International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
www.florajournal.com
IJHM 2023; 11(4): 51-57
Received: 09-05-2023
Accepted: 15-06-2023

Muaaz Alajlani
Faculty of Pharmacy, Al-Sham Private University, Damascus, Syria

Corresponding Author:
Muaaz Alajlani
Faculty of Pharmacy, Al-Sham Private University, Damascus, Syria
Email:
muaaz.alajlani.foph@aspu.edu.sy

Antifungal property of medicinal plants: A comprehensive review

Muaaz Alajlani

DOI: https://doi.org/10.22271/flora.2023.v11.i4b.880

Abstract
Fungal infections pose a significant global health burden, affecting millions of individuals each year. Conventional antifungal therapies often suffer from limitations such as drug resistance and adverse side effects. As a result, researchers have turned their attention to natural remedies, particularly medicinal plants, in search of novel antifungal agents. This review article aims to provide an up-to-date and detailed examination of the antifungal properties of various medicinal plants, exploring their active compounds, mechanisms of action, and potential applications in combating fungal infections.

Keywords: Medicinal plants, natural products, antifungal

1. Introduction
Fungal infections, including candidiasis, aspergillosis, dermatophytosis, and systemic mycoses, have emerged as a major health concern worldwide. The incidence of fungal infections has risen due to factors such as immunosuppression, broad-spectrum antibiotic use, and increased population of immune compromised individuals [1]. Consequently, the rise in antifungal resistance has underscored the urgency of finding alternative and effective therapeutic options. Medicinal plants have been used for centuries in traditional medicine to treat various ailments, including fungal infections. The vast diversity of bioactive compounds present in these plants has drawn the attention of researchers towards exploring their potential as natural antifungal agents [2]. This comprehensive review aims to collate and analyze the latest scientific evidence on the antifungal properties of medicinal plants, shedding light on their mechanisms of action and potential applications in clinical settings [3].

2. Methods
An extensive literature search was conducted using reputable academic databases, including PubMed, Scopus, and Web of Science. The search keywords included "antifungal," "medicinal plants," "phytochemicals," and "mechanism of action." Only peer-reviewed articles published between 2010 and 2023 were considered to ensure the inclusion of up-to-date information. The selected studies focused on investigating the antifungal activity of medicinal plants against various fungal pathogens. The methodologies employed in the studies, including minimum inhibitory concentration (MIC) assays, time-kill assays, and animal models, were also examined to assess the robustness of the findings.

3. Medicinal plants and their antifungal properties
A complete description of the medicinal plants including their constituent (Table 1) and their antifungal properties is elaborated for each medicinal plant in this review.

3.1. *Aloe vera* (*Aloe barbadensis miller*)
Aloe vera, a succulent plant belonging to the family Asphodelaceae, has been revered for its diverse medicinal properties across various cultures for centuries. It is commonly known as the "wonder plant" due to its extensive therapeutic potential. The gel extracted from the fleshy leaves of *Aloe vera* contains a plethora of bioactive compounds, including anthraquinones, anthrones, and polysaccharides, which have been extensively studied for their pharmacological activities, including potent antifungal properties [1]. Among the bioactive compounds present in *Aloe vera*, a hydroxyanthraquinone called aloe-emodin has been identified as a significant contributor to its antifungal effects. Aloe-emodin has shown remarkable efficacy against various fungal pathogens, particularly Candida species and dermatophytes.

This compound acts by inhibiting the biosynthesis of ergosterol, a crucial component of fungal cell membranes. Ergosterol is essential for maintaining membrane integrity and fluidity, and its disruption leads to severe impairment of fungal cell viability [2]. Aloe-emodin's inhibitory action on ergosterol biosynthesis sets off a chain of events that culminate in the disruption of the fungal cell membrane, rendering it susceptible to osmotic stress and eventual cell death. Furthermore, *Aloe vera* contains another bioactive compound known as aloin, which exhibits immunomodulatory effects. Aloin has been shown to enhance the immune response by stimulating the activity of macrophages and promoting the secretion of cytokines, such as interleukins and tumor necrosis factor-alpha [3]. Macrophages play a pivotal role in the host's defense against fungal infections, as they act as phagocytes and initiate the inflammatory response by releasing pro-inflammatory cytokines. By boosting the immune response, aloin aids in combating fungal infections more effectively and expedites the process of pathogen clearance.

Apart from its direct antifungal effects, *Aloe vera*'s polysaccharides have also been shown to contribute to its therapeutic potential. These polysaccharides possess immunomodulatory properties, promoting the activation of various immune cells, including T lymphocytes and natural killer cells, thereby strengthening the host's immune defense against fungal invaders [4].

Aloe vera's antifungal properties have been evaluated against various fungal species, including *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*, among others. *In vitro* studies using various experimental models, such as minimum inhibitory concentration (MIC) assays and time-kill kinetics, have consistently demonstrated its effectiveness in inhibiting fungal growth and replication [5]. Moreover, *in vivo* studies in animal models have shown promising results in terms of reducing fungal burden and improving the overall outcome of fungal infections [6]. The multifaceted antifungal activity of *Aloe vera*, coupled with its immunomodulatory effects, makes it a promising candidate for the development of natural antifungal therapies. However, before clinical application, further research is needed to explore its safety and pharmacokinetic properties in human subjects. Additionally, synergistic interactions with conventional antifungal drugs should be investigated to assess the potential for combination therapy, which may enhance treatment efficacy and mitigate the emergence of drug-resistant fungal strains. Overall, *Aloe vera* stands as a valuable natural resource in the ongoing battle against fungal infections and offers an exciting avenue for future antifungal drug development.

3.2. Garlic (*Allium sativum*)

Garlic, known for its pungent aroma and distinct taste, has been utilized for centuries in traditional medicine for its various health benefits. The medicinal properties of garlic can be attributed to its rich content of organosulfur compounds, with allicin being the primary bioactive component responsible for its potent antifungal activity against both yeast and filamentous fungi [7]. Allicin, a highly reactive and unstable compound, is formed when garlic is crushed or chopped. It exerts its antifungal effects through multiple mechanisms, with a primary target being the ergosterol biosynthesis pathway in fungal cells. Ergosterol, a sterol component of fungal cell membranes, is vital for maintaining membrane fluidity and integrity. Allicin inhibits crucial enzymes involved in the synthesis of ergosterol, such as squalene epoxidase and 14α-demethylase, which are encoded by ERG1 and ERG11 genes, respectively [8]. By disrupting ergosterol production, allicin leads to alterations in fungal membrane structure and function, ultimately compromising the integrity of the cell membrane and causing cell death. Furthermore, garlic's antifungal properties extend beyond the direct inhibition of fungal growth. It has been found to effectively inhibit biofilm formation, a critical virulence factor in fungal infections. Biofilms are complex, multicellular communities of microorganisms encased in a protective extracellular matrix, which enhances their resistance to antifungal agents and the host's immune response. Garlic's ability to interfere with biofilm formation and disperse existing biofilms contributes to its efficacy in combating persistent and recurrent fungal infections [9]. The broad-spectrum antifungal activity of garlic has been demonstrated against various pathogenic fungi, including Candida species (*Candida albicans*, *Candida glabrata*, *Candida tropicalis*) and filamentous fungi like *Aspergillus fumigatus*. *In vitro* studies using agar diffusion assays, broth micro dilution assays, and time-kill kinetics have consistently shown its efficacy in inhibiting fungal growth [10]. Furthermore, animal models have provided evidence of garlic's antifungal efficacy *in vivo*, substantiating its therapeutic potential for the treatment of fungal infections [11]. In addition to its direct antifungal effects, garlic has been reported to modulate the host's immune response, which plays a pivotal role in defense against fungal infections. Garlic's immunomodulatory properties are attributed to various components, including diallyl disulfide, S-allylmercaptocysteine, and ajoene, which can stimulate immune cells and enhance the production of cytokines such as interleukins and interferons [12]. By bolstering the immune response, garlic complements its direct antifungal effects, promoting a comprehensive defense against fungal pathogens. Garlic's natural antifungal properties offer significant advantages, including a reduced risk of developing drug resistance compared to conventional antifungal agents. However, to harness garlic's full potential as an antifungal agent, further research is needed to optimize its formulation, dosage, and delivery methods for clinical use. Additionally, investigating its potential synergistic effects with other antifungal agents could lead to combination therapies that enhance treatment outcomes and reduce the required dosages, minimizing potential side effects.

3.3. Neem (*Azadirachta indica*)

Neem (*Azadirachta indica*), an evergreen tree native to the Indian subcontinent, has been a cornerstone of traditional medicine for centuries, known for its diverse therapeutic properties. Among its various bioactive constituents, neem extracts contain an array of compounds such as limonoids, nimbin, nimbidin, and azadirachtin, which have been attributed to its potent antifungal activity [13]. Azadirachtin, a major active component present in neem, has shown remarkable antifungal effects against a wide range of pathogenic fungi, including Candida species and *Aspergillus fumigatus* [14]. The antifungal mechanism of azadirachtin involves disrupting fungal cell membranes by targeting key enzymes in the sterol biosynthesis pathway. Specifically, azadirachtin inhibits 24-methylenedihydrolanosterol acetyltransferase (24-MDT), an enzyme crucial for the conversion of lanosterol to 24-methylenedihydrolanosterol in the ergosterol biosynthesis pathway [15]. This disruption

ultimately leads to a decrease in ergosterol levels, impairing the structural integrity of the fungal cell membrane and causing cell death. Ergosterol, a sterol unique to fungal cell membranes, plays a vital role in maintaining membrane fluidity and integrity. Its depletion by azadirachtin leads to the accumulation of toxic sterol intermediates and altered membrane structures, which affects membrane permeability and disrupts essential cellular functions. Consequently, the loss of ergosterol and the accumulation of toxic sterols disrupt the osmotic balance of the fungal cell, leading to cellular damage and eventual cell death [16]. In addition to its direct antifungal effects, neem-derived compounds exhibit immunomodulatory properties, which play a vital role in the host's defense against fungal infections. Various components in neem, such as polysaccharides, nimbidin, and nimbin, have been shown to stimulate immune cells and enhance the production of cytokines and chemokines, including interleukins and tumor necrosis factor (TNF)-alpha [17]. These immunomodulatory effects bolster the host's innate immune response, promoting phagocytosis and the activation of immune cells, thereby aiding in the elimination of fungal pathogens. Moreover, neem's immunomodulatory properties extend to the regulation of the adaptive immune response, which involves T-cell activation and the production of specific antibodies against fungal antigens. This multifaceted immunomodulatory activity contributes to the comprehensive defense against fungal infections, enhancing the overall antifungal efficacy of neem-based treatments.

Furthermore, neem's antimicrobial activity is not limited to fungi alone; it also exhibits broad-spectrum effects against bacteria and viruses, making it a comprehensive therapeutic option for various infectious diseases. Beyond its antifungal and immunomodulatory properties, neem has also shown antioxidant and anti-inflammatory effects. These properties are of particular significance in fungal infections, as the host's immune response can lead to oxidative stress and tissue damage. The antioxidant compounds in neem scavenge reactive oxygen species (ROS), reducing oxidative damage and inflammation in infected tissues [18]. By mitigating the inflammatory response, neem aids in tissue repair and contributes to the resolution of fungal infections. Neem's antifungal potential offers significant advantages in combating drug-resistant fungal infections, as the multifaceted mechanisms of action make it less susceptible to the development of resistance compared to single-target antifungal drugs. Furthermore, neem's bioactive compounds work synergistically to enhance its overall antifungal efficacy, further reducing the risk of resistance development. To optimize neem's potential as an antifungal agent, further research is warranted to explore its safety, pharmacokinetics, and formulation for clinical use. Clinical trials evaluating the efficacy of neem-based formulations, alone or in combination with existing antifungal drugs, are essential to establish its role as a natural antifungal therapy in modern medicine.

3.4. Tea Tree (*Melaleuca alternifolia*)

Tea tree (*Melaleuca alternifolia*), a native plant of Australia, is renowned for its essential oil with broad-spectrum antimicrobial properties, making it a popular natural remedy for various infections, including fungal infections [19]. The major active constituent responsible for its potent antifungal effects is terpinen-4-ol, which has shown efficacy against both dermatophytes and Candida species [20]. The antifungal mechanism of terpinen-4-ol involves its ability to disrupt fungal cell membranes, a critical structural barrier that plays a pivotal role in maintaining cellular integrity and function. Terpinen-4-ol interacts with the lipid components of the fungal cell membrane, leading to the destabilization of the membrane structure and increased permeability. This disruption ultimately results in the leakage of essential cellular components, loss of ion homeostasis, and subsequent cell death [21]. Moreover, tea tree oil's anti-biofilm activity holds promising implications in the management of biofilm-associated fungal infections, which are known to be particularly resistant to conventional antifungal treatments. Biofilms are complex communities of microorganisms encased in a protective extracellular matrix, making them highly resistant to immune defenses and antimicrobial agents. Tea tree oil's lipophilic nature allows it to penetrate deep within the biofilm matrix, effectively targeting and inhibiting fungal growth within the biofilm. By disrupting the biofilm structure, tea tree oil not only prevents the formation of new biofilms but also aids in the eradication of existing ones [22].

Furthermore, tea tree oil's multifaceted properties make it a versatile antifungal agent, as it not only directly targets fungal cells but also combats the biofilm-associated virulence of fungal infections. This dual action significantly enhances its effectiveness in treating persistent and recurrent fungal infections. However, it is essential to consider the potential irritant or sensitizing effects of tea tree oil, especially when applied topically. Dilution of the essential oil and patch testing are recommended to ensure its safe use without adverse reactions [23].

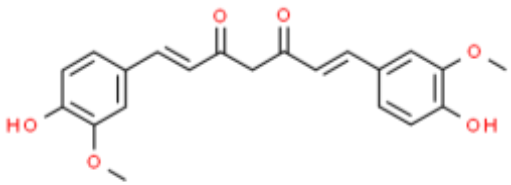
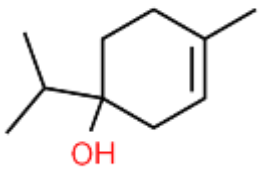
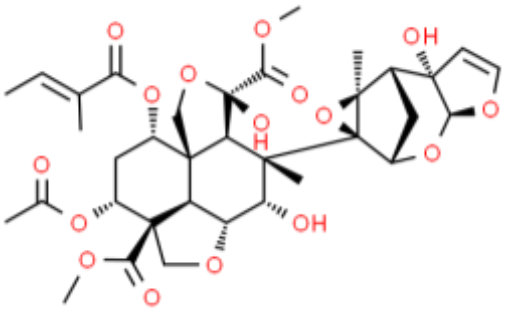
Despite tea tree oil's promising antifungal potential, further research is necessary to optimize its formulation and explore its clinical applications. Large-scale clinical trials evaluating the efficacy and safety of tea tree oil, alone or in combination with conventional antifungal agents, are needed to establish its role in evidence-based antifungal therapies [23, 24].

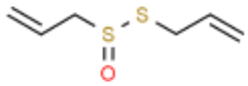
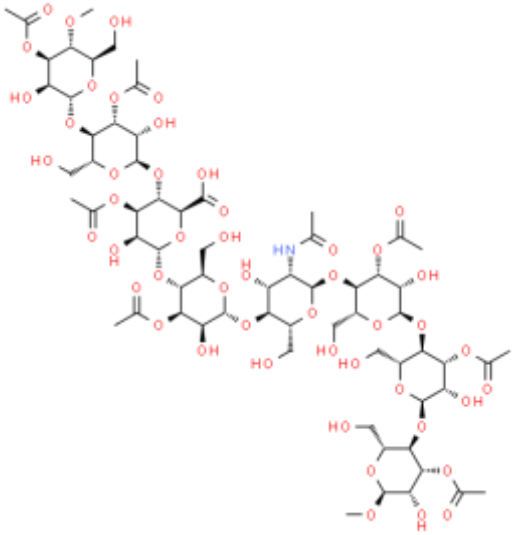
3.5. Turmeric [*Curcuma longa*)

Turmeric [*Curcuma longa*) is a flowering plant that has been used for centuries in traditional medicine and culinary practices. Its primary bioactive compound, curcumin, has drawn significant attention from the scientific community due to its diverse pharmacological properties, including potent antioxidant, anti-inflammatory, anticancer, and antiviral activities. Additionally, research has revealed that curcumin exhibits remarkable antifungal properties, making it a promising candidate for the development of novel antifungal therapies [25]. Curcumin's antifungal effects have been studied extensively, and it has demonstrated efficacy against various fungal pathogens, including Candida species and *Aspergillus fumigatus* [26]. One of the key mechanisms through which curcumin exerts its antifungal activity is by interfering with crucial intracellular processes within fungal cells. It has been found to disrupt the generation of reactive oxygen species (ROS) in these cells. ROS are highly reactive molecules involved in cellular signaling and stress responses. Fungal cells rely on balanced ROS levels for their normal functioning, and curcumin disrupts this balance, leading to oxidative stress and subsequent cell damage. The perturbation of ROS levels contributes to the impaired growth and survival of fungal pathogens [27]. Moreover, curcumin targets the mitochondria, the energy-producing powerhouses of the cell, to exert its antifungal effects. Mitochondria play a crucial role in fungal metabolism, and curcumin disrupts the process of oxidative phosphorylation, leading to mitochondrial dysfunction. This disruption compromises the energy production necessary for fungal growth and survival,

contributing to their demise [27-28]. In addition to its direct impact on fungal cell physiology, curcumin also modulates key cell signaling pathways. These pathways regulate essential cellular processes such as growth, differentiation, and responses to external stimuli. By interfering with these signaling pathways, curcumin disrupts vital cellular functions in fungi, further inhibiting their proliferation and pathogenicity [29]. One remarkable aspect of curcumin's antifungal activity is its ability to inhibit the expression of virulence factors in fungi. Virulence factors are molecules that enhance the ability of pathogens to infect host tissues and evade the host's immune response. By down regulating the expression of these factors, curcumin reduces the pathogenicity of fungal strains, making infections less severe and easier to manage [28]. The potential of curcumin as an adjunct therapy with conventional antifungal drugs has also been explored. When used in combination with standard antifungal medications, curcumin has shown synergistic effects. This means that the combination enhances the overall antifungal activity, enabling the use of lower effective dosages of the drugs while reducing the risk of drug-resistant fungal strains emerging [30]. Despite these promising findings, the translation of curcumin's antifungal properties to clinical applications requires addressing several challenges. One significant obstacle is its limited bioavailability, as curcumin is poorly absorbed and rapidly metabolized in the body. Researchers are exploring various strategies, such as nanoparticle formulations and curcumin analogs, to improve its bioavailability and therapeutic efficacy.

Table 1: Plants and their chemical components with corresponding mechanism of action:

Plant	Chemical Components principal bioactive compound	Mechanism of action	Reference
Curcuma longa (Turmeric):	Curcumin  Demethoxycurcumin Bisdemethoxycurcumin	disrupting the cell membrane integrity, generating reactive oxygen species, and modulating cell signaling pathways in fungi	[27]
Melaleuca alternifolia	Terpinen-4-ol  α-Terpineol 1,8-Cineole (Eucalyptol)	disrupts the fungal cell membrane	[14]
Azadirachta indica	Azadirachtin  Nimbin salannin	disrupts the cell membrane and inhibits fungal growth	[9]
Allium sativum	Allicin	disrupts the cell membrane and alters cellular processes	[8]

	 Ajoene Diallyl sulfide		
Aloe barbadensis miller	Aloin Acemannan  Cinnamic acid	modulates the immune response and improve host's immune system	[5]

4. Mechanisms of action

4.1. Disruption of fungal cell membrane

A significant number of medicinal plants exert their antifungal effects by disrupting fungal cell membranes. Compounds such as polyphenols, terpenes, and alkaloids present in these plants interact with the fungal cell membrane, leading to the leakage of cellular contents and eventual cell lysis. This mechanism is particularly effective against various pathogenic fungi, including Candida species and dermatophytes. For instance, the polyphenols in *Aloe vera* and the terpenes in tea tree oil have been shown to destabilize fungal membranes and compromise their structural integrity [20]. The disruption of the fungal cell membrane is a critical step in the antifungal action of these medicinal plants.

4.2. Inhibition of fungal adhesion

Several medicinal plants prevent fungal colonization by interfering with the adhesion of fungal cells to host tissues. For instance, *Aloe vera* and its components can inhibit the adhesion of Candida cells to epithelial cells, reducing the ability of fungi to establish infection and propagate. This inhibition of fungal adhesion is a crucial step in preventing the initial stages of fungal infection [31]. The inhibition of adhesion prevents the fungi from establishing a foothold in host tissues and aids in the clearance of the pathogen by the immune system.

4.3. Modulation of host immune response

Certain plant compounds possess immunomodulatory properties, enhancing the host's immune response against fungal infections. *Aloe vera* and Neem extracts, for example, have been shown to modulate immune cell activity and cytokine production, promoting an effective antifungal immune response. These immunomodulatory effects help the host in controlling fungal growth and reducing the severity of infections [32]. By boosting the immune response, these medicinal plants assist the host in clearing the fungal infection and preventing its spread.

5. Clinical applications and future perspectives

The antifungal properties of medicinal plants hold significant promise in the development of new therapeutic strategies against fungal infections. However, before their widespread clinical application, further research is essential to evaluate their safety, pharmacokinetics, and efficacy in human subjects. Standardization of herbal extracts and large-scale clinical trials are necessary to validate the efficacy and establish appropriate dosing regimens. Moreover, investigating the potential synergistic effects of medicinal plant-derived compounds with existing antifungal drugs could lead to more effective treatment options, especially in cases of drug-resistant fungal infections.

5.1 Safety evaluation

Safety evaluations of medicinal plant-derived compounds are critical to ensure their clinical applicability. While many of these compounds have been traditionally used without reported severe adverse effects, rigorous toxicological studies are essential to identify any potential risks. For instance, studies have shown that curcumin exhibits low toxicity and is generally well-tolerated, even at higher doses [33]. However, higher concentrations of certain compounds may have unintended effects, and comprehensive safety assessments are necessary to determine the maximum safe dosages for

therapeutic use.

5.2 Pharmacokinetic studies

Understanding the pharmacokinetic properties of medicinal plant-derived compounds is essential for optimizing their therapeutic potential. Pharmacokinetic studies of curcumin have shown relatively low oral bioavailability due to poor absorption and rapid metabolism [28]. Encapsulation of curcumin in nanosystems has been explored to improve its bioavailability, resulting in enhanced antifungal activity [34]. Similarly, pharmacokinetic investigations of other medicinal plant-derived compounds can provide valuable insights into their absorption, distribution, metabolism, and excretion, aiding in the design of effective dosing regimens.

5. 3 Standardization of herbal extracts

Standardization of herbal extracts is crucial for ensuring consistency and reproducibility of the antifungal activity across different preparations. Analyzing the content of active compounds in the extracts and setting quality control parameters are essential steps in achieving standardized formulations. For instance, a study assessing the composition of curcuminoids in commercial turmeric extracts found significant variations in curcumin content, emphasizing the importance of standardization [35].

5. 4 Large-scale clinical trials

To validate the efficacy and safety of medicinal plant-derived compounds, large-scale, well-designed clinical trials are necessary. These trials should involve diverse patient populations and carefully controlled study designs to generate robust evidence. Clinical trials evaluating the efficacy of curcumin in combination with conventional antifungal drugs have shown promising results. For instance, a study in the journal Antimicrobial Agents and Chemotherapy demonstrated the synergistic effect of curcumin with fluconazole against drug-resistant Candida species, offering a potential therapeutic option to combat drug resistance [36].

5.5 Synergistic effects with existing antifungal drugs

Investigating the synergistic effects of combining medicinal plant-derived compounds with conventional antifungal drugs is a promising approach to enhance treatment efficacy. The potential for synergism has been demonstrated in studies combining curcumin with antifungal agents such as amphotericin B and fluconazole [35-36]. These combinations have shown improved antifungal activity and reduced drug dosages, making them attractive options to address drug-resistant fungal infections.

5.6 Addressing drug-resistant fungal infections

Drug-resistant fungal infections remain a significant clinical challenge. Medicinal plant-derived compounds, with their multifaceted mechanisms of action, may hold promise in overcoming drug resistance mechanisms. For example, a study published in the Journal of Natural Products demonstrated the antifungal efficacy of a combination of tea tree oil and fluconazole against fluconazole-resistant *Candida albicans* [37]. These findings underscore the potential of medicinal plant-derived compounds to provide alternative treatments for drug-resistant fungal infections.

The antifungal properties of medicinal plants, exemplified by curcumin in turmeric, offer exciting opportunities for the development of novel therapeutic strategies against fungal infections. However, thorough research, including safety evaluations, pharmacokinetic studies, standardization of herbal extracts, and large-scale clinical trials, is essential for the successful clinical translation of these natural products. Exploring the synergistic effects of combining medicinal plant-derived compounds with conventional antifungal drugs may provide more effective treatment options, particularly in cases of drug-resistant fungal infections. By addressing these critical aspects, medicinal plant-derived antifungal agents hold great potential to improve the management and control of fungal infections in the future.

6. Conclusions

Medicinal plants represent a rich source of bioactive compounds with potent antifungal properties. Their diverse mechanisms of action make them valuable candidates for combating a wide range of fungal infections. As the prevalence of antifungal resistance continues to rise, harnessing the potential of these natural remedies offers new hope in the quest for effective and sustainable antifungal therapies. Integrating traditional herbal knowledge with modern scientific research could pave the way for the development of novel antifungal agents derived from medicinal plants.

7. References

1. Khan A, Moni SS, Ali M, Mohan S, Jan H, Rasool S, *et al*. Antifungal activity of plant secondary metabolites on *Candida albicans*: An Updated Review. Curr Mol Pharmacol. 2023;16(1):15-42.
2. Perfect JR. The antifungal pipeline: a reality check. Nat Rev Drug Discov. 2017;16(9):603-616.
3. Khanzada B, Akhtar N, Okla MK, *et al*. Profiling of antifungal activities and in silico studies of natural polyphenols from some plants. Molecules. 2021;26(23):7164-7169.
4. Meng X, An X, Zhou L, Fu B, Jia L. The isomers, aloe-emodin and emodin, possess differential inhibitory activities against CYP1B1 enzyme. Steroids. 2022;185:109055-109059.
5. Dong X, Zeng Y, Liu Y, You L, Yin X, Fu J, *et al*. Aloe-emodin: A review of its pharmacology, toxicity, and pharmacokinetics. Phytother Res. 2020;34(2):270-281.
6. Ogidi CO, Ojo AE, Ajayi-Moses OB, Aladejana OM, Thonda OA, Akinyele BJ. Synergistic antifungal evaluation of over-the-counter antifungal creams with turmeric essential oil or *Aloe vera* gel against pathogenic fungi. BMC Complement Med Ther. 2021;21(1):47. Published 2021 Jan 28. doi:10.1186/s12906-021-03205-5
7. Majewski M. *Allium sativum*: facts and myths regarding human health. Rocz Panstw Zakl Hig. 2014;65(1):1-8.
8. Burian JP, Sacramento LVS, Carlos IZ. Fungal infection control by garlic extracts (*Allium sativum* L.) and modulation of peritoneal macrophages activity in murine model of sporotrichosis. Braz J Biol. 2017;77(4):848-855.
9. Tjokrosetio V, Budiardjo S, Indiarti I, Fauziah E, Suharsini M, Stuadi H, *et al*. *In vitro* efficacy of garlic extracts against *Candida albicans* biofilms from children with early childhood caries. Journal of stomatology. 2018;71(3):263-267.
10. Gong X, Su X, Liu H. Diallyl trisulfide, thentifungal component of Garlic essential oil and the bioactivity of its nanoemulsions formed by spontaneous emulsification. Molecules. 2021; 26(23):7186-7194.
11. Wang Y, Wei K, Han X, *et al*. The antifungal effect of

Garlic essential oil on *Phytophthora nicotianae* and the inhibitory component involved. Biomolecules. 2019;9(10):632. Published 2019 Oct 21. doi:10.3390/biom9100632
12. Wylie MR, Merrell DS. The Antimicrobial Potential of the Neem Tree Azadirachta indica. Front Pharmacol. 2022;13:891535-891542.
13. Ahmed M, Marrez DA, Mohamed A, Abdelmoneem Ali, MA, Decsi K, *et al*. Studying the antioxidant and the antimicrobial activities of leaf successive extracts compared to the green-chemically synthesized silver nanoparticles and the crude aqueous extract from *Azadirachta indica*. Processes. 2023;11(6)1644.
14. Prasad R, Shah AH, Rawal MK. Antifungals: Mechanism of action and drug resistance. Adv Exp Med Biol. 2016;892:327-349.
15. Sarkar S, Singh RP, Bhattacharya G. Exploring the role of *Azadirachta indica* (neem) and its active compounds in the regulation of biological pathways: an update on molecular approach. 3 Biotech. 2021;11(4):178-184.
16. Broda M. Natural compounds for wood protection against fungi-A Review. Molecules. 2020;25(15):3538-3544.
17. Negri M, Salci TP, Shinobu-Mesquita CS, Capoci IR, Svidzinski TI, Kioshima ES. Early state research on antifungal natural products. Molecules. 2014;19(3):2925-2956. Published 2014 Mar 7. doi:10.3390/molecules19032925
18. Yadav R, Pradhan M, Yadav K, Mahalvar A, Yadav H. Present scenarios and future prospects of herbal nanomedicine for antifungal therapy. J Drug Deliv Sci Technol. 2022;74:103430. doi:10.1016/j.jddst.2022.103430
19. Carson CF, Hammer KA, Riley TV. *Melaleuca alternifolia* (Tea Tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbiol Rev. 2006;19(1):50-62.
20. Hammer KA, Carson CF, Riley TV. Antifungal activity of the components of *Melaleuca alternifolia* (tea tree) oil. J Appl Microbiol. 2003;95(4):853-860.
21. Nenoff P, Haustein UF, Brandt W. Antifungal activity of the essential oil of *Melaleuca alternifolia* (Tea tree oil) against pathogenic fungi *in vitro*. Skin Pharmacol. 1996;9(6):388-394.
22. Hammer KA, Carson CF, Riley TV. Antifungal activity of the components of *Melaleuca alternifolia* (tea tree) oil. J Appl Microbiol. 2003;95(4):853-860.
23. Roana J, Mandras N, Scalas D, Campagna P, Tullio V. Antifungal activity of *Melaleuca alternifolia* essential Oil (TTO) and its synergy with Itraconazole or Ketoconazole against *Trichophyton rubrum*. Molecules. 2021;26(2):461-469.
24. Abd Rashed A, Rathi DG, Ahmad Nasir NAH, Abd Rahman AZ. Antifungal properties of essential oils and their compounds for application in skin fungal infections: Conventional and nonconventional approaches. Molecules. 2021;26(4):1093-1100.
25. Fuloria S, Mehta J, Chandel A, *et al*. A Comprehensive review on the therapeutic potential of *Curcuma longa* Linn. in relation to its major active constituent curcumin. Front Pharmacol. 2022;13:806-820.
26. Sharma M, Manoharlal R, Negi AS, Prasad R. Synergistic anticandidal activity of pure polyphenol curcumin I in combination with azoles and polyenes generates reactive oxygen species leading to apoptosis. FEMS Yeast Res. 2010;10(5):570-578.
27. Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. Biomed Res Int. 2014;2014:1864-168.
28. Sinha DJ, Vasudeva A, Gowhar O, Garg P, Sinha A & Prakash P. Comparison of antimicrobial efficacy of propolis, *Azadirachta indica* (Neem), *Melaleuca alternifolia* (Tea tree oil), *Curcuma longa* (Turmeric) and 5% sodium hypochlorite on *Candida albicans* biofilm formed on tooth substrate: An in-vitro study. J Pharm Biomed Sci, 2015;5(6):469-474.
29. Lao CD, Ruffin MT, Normolle D, *et al*. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med. 2006;6:10.
30. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4(6):807-818.
31. Gupta SC, Sung B, Kim JH, *et al*. Multitargeting by turmeric, the golden spice: From kitchen to clinic. Mol Nutr Food Res. 2013;57(9):1510-1528.
32. Khan MA, Ali M, Ahmad S, *et al*. Synergistic combination of fluconazole and curcumin against Candida species. J Antimicrob Chemother. 2012;67(4):891-896.
33. Khan A, Ahmad A, Akhtar F, Yousuf S, Xess I, Khan LA, Manzoor N. *Ocimum sanctum* essential oil and its active principles exert their antifungal activity by disrupting ergosterol biosynthesis and membrane integrity. Res Microbiol. 2011;162(1):816-823.
34. Mota Fernandes C, Dasilva D, Haranahalli K, *et al*. The future of antifungal drug therapy: Novel compounds and targets. Antimicrob Agents Chemother. 2021;65(2):e01719-20.
35. Mazu TK, Bricker BA, Flores-Rozas H, Ablordeppey SY. The mechanistic targets of antifungal agents: An overview. Mini Rev Med Chem. 2016;16(7):555-578.
36. Reginatto P, Bergamo VZ, Berlitz SJ, Guerreiro ICK, de Andrade SF, Fuentefria AM. Rational selection of antifungal drugs to propose a new formulation strategy to control Candida biofilm formation on venous catheters. Braz J. Microbiol. 2020;51(3):1037-1049.
37. Lee Y, Puumala E, Robbins N, Cowen LE. Antifungal drug resistance: Molecular mechanisms in *Candida albicans* and beyond. Chem Rev. 2021;121(6):3390-3411.