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Nature's Pharmacy: Plant-Based Antifungal Agents and Their Therapeutic Potential

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Abstract

Antifungal resistance has increased dramatically over the last 10 years, causing serious problems for healthcare because of higher morbidity and death. The urgent need for new treatments is highlighted by the scarcity of effective antifungal medications, their toxicity, and the rise of resistant strains. Since many plants have bioactive secondary metabolites with strong antifungal qualities, including alkaloids, flavonoids, terpenoids, phenolics, and saponins, ethnobotanical sources offer a viable path. Plants with notable antifungal action, such as Bridelia retusa, Hypoestes serpens, and Piper crassinervium, have been used in traditional medicine. These phytochemicals work by causing oxidative stress, blocking ergosterol synthesis, and rupturing fungal membranes. Recent developments in nanotechnology have improved the clinical potential of plant-derived chemicals by increasing their stability, bioavailability, and targeted delivery. Nevertheless, issues with bioavailability, standardization, and regulatory approval still exist. Finding safe, efficient, and long-lasting antifungal medicines to counteract growing resistance may be made easier by combining ethnobotanical knowledge with contemporary scientific study.

Keywords: Antifungal resistance, *Bridelia retusa*, Flavonoids, *Hypoestes serpens*, nanotechnology, phytochemicals, *Piper crassinervium*, Plant-derived antifungal agents, Terpenoids

INTRODUCTION

Over the last ten years, there has been a notable rise in antifungal agent resistance occurrence [1]. Something harmful to fungal cells may also be harmful to host cells because humans and fungi share some molecular mechanisms. Current medical issues are represented by patients with diabetes, AIDS, organ transplant recipients, and chemotherapy patients [1]. Serious problems with the medications now used to treat fungal infections include harmful side effects and the emergence of fungal resistance. For almost 30 years, amphotericin B, a broad-spectrum medication, was the only treatment available. It is one of the few medications that truly destroys fungal cells, but it can seriously harm patients' kidneys. Imidazoles and triazoles, which were significant developments in the late 1980s and early 1990s, respectively, work by blocking the fungal cell's functions; however, they frequently cause infection recurrence and drug resistance [2]. Fungal illnesses have become more common in recent decades, and several fungi have emerged as opportunistic pathogens. Although there are plant species that can treat antifungal diseases and antifungal chemicals found in nature, their clinical applications are restricted because there are not enough clinical studies or antifungal compounds available. It is imperative that both industry and academics step up their efforts to find or create new antifungal medicines, including compounds derived from plants, to develop innovative approaches to the detection and treatment of fungal illnesses. The Euphorbiaceous family tree *Bridelia retusa* (L) Spreng. is a moderately sized tree that may grow up to 20 meters in height. It can be found growing across the Himalayas, from Nepal to the hills of Assam, Meghalaya, Manipur, and Arunachal Pradesh, as

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well as in South India and Sri Lanka. Its leaves are used as fodder and are simple, alternating, oval, acute or acuminate, hairy, and prominently veined. The stem is pointed and armed. It is used to tan its dark gray bark. The petite, unisexual flowers are arranged in axillary spikes. The fruit is a drupe with a solitary seed and a diameter of 5 mm [3–5]. Research to validate the use of folk medicine has already been conducted for a long time. For many ages, medicinal plants have provided a vast array of physiologically active chemicals that are widely employed as pure or crude materials to treat a variety of illnesses. Out of the estimated 250,000–500,000 plant species on Earth, humans consume just about 10% of them [6]. The chemical diversity present in synthetic libraries is complemented by that of natural materials. However, due to the lengthy evolutionary selection process, natural products have a higher range of ring systems and are sterically more complex. As a result, methods for the manufacture of natural product-like libraries through the diversification of natural product mixes by combinatorial biosynthesis and related techniques can be developed, as well as strategies to exploit natural sources. As conventional antibiotics lose their efficacy, mainstream medicine is becoming more accepting of the use of antimicrobials and other medications made from plants [7]. Numerous substances that have been isolated from plants, including indole derivatives, hydroxydihydrocornin-aglycones, and dimethyl pyrrole, have been shown to exhibit antifungal properties [8]. Nevertheless, it has not yet proven feasible to turn these compounds into effective antifungal medications. Important antifungal chemicals that have been identified from higher plants are attempted to be covered in this review. Flavones are phenolic compounds with a single carboxyl group; a flavonol is created when a 3-hydroxyl group is added. *Selaginella tamariscina*'s amentoflavone (4) shown strong antifungal activity (IC50 value of 18.3 mg/ml) against several harmful fungal strains while having very little hemolytic effect on human erythrocytes [9]. All tested dermatophytes were susceptible to the antifungal action of the four compounds from *Piper solmsianum*: eupomatenoid-3, eupomatenoid-5 (5), conocarpan (6), and orientin (7). Their MIC values ranged from 2.0 to 60.0 mg/ml, and their potency was comparable to that of the common antifungal medication ketoconazole [10]. Because of its therapeutic benefits, *Inula viscosa* is currently utilized as a common medication. Even at low doses (10 mg/ml), the plant's flavonoids, azulenes, sesquiterpenes, and essential oils demonstrated a strong antifungal effect against dermatophytes. The higher antifungal activity of the leaf extracts may be explained by the high amounts of the sesquiterpene carboxyeudesmadiene [11]. According to reports, coumarins excite macrophages, which may have an indirect detrimental effect on infections. The phenolic compounds known as coumarins are composed of α-pyrone and benzene rings bonded together. Their antithrombotic, anti-inflammatory, and vasodilatory properties, as well as their application in preventing human cold sore recurrences caused by HSV-1, have mostly contributed to their notoriety [12]. Isolated from *Clausena excavata*, clauszoline J (15), dentatin, nor-dentatin, and carbazole derivatives, as well as clausenidin (14), demonstrated antimycotic action (MIC = 50 mg/ml). Additionally, a synthetic coumarin called O-methylated clausenidin (MIC = 50 mg/ml) showed considerable antimycotic efficacy [13]. 1-Tigloyloxy-8bH,10bH-eremophil 7(11)-en-8a,12-olide, a bioactive eremophilanolide (16), was isolated from Senecio poepigii and demonstrated antifungal characteristics [14]. Baccharis pedunculata's dichloromethane leaf extract included a prenylated coumarin, which was found to be the cause of the antifungal action against a few human pathogenic fungi [15]. According to a 1977 study, 30% of essential oil derivatives tested so far inhibited bacteria, whereas 60% inhibited fungi [16]. According to reports, the main oils' constituents – cineole, geranial, carvacrol, thymol, p-cymene, and 1,8-cineole – have antifungal properties. When coupled with ketoconazole, the antifungal properties of the essential oil from Agastache rugosa and its primary constituent, estragole, were found to have notable synergistic effects [17]. The essential oil from the leaves of *Litsea cubeba* has α-cis-ocimene [18]. 3,7 dimethyl-1,6-octadien-3-ol [19] and n-trans-nerolidol [20] shown clear antifungal properties, with MICs for used pathogenic fungi ranging from 0.03 to 0.4 ml/ml and for molds from 1.0 to 2.0 ml/ml [21].

Fungal illnesses have become more common in recent decades, and several fungi have emerged as opportunistic pathogens. Although there are plant species that can treat antifungal infections and produce antifungal compounds in nature, their therapeutic applications are restricted because there are not enough antifungal compounds on the market and there is not enough clinical research on them. It is imperative that both industry and academics step up their efforts to find or create new antifungal

medicines, including compounds derived from plants, to develop innovative approaches to the detection and treatment of fungal illnesses. The quest for novel chemicals with possible antifungal properties is urgent, and it is anticipated that global expenditures on the development of novel antifungal drugs will rise in the coming years. In recent years, a lot of research has been done on new sources, particularly antifungal chemicals produced from plants. Here, we will talk about certain therapeutic herbs that have been purified recently that have antifungal action against pathogenic fungal species, including *Bridelia retusa*, *Hypoestes serpens*, and *Piper crassinervium*.

Bridelia retusa

In the traditional medical system, *Bridelia retusa* is used as an astringent and to treat rheumatism [22]. Additionally, it soothes vitiated pitta, vata, diarrhea, nausea, hemorrhoids, bleeding, menorrhagia, leukorrhea, arthritis, diabetes, wounds, ulcers, and poisoning. Additionally, it has been reported that the plant possesses antibacterial and contraceptive properties against *Salmonella* typhi, *Shigella dysenteriae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus* [23, 24]. Its bark's aqueous and alcoholic extracts were examined for their immediate anti-inflammatory properties in rat paw edema caused by carrageenan [25].

Hypoestes serpens

The herbaceous plant *Hypoestes serpens* (Vahl) R. Br., which belongs to the Acanthaceae family, thrives in Madagascar's central area [26, 27]. There are over 2,500 species and 250 genera in the H. serpens family. Its leaves are simple and opposite and decussate without stipules. Brightly colored bracts accompany zygomorphic, bisexual flowers. The corolla is sympetalous, typically 5-merous, primarily zygomorphic, and typically 2-lipped, while the calyx is profoundly 4–5 lobed or occasionally drastically reduced with more frequent minute teeth. There are typically four didynamous stamens in the androecium. A single compound pistil with two carpels, a single style, and a superior ovary with two locules – each often containing two to ten axile ovules in one or two collateral vertical tiers – make up the gynoecium. Typically, an annular nectary disk is located around the ovary's base. Usually, the fruit is a loculicidal capsule that is elastically dehiscent [28]. Malagasy folk medicine uses a decoction of H. serpens leaves to treat infected vaginitis and excessive blood pressure [26, 27]. Its leaves' defatted chloroform extract has been used to isolate fusicoccane diterpene, which was found to have a relaxing effect on isolated rat aorta [29].

Piper crassinervium

A branching shrub or small tree that can grow to a height of 2–5 meters, *Piper crassinervium* is a member of the Piperaceae family and is commonly found in the Atlantic Forest (Brazil), Peru, Colombia, and Ecuador [30]. It has pubescent and alternating leaves. The lateral veins are ascending-arching and connect to the leaf blades by a fainter ladder-like tertiary vein, while the leaf blades are clearly pinnately veined. Sessile flowers are carried on the rachis' surface. It has white hair on the border of its flowery bracts. It has three (–4) stigmas, two (–6) stamens, and (2–). Sessile fruit [31], there are over 1950 species and 14 genera in the Piperaceae family [32]. Piper and Peperomia are the most prevalent of them, with over 700 and 600 species, respectively [33]. Using 2,2-azo-bis(2-amidinopropane) (ABAP) as a peroxyl radical source, the antioxidant potential of prenylated hydroquinones and prenylated 4-hydroxy-benzoic acids from *P. crassinervium* fruits was recently observed in terms of their ability to suppress both DPPH (2,2-diphenyl-1-picrylhydrazyl) radical and chemiluminescence generated from luminol [34].

Antifungal Resistance

Clinicians tasked with treating patients at high risk for invasive mycoses are increasingly concerned about antifungal resistance. After exposure, acquired mechanisms may lead to the development of resistance to currently available antifungal drugs. Yes, to these medications. Increased azole resistance in isolates of non-Candida albicans, azole resistance in Aspergillus fumigatus, and echinocandin resistance in C. glabrata are recent developments in acquired antifungal resistance [35–37]. As mentioned earlier, the most common non-*C. albicans* species that cause infections might differ geographically, and azole

resistance rates can also differ amongst institutions. Clinicians' prescription practices for the management of invasive candidiasis as well as its prevention may have an impact on this [38].

ETHNOBOTANICAL SOURCES OF ANTIFUNGAL COMPOUNDS

A wealth of antifungal compounds derived from plants that have historically been used to treat fungal infections worldwide can be found in ethnobotanical sources. Fungal growth is inhibited by bioactive secondary metabolites found in many plants, including phenolics, flavonoids, alkaloids, saponins, and essential oils. For instance, *Lawsonia inermis* (henna) and *Azadirachta indica* (neem) are extensively researched for their antifungal qualities, which work well against a variety of fungal species. Thymoquinone, a compound found in Nigella sativa (black seed), also has potent antifungal properties. Other plants that exhibit inhibitory effects on fungi that cause skin and systemic infections include *Aristolochia longa*, *Combretum latifolium*, and several Ethiopian medicinal plants. These plants are frequently utilized in traditional medicines in a variety of forms, including powders, oils, and aqueous extracts. Usually, their methods entail rupturing fungal cell walls or interfering with fungal metabolism [39].

The fact that ethnobotanical antifungal plants come from a variety of geographical areas emphasizes how worldwide plant-based antifungal resources are. Scientific studies that isolate and identify the key phytochemicals responsible for efficacy have validated these plants' antifungal activity. These plants serve as the foundation for creating safer and more affordable antifungal medications, which is crucial given the rise in antifungal resistance. Overall, modern research and ethnobotanical knowledge continue to identify promising plants with strong antifungal properties, promoting the sustainable use and preservation of traditional medicinal plants [39].

PHYTOCHEMICALS WITH ANTIFUNGAL ACTIVITY

Terpenoids, flavonoids, alkaloids, phenolics, and saponins are some of the main classes of phytochemicals that have antifungal properties. These substances mainly work against fungi by rupturing their cell membranes, blocking important enzymes, stopping the growth of biofilms, and interfering with the synthesis of fungal cell walls [40].

Alkaloids are nitrogen-containing substances that interfere with the integrity of fungal membranes and inhibit the activity of fungal enzymes. Examples of alkaloids that target metabolic pathways to inhibit fungal growth include berberine and jatrorrhizine. Fungal RNA/protein synthesis and cell wall synthesis are inhibited by flavonoids, which also interact with fungal membranes to change permeability and cause leakage. Well-known examples of terpenoids, which include monoterpenes, sesquiterpenes, and diterpenes, include eugenol (clove oil) and carvacrol (oregano oil), which damage hyphal tissue and cause ion leakage by disrupting fungal membranes. Fungal cell lysis results from saponins' disruption of membrane integrity. Fungal proteins and enzymes are bound by phenolic compounds, which impair cellular processes and membrane integrity [41].

Numerous phytochemicals target ergosterol, a crucial component of fungal membranes, at the molecular level, impairing membrane stability and allowing cell contents to seep out. Additional mechanisms include the inhibition of ergosterol biosynthesis-related enzymes, such as 14-α demethylase, which is essential for fungal growth. Moreover, phytochemicals can cause oxidative stress in fungal cells and interfere with the formation of biofilms, which shields fungi from antifungal medications. Additionally, some enhance antifungal defense by modifying host immune responses [41].

FORMULATION INNOVATIONS

The delivery and effectiveness of plant-based antifungal phytochemicals have been greatly enhanced by recent developments in nanotechnology. The bioavailability, stability, and targeted delivery of phytochemicals, like curcumin, quercetin, eugenol, and berberine, are improved by nanoformulations, like lipid nanoparticles, liposomes, and nanomicelles, which also address problems like poor solubility and fast metabolism. These nanosystems provide controlled and sustained drug release, lessen systemic toxicity, and enable deeper penetration into fungal cells.

Research shows that nanoencapsulation improves antifungal activity by dramatically reducing the minimum inhibitory concentration (MIC) of phytochemicals against fungi like Aspergillus fumigatus and Candida albicans. Lipid nanoparticles loaded with curcumin, for instance, exhibit a 48-hour duration of release, increasing therapeutic efficacy while reducing adverse effects. To further enhance antifungal effects, liposomal, and polymeric nanoparticles have also been used to deliver antifungal agents like natamycin and hexaconazole.

In addition to enhancing the pharmacokinetics of herbal compounds, nanoformulation techniques make it possible for combination therapies that can fight drug resistance. This novel strategy has the potential to overcome the drawbacks of conventional formulations and create strong, secure, and efficient antifungal treatments, particularly for systemic infections.

CHALLENGES AND FUTURE DIRECTIONS

Regulatory approval, bioavailability, and standardization are among the difficulties in using phytochemicals as antifungal agents. Geographical, environmental, genetic, and harvesting factors can all significantly alter the plant extract chemical makeup, resulting in varying potencies and levels of efficacy. Because of this variability, it is challenging to guarantee consistent therapeutic results when extract preparation and dosage are complicated. Standardization is made more difficult by the complexity of phytochemical mixtures, which can have unforeseen antagonistic or synergistic effects. Additionally, many phytochemicals' clinical efficacy is limited by their rapid metabolism and poor bioavailability.

The strict safety and efficacy requirements for plant-based antifungals make regulatory approval extremely difficult. Widespread adoption is frequently hampered by the lack of solid clinical trial data to back up traditional medicinal claims. Concerns about toxicity and contamination make it difficult for many botanical products to meet quality control standards [41].

The necessity of thorough clinical trials and safety profiling to confirm antifungal efficacy and detect possible side effects is emphasized in future directions. To increase reproducibility, research should concentrate on creating standardized extraction and formulation methods. Delivery and stability of bioactive compounds can be improved by developments in biotechnology and analytical technologies, including nanotechnology. For the development of safe, efficient, and standardized plant-based antifungal treatments, cooperation between researchers, regulatory bodies, and industries is crucial in addressing ethical, environmental, and commercial issues [41].

CONCLUSION

Antifungal resistance has grown over the last decade, posing a serious global health threat and affecting rates of morbidity and mortality, particularly for vulnerable groups like AIDS patients, diabetic patients, organ transplant recipients, and chemotherapy patients. Because fungi and their hosts share molecular pathways, antifungal treatments must target fungal cells without endangering human cells. Even though they are generally effective, traditional antifungal medications, like amphotericin B, have major adverse effects such as nephrotoxicity. Although they initially increased treatment options, newer classes, like imidazoles and triazoles – which were developed between the late 1980s and early 1990s – have resulted in problems like recurring infections and growing drug resistance. These difficulties highlight the pressing need for novel antifungal treatments, especially considering the increasing frequency of opportunistic fungal infections.

Numerous phytochemical classes, including alkaloids, flavonoids, terpenoids, phenolics, and saponins, are among the many and mainly unexplored sources of novel antifungal compounds found in medicinal plants. Through a variety of mechanisms, including disrupting fungal membranes, inhibiting important enzymes, preventing biofilm formation, and modulating host immune responses, these natural compounds exhibit antifungal properties. In vitro studies have confirmed the strong antifungal properties of plants, such as *Bridelia retusa*, *Hypoestes serpens*, and *Piper crassinervium*, as well as essential oils from different species. Phytochemicals fight fungal infections and lower toxicity risks by targeting components unique to fungi like ergosterol and 14-α demethylase.

But there are still a lot of obstacles in the way of turning phytochemicals into effective antifungals. Standardization and reproducibility of extracts are jeopardized by variations in plant composition brought on by harvesting, genetic, and environmental factors. Numerous phytochemicals have poor bioavailability and fast metabolism, and complex mixtures can result in unpredictable interactions. These problems are made worse by regulatory obstacles, which prevent approval and adoption due to a lack of thorough clinical trials and worries about toxicity, safety, and quality control.

A promising remedy for many of these issues is nanotechnology. Lipid nanoparticles, liposomes, and nanomicelles are examples of nanoformulations that improve solubility, stability, bioavailability, and targeted delivery of phytochemicals. To provide controlled release and minimize side effects, nanoencapsulation lowers the minimum inhibitory concentrations of antifungal compounds against pathogens such as Aspergillus fumigatus and Candida albicans. Furthermore, combination therapies made possible by nanotechnology can help improve outcomes and overcome drug resistance, particularly in cases of systemic fungal infections.

Finding and improving plant-based antifungals will require combining ethnobotanical knowledge, phytochemistry, biotechnology, and nanotechnology. While genetic and metabolic engineering of plants or their endophytes may increase the production of active constituents, high-throughput screening and artificial intelligence tools can speed up the identification of powerful compounds. To create standardized extraction techniques, carry out reliable clinical trials, and guarantee safety and efficacy, cooperation between researchers, regulatory bodies, and industry stakeholders is crucial.

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