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Beyond Synthetic Drugs: Evaluating the Therapeutic Landscape of Antifungal Phytomedicines

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ABSTRACT

Most of the conventional synthetic antifungal agents are highly toxic and hence, they need to be replaced by safer alternatives. Medicinal flora, therefore, provides a sustainable source of bioactive molecules that have the potential to act as novel antifungal agents. The present review aims to provide a detailed review of medicinal plants and their derived phytochemicals that can be used as valuable scaffolds to derive bioactive molecules that target fungal infections by acting at multiple sites. Various bioactive plant-derived molecules were reported to affect fungal cell membrane integrity, biofilm formation, mitochondrial functions, and ultimately genomic reprogramming via S-adenosyl-L- methionine (SAM) pathway. In addition, efficient drug delivery system like nanohydrogels to stabilize plant-derived bioactive extracts is also discussed in this review. The integration of ethnobotany with genomics and nanotechnology to develop therapeutic potential of medicinal plants-derived bioactive molecules to combat fungal infections to produce drugs with resistance against fungal infections is also discussed.

Keywords: Antifungal resistance, Medicinal plants, Phytochemicals, Biofilms, Nanotechnology.

1. INTRODUCTION

Fungal infections that were previously considered to be of little importance to man, in relation to the incidence of viral and bacterial infections are now of worldwide importance, with estimates suggesting that they are responsible for some 150 million new infections and 1.5 million deaths worldwide each year (Birnie et al., 2024). The increasing incidence of immunodeficiency diseases such as HIV/AIDS, diabetes, etc. and the absence of effective remedies against certain fungal infections are all contributing to the emergence of drug resistance in the four classes of synthetic drugs employed against the various types of fungal infections. Plant-based fungicides offer great potential in the development of novel safe fungicides. This review aims at highlighting the use of some medicinal plants and their mechanisms of actions for controlling human and plant diseases caused by fungi.(*Global Burden of Fungal Infections And*, n.d.)

2. PHYTOCHEMICAL CLASSIFICATION AND BIOACTIVE COMPOUNDS IN ANTIFUNGAL HERBS

2.1. Phenolic Compounds, Flavonoids, and Anthraquinones

Phenolic compounds are significant plant secondary metabolites having an aromatic ring with hydroxyl group and they possess wide spectrum of antifungal activities. Azole toxicity towards fungi is due to hydroxyl group present at specific position in azole molecules which cause denaturation of proteins and membrane disruption. Among all phenolic compounds, flavonoids are the most predominant compounds which are responsible for the inhibition of growth of Candida and Aspergillus by interacting with proteins and causing damage to cell wall and hence, flavonoids have synergistic activity towards azoles by targeting ERG11 gene. A variety of antifungal anthraquinones and their glycosides were isolated from Rumex japonicus and were reported to have antifungal activities towards dermatophytes especially chrysophanol and emodin.(Edri et al., 2023)

Table No. 1.1: Representative Phytochemicals: Sources and Primary Biological Functions.

Phytochemical Subclass	Representative Compounds	Exemplary Plant Sources	Primary Biological Function
Flavonoids	Quercetin, Rutin, Apigenin	*Allium cepa*, *Camellia sinensis*	Inhibition of protein synthesis; ERG11 downregulation
Anthraquinones	Emodin, Aloe-emodin, Rhein	*Rumex japonicus*, *Cassia alata*	Disruption of cell wall and membrane; ATP depletion
Phenolic Acids	Rosmarinic acid, p-Coumaric acid	*Rosmarinus officinalis, Melissa officinalis*	Reduction of biofilm exopolysacc harides (EPS)
Tannins	Gallotannins, Ellagitannins	*Punica granatum, Cinnamomum spp.*	Protein precipitation; enzyme inhibition

Phenolics are a large group of compounds with diverse structures, and as a result they are involved in a variety of inhibitory activities. Therefore, gallotannins which are constituents of the fruit extracts of Pomegranate (Punica granatum) have a high affinity for proteins and they inhibit fungal SAPs (Secreted Aspartic Proteinases) and keratinases, which are important enzymes for the pathogenicity and for the softening of plant tissues.(Pilevar et al., 2024)

2.2 Terpenoids and Volatile Constituents of Essential Oils

Several species of medicinal plants which contain large amount of carvacrol and thymol, such as thyme (Thymus vulgaris) and oregano (Ligusticum or Thymus x hybrida) essential oils, exhibit strong antifungal activity towards different Candida species via affecting membrane integrity, and towards Aspergillus flavus via affecting the levels of ergosterol. Thymol induces disturbances in intracellular calcium homeostasis by depressing expression of calcium transporters, which exerts cytotoxicity to cells. Terpenes such as beta-caryophyllene, limonene and sabinene in Piper nigrum (black pepper) and Syzygium aromaticum (clove) affect the fungal cell membrane and envelope structure.(Calegari- Alves et al., 2025)

Table No. 1.2: Major Terpenoids in Essential Oils and Their Documented Antifungal Effects.

Essential Oil Source	Major Terpenoid	MIC Range	Documented Antifungal Effect
Cinnamomum zeylanicum	Cinnamaldehyde	0.01 ug/mL	Germ tube inhibition; cell wall damage
Eucalyptus globulus	1,8-Cineole	0.05 ug/mL	Membrane disruption; synergistic with azoles
Cymbopogon spp.	Citral / Lemongrass oil	0.06 ug/mL	Biofilm inhibition; cytoplasmic
			leakage
Mentha piperita	Menthol / Peppermint oil	0.08 ug/mL	High potency against Candida spp.

Air stability is a common limitation to the biological applicability of many bioactive VOCs. Due to their aerosolization properties, bioactive VOCs represent interesting therapeutic strategies for the treatment of respiratory fungal infections and have shown great efficacy as air vector for the room air disinfection by nebulization. However, they are prone to autoxidation and epimerization and therefore need to be incorporated into nanotechnology-based formulations which will provide prolonged activity at the target site, such as with polysaccharide nanohydrogels.

2.3 Alkaloids, Glycosides, and Saponins in Medicinal Flora

Table No. 2.3.1: Chemical Classification and Mechanistic Insights of Key Plant-Derived Compounds.

Plant Species	Key Compound	Chemical Class	Mechanism Highlight
Berberis spp.	Berberine	Alkaloid	HSF1 inhibition; Calcineurin pathway disruption
Kalopanax pictus	Kalopanaxsaponin A	Saponin	Mitochondrial respiratory chain interference

Phenolic compounds are significant plant secondary metabolites having an aromatic ring with hydroxyl group and they possess wide spectrum of antifungal activities. Azole toxicity towards fungi is due to hydroxyl group present at specific position in azole molecules which cause denaturation of proteins and membrane disruption. Among all phenolic compounds, flavonoids are the most predominant compounds which are responsible for the inhibition of growth of Candida and Aspergillus by interacting with proteins and causing damage to cell wall and hence, flavonoids have synergistic activity towards azoles by targeting ERG11 gene. A variety of antifungal anthraquinones and their glycosides were isolated from Rumex japonicus and were reported to have antifungal activities towards dermatophytes especially chrysophanol and emodin.

Table No. 2.3.2: Plant Species and Their Key Bioactive Compounds with Mechanistic Insights.

Asparagus racemosus	**Saponins**	**Saponin**	**Perforation of lipid bilayers;low hemolysis**
Allium sativum	Allicin	Organosulfur	Inhibition of cysteine proteinases and thiol-containing enzymes

It is highly unlikely that a single class of phytochemicals (such as phenolics, terpenoids or alkaloids) is going to yield a new antifungal drug molecule. Instead, the field is poised to take a more holistic approach, where drugs that target the plurality of biological processes important for growth and survival in fungi are used in combination. Instead of targeting a single pathway in the pathogen, we will need to apply a combination drug therapy to inhibit the various pathways that need to be inactivated to achieve a therapeutic effect. This approach should decrease the likelihood that resistant pathogens will emerge.(Xiao et al., 2024)

3. MECHANISMS OF ACTION AND BIOLOGICAL PATHWAYS OF HERBAL ANTIFUNGALS

Molecular communication between bioactive plant compounds and fungal cells is a key aspect of natural medicine for which there is little scientific basis. While synthetic drugs act on one enzyme in a metabolic pathway, bioactive compounds from plants that form the basis of phytotherapy often interact with several targets in the cells affecting a number of important organelles and pathways.(Contreras-Martínez et al., 2023)

3.1 Disruption of Fungal Cell Membrane Integrity and Permeability

Fungal plasma membrane (PM) is an organelle that maintains fundamental cellular processes. The fungal PM membrane has a high sterol content, almost exclusively composed of ergosterol. Ergosterol is involved in the structure, physical properties and catalytic functions of membrane proteins. Many antifungal compounds including plant derived carvacrol and eugenol interfere with ergosterol synthesis by affecting the activity of the erg25, erg11 and erg24 proteins. The 14α-demethylase enzyme, CYP51, is responsible for catalyzing the lanosterol to ergosterol conversion reaction. Inhibition of the enzyme results in decreased ergosterol levels and accumulation of lanosterol thereby affecting membrane integrity. Some of the lipophilic parts of the structures of various antifungal compounds can cause an increase in lipid fluidity by insertion between lipid molecules of the bilayer. Also, some lipophilic parts can form aqueous channels thereby affecting ion and molecule leakage out of the cell causing cellular metabolic dysfunction and thus cell death. (Romo et al., 2019)

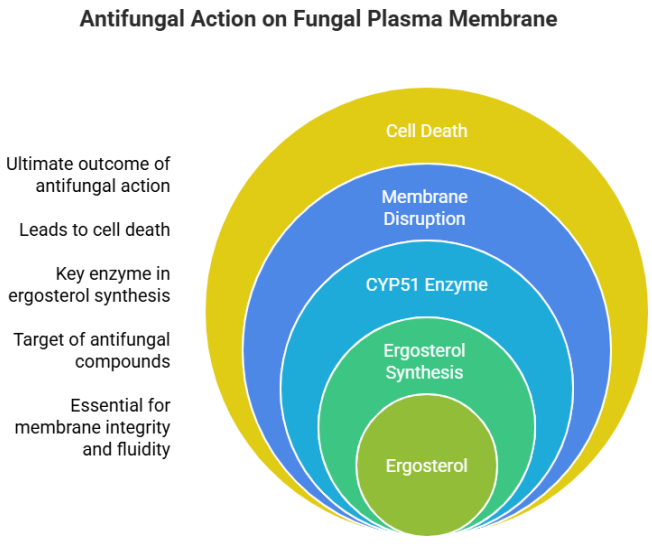

Fig. No. 3.1 Mechanism of Antifungal Action Targeting Ergosterol Biosynthesis and Fungal Plasma Membrane

3.2 Inhibition of Biofilm Formation and Morphological Transformation

Biofilms formed by Candida albicans are a polymorphic fungus, which is a common source of the majority of the human fungal pathogens and is associated with the development of relapsing infections and resistance to chemotherapeutic drugs. Transition from yeast to hypha or vice versa is a crucial morphological change that allows the fungus to establish infection in the host tissues. While yeast cells are commonly associated with the development of systemic infections, hyphae are necessary for the adherence of the fungus to host surfaces. Although most plant derived phytochemicals have been reported to have antifungal properties, commonly known as garlic has not been investigated for its effect on Candida albicans. Moreover, active ingredients of garlic such as allicin and cinnamaldehyde have been reported to inhibit the formation of germ tubes and biofilms. In this study, we investigated the potential use of berberine hydrochloride (BBH) alone and in combination with fluconazole for its possible antifungal effects. In addition, our study demonstrated that rosmarinic acid of rosemary is effective in eradicating biofilms formed by Candida albicans by decreasing the amount of ECM i.e., exopolysaccharides. (Ivanov et al., 2022)

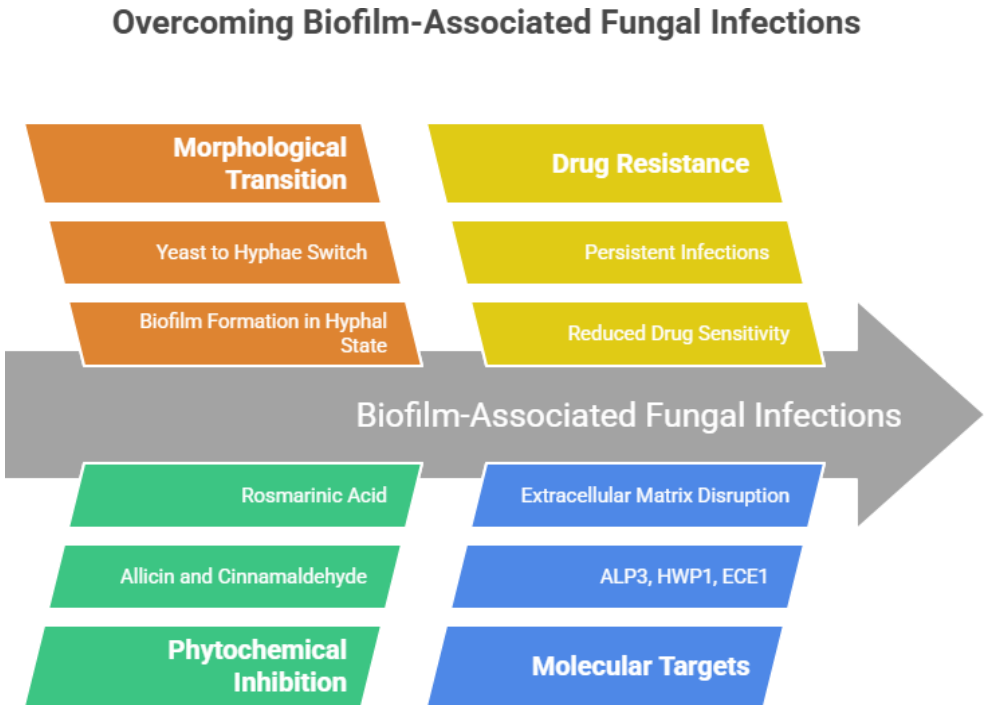

Fig. No. 3.2: Mechanistic Overview of Biofilm Formation and Phytochemical Intervention.

3.3 Molecular Targets and Genomic Responses in Pathogenic Fungi

In our research we have characterized the gene expression reprogramming in fungi upon treatment with herbal extracts by using transcriptomics and RNA sequencing (RNA-seq) approaches. Here, we investigated the impact of isoespintanol (ISO), a monoterpene compound isolated from Oxandra xylopioides leaf extract on Candida tropicalis genes expression. The results obtained demonstrated that 186 genes were differentially expressed in C. tropicalis upon ISO treatment and that 85% of them were over-expressed as a general stress response. (Dhamgaye et al., 2014)

Table No. 3.3: Molecular Targets of Bioactive Agents and Their Genomic and Physiological Effects.

Molecular Target	Bioactive Agent	Genomic / Physiological Effect
ERG11 Gene	Flavonoids (Rutin)	Reduction in ergosterol synthesis enzymes
HSF1 Factor	Berberine	Collapse of thermal adaptation and CW integrity
Mitochondrial Complex III/IV	Arylamidine T-2307	Selective ATP depletion in yeast vs. mammals
SAM Pathway	Isoespintanol (ISO)	Downregulation of methyl donors;epigenetic disruption
Ca2+ Pumps (YVC1, PMC1)	Berberine + FLC	Cytoplasmic Ca2+ overload; apoptosis

We identified the S-Adenosylmethionine (SAM) pathway disruption and associated its key player SAM which serves as the methyl donor for DNA and protein methylation. ISO affected the genes related to SAM pathway, thereby down-regulated the expression of genes like TRM7, TRM2 and DOT1, a chromatin silencing and tRNA modification enzyme. The down-regulation of these genes inhibited SAM pathway which is responsible for gene expression and stress response in ISO-treated cells (Yu et al., 2023). We also observed the disruption of mitochondrial membrane potential and an increased reactive oxygen species (ROS) in the presence of ISO-treated compound solution, which lead to DNA fragmentation and nuclear condensation, a common characteristic of apoptosis. In contrast to their fungistatic effects towards different fungal strains, all strains were found to be sensitive to herbal compounds.

4. THERAPEUTIC APPLICATIONS AND SYNERGISTIC POTENTIAL OF HERBAL EXTRACTS

Use of herbal antifungal drugs in clinics and industries is in developing stage due to the increasing realization of the limitations of synthetic chemistry. Apart from drug delivery systems, they are also used as biopesticides in agriculture (Yang et al., 2023).

4.1 Management of Drug-Resistant Candida Species and Clinical

Mycoses

Candida auris, a super-fungus causing severe fungal infection has triggered the search for alternative therapeutic strategies for the management of MDR (multi-drug resistant) fungal infections. Over the years, plant extracts exhibiting antifungal activity have been reported. In the present investigation, glycolic extracts of Rosa centifolia, Curcuma longa and Punica granatum were assessed for their effect on biofilms of Candida auris, Candida glabrata and Candida albicans. All the plant extracts showed biofilm disruption activity against all the three Candida species. The combination of Rosa centifolia and Curcuma longa extracts showed maximum biofilm disruption activity along with maximum fungicidal activity against all the three Candida species. Plant derived bioactive compounds are often restricted to laboratory studies due to their poor aqueous solubility and instability. Their therapeutic application is further restricted due to their low bioavailability, short half-life and frequent dosing which poses significant clinical challenges. Using nanotechnology, these limitations can be successfully addressed by using polysaccharide-based nanohydrogels for the delivery of phytochemicals (Li et al., 2025). The encapsulation of plant derived bioactive compounds in nanohydrogels could be used for site specific delivery of phytochemicals at the infection site i.e. the skin. This could be highly beneficial for the management of localized fungal infections such as onychomycosis and dermatophytoses while reducing the systemic side effects.

4.2 Applications in Agricultural Biopesticides and Food Preservation

Plant pathogens like Aspergillus and Fusarium are responsible for production of mycotoxins that have harmful health effects on human beings. They are controlled by the application of Chemical synthetic fungicides which leads to environmental degradation like soil degradation and bioaccumulation of pesticides in the food chain (Balusamy et al., 2023). Hence, there is need for safer fungicides. Plant-based fungicides are gaining importance for management of plant diseases in an eco-friendly manner. Plant extracts and essential oils have been studied for controlling plant pathogens. Biopesticide cinnamaldehyde showed strong fungicidal activities against wood decaying fungi and Fusarium moniliforme. Although plant-based fungicides have a long history with many testimonies of their efficacy, there is always need for the development of standardized methods for isolation of active compounds. Moreover, they may favor the growth of non- target fungi. With the recent data profiling of 15 plant species using agricultural waste like bergamot peels, this may lead to the development of green fungicides. In addition, herbal constituents have shown great pharmacological potential especially as chemosensitizers in conjunction with the conventional drugs (Deresa & Diriba, 2023).

Table No. 4.2: Plant-Derived Products (PIPs) Targeting Agricultural and Environmental Pathogens (Morea et al., 2025).

Pathogen Category	Representative Pathogen	Host Crop / Environment	Effective Botanical Product (PIP)
Soilborne (SBP)	*Agroathelia rolfsii*	Tomato	EP5-Protect (Commercial Induction)
Fruit Rot (FRP)	*Monilia fructicola*	Peach	*Punica granatum* (Pomegranate)
Wood Decay (WDP)	*Coniella granati*	Pomegranate Tree	*Solanum lycopersicum* (Leaf/Stem)
Trunk Disease (TD)	*Phaeomoniella chlamydospora*	Grapevine	*Bergamot / Artichoke*
			Waste PIPs

4.3 Synergistic Interactions with Conventional Antifungal Pharmaceuticals

β-lactamase inhibitors act as a chemosensitizer (CS). They improve antibiotic activity on resistant bacteria. Candida cells present

multi resistance to azoles due to the activity of multi drug efflux pumps, namely CDR1 and CDR2. Plant derived compounds known to inhibit drug efflux pumps include eucalyptal D, geraniol and magnolol, thereby promoting azole accumulation in the fungal cells. Ginger compound 6-Shogaol leads to a down- regulation of the efflux pump genes (Li et al., 2025). Combination of berberine and fluconazole were found to induce mitochondrial dysfunction in wild-type Candida albicans while azole-resistant strain recovered mitochondrial functions by intracellular calcium ions mediated through the calcium-regulated genes, YVC1 and PMC1. At therapeutic concentrations, these drugs have shown enhanced fungicidal effects and a reduced host toxicity.(Yamasaki & Van Eeden, 2018)

Table No. 4.3: Herb–Drug Combinations: Mechanistic Basis and Therapeutic Outcome

Synthetic Drug	Herbal Partner	Synergistic Mechanism	Outcome
Fluconazole	Berberine	Calcineurin inhibition; Ca^{2+} overload	Reversal of MDR in *Candida*
Amphotericin B	Berberine	Inhibition of filamentation & co-adhesion	Treatment of mixed biofilms
Fluconazole	Gypenosides	Arrest of blastospore germination	Early biofilm prevention
Azoles (Various)	Apigenin + Rutin	Suppression of ERG11 expression	Reduced drug dosage requirement

5. CONCLUSION

Antifungal plant sources represent vast bioresources for development of plant derived drugs against various fungal infections for which the synthetic chemicals are fast losing their efficacy. The present review paper is concerned with plant bioresources like essential oils and their constituents as well as alkaloids such as berberine having proven records of their activities against various plant pathogenic fungi. However, there are many constraints which are restricting their clinical and commercial utilization. In the present review, we have suggested that metabolomics and structure-based drug designing for fungal specific enzymes may yield plant derived drugs with desired efficacy. In addition, the nanotechnology may also be employed for safe delivery of volatile plant derived phytochemicals and may utilize the agricultural waste for preparation of fungicides contributing thereby towards sustainable development through circular economy. The integration of ethnobotany with modern tool of molecular biology may also lead towards the development of newer generation of fungicides for controlling the global fungal diseases.

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