevated levels of reactive oxygen species (ROS), such as hydrogen peroxide, superoxide anions, hydroxyl radicals, and singlet oxygen can severely compromise overall fungal cell viability. The persistence of ROS levels above a threshold value can prompt yeast cells to enter an irreversible apoptotic-like death program, leading to the activation of various downstream markers. These markers include phosphatidylserine exposure, mitochondrial membrane depolarization, cytochrome c release, caspase-like activity, and DNA fragmentation. Such cell death pathways can also follow exposure to conventional antifungal agents. Induction of apoptosis-like cell death often accompanies the arrest of the cell cycle, frequently at the G1 phase; the inhibition of DNA replication; and the inhibition of the activity of critical components of the mitogen-activated protein (MAP) kinase pathways involved in cell cycle regulation. (Li *et al*., 2025) [32]; (Abubakar *et al*., 2026) [1]

3.4. Modulation of virulence factors

The virulence behavior of *Candida species* manifests in various ways: the ability to adapt to different environments (morphological changes), the secretion of hydrolytic enzymes, pH sensing and regulation, metabolic adaptation, resistance to environmental stress, expression of heat shock proteins, and scavenging of metal ions (Martins *et al*., 2015) [39]. A prominent virulence strategy is to modulate the cell cycle of macrophages that engulf the fungus and delay their division, thereby restraining the immune system response (Lone and Ahmad, 2020) [3]. These capabilities enable *Candida species* to exit the commensal phase, survive in the host and establish opportunistic infections. C. glabrata, C. parapsilosis and C. tropicalis share epidemiological and pathogenic traits, whereas C. krusei and C. auris have a broad distribution, intrinsic resistance and limited treatment options. The inhibition of virulence factors must also be taken into account for a full evaluation of susceptibility profiles. (Chew *et al*., 2023) [13]; (Gabaldón, 2024) [20]

4. Susceptibility Profiles of *Candida species* to Plant-Derived Agents

The antifungal susceptibility of different *Candida species* to plant-derived natural agents has been studied extensively (Martins *et al*., 2015) [39]. An overview of the available data is presented below, with individual *Candida species* arranged in order of their clinical relevance and global distribution. (Martins and Silva, 2023) [38]. The broadest range of antifungal activity was observed with terpenoids, essential oils, and alkaloids. Resistance to plant-derived agents has been documented, with chemical indexing indicating a capacity for cross-resistance to certain antifungals. (Osorio *et al*.2026; Pradhan *et al*.2026) [45, 48]. *Candida glabrata* Plant-derived agents demonstrated antifungal activity against *Candida glabrata* within a MIC range of 0.06 to 2500 µg/mL and an MEC range of 0.006 to 1250 µg/mL. However, the maximum observed MIC of 2500 µg/mL indicates the potential for extreme tolerance among certain agents. The low MEC values suggest the corresponding opportunity for cross-resistance to other antifungals in formulations with limited Candida activity (Esmaeili *et al*., 2025) [18]. *Candida tropicalis* Plant-derived agents also exhibited antifungal activity against *Candida tropicalis*, with reported MIC values between 0.1 and 4000 µg/mL. Multiple candidate agents have been documented (Shathan *et al*., 2026) [55]. *Candida parapsilosis* The MIC and MEC values for *Candida parapsilosis* range from 50 to >10,000 µg/mL and 25 to >50,000 µg/mL, respectively. The data indicate a general trend of elevated resistance, corroborated by a limited selection of active agents. (Floyd *et al*., 2024) [19]. *Candida krusei* a high intrinsic resistance to plant-derived antifungal agents has been documented for *Candida krusei*. The susceptibility profile obtained for this species overlaps partially with those of other *Candida species* exhibiting similar resistance. (Gómez-Gaviria *et al*., 2022) [22]. Non- albicans Candida Increasing infections due to non-albicans *Candida species* remain a notable concern worldwide. Antifungal susceptibility data for various emerging Candida pathogens is provided to facilitate the selection of candidate agents for further investigation and to aid understanding of critical cross-species differences. (Katsipoulaki and Stapper, 2024) [28]

4.1. *Candida albicans*

Candida albicans is a common opportunistic pathogen and the crucial causative agent of candidiasis that affects humans. It colonizes mainly the gut, oral cavity, and vagina, but it can also cause intravascular candidiasis. It is associated with high mortality rates. It is commonly isolated from nosocomial infections. In the case of candidemia the patient may require central venous catheter, parenteral nutrition or broad-spectrum antibiotics among the other risk factors, which increases the chance for C. albicans infection (Rajput and Karuppayil, 2013) [5]. The major mode of action of azoles and polyene is either by interfering with the ergosterol synthesis or by binding directly to the cell membrane steroids like ergosterol. Resistance mechanisms for C. albicans against azole like fluconazole which is commonly used by many doctors for treatment are efflux of drug by Cdr1 and Mdr1 pumps present on the cytoplasmic membrane and alteration of target enzyme, Lanosterol 14 alpha-demethylase. (Katsipoulaki and Stappers, 2024) [28]

4.2. *Candida glabrata*

Candida glabrata, the second most common species of Candida implicated in clinical infections, is responsible for approximately 15% of invasive candidiasis cases in non-neutropenic patients and 37% of cases in neutropenic patients. Elevated minimal inhibitory concentration–minimal effective concentration (MIC/MEC) values have been reported against a variety of classes of compounds extracted from plant sources, indicating that C. glabrata exhibits high levels of tolerance to a diverse range of plant-derived antifungal agents. Furthermore, C. glabrata possesses the ability to develop tolerance towards azoles and echinocandins in the presence of antifungal agents, including those derived from plants. Beta-escin has been found to alleviate azole resistance in C. glabrata by affecting biofilm-associated virulence parameters. C. glabrata shows resistance to azole antifungals, making infection management challenging. Several plant extracts and polyphenolic compounds, especially flavonoids, demonstrate antimicrobial activity against C. glabrata and exhibit higher antioxidant levels than fluconazole. Among 18 polyphenols screened for activity

against C. glabrata, myricetin and baicalein inhibited the growth of all tested *Candida species*, with effects on C. glabrata surpassing those of fluconazole. At tested concentrations, other polyphenols monitored did not demonstrate antifungal activity (Aranda *et al*., 2015) [51]; (Gómez-Gaviria *et al*., 2022) [22]; (Long and Li, 2024) [35]

4.3. *Candida tropicalis*

Plant-derived antifungal agents exhibit variable activity against *Candida tropicalis*, with minimum inhibitory concentrations (MIC) ranging from 2 to 22 mg/mL, and minimum effective concentrations (MEC) from 1.28 to 17.6 mg/mL (Alam and Khan, 2021) [65]. Most of the reported antifungal activity against C. tropicalis is observed for essential oils, particularly from Melaleuca and Thymus species, and selected extracts show moderate efficacy (Khodavandi *et al*., 2018) [29]. Studies indicate that essential oils, alkaloids, terpenoids, and flavonoids from several plant species are active against C. tropicalis. Reported extracts with antifungal effects include those from Allium sativum (garlic), Allium cepa (onion), Cinnamomum zeylanicum (cinnamon), Euphorbia tirucalli (pencil tree), Fumaria parviflora (fumitory), and Glycyrrhiza glabra (liquorice). (Gómez-Gaviria *et al*., 2022) [22]

4.4. *Candida parapsilosis*

Candida parapsilosis is recognized as an opportunistic pathogen in humans, implicated in various clinical infections (Felipe *et al*., 2017) [16]. Access to microorganisms through implanted medical devices is frequent, and *Candida parapsilosis* has a remarkable ability to form biofilms, which contributes to its pathogenicity. The nascent knowledge of this fungus has directed attention to its interactions with the host immune system and its biofilm formation. The virulence factors associated with *Candida parapsilosis*, such as protease and phospholipase activities, have been under investigation. The prevention and treatment of these infections are essential since the associated risk groups include preterm neonates and immunocompromised individuals (Gabaldón, 2024) [20]

4.5. *Candida krusei*

Antifungal susceptibility profiles of *Candida krusei* strains to plant-derived agents; emphasis on intrinsic resistance (Esmaeili *et al*., 2025) [18]. The intrinsic resistance of *Candida krusei* to fluconazole limits treatment options. Susceptibility data for this species reflect a broad range of plant-derived antifungal activity; however, C. krusei possesses the highest MIC/MEC and least information is available for plant-derived agents. Essential oils from Cinnamomum cassia, Cinnamomum verum, Eucalyptus citriodora, Eucalyptus globulus, and oil of thyme exhibited lower antifungal activity against C. krusei. (Yang *et al*.2024) [62]
In a study of vanillin and related aromatic aldehydes, C. krusei displayed a relatively high tolerance similar to that of C. glabrata. Aloe extracts from both Aloe vera and Aloe species inhibited C. krusei, but the corresponding MIC and MEC values remained in the range indicative of moderate activity. Extracts with moderate antifungal activity included Bactris gasipaes pulp oil, bovine casein, Durio zibethinus seed oil, palm oil, Ricinus communis oil, and haze oil from Pseudomonas putida TIGP, as well as pentamethylenetetramine and α-hydroxypentamethylindane. Extracts with marginal activity against C. krusei included oils from rubber, palm, mulberry, hickory, hazelnut, rambutans, redhibis, griddle, Bactris gasipaes pulp, durian skin, and diverse microbial sources. Percent inhibition values from these studies are compiled (Rezazadeh *et al*., 2016) [50]; (Rajput and Karuppayil, 2013) [5]; (Alam and Khan, 2021) [65].

4.6. Non-albicans *Candida species* of emerging concern

Non-albicans *Candida species* have emerged as significant opportunistic pathogens responsible for an increasing proportion of systemic infections. Besides C. tropicalis and C. parapsilosis, other non-albicans Candida such as C. krusei, C. auris, C. dubliniensis, C. floricola, and C. guilliermondii are also involved. The worldwide incidence of candidiasis due to C. krusei has risen sharply. Cross-resistance between fluconazole and newer triazoles (voriconazole and posaconazole) in C. krusei further complicates therapy as it has intrinsic resistance to fluconazole. C. auris, first reported in 2009, is an urgent health threat due to its multidrug-resistant profile, environmental persistence, and prompt transmission among patients (Rezazadeh *et al*., 2016) [50].
Non-albicans *Candida species* capable of acquiring antifungal resistance and evading the immune response have been given increased attention. Considerable variation in susceptibility profiles has been reported among clinical isolates of non-albicans Candida to widely used antifungals. Significant percentages of isolates resistant to fluconazole, amphotericin B, and echinocandins have been documented in C. tropicalis, C. parapsilosis, and C. glabrata, respectively. The identification of these opportunistic yeast species as clinically relevant pathogens underscores the need for ongoing surveillance of antifungal susceptibility and the exploration of new bioactive compounds to combat fungal infections. Plant-derived antifungal agents represent a promising alternative approach against some *Candida species* and efforts are ongoing to determine the range of activity, including against non-albicans Candida (Gómez-Gaviria *et al*., 2022) [22]

5. Methodological Considerations in Susceptibility Testing

Uncertainties remain in the performance of susceptibility tests for plant-derived agents against Candida spp. In the absence of frameworks supporting plant extracts, adherence to established reference methods facilitates data comparison. Research adopts two assay designs endorsed by the Clinical Standards and Laboratory Institute: the broth microdilution (Cilo and Ener, 2021) [14] and the agar dilution method (Rezazadeh *et al*., 2016) [50]. Both formats demand careful adaptation for use with extracts. Initial concentrations commonly range from 4000 to 16000 µg/mL, with no guidance on further dilutions. Analysis of individual extract susceptibility in microdilution assays shows interspecies variation, indicating agent predisposition rather than universal interpretative criteria. Consequently, a two-category system—active or non-active—guides extract evaluation across multiple species. (Nasim *et al*., 2022) [44].
Plant-derived compounds and extracts tested against *Candida species* typically lack species identification, complicating cross-study comparison. Over 70 studies document Candida plant-derived agent susceptibility, yet branching extends from only one congeneric species. Reproducibility remains intrinsically problematic, X200 sequence variation incurring alterations in chemical composition. Even standardized

commercial preparations exhibit batch to batch divergence, including—despite rigorous physicochemical evaluations readily perceptible interlot fluctuations in tea extract from a single manufacturer. Quality-assurance measures are thus paramount, yet remain under-explored in the scientific literature. Only one report provides chromatographic profiles and bioassays on multiple batches, another noting candidacidal absence and phytochemical diversity in undecaprenyl diphosphate synthase inhibitors. (Gómez-Gaviria *et al*., 2022) [22]; (Dantas *et al*., 2025) [15]

5.1. *in vitro* Assay Designs and Standards

The most widely used reference standard for broth microdilution antifungal susceptibility testing, the CLSI M27-A3 document, specifies testing conditions for the following yeast and yeast-like species: *Candida albicans*, C. guilliermondii, C. kefyr, C. parapsilosis, C. tropicalis, Cryptococcus neoformans, C. laurentii, Geotrichum capitatum, Hanseniaspora uvarum, Kluyveromyces marxianus, K. lactis, Pichia anomala, P. kudriavzevii, P. pastoris, P. stipitis, Rhodotorula glutinis, and Saccharomyces cerevisiae. Numerous studies evaluated the activity of plant extracts, oils, and essential oils against Candida spp. and other yeast based on CLSI M27. However, plant-based preparations possess a distinct nature and physicochemical properties requiring the development of dedicated methodologies, such as those defined (Cilo and Ener, 2021) [14] guidelines for herbal medicines or Endocrine Disruptor Screening Program (EDSP) (Cilo and Ener, 2021) [14]. Batches exhibit variability in composition and concentration, including uptake by complex matrices (Serrano *et al*., 2023) [53]. Establishing water solubility, pH, evaporative weight, or the presence of surfactants presents other assessment challenges (Madrid *et al*., 2026) [37].

5.2. Concentration Ranges and Interpretation of Antifungal Activity

Concentration ranges and interpretation of antifungal activity are critical for evaluating efficacy (Souza-Moreira *et al*., 2013) [36]. Methods such as ergosterol quantitation and resazurin metabolism assays are used to assess antifungal susceptibility. Studies focus on mechanisms of action, including effects on cell wall synthesis and virulence factors. Various natural products and plant extracts have been tested for antifungal activity, with some showing promising results. Standardized protocols and susceptibility testing methods are essential for consistent evaluation (Herman and Przemysław, 2021) [25].

5.3. Reproducibility and Challenges in Plant-Derived Preparations

Standardization and characterization of plant-derived antifungal agents remain particularly challenging due to the complex phylogeny and chemical variability within these organisms (Martins *et al*., 2015) [39]. The chemical composition of plant extracts may differ significantly due to cultivation techniques, climate, plant part utilized, and the precise method of extraction. These factors introduce batch-to-batch variability, complicating evaluation of antifungal activity across different studies. Reproducibility is further hampered by variation in assay design and interpretation, the lack of established pharmacopoeial procedures for plant-based agents, and the additional challenges posed when multiple active constituents are present (Herman and Przemysław, 2021) [25]. Quality-control measures, such as chemical-standardization protocols, characterization of bioactive compounds, and activity screening of raw materials and extracts, are essential to enable reliable evaluation of plant-derived antifungal agents. Ensuring the stability of bioactive compounds during storage, processing, and formulation is a further concern. Analyses that inform on active-principle identity, concentration, and stability before, during, and after extraction, together with appropriate standardization and quality-control steps, can help to establish the reliability of plant-based antifungal treatments and improve therapeutic confidence in these preparations. (Alsalih, 2025) [4]; (Muley *et al*.2026) [43]

6. Synergistic and Combination Approaches

Candida spp. show different susceptibility profiles to plant-derived antifungal agents and different cross-resistance patterns to fluconazole. Despite the need to address the limitations of current systems, *in vitro* testing of plant-derived antifungal agents on Candida is important for identification of broad-spectrum activity, activity against emerging pathogens, and the discovery of multitarget strategies that are difficult to achieve with chemically synthesized agents (Herman and Przemysław, 2021) [25]. Taking this wider perspective, an overview is provided of combinations of plant-derived antifungal agents with conventional antifungals, the possible concomitant administration of plant-derived agents, and the potential for natural product-derived hybrid compounds. Plant-derived agents identified in such action combinations include compounds that target *Candida species* at various different steps in their pathogenicity. An adjunctive approach attending to different targets within the same life cycle raises the prospects of combinatorial plant-derived strategies that could play an important role in antifungal therapy (Zapata-Zapata *et al*.2022) [64].

6.1. Plant-Derived Agents with Conventional Antifungals

The prevalence of emerging resistance also promotes interest in plant-derived alternatives that can augment existing therapies. Various plant extracts and fractions exhibit synergistic activity against resistant microorganisms when combined with standard antifungal agents. Such combinations may lower the effective doses of classical drugs and thereby reduce their associated toxicity (Herman & Przemysław, 2021) [25]. A systematic review of the scientific literature identifies 10 phytochemicals from plants that retain antifungal activity against *Candida species* even when combined with representative conventional antifungal agents. Montelukast, sulfamethoxazole, drospirenone, and ibuprofen demonstrate synergistic interactions with promising natural antifungal agents. Combination therapy may help to combat the emergence of resistance, and products of vegetable origin possessing additional health benefits would be especially favorable (Martins *et al*., 2015) [39].

6.2. Multitarget Strategies and Combinatorial Effects

Multitarget strategies and combinatorial effects. Several plant-derived natural antifungal compounds exhibit interactions with classical antifungal drugs, encompassing synergy, antagonism, and additive effects (Herman and Przemysław, 2021) [25]. Data for Candida spp. indicate low-probability synergy, common antagonism, and cases of additive action. Microscopy reveals that combinations of the

flavonoid quercetin with conventional antifungal agents exerted effects distinct from those of each drug alone on cellular morphology. Such observations support the multitarget nature of the agents' actions and the potential for combotherapy. (Long & Li, 2024) [35]; (Adewole *et al*., 2026) [2]. Antifungal plant-derived agents can act alongside conventional synthetic antifungals. Comprehensive evidence exists for combinatorial testing—plant-derived agents exhibit additive, synergistic, and antagonistic effects in combination with synthetic antifungals against Candida fungi. Multitarget action is hypothesized to underpin these observations, supported by distinct cytological changes in treated cells that differ from those resulting from plant-derived agents acting alone (Tian *et al*., 2022) [59]

7. Safety, Toxicology, and Pharmacokinetic Considerations

Plant extracts commonly garner popular support as herbal folklore, yet their inherent biochemical diversity often delineates significant cytotoxicity and pharmacological incompatibility risks (Martins *et al*., 2015) [39]. Understanding the novel pharmacodynamics of plant-derived antifungals remains paramount for realizing their potential. Bioavailability and fundamental pharmacokinetic parameters (absorption, distribution, metabolism, excretion) closely correlate to cytotoxicity, underscoring the merit of conservative dose applications. Compounds with narrower cytotoxicity profiles in anti-Candida evaluation present opportunities for synergistic combination refinement (Khwaza and Aderibigbe, 2023) [30]. The cytotoxicity of selected plant-derived compounds predominates comparatively over the host cells. The safety edge of plant-derived antifungals may extend to monitoring adverse interactions due to their natural occurrence. However, thorough scrutiny of toxicological parameters and formulation of safe dosages warrant urgent prioritization before progression toward other research phases (Torres *et al*., 2023) [60]; (Jalendiran *et al*.2026) [26]

7.1. Cytotoxicity and Selectivity Indices

Cytotoxicity and selectivity indices are important aspects of the phytochemical class with antifungal activity against Candida. Plant-derived agents have been shown to inhibit growth or viability of *Candida species* without affecting the viability of mammalian cells (Rajput and Karuppayil, 2013) [5]. Cytotoxicity assays using macrophage, mammalian, or human cell lines and a wide variety of plant-derived antifungal agents have reported CC50 values ranging from 0.78–6651 µg/mL against various Candida spp. Growth inhibition of *Candida species* reflected selective action of the extracts, with selectivity indices determined as the ratio of the CC50 to the minimum inhibitory concentration (MIC) or minimum effective concentration (MEC) (Casanova *et al*., 2015) [6]. Significant variation in selectivity indices was noted, with intrinsic permissiveness of the target species influencing the establishment of robust activity categories. Cadalene and eugenol exhibited the greatest selectivity indices against C. albicans, while garcinol, di-coumaroyl-erythritol, and γ-sitosterol displayed broad-spectrum action across several non-albicans species with selective indices greater than 200. Hexane, ethyl acetate, and methanolic extracts from several species demonstrated selective action against multiple pathogens, consolidating potentially concatenated strategies aimed at positioning plant-derived agents as promising antifungal candidates for emerging Candida pathogens (Shariati *et al*.2022) [54]. The urgent need to target biofilms helps position Cadalene, Eugenol, and Hexane Extract of Lantana Camara as particularly relevant candidates for further characterization. (Liambila, 2023) [34]

7.2. Pharmacokinetics and Bioavailability

Plant-based antifungal agents have gained attention due to the increase in resistance of pathogenic strains. Bioavailability and clinical benefits of the bioactive components in other biological systems may influence the path for development and research on the antifungals. These compounds, including essential oils, volatile oils, phenolic compounds, flavonoids, alkaloids, and terpenoids, have a wide range of pharmacological activities. There are various mechanisms by which phenolic compounds treat infections, one of which involves the inhibition of the growth of fungi and bacteria. Active components found in herbs can limit biofilm formation when used alongside antifungal agents, thereby blocking the adhesion of yeast to non-shedding collagen substrates and the oral biofilm (Herman and Przemysław, 2021) [25]. Some studies focused on the effect of bioactive components from natural sources and their combinations, including plant extracts, on drug-resistant *Candida species*. Cinnamaldehyde, eugenol, and carvacrol showed candidacidal activity against various *Candida species* (Martins *et al*., 2015) [39]. Pharmacokinetics and bioavailability of antifungal agents are vital for successful treatment of *Candida albicans* infections. Considerable differences in the pharmacokinetics of antifungal agents in clinical practice have been observed and similar pattern may occur for plant-derived antifungal agents and other antifungals (Khwaza and Aderibigbe, 2023) [30]. The variations in pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion may affect the antifungal susceptibility of plant-derived compounds on the fungi. (Pereira *et al*., 2022) [46]; (Branda *et al*., 2025) [8]

7.3. Potential Adverse Interactions and Standardization Needs

Plant-derived antifungal agents can have pharmacokinetic interactions with conventional antifungals and other medicines. For instance, bergamot essential oil can affect the metabolism of coadministered drugs that undergo cytochrome P450-mediated biotransformation and thus potentially impair antifungal efficacy (Rajput and Karuppayil, 2013) [5]. Cytotoxicity, selectivity indices, and pharmacokinetic parameters have been described for only a minority of plant-derived antifungals (Herman and Przemysław, 2021) [25]. Limited conclusions can therefore be drawn regarding their therapeutic windows, since more-selective agents with lower MIC/MEC50 values may be less suitable than those for which higher MOL/MOC50 ratios are reported (Jalendiran *et al*.2026) [26].
To be considered relevant for their use against Candida infections, the antifungal activity of plant-derived agents has to be accompanied by satisfactory bioavailability following the route of administration envisaged. Reports on plant-derived antifungal agents frequently focus on *in vitro* activity. Other critical pharmacokinetic information relating to bioavailability, distribution, metabolism, and excretion is rarely available. Candidates with characterized oral bioavailability and good systemic distribution include thymol, eugenol, and curcumin. The limited number of plant-

derived agents under investigation means that systematic characterization of their absorption, distribution, metabolism, and excretion remains urgently needed. (Alsalih, 2025) [4]; (Abubakar *et al*., 2026) [1]

8. Conclusion

The present review compiles *in vitro* Candida susceptibility data for plant-derived antifungal agents to aid knowledge transfer within the field. *Candida species* continue to pose significant clinical challenges, especially in immunocompromised individuals. Emergence of resistance to fluconazole the most widely prescribed systemic antifungal agent has been documented in several species. Combinations of plant-derived agents with conventional antifungals, multitarget approaches, and the potential use of non-albicans species such as *C. guilliermondii, C. norvegensis, and C. utilis* warrant further exploration. Plant-derived agents exhibit diverse structures, mechanisms of action, and activity spectra that could complement existing antifungal regimens and warrant comprehensive investigation. (Martins-Santana *et al*.2023; Posteraro *et al*.2025)

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