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A Comprehensive Review of Plant Based Extracts for Preventing and Controlling *Candida albicans*

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Authors' contributions

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Review Article

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ABSTRACT

A common fungal pathogen *Candida albicans* can cause infections ranging from simple mucosal infections to serious systemic illnesses especially in people with weakened immune systems. Normally found in the human microbiome it turns harmful when the immune system is weakened. Its dimorphism—the capacity to transition between hyphal, and yeast forms—is a primary factor

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contributing to its pathogenicity, and is essential for both tissue penetration, and dissemination. This transition is crucial for tissue invasion, biofilm formation, and dissemination within the host. The infection mechanism involves adhesion to host cells, biofilm formation, epithelial invasion, and bloodstream dissemination. Furthermore, *Candida albicans* may use different carbon sources to adapt metabolically increasing its survival in a variety of host environments. Recent study revealed that *Candida albicans* possesses a parasexual cycle that allows for genetic diversity without requiring sexual reproduction. Plant-based remedies have become viable substitutes for conventional pharmaceutical antifungals with benefits including a decreased chance of drug resistance, fewer side effects, and cheaper expenses. Plant extracts offer several advantages, including a reduced likelihood of resistance development, fewer adverse side effects, and lower treatment costs. In particular, herbal medicines are emerging as safer, more sustainable options for managing *C. albicans* infections. As a result, plant based treatments are becoming increasingly recognized for their role in supporting antifungal therapy and enhancing overall treatment efficacy. In treating *Candida albicans* infections, herbal medicine is becoming more and more recognized as a useful tool due to its ability to offer safer, and more sustainable treatments. This pathogen can severely reduce crop yield and quality, posing a significant threat to global food security and agricultural economies, particularly in regions where these crops are staples. This review as an attempt to study their potential to address some of the limitations of current antifungal therapies, such as toxicity and resistance against *C. albicans* makes them an important area of research.

Keywords: Candida albicans;candidiasis; dimorphism; parasexual cycle; plant extract.

1. INTRODUCTION

Based on contemporary estimates, there are 8.7 million eukaryotic species on Earth, of which fungus comprise about 7% (611,000 species) (Mayer et al. 2013). Among them,approximately 600 species of fungi are known to be harmful to humans. Fungal infections are more severe because they affect the third layer of the skin and they affect keratin tissue which includes skin, nails, and hair (Kaur et al. 2021). *Candida albicans* is one ofthe most prevalent human pathogens among fungal species (Tsui et al. 2016). Candidiasis refers to infections caused by fungi of the genus *Candida*. These infections can be invasive (bloodstream, and deep-seated candidiasis), cutaneous, or mucosal (oral, esophageal, and vulvo vaginal candidiasis) (Geraldi et al. 2022). In people with weakened immune systems, this normally benign commensal fungus can turn into an opportunistic pathogen (Kabir et al. 2012). The two most significant morphological forms of *Candida albicans* that influence its pathogenicity are yeast, and hyphal cells (Guevara-Lora et al. 2020). The commensal, and pathogenic phases of *Candida albicans* are determined by the transition from yeast to hyphae, which can also result in tissue infection, host-cell adhesion, macrophage evasion, and the formation of clinically significant biofilm communities (Guevara-Lora et al. 2020). In different countries, *Candida albicans* causes >90% of cases of mucosal candidiasis, and >40% of invasive candidiasis, respectively. The most important risk factors for infections caused by *Candida albicans* are antibiotic therapy, followed by central venous access,neutropenia, surgery, urinary catheter,parenteral nutrition, and certain diseases like hematologic malignancy,solid cancer, prematurity,neurologic disease, heart disease, trauma, organ transplant, gastrointestinal disease, pulmonary disease, genetic disease/congenital malformation, vascular disease, HIV, renal disease, liver disease, diabetes mellitus, and pancreatic disease (Dadar et al. 2018). Due to the widespread, and overuse of limited antifungal drugs, the search for alternatives against *Candida albicans* is ongoing, especially in plants, and natural herbs as the diversity of plants provides a wide range of important sources of biologically active molecules with enormous potential antifungal properties such as alkaloids, phenols, tannins, and terpenoids (Martins et al. 2015).

This review discusses the pathogenic mechanisms of *Candida albicans*, including its parasexual cycle, infection-causing potential, and the range of diseases it may cause. The study also looks at plant extracts that have been proven to be beneficial in treating *Candida albicans* infections, highlighting the benefits of employing plant-based remedies rather than traditional pharmaceutical medications to treat these infections. The review emphasizes how, in comparison to manufactured drugs, plant

extracts provide a less harmful, more affordable, and less invasive substitute.

2. METHODOLOGY

The data on *Candida albicans*, a crucial human fungal pathogen, and how plant-based extracts can prevent it were gathered from available literature publications using several scientific literature search engines, such as PubMed, Springer, ResearchGate, Google Scholar, ScienceDirect, MDPI, Web of Science, Academia.edu, and Scopus. The terms "*Candida albicans*", "Candidiasis", "dimorphism", "parasexual cycle", and "plant extract" were applied during the investigation. Only 72 references were included in this study out of the approximately 300 papers that were reviewed in the literature.

3. PARASEXUAL CYCLE OF *Candida albicans*

Candida albicans, a human pathogenic fungus, has long been thought to be a diploid, asexual organism. But according to recent research, the creature developed mating-competent forms of tetraploid mating products.A non-meiotic ploidy reduction mechanism that produces genetically distinct kids is known as 'parasex'. It was initially employed in 1953 by Guido Pontecorvo, an Italian geneticist who was studying *Aspergillus nidulans*(Pontecorvo et al. 1953).

The belief that Candida albicans solely reproduced asexually persisted for a long time. The *Candida* genus was formerly classed as a Deuteromycetes (imperfect fungus) due to its apparent lack of a reproductive cycle, but it was later moved to the Saccharomycetes (Hibbett et al. 2007). It is theoretically possible for a parasexual mechanism, a sexual process, or both to complete the life cycle of *Candida albicans*(Forche et al. 2008).An important opportunistic pathogen, *Candida albicans* may infect almost every organ in the body and can cause both life-threatening invasive infections and crippling mucosal infections.

Previously, species of *Candida* were described as having the ability to produce true hyphae or pseudohyphae but not sexual reproduction (Reedy and Heitman 2014).The yeast*Candida albicans*, exhibiting commensalism, and then it sometimes proves to be opportunistic inside the human body, can mate, but it is an extremely complicated process. Most isolates are diploid, carrying both mating-type-like (MTL) locus alleles, which inhibit mating. Despite appearing incapable of meiosis, deletion of a whole copy of chromosome 5 (chr 5), which contains the MTL locus, or localized loss of heterozygosity (LOH) produces MTL-homozygotes capable of mating. To achieve this, they must experience an epigenetic shift from the "white" phenotype to the "opaque" phenotype, which is capable of mating (Miller and Johnson2002, Alby et al. 2009, Heitman2010, Xie et al. 2013).A small proportion of mating events produces fusants having genetic markers from both parents(Bennett et al. 2005).

When diploids mate to create tetraploids, a physiological/epigenetic transition from the typical "white" phase to an "opaque" condition is required. These tetraploids can revert to a near-diploid state under certain stressors, but many of them have at least one extra (aneuploid) chromosome, and some have undergone events of recombination that require Spo11, a protein required for meiotic recombination to occur in organisms with true meiosis.This transition between diploid, and tetraploid generations, followed by a return to near-diploids without the use of traditional meiosis, is known as the "parasexual cycle"(Berman and Hadany 2012).

The genome of *Candida albicans* contains a number of "meiosis-specific" genes, but no meiotic program has been found. Alternatively, it is possible to cause efficient, random chromosome loss in tetraploid mating products, which frequently results in ploidy strains that are diploid or nearly diploid. When examined the genotypes that result from the parasexual cycle of *Candida albicans* using comparative genome hybridization arrays, and SNP. It was shown that at least one meiosis-specific gene has been reprogrammed to facilitate genetic recombination during the alternate parasexual life cycle of *Candida albicans*, and that deletion of SPO11 blocked genetic recombination between homologous chromosomes during the parasexual cycle (Fig. 1)(Forche et al. 2008).

4. PATHOGENICITY OF *Candida albicans*

The most prevalent human pathogen among fungal species is *Candida albicans*, which can cause illnesses ranging from minor mucosal infections to serious systemic infections (Jabra-

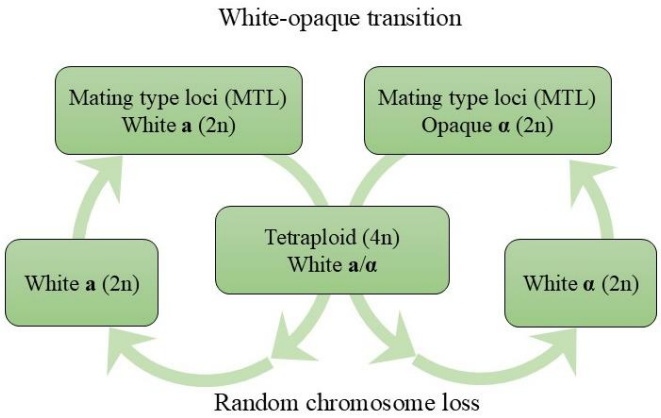

Fig. 1. Parasexual cycle of *Candida albicans*

Rizk et al. 2016). Healthy people's gastrointestinal system, mouth cavity, and reproductive tract are asymptomatically colonized by *Candida albicans* as a component of the commensal human microbiota (Mason et al. 2012). *Candida albicans* infections can primarily be classified into mucosal and systemic infections. People with normal immune function may experience mucosal candidiasis, particularly vulvovaginal candidiasis (VVC); however, individuals with compromised immune systems are at greater risk for more frequent, severe, or recurrent mucosal infections. Systemic candidiasis affects body parts which are in sterile condition, includes the central nervous system (CNS), along with liver, heart,spleen, and/or kidneys, as well as the bloodstream (Lopes and Lionakis 2022).

In reaction to different environmental factors from the host, *Candida albicans* can switch its form between yeast (individual oval cells) and filaments or hyphae (stretched cells joined together) reversibly, a process associated with the organism's virulence, and capability to cause disease (Mitchell 1998), and this ability to change between these two phases i.e. yeast, and hyphae are known as dimorphism. The filamentous (hyphal) form is responsible for invading tissues and causing disease, while the yeast form plays a role in spreading the infection, indicating that both forms operate independently (Seman et al. 2018). The morphological characteristics of *Candida albicans* are affected by several environmental factors, for instance, the temperature of the host, pH levels, availability of nutrients, and quorum sensing mechanisms (Lu et al. 2014).

The general procedure of invasion of tissue by *Candida albicans* can be outlined as follows (Fig. 2)-

Adhesion to the cell surface: The diverse surfaces that *Candida albicans* can inhabit, such as human mucosal tissues, and various medical equipment, and instruments, highlight the critical significance of the factors that are involved in adhesion, and invasion in the success of the pathogen (Lopes and Lionakis 2022).Adhesins represent a distinctive class of proteins present in *Candida albicans* that promote adhesion to host cells, abiotic surfaces, and other microorganisms (Garcia et al. 2011). Adhesins along with invasins (Als and Hwp1 families) mediates hyphal extension followed by host cell active penetration (Liu and Filler 2011). To invade host cells *Candida albicans* use two different mechanisms-induce endocytosis, and active penetration (Zakikhany et al. 2007). Induce endocytosis occurs with the help of adhesins, and invasins without the direct activity of the viable fungal hyphae (Dalle et al. 2010). However, active penetration is a process in which viable fungal hyphae is fully involved in the process of invasion (Wächtler et al. 2011).

Biofilm formation: A sequence of occurrences contributes to the creation of biofilms, which begins when yeast cells adhere to the surface, then came their multiplication, the formation of hyphal cells in the biofilm’s upper layer, the buildup of extracellular matrix materials, and finally, the of yeast cellsrelease for the purpose of infecting surrounding areas from the biofilm structure (Finkel and Mitchell 2011). According to in vitro studies, biofilm growth takes place over the course of 24 to 48 hours in a sequence of

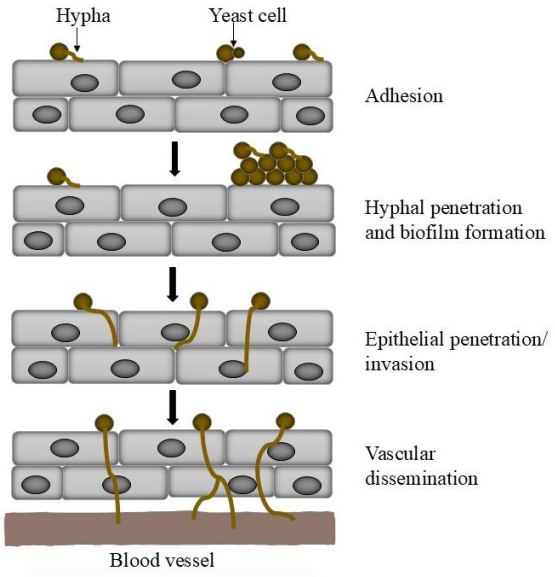

Fig. 2. Different stages of *Candida albicans* tissue invasion

consecutive phases (Mathe and Dijck 2013). In the very first stage, a single fungal yeast cell adheres to the surface and form the layer of basal yeast cell, known as adherence stage (Tournu and Dijck 2012). The next step is the initiation step where cell proliferation occurs, and hyphae are formed for invasion. The next stage is the maturation phase where extracellular polysaccharide matrix is accumulated that indicates the maturation of biofilm. The last stage is the dispersal stage where yeast cell that are not attached to the surface are released to colonize the surrounding tissues (Tournu and Dijck 2012).

Epithelial penetration/invasion by hyphae: The production of hypha-associated proteins, which are known to cause damage and are with activate immune responses, occurs alongside the formation of hyphae. Furthermore, hyphae of *Candida albicans* release hydrolases that facilitate penetration into epithelial tissues and assist in obtaining extracellular nutrients. *Candida albicans* released proteinases, phospholipases, and lipases, which are the example of hydrolases.A ten members group of secreted aspartic proteinases (Saps) , out of which some secreted (Sap1–8) while others remain intact to the surface of the cell (Sap9–10) (Lopes and Lionakis 2022)

Vascular dissemination: After escaping from the host immune system and forming biofilm the fungus enters the blood stream. Candidaemia is a disorder caused by the presence of *Candida* in the blood. The yeast spreads from the blood to the body's essential organs, where it results in systemic infections. Adhesins, cytolytic proteins, phenotypic flipping, and extracellular hydrolytic enzymes all significantly aid in the spread of candidiasis, in certain condition infection proceeds without the formation of biofilm (Mba and Nweze 2020).

Metabolic adaptation and nutrient acquisition: When pathogenic fungus infects various host habitats, this metabolic flexibility is very crucial (Mayer et al. 2013). For *Candida albicans*, the preferred source of carbon is glucose (Man et al. 2017). In contrast, fungal growth occurs in most internal sites of colonization when glucose is limited. To adapt to such type of conditions, *Candida albicans* uses carboxylic acids like lactate as an alternate route for carbon usage in addition N-acetylglucosamine (GlcNAc) and amino acids (Williams and Lorenz 2020).Although it is believed thatpathogenesis, and host colonization are influenced by gluconeogenesis, glycolysis, and starvation responses, their precise roles may vary greatly depending on the niche, and are still not fully understood (Mayer et al. 2013).

5. ROLE OF IMMUNE DEFENSE SYSTEM

The body's innate immune system plays a crucial role in the early defense against *Candida albicans* infections. When *C. albicans* is detected, the immune system initiates a rapid response to contain and eliminate the pathogen.

Table 1. Different diseases caused by *Candida albicans*

Sl.No.	Disease	Reference
1.	Esophageal candidiasis (EC)	(Ou et al. 2014)
2.	Vulvovaginal Candidiasis (Yeast Infection)	(Eckert 1998)
3.	Oral Candidiasis	(Takakura et al. 2003)
4.	Fatal candidemia	(Cheng et al. 2005)
5.	Chronic Mucocutaneous Candidiasis	(Zhang et al. 2020)
6.	Infective endocarditis	(Mamtani et al. 2020)
7.	Invasive Candidiasis	(Pappas et al. 2018)
8.	Cutaneous Candidiasis	(Palese et al. *2018*)
9.	Onychomycosis	(Elewski 1998)
10.	Endophthalmitis	(Durand 2013)
11.	Intestinal candidiasis	(Cater 1995)
12.	Meningitis	(Nguyen and Yu 1995)

Toll like receptors (TLRs) and C type lectin receptors (CLRs) on immune cells recognize conserved pathogen associated molecular patterns (PAMPs) on *C. albicans*. This recognition triggers the activation of immune cells and the initiation of an inflammatory response. Neutrophils are the first responders and are crucial for killing *C. albicans* through phagocytosis (engulfing the pathogen) and subsequent destruction within the phagosome using reactive oxygen species (ROS) and enzymes like myeloperoxidase. Macrophages also phagocytose *C. albicans* and play a role in cytokine production to modulate the immune response. Dendritic cells capture the fungus and present antigens to T cells, which helps bridge the innate and adaptive immune responses. Upon recognition of *C. albicans*, immune cells release various proinflammatory cytokines to recruit additional immune cells to the site of infection. These cytokines enhance the immune response and help control the spread of the pathogen. There is also report on Neutrophils release neutrophil extracellular traps (NETs), which are weblike structures composed of DNA, histones, and antimicrobial proteins that trap and kill *C. albicans*.

6. CURRENT TREATMENT STRATEGIES

Many strategies have been taken to prevent the pathogenesis of *Candida albicans*. Many plant species have been found to have anti-*Candida* activity. The most common Indian spices like clove (*Syzygiumaromaticum* L.), Indian gooseberry (*Phyllanthus emblica* L.), andgarlic (*Allium sativum* L.). To test the antimicrobial activity of these spice extract against *C. candida*, samples from several patients with Candidiasis were isolated and cultured. All these three spices have been used as basic spices in India has many traditional uses and also some medicinal values that people of India using since ages. Aqueous solution of these spice extracts was used to test the antimicrobial activity against *C. albicans,* and the compound found to be present are allicin, ellagic acid, and gallic acid (Sadanandan et al. 2023)

Plants based extract as antifungal agents: Several studies have demonstrated thathow well plant metabolites work as strong antifungal agents, which have been shown toprevent the growth, and change the virulence of many *Candida* species in their hyphal, planktonic, and biofilm-forming forms (Guevara-Lora et al. 2020). Despite the development of numerous antifungal medications that primarily attack the fungal cell wall as well as plasma membrane, these pathogens have evolved novel defense mechanisms that make them resistant to standard treatment, which increases the incidence of candidiasis, and enforces the urgent need for an intensified search for new specifics that could be helpful, alone or synergistic with traditional drugs in controlling *Candida* pathogenicity. There are significantly fewer antifungal agents available in clinical settings than antibacterial medications. Polyenes, azoles, allylamines, and echinocandins are the four main groups of antifungal chemicals. Furthermore, there are a variety of antifungal substances that do not fall within one of the major categories, such griseofulvin, and flucytosine (Richardson 2022).

7. WHY PLANT BASED ARE BETTER THAN PHARMACEUTICAL DRUGS?

The utilization of plants as a primary source of medicinal remedies can be traced back to early civilizations of the world (Subramoniam 2014,

Table 2. Plant extract used against *Candida albicans*

Sl.No.	Latin name of plant extracts used	Reference
1.	*Achillea santolina*, *Salvia dominica*,*Salvia officinalis*	(Hassawi and Kharma 2005)
2.	*Murraya koenigii*,*Camellia sinensis*	(Doddanna et al. 2013)
3.	*Eucalyptus globulus*,*Mentha piperita*	(Agarwal et al. 2010)
4.	*Piper capense*, *Syzygium cordatum*,*Tabernae montana elegans*	(Steenkamp et al. 2007)
5.	*Achillea millefolium*,*Mikania glomerata*,*Stachysbyzantina*	(Duarte et al. 2005)
6.	*Curtisia dentata*	(Shai et al. 2008)
7.	*Juglans regia*,*Rubusulmi folius*, *Pterospartum tridentatum*	(Martins et al. 2015)
8.	*Cuminum cyminum*, *Zataria multiflora*, *Thymus kotschyanus*, *Plargonium graveolens*	(Naeini et al. 2009)
9.	*Albizia anthelmintica*, *Balanitesaegyptiaca*, *Plectranthus barbatus*	(Runyoro et al. 2006)
10.	*Rosmarinus officinalis* ,*Echinophora platyloba*	(Jahani et al. 2016)
12	*Curcuma longa*, *Zingiber officinale* var. *rubrum*	(Geraldi et al. 2022)
13	*Dodonaea viscose* var. *angustifolia*	(Patel and Coogan 2008)

Shakya 2016, Chaachouay and Zidane 2024). In the view of modern medical sciences, herbal medications ought to be universally recognized (Karimi et al. 2015), and commercially feasible. However, comparatively speaking, developing such phytomedicines based on ethnomedical leads is easier and more pertinent to our economic conditions than developing pure chemical entity drugs (Subramoniam 2014). Research on herbal drugs and the creation of beneficial medical products from locally sourced plants would advance healthcare (van Wyk and Prinsloo 2020), and economic development, including the emergence of enterprises centered around herbal drugs (Subramoniam 2014). In the present pharmaceutical market, allopathic drugs being used in order to treat variousillnesses with greater success rates. However impulsive use of synthetic drugs resulted in severe adverse side effects as well (Nisar et al. 2018, Jha et al. 2023) (Nisar et al. 2018, Jha et al. 2023). In their study, Nisar et al. (2018) mentioned that, some common synthetic medicines like Aspirin, Enoxaparin, Clopidogrel, Naproxen, Diclofenac, Warfarin, and Ibuprofen are linked to minor side effects (such as headache or back pain) to significant ones (haemorrhaging, respiratory difficulties, and excessive bleeding, etc.). Several examplesin the available literature regardingside effects of pharmaceutical drugs. For instance, Paracetamol, a well-known febrifuge medication, butits primary adverse consequence isliver toxicity (Nisar et al. 2018). This encouraged researchers to focus on investigating herbal substitutes that have fewer adverse effects.These herbal medications' safety and toxicity profiles have never been confirmed.Besides, being a less expensive and safer option, utilizing herbs could reduce the prevalence regarding resistance to drugs and alter the immunological system to prevent illnesses linked to viruses (Yasmin et al. 2020). Therefore, in order to enhance the level of safety, effectiveness, and herbal medication's quality, WHO initiated a strategy on conventional medicine plan (2014-2023) (Jha et al. 2023).

8. MECHANISMS OF ANTIFUNGAL ACTION: DESCRIBE HOW PLANT COMPOUNDS DISRUPT CELL WALLS, INHIBIT BIOFILM FORMATION, OR AFFECT METABOLIC PATHWAYS

The fungal cell wall is an essential structure for maintaining cellular integrity, and it is a prime target for antifungal agents. The primary components of the fungal cell wall include chitin, glucans, and mannans, which provide strength and protection. Many plant derived compounds are known to disrupt the synthesis or integrity of these components, leading to cell wall damage and fungal cell death. Chitin is a major component of the fungal cell wall, and its synthesis is crucial for maintaining structural integrity. Several plant compounds, such as flavonoids and phenolic acids, have been shown to inhibit chitin synthesis, weakening the cell wall and making the fungus more susceptible to environmental stresses. Flavonoids like quercetin have been shown to inhibit chitin biosynthesis in

C. albicans by targeting the chitin synthase enzyme, thereby disrupting cell wall integrity. This results in the accumulation of chitin precursors and disruption of the cell wall structure. Cinnamic acid, a phenolic compound found in cinnamon, interferes with cell wall formation in *C. albicans*, likely through inhibition of chitin and glucan synthesis. β glucan is another major component of the fungal cell wall, particularly important in the structural integrity of Candida species. Disruption of βglucan biosynthesis can compromise the cell wall and trigger an immune response in the host. Berberine, an alkaloid derived from Berberis species, has been found to interfere with βglucan synthesis in *C. albicans*, leading to compromised cell wall integrity and increased susceptibility to immune system attack (Devi et al., 2017). Many plant compounds also disrupt the fungal cell membrane, leading to leakage of intracellular contents and cell death. Terpenoids, including thymol from Thymus vulgaris, and eucalyptol from Eucalyptus spp., have been shown to alter membrane fluidity, affecting membrane bound enzymes and proteins. Alkaloids such as berberine have been shown to inhibit ergosterol biosynthesis in *C. albicans* by targeting the enzyme lanosterol 14αdemethylase, a key enzyme in the ergosterol synthesis pathway. Menthol, a monoterpene found in peppermint, has been shown to induce ROS production in *C. albicans*, causing damage to fungal DNA and proteins, which ultimately inhibits fungal growth. Curcumin, a polyphenolic compound found in turmeric, induces oxidative stress and mitochondrial dysfunction in *C. albicans*, leading to cell death through the generation of ROS and impairment of fungal metabolism. Gallic acid, a phenolic compound found in tea and other plants, inhibits the glycolytic pathway in *C. albicans*, reducing its ability to generate energy and impeding its growth.

9. CHALLENGES AND LIMITATIONS OF PLANT BASED ANTIFUNGAL AGENTS

Many plant derived compounds have poor bioavailability, meaning they are not efficiently absorbed into the bloodstream or tissues, limiting their therapeutic potential. For example, compounds such as curcumin and berberine have potent antifungal properties in laboratory settings but are poorly absorbed and rapidly metabolized in the body, reducing their effectiveness against systemic infections. The ability of plant compounds to penetrate infected tissues, especially in immune-compromised patients, is another challenge. Fungal biofilms, commonly associated with Candida and other fungal pathogens, form a protective barrier, making it difficult for antifungal agents to reach the fungal cells. While plant based antifungal agents are often touted for their lower toxicity compared to synthetic drugs, many natural compounds can still cause adverse effects when used at high doses or over extended periods. The safety profiles of many plant derived compounds are not well established, especially with prolonged use. Some plant compounds, such as berberine (from Berberis spp.), have been associated with liver toxicity in animal studies when used at high concentrations. Long term use of certain plant extracts might lead to adverse reactions, limiting their clinical application. Natural compounds can also trigger allergic reactions or hypersensitivity in certain individuals. For example, thymol and eugenol, found in Thymus vulgaris (thyme) and Cinnamomum verum (cinnamon), respectively, have shown allergenic potential in some users. The interactions between different plant derived compounds can result in either synergistic or antagonistic effects. Synergistic combinations of plant compounds can improve efficacy, but in some cases, interactions may reduce the activity of the primary antifungal agent. Understanding the pharmacological synergy between various plant compounds is a challenge that requires further research.

10. CHALLENGES IN STANDARDIZING PLANT EXTRACTS DUE TO VARIABILITY IN PLANT CHEMISTRY

The genotype of a plant species plays a significant role in the composition of bioactive compounds. Even within the same species, variations in the expression of key biosynthetic pathways can lead to differences in the concentrations of secondary metabolites, such as alkaloids, flavonoids, and terpenoids. Factors such as soil composition, climatic conditions, and elevation can significantly affect the concentration and profile of bioactive compounds. Environmental stressors such as drought, pest infestations, or pathogen exposure can also trigger the production of certain metabolites, leading to variations in the chemical composition of the plant and potentially affecting its antifungal efficacy. The stage of harvest and the specific part of the plant used for extraction (e.g., leaves, roots, bark, or flowers) can also lead to significant variability. Postharvest

handling, including drying and storage conditions, can also significantly influence the chemical profile of plant extracts. High temperatures and improper storage conditions can degrade volatile compounds, especially in extracts like essential oils, reducing their potency. Inadequate drying methods can lead to microbial contamination, further altering the extract's composition.

11. POTENTIAL FOR ALLERGIC REACTIONS OR TOXICITY: CONSIDER THE SAFETY AND POTENTIAL SIDE EFFECTS OF PLANT BASED TREATMENTS

Allergic reactions to plant based compounds occur when the immune system responds abnormally to natural substances, triggering inflammatory responses that can range from mild irritation to severe anaphylaxis. Many essential oils contain volatile compounds that can act as sensitizers for allergic reactions. Individuals with allergies to related plant species (e.g., Asteraceae family) may be at increased risk of developing allergic reactions to flavonoid rich extracts. Some plant derived compounds have been associated with hepatotoxicity (liver damage), particularly when consumed in large amounts or over extended periods. Kava (Piper methysticum), a plant used for its anxiolytic and sedative effects, has been linked to severe hepatotoxicity, including liver failure. These concerns have led to regulatory restrictions on the use of kava in several countries. Certain plant compounds have been found to exert neurotoxic and cardiovascular effects, especially when consumed in large quantities or in improper formulations.

12. DISCUSSION AND FUTURE DIRECTIONS

Disease causes by *Candida albicans* becomes a major problem for human being. There are many drugs available for the treatment of systemic and superficial mycoses, but in limited number, and *C. albicans* becomes resistant to these drugs because of continuous use of these drugs against *Candida* sp. So, it is become necessary to find alternative to tackle with this problem and plant-based extract seems to be effective in this case to deal with *Candida albicans* pathogenicity in the molecular level. To search new drugs based on plant extract, agar diffusion method, autobiography, agar or broth dilution assays are most commonly used. While using these methods, different dilution series of plant sample are prepared and mixed with culture medium and then fungal inoculums inoculated in these culture media. The culture media are then incubated in particular temperature, and after that the minimum inhibitory concentration i.e. the lowest compound concentration showing no visible growth of fungus is recorded.

As the biofilm formation is the main problem of *Candida* pathogenesis, development of new antifungals is must needed. Studies on different transcription factors, quorum sensing molecules, host response to adhesion, and changes in lipid profiling have cleared the complex mechanism behind the biofilm formation.

Many studies on phenolic compound have shown their effect on *C. albican's* because of these compounds having anti-adhesion, antibiofilm effects. So, looking forward on more phenolic compounds and their activities against *C. albicans* can be really helpful (Teodoro et al. 2015).

Dubey and Singla (2019) have suggested various natural compounds from classes of terpenoids, alkaloids etc. which showed prevention of biofilm formation by *C. albicans*. Different report on bioactive compound showed that thymol and carvacrol, interfere with the structural integrity of cell membrane. Allicin, and cinnamaldehyde also have shown effective results against *Candida* causing disease.

The main mechanism of *Candida* pathogenicity is by the initiation process involving adhesion of pathogens to surface, so, discovery of molecules that can prevent this initiation step can be more useful in prevention of their growth, as there are still researches are going on to found effective biomolecules that can prevent the initiation of *C. albicans* infection (Martin et al. 2021).

13. CONCLUSION

The incidence of potentially lethal fungal infections has increased throughout the last 20 years. The majority of these infections are caused by *Candida* species, primarily *Candida albicans*. In warm-blooded animals' and most people's gastrointestinal, and urogenital tracts, as well as in the mouth cavity and skin, this fungus usually exists as a benign symbiotic microbe. The fourth most prevalent kind of bloodstream infection, *Candida albicans*, has a variety of severity, epidemiology, and antifungal susceptibilities.

Despite their extensive spectrum, including biofilm formation, dimorphism, adhesion protein expression,thigmotropism, and the production of extracellular hydrolytic enzymes, it is crucial to understand the precise components and mechanisms underlying *C. albicans*' pathogenicity (Shradha et al. 2023).

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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