

<https://africanjournalofbiomedicalresearch.com/index.php/AJBR>

Afr. J. Biomed. Res. Vol. 27(3s) (September 2024); 258-268

Research Article

Phytochemicals: Investigating Bioactive Compounds for Antifungal Uses and Quality Issues in Functional Foods and Therapeutics

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Abstract

The medicinal potential and functional dietary and nutraceutical uses of phytochemicals, which are naturally occurring substances sourced from plants, have attracted considerable study. With an emphasis on their bioactivity and possible in the fight against fungal infections, this review delves into the various functions of phytochemicals, including terpenoids, saponins, phenolic compounds, coumarins, and alkaloids. Terpenoids, which can be found in plants like *Artemisia* and *Cannabis*, have antifungal qualities that show promise. On the other hand, phenolic compounds and saponins are very effective against a variety of fungal infections. Our understanding of natural antifungal mechanisms is further enhanced by coumarins and alkaloids, such as those found in *Phyllanthus amarus* and *Alstonia scholaris*. A new avenue for increasing therapeutic efficacy has been identified in the review: the synergistic effects of mixing phytochemicals with conventional antifungal medications. Notwithstanding these benefits, there are still obstacles to overcome in terms of standards, toxicity, and production. Research in the future should be on finding better ways to make phytochemicals, making sure they are of high quality, and looking for new ways to combine them to treat fungal infections.

Keywords: Antifungal Agents, Phytochemicals, Terpenoids, Standardization, Synergistic Combinations, Toxicologys

Received: 10/07/2024 Accepted: 09/08/2024

DOI: <https://doi.org/10.53555/AJBR.v27i3S.1945>

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1. Introduction

Fungal infections, especially in people with weakened immune systems, have recently emerged as a major issue in world health. *Aspergillus*, *Candida*, and *Cryptococcus* are among the most dangerous invasive fungal infections (IFDs), which cause 1.5 million fatalities yearly [1]. Present antifungal treatments have their limits, which contributes to the rising prevalence of these illnesses. Side effects include liver damage and medication interactions are common with conventional antifungal drugs like echinocandins, azoles, and polyenes [2]. In addition, resistant fungal strains have emerged as a result of these medications' abuse and misuse, which further complicates treatment attempts [3]. The immediate necessity for new therapeutic strategies is underscored by the small number of antifungal classes and their diminished effectiveness as a result of resistance [4]. To overcome these obstacles, scientists must keep digging for new antifungal drugs and ways to enhance current treatment plans. There has been a lot of interest in phytochemicals derived from plants as a possible alternative medicine because of its medicinal and health effects. Antioxidant, anti-inflammatory, and anti-cancer characteristics are associated with flavonoids, a class of naturally occurring phenolic chemicals present in a wide variety of foods and drinks. Research has shown that eating foods high in flavonoids can lower your chance of developing chronic diseases like diabetes, heart disease, and neurological disorders [5]. Plant nitrogen compounds known as alkaloids have several medicinal uses, such as pain relief, inflammation reduction, and antimicrobial protection. For ages, alkaloids such as quinine and morphine have been part of traditional medicine. The immune-boosting, cholesterol-lowering, and anti-cancer benefits of saponins—glycosides having soap-like characteristics—are well-known. The anti-inflammatory characteristics of saponins have made them a viable treatment candidate for rheumatoid arthritis [6]. One class of plant phytochemicals called polyphenols helps ward off diseases caused by oxidative stress because of its potent antioxidant capabilities. Additionally, polyphenols have anti-carcinogenic and anti-inflammatory properties. Terpenoids are a big group of organic compounds with anti-inflammatory, antimicrobial, and anti-cancer effects. They are produced from five-carbon isoprene units. A variety of terpenoids have medicinal and nutritional uses in traditional medicine. There is continuing research that supports the efficacy and safety of these phytochemicals, making them a potential alternative to conventional therapy [7]. *Mimosa pudica* L. [8], *Cyperus scariosus* [9], monkeypox [10], epilepsy [11], COVID-19 [12, 13], *magnifera indica* [14], *Solanum*

lycopersicum L. phytoconstituents [15], phytochemicals derived from *Daucus carota* [16], conjunctivitis [17], and other plant-related diseases or conditions have been studied and reported in the literature. The creation of patches containing the antimicrobial ingredient *Ocimum santum* Linn [18]. The growth or degradation of certain soil contents is also caused by fungi [19]. Spring Green Gram *Vigna* Insects That Cause Pest Problems [20]. Antimicrobial resistance (AMR) is a major concern for global health; if left unchecked, it could result in 10 million deaths per year by 2050, making healthcare-associated infections (HAIs) and AMR a double-edged sword [21, 22]. In order to prevent serious consequences and higher healthcare expenses, effective infection control is vital in the case of healthcare-associated infections (HAIs) [23]. Thorough hand hygiene can cut healthcare-associated infections (HAIs) in half, and improved environmental cleaning techniques can drastically cut down on pathogen contamination on surfaces. For early outbreak detection, it is vital to continuously monitor infection rates and resistance patterns. Advanced data analytics can then be used to assist timely interventions [24]. Furthermore, healthcare providers can improve patient safety and lessen the impact of healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) by education and training on infection management measures [25]. With an emphasis on their bioactivity and possible in the fight against fungal infections, this review delves into the various functions of phytochemicals, including terpenoids, saponins, phenolic compounds, coumarins, and alkaloids. Terpenoids, which can be found in plants like *Artemisia* and *Cannabis*, have antifungal qualities that show promise. On the other hand, phenolic compounds and saponins are very effective against a variety of fungal infections. Our understanding of natural antifungal mechanisms is further enhanced by coumarins and alkaloids, such as those found in *Phyllanthus amarus* and *Alstonia scholaris*. A new avenue for increasing therapeutic efficacy has been identified in the review: the synergistic effects of mixing phytochemicals with conventional antifungal medications. Notwithstanding these benefits, there are still obstacles to overcome in terms of standards, toxicity, and production. Research in the future should be on finding better ways to make phytochemicals, making sure they are of high quality, and looking for new ways to combine them to treat fungal infections fig no.1: Demonstrating the antifungal activity of various plants and their bioactive compounds.

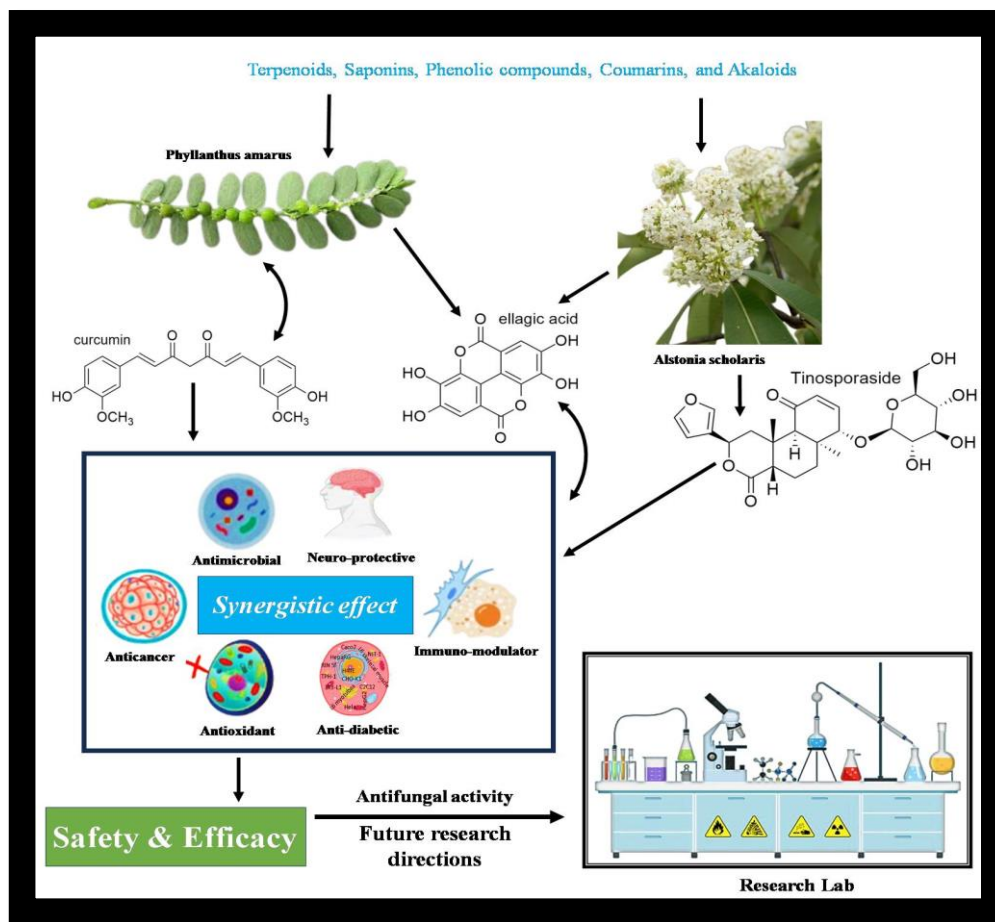


Figure No.1: Demonstrating the antifungal activity of various plants and their bioactive compounds

2. Phytochemicals: Bioactive Compounds for Health and Disease Prevention

2.1 Functional Foods and Nutraceuticals

Phytochemicals are bioactive substances derived from plants that plants use to defend themselves. Over a thousand phytochemicals have been identified so far, and they can be found in a wide variety of foods including whole grains, fruits, vegetables, nuts, and herbs. Dietary fibers, certain polysaccharides, phytosterols, carotenoids, isoprenoids, and saponins are a few of the important phytochemicals. In addition to their antioxidant properties, these phytochemicals show antiviral, antiallergic, antispasmodic, antihelmintic, antidiarrheal, and antimicrobial actions [26, 27]. Additionally, they aid in controlling gene transcription, improving immunity, and protecting against malignancies of the lung and prostate [28-32]. Functional food dimensions have been elevated thanks to the current emphasis on translational research. Functional foods and nutraceuticals rely heavily on phytochemicals, which are extracted from plants.

3. Terpenoids: Bioactive Compounds with Therapeutic and Toxicity Potential

Plants, bacteria, mammals, insects, marine life, and endophytes are all potential places to find terpenoids, which are secondary metabolites. There are about 40,000 known terpenoids, and researchers are only scratching the surface of this vast family. Cancer is just

one of many diseases that can benefit from the therapeutic and preventative potential of terpenoids, the majority of which have physiologically active variants. There are a number of anti-inflammatory, anti-fungal, antibacterial, antiviral, antiparasitic, antispasmodic, antiallergic, and antihyperglycemic characteristics exhibited by terpenoids [33]. The human neurological system and functional capacity are particularly vulnerable to the effects of certain poisonous terpenoid variants [34]. The structural organization of carbons and the number of C₅H₈ isoprene units (2-methylbuta-1,3-diene) are the two main criteria used to classify terpenoids. Terpenoids are mostly composed of compounds with a single isoprene unit. A hemiterpene molecule has five carbon atoms and one isoprene unit. From monoterpenes onward, each succeeding class gains five carbons and one isoprene unit.

4. Terpenoids: Therapeutic Potential and Antifungal Activity

The terpenoids found in cannabis have several uses, including fighting off parasites like malaria and fungus. Terpenoids found in cannabis hash oil from medicinal varieties outperformed those in essential oil from fiber varieties in terms of antibacterial activity [35]. Oregano extract contains the terpenoid phenols carvacrol, thymol, and eugenol, all of which possess strong antifungal properties. On top of that, terpenoid phenols work wonders on both planktonic cells and the

multidrug-resistant *Candida albicans* biofilms [36]. With a minimum inhibitory concentration (MIC) of less than 0.03%, carvacrol showed the most potent antifungal action against *C. albicans* biofilms among all terpenoid phenols. Not only did the terpenoid phenols suppress biofilms of *Candida albicans*, but they were also effective against *C. glabrata* and *C. parapsilosis* [37]. *Artemisia annua* chloroform extract antifungal fractions produced oleanolic acid, β -sitosterol, stigmasterol, two cadinane derivatives (arteannuin B and artemisinin), and oleanolic acid. One human (*C. albicans*) and four plant pathogenic fungi (*Gaeumannomyces graminis* var. *tritici*, *Rhizoctonia cerealis*, *Gerlachia nivalis*, and *Verticillium dahliae*) were shown to be antifungal by arteannuin B, a primary sesquiterpenoid in *A. annua* [38]. Sunflower terpenoids suppressed the formation of hyphae, making them antifungal against *Verticillium dahliae* and *Sclerotinia sclerotiorum*. Anthocyanin, arundifungin, enfumafungin, and ascosteroside are all new natural compounds. By inhibiting (1,3)- β -Dglucan synthase, an oral antifungal drug may be developed. Terpenoids showed antifungal activity that was on par with that of commercially available drugs like MK-0991 and L-733560. Additionally, a number of harmful *Candida* and *Aspergillus* strains were preferentially suppressed by the four terpenoids (ascosteroside, ergokonin A, arundifungin, and enfumafungin). For example, sorbitol's antifungal activity, a shift in shape, and the antifungal spectrum all point to terpenoids interfering with the glucan fungal cell wall assembly [39].

5. Saponins: Versatile Phytochemicals with Antifungal Properties

When saponins, a type of phytochemical, are dissolved in water, they form foam, which is one of their sensory qualities. One or more carbohydrate chains (sugar) are connected to an aglycone (sterol or common triterpene) unit in saponins, making them glycosides. A triterpenoid saponin is the most common type of saponin; these compounds have a hydrophilic end and a lipophilic or hydrophobic end. Monocotyledons are the usual places to find steroidal saponins. Oats, asparagus, spinach, peanuts, beans, and tea are some of the natural foods that contain saponins [40]. Saponins' primary function in plants is defense against diseases and animals. The commercial value of these compounds is significant because of their many uses in medicine, cosmetics, foaming agents, sweeteners, and flavor modifiers [41].

6. Phenolic and Saponin Antifungals: Natural Defenders with Therapeutic Potential

Extract of saponins from *Dioscorea panthaica* roots in a test against *Candida albicans*, Prain et Burk (HSE, or Huangshanyao saponin extract) was used. Between 16 and 64 $\mu\text{g/mL}$ of HSE, *C. albicans*' planktonic growth, biofilm formation, and development are inhibited. In addition, 64-256 $\mu\text{g/mL}$ of HSE could prevent the development of extracellular exopolysaccharide (EPS) and reactive oxygen species (ROS) in constructed biofilms. It was also tested for cytotoxicity against

humans using Chang's liver cells, however the IC₅₀ value was approximately 256 $\mu\text{g/mL}$, indicating modest cytotoxicity [42]. Tests were conducted to determine the antifungal activity of *Sapindus mukorossi* extract against two significant fungal infections globally: *Venturia inaequalis* and *Botrytis cinerea*. At a concentration of 1% v/v, the spray extract dramatically decreased symptoms of *V. inaequalis* and sporulation on the leaves of apple seedlings by 99% ($P < 0.05$). On average, a 63% reduction in disease severity was observed when grapes were treated with 1% v/v extract. Among the saponins found were oleanolic acid-hexosyl-deoxyhexosyl-hexoside and sapindoside B (hederagenin-pentosylhexoside) [43]. Are phenolic compounds what they claim to be? Plants and microbes release naturally occurring phenolic chemicals. They include at least one phenolic group and have a low molecular weight. These are the secondary metabolites that plants make naturally during growth and also when exposed to certain stresses, such as UV light or an injury [44]. Among the most well-known phytochemicals, phenolic compounds have far-reaching effects on plant shape and physiology. In addition to influencing the flavor and hue of the plant's fruits, these chemicals play an important role in development and generation by providing protection from infections and predators. The pentose phosphate, shikimate, and phenylpropanoid pathways in plants are the sources of these chemicals [45]. Isolated phenolic compounds from medicinal herbs and food plants include phenolic acids, flavonoids, tannins, stilbenes, curcuminoids, coumarins, lignans, quinines, and many more [46].

7. Essential phytochemicals for plant defense, development, and therapy

Plants and microbes release naturally occurring phenolic chemicals. They include at least one phenolic group and have a low molecular weight. They are the plant's secondary metabolites, created naturally throughout growth and also replicated in response to stressors like UV light and wounds [47]. Among the most well-known phytochemicals, phenolic compounds play a pivotal role in plant morphology and physiology. In addition to influencing the flavor and hue of the plant's fruits, these substances play an important role in development and generation by protecting them from predators and diseases. The pentose phosphate, shikimate, and phenylpropanoid pathways in plants are the sources of these chemicals [48]. Plants with medicinal and culinary uses contain phenolic chemicals such as acids, tannins, stilbenes, curcuminoids, coumarins, lignans, quinines, and many more [49].

8. Evaluation of Phenolic-Rich Plant Extracts and Compounds' Antifungal Activity

A number of investigations have sought to ascertain the antifungal efficacy of aqueous, ethanolic, methanolic, hydroalcoholic, acetone, and dimethyl sulfoxide (DMSO) polar plant extracts. After aqueous, methanolic, and ethanolic extracts, the most researched are these three types of solutions [50]. A potentilla

simplex Michx., an aqueous phenolic extract from *Epilobium angustifolium* L., and a *Fragaria virginiana* Duchesne showed promising antifungal activity. Of the three fungal pathogens tested, *Fragaria virginiana* showed the most activity against *Betula alleghaniensis* Britt., *Alnus viridis* DC., and *Solidago gigantea* Ait [51]. Using *Candida* planktonic and biofilm cells as targets, Alves et al. (2014) investigated the antifungal effects of four phenolic compounds isolated from flowers in northeastern Portugal: gallic acid, catechin, luteolin, and quercetin. According to the minimum inhibitory concentration (MIC) values, gallic acid was the most effective against every species of *Candida*. Similarly, catechin inhibited the growth of *Candida albicans* cells from the American Type Culture Collection (ATCC) 90028. Furthermore, quercetin and gallic acid had shown very little efficacy against biofilms of *Candida* species [52]. Using filamentous fungi from the genera *Fusarium*, *Aspergillus*, and *Penicillium*, Zabka and Pavela evaluated the antifungal effectiveness of 21 phenolic components derived from essential oils and plant compounds. The two most effective compounds were found to be thymol and carvacrol. The thymol MIC₅₀ values varied between 30 and 52 µg/mL. The values of MIC₁₀₀ for thymol varied between 76 and 255 µg/mL, in that order. The MIC₁₀₀ values for carvacrol varied between 131 and 262 µg/mL, while the MIC₅₀ values varied between 37 and 76 µg/mL [53]. Antifungal activity against *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton mentagrophytes*, and *T. rubrum* was demonstrated in fungal cultures in the presence of different doses of baicalein derived from *Ou-gon* extracts. The antifungal activity of wogonin, which was extracted from the same plant, was seen against all fungi with the exception of *Candida albicans* [54].

9. Coumarins: Multifunctional Bioactivities and Antifungal Potential

Coumarins, as their name suggests, are a kind of benzopyrone consisting of a benzene ring fused to an apyrone ring. They are obtained from the *Coumarouna odorata* plant. There is an abundance of coumarins in angiosperms, and there are thousands of them. There are more than 150 species of plants that contain them, spread across nearly 30 families. Some bacteria contain them, and they are primarily secondary metabolites of plants. Furthermore, coumarins have demonstrated potent antifungal activity in addition to their antioxidant, antiinflammatory, antifilarial, antiulcerogenic, trypanocidal, antibacterial, anticancer, and antiHIV properties. The structural diversity of coumarins allows for their classification into four distinct families. Two rings are present in coumarin derivatives, also known as simple coumarins, which have aliphatic, hydroxyl, or benzopyrone groups replaced at locations C7, C6, and C3. Isocoumarin derivatives, which consist of benzene rings and α -isopirone, have substituents at locations C3, C6, C7, and C8 and constitute the second group of coumarins. Many fungal species, including *Artemisia*, *Aspergillus*,

Fusarium, *Penicillium*, and *Streptomyces*, as well as a small number of plant families, including Leguminosae, Myrtaceae, and Compositae, are responsible for their isolation. A coumarin ring linked with a furan ring at the C6-C7 position (psoralen type) or the C7-C8 position (angelicin type) makes up the furanocoumarin derivatives, the third category. Last but not least, we have pyranocoumarin derivatives, which are xanthyletin-type or seselin-type depending on whether the condensation occurs at the C6-C7 or C7-C8 position [55].

10. Coumarins' Antifungal Effects on Pathogenic Fungi

Osthole is a coumarin derived from medicinal herbs such as *Peucedanum ostruthium*, *Angelica pubescens*, and *Cnidium monnieri*. *Osthonium graminearum*, *Botrytis cinerea*, *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, and *Phytophthora capsici* are among the most dangerous fungi that can be treated with osthole. The antifungal efficiency of psoralen, imperatorin, and ostruthin is the highest compared to all the coumarins [56]. Byosthol, a coumarin derivative found in celery plants, shows antimicrobial efficacy against *R. solani*, *P. capsici*, *B. cinerea*, *S. sclerotiorum*, and *F. graminearum* [57]. You may find the two kinds of coumarins that are antifungal in Table 1. The antifungal action of pyranocoumarin (PDP) found in *Psoralea corylifolia* was demonstrated in a study by Srinivasan and Sarada (2012). A molecular docking study using Tri101, trichothecene 3-Oacetyltransferase's X-ray crystal structures from the Protein Data Bank suggested a potential mechanism for their antifungal activity against the plant pathogen *Fusarium* sp., in addition to their capacity as an antifungal agent against *Fusarium* sp. When tested against *Fusarium oxysporum*, *Fusarium moniliforme*, and *Fusarium graminearum*, the PDP showed a minimum inhibitory value of 1 mg/mL. Molecular docking analysis has revealed a strong binding affinity for the target protein, which, once bound, will halt the acetylation process and ultimately kill the fungus. Within twenty-four hours of exposure, coumarin caused structural disarray, decreased cytoplasmic volume, and changes to the cell wall and membrane of *Candida albicans*. Coumarin (1,2-benzopyrone) has not yet had its mode of action shown. The exact mechanism that silver (I)-coumarin complexes used to combat *Candida albicans* was to impair cytochrome c production, which may also cause apoptosis [58]. This led to dysfunction in respiration and ergosterol synthesis. The effects of coumarin on cell growth suppression and strain viability decrease were investigated by Jia et al. (2019) through experiments that determined yeast apoptosis through phosphatidylserine (PS) externalization, DNA fragmentation, cytochrome c release, and metacaspase activation. Their findings investigated how coumarin affected PS exposure on the outer leaflet, DNA degradation and nuclear compaction, cytochrome c release, and metacaspase activation, indicating that coumarin caused *C. albicans* to undergo apoptosis.

Coumarins harm *Candida albicans* cells by penetrating the fungal cell wall, causing the contents of the cell to leak out and necrosis to develop, as has been previously shown [59].

11. Alkaloids: Structural Diversity, Bioimportance, and Antifungal Properties

Alkaloids, a structurally diverse class of chemicals, are produced from amino acids and have a nitrogen atom in the heterocyclic ring. Alkaloid names come from al-qali, the plant from which soda was initially isolated. Alkaloids make up 20% of plant-based secondary metabolites and are antibacterial, anticancer, narcotic, poisonous, and stimulating. Alkaloids from plant genera number over 12,000 now. This amount renders this natural product class physiologically significant [60]. There are many antifungal alkaloids. They block protein synthesis, intercalate fungal DNA, and enhance fungi inhibitor production in a pleiotropic manner. Morphine, extracted from *Papaver somniferum* in 1805, was the first medically valuable alkaloid [61]. Antifungal activity of *Chelidonium majus* alkaloid phenanthridine against clinical drug-resistant yeast isolates. Bibenzylisoquinoline alkaloids like cycleanine and cocsoline from *Albertisia villosa* are antibacterial, antifungal, and antiparasitic in addition to being cytotoxic [62].

12. Alkaloids' Antifungal Properties: From *Phyllanthus amarus*, *Alstonia scholaris*, and *Amaryllidaceae*

Allosecurinine is an alkaloid derived from the *Phyllanthus amarus* Linn. plant, which belongs to the Euphorbiaceae family. In 2007, Singh et al. investigated its antifungal effects. Even at extremely low concentrations, the alkaloid hindered the moderate spore germination of several species, including *Curvularia lunata*, *Curvularia* sp., *Collectotrichum* sp., *C. musae*, and *Heterosporium* sp. [63]. *Alstonia scholaris* has seven monoterpene indole alkaloids in its ethanolic leaf extract. The antifungal potential of the obtained compounds was evaluated in vitro against five different types of fungus. *Gibberella pulicaris* and *Cercospora nicotianae* were two fungus strains that the extract shown antifungal efficacy against [64]. In their study on the anti-yeast action of alkaloids, Miroslav et al. (2015) focused on six species of *Amaryllidaceae*. Results from retention indices, retention periods, and mass spectra allowed for the identification of sixteen of the twenty-five alkaloids detected. *Candida albicans*, *Candida glabrata*, *Candida dubliniensis*, and *Lodderomyces elongisporus* were examined in the antimicrobial assay. Although no antibacterial activity was discovered, the six extracts and 19 alkaloids from the *Amaryllidaceae* family demonstrated promising anti-yeast characteristics. *Narcissus jonquilla* cv. is one of the alkaloidal extracts. The most efficient anti-yeast strain was Baby Moon, with MIC values of 128 and 192 µg/mL, respectively. *Leucojum aestivum*, *Narcissus poeticus* var. *recurvus*, and *N. canaliculatus* were the next strains, according to reference 65.

13. Antifungal Phytochemicals Disrupt Fungal Structures and Metabolism

Plants produce antifungal phytochemicals. Through diverse ways, they suppress fungal pathogen growth and dissemination. Key mechanisms and important studies are listed below: Antifungal phytochemicals like saponins and essential oils damage fungal cell membranes, killing cells. The interaction of these chemicals with membrane sterols often causes disruption [66]. Polyphenols prevent the formation of fungal cell wall components like chitin and glucans. This weakens the cell wall and makes fungus more sensitive to environmental stress [67]. Alkaloids and flavonoids suppress fungal growth and reproduction by blocking nucleic acid synthesis. They attach to DNA or RNA, inhibiting replication and transcription [68]. Terpenoids can cause mitochondrial malfunction in fungus, causing energy loss and cell death. This is frequently done by altering mitochondrial membrane potential [69]. Many antifungal phytochemicals impede fungal metabolic enzymes. Tannins can block enzymes including β -glucosidase and proteases, which are essential for fungal growth and pathogenicity [70]. Antifungal phytochemicals can fight fungal infections in several ways, making them promising candidates for novel antifungal medicines.

14. Neem and Tulsi Antimicrobial and Antifungal Effects: Clinical and In-Vitro Studies

Research on the antibacterial properties of neem has been thorough. Extensive research has demonstrated its effectiveness in combating a range of illnesses, from skin disorders to dental plaque. One study showed that neem extract inhibited the growth of harmful bacteria, highlighting its antibacterial effect. The antifungal effects of neem have been validated by in-vitro research. Several bacterial strains, including *Escherichia coli* and *Staphylococcus aureus*, were effectively inhibited by the neem leaf methanolic extract. [71]. Because of its medicinal qualities, tulsi has a long history of usage in traditional medicine. Results from clinical research show that it can alleviate stress, boost the immune system, and cure respiratory problems. Researchers have found that tulsi extracts are highly effective against common fungal infections, including *Candida albicans* and *Aspergillus niger*, in in vitro tests [72].

15. Flavonoids, Terpenoids, and Essential Oils Effectively Fight Multiple Fungal Pathogens

The antifungal activity of these chemicals is quite strong. Plant flavonoids, for instance, have shown promise in combating fungi including *Aspergillus fumigatus*, *Candida albicans*, and *Trichophyton rubrum* [73]. By penetrating fungal cell membranes, terpenoids have shown antifungal capabilities. Their effectiveness against diseases such as *Alternaria alternata* and *Fusarium oxysporum* has been demonstrated in studies [74]. Clove and cinnamon essential oils, for example, have been shown to effectively halt the development of botrytis and penicillium, two fungal diseases [75].

16. Chalcone-Derived Compounds and Phytochemical Combinations Improve Conventional Antifungal Effectiveness

Studies have demonstrated that chemicals produced from chalcones can improve the effectiveness of more traditional antifungal medications, such as fluconazole and itraconazole. Synergistic effects against dermatophytes and *Candida* spp. have been demonstrated by these combinations, which reduce the dosages of each treatment individually [76, 77]. Phytochemicals combined with traditional antifungal medications have shown to increase efficacy while decreasing toxicity, as shown in several examples in the Antifungal Synergistic Drug Combination Database (ASDCD) [78]. These results demonstrate that phytochemicals have promising future use as antifungal agents, either alone or in conjunction with more traditional medications.

17. Phytochemicals Outperform Conventional Antifungals in Safety, Resistance, and Accessibility

There are a number of benefits to using phytochemicals instead of more traditional antifungal medications. Synthetic antifungal agents, such as azoles and polyenes, can cause serious side effects, including toxicity to the liver, kidney damage, and gastrointestinal problems; in contrast, natural compounds, such as tulsi and neem extracts, are generally well-tolerated and produce few adverse reactions. Fungal infections are less likely to develop resistance to phytochemicals because of their diverse chemical structures and various modes of action. For example, essential oils are rich in a variety of bioactive chemicals that inhibit fungal resistance. *Candida auris* and other fungus strains that are resistant to synthetic antifungal medications have emerged as a result of their overuse and misuse. Plus, many phytochemicals are produced by plants that are already in the area, which makes them more accessible and economical, particularly in underdeveloped areas. In India and other Asian countries, you may easily find tulsi and neem. The high cost of treatment is a major obstacle for patients in underdeveloped nations, as synthetic antifungal medications are not always easily accessible or affordable in areas with little resources. In contexts where resources are scarce, these benefits underscore the possibility of phytochemicals as substitutes or adjuncts to traditional antifungal treatments [79, 80].

18. Quality, Safety, and Production Challenges of Phytochemicals: Standardization, Toxicology, production advances

It is critical to guarantee that phytochemical extracts are of high quality and consistent. All stages of the growing, harvesting, and manufacturing operations are subjected to rigorous quality controls to ensure that standardized extracts are of consistent quality and contain consistent quantities of required components [81]. Finding out how high-quality herbal products are requires a battery of analytical procedures, some of which include chemical and phytochemical testing [82].

In small dosages, phytochemicals are usually harmless, but in large quantities, they become hazardous. Phytotoxins are a class of phytochemicals that can induce cancer, hepatotoxicity, and nephrotoxicity [83]. To guarantee their safe usage, it is crucial to know their pharmacology and toxicity. [84]. The high production costs, vulnerability to pests and diseases, and large-scale land usage requirements are some of the obstacles to the widespread production of phytochemicals. Also, these chemicals aren't always best suited for chemical synthesis because of all the procedures and harsh conditions involved [85]. The development of phytochemicals in heterologous systems, as well as ciprofloxacin compounds with broad antimicrobial activity, is an area of active investigation in metabolic engineering and synthetic biology [86, 87].

Conclusion

Because of their wide range of bioactive characteristics, phytochemicals hold great promise as future antifungal drugs and functional food ingredients. A number of these substances have shown antifungal effectiveness against both common and resistant fungal infections; they include terpenoids, saponins, phenolic compounds, coumarins, and alkaloids, each of which has its own specific purpose. They have therapeutic promise due to their capacity to supplement standard antifungal therapies with synergistic mixtures of phytochemicals. Still, a major obstacle is making sure phytochemical products are safe, high-quality, and affordable. The successful integration of phytochemicals into mainstream treatments and nutraceuticals will depend on addressing these challenges through increased standardization, understanding toxicological profiles, and advancing production procedures.

Future Directions

Improving yield and purity, which can lower costs and increase accessibility, is crucial for optimizing phytochemical production. Additional advancements in metabolic engineering and synthetic biology are necessary for this. Consistent quality and therapeutic efficacy, in accordance with regulatory norms and safety, can be achieved through the development of strong standardization processes and quality control systems. Safer treatment solutions can only be developed with the help of thorough toxicological studies that can detect possible side effects and set safe usage guidelines. It is recommended that clinical trials and in-vitro investigations evaluate new phytochemical combinations with traditional antifungal drugs in order to increase efficacy and decrease resistance. Further investigation into various under-studied plant sources for the development of novel phytochemicals possessing antifungal properties is of the utmost importance. In settings with limited resources, increasing production and enhancing availability will be greatly aided by tackling production hurdles like pest control and high prices.

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