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"Harnessing the Antifungal Power of Terpenoids and Coumarins: A Natural Approach to Combat Fungal Infections"

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Abstract:
Fungal infections pose a significant challenge to public health and agriculture, necessitating the search for effective and safer antifungal agents. Phytoconstituents, particularly terpenoids and coumarins, have gained attention due to their diverse bioactivities, including antifungal properties. This review explores the antifungal potential of selected terpenoids and coumarins, focusing on their mechanisms of action, spectrum of activity, and structure-activity relationships. Terpenoids, known for their membrane-disrupting and enzyme-inhibiting capabilities, exhibit promising antifungal efficacy against pathogenic fungi. Similarly, coumarins, with their ability to interfere with fungal growth and oxidative stress pathways, have shown broad-spectrum antifungal activity. This review also highlights recent studies, challenges in clinical translation, and future prospects for developing plant-derived antifungal agents. Understanding the molecular interactions and synergistic effects of these phytochemicals can aid in the design of novel antifungal therapies with enhanced efficacy and reduced resistance.

Keywords: Antifungal activity, Phytoconstituents, Terpenoids, Coumarins, Natural products, fungal infections.

Introduction:

Fungi are eukaryotes; they have a membrane surrounding their nucleus, their cells are much larger than bacteria and their molecular processes closely resemble those of plants and animals. A fungus is a vegetative organism. The most common species like *Aspergillus* and *Candida* are found everywhere on earth. Gardens, playgrounds, houses, hotels, hospitals and even the skin and mucous membranes have been identified as sources of fungi that caused life-threatening infections. In the course of time more than 69.000 species of fungi have been described while it has been estimated that the total number of fungal species is of the order of 1.5 million. They range from giant puff-balls mushrooms- sometimes edible, often poisonous- to moulds and yeasts only visible by microscope [1].

Table 1: WHO's Priority Fungal Pathogen List (Adapted)

Pathogen	**Category**	**Common Infections**
Candida auris	Critical	Bloodstream infections, multidrug resistance [2]
Aspergillus fumigatus	High	Pulmonary aspergillosis, affects immunocompromised patients[2]
Cryptococcus neoformans	High	Meningitis, lung infections [2]
Fusarium spp.	Medium	Eye infections, onychomycosis, systemic infections [3]
Mucorales (Rhizopus, Mucor)	Medium	Mucormycosis, severe fungal infections in diabetics [3]

Fungal pathogens employ various mechanisms to evade the host immune system and to progress the severity of infections. Opportunistic and systemic infections, fungal pathogens such as Candida, Aspergillus, Fusarium, Mucorales and molds can cause healthcare-associated infections (HAI) in patients with underlying diseases [4].Over 150 million people have severe fungal infections, which lead to approximately more than one million deaths per year [5]. Kingdom Fungi is diverse and includes different types of organisms such as molds, yeasts, mushrooms, polypores, plant parasitic rusts, and smuts. Fungi can affect human health directly, but also indirectly affect animal and plant health. Phytopathogenic fungi are the ones infecting agricultural crops and forestry trees with a high impact on human nutrition, life quality, and economy, as they may compromise production/yields and quality. The most relevant mycotoxins harmful to human health are aflatoxins [6].

Limitations:

Traditional methods often misidentify *Candida auris* due to its similarity to other *Candida species*, leading to incorrect treatment. Advanced techniques like MALDI-TOF MS and genetic sequencing improves accuracy. *Candida auris* causes hospital outbreaks due to its persistence on surfaces and resistance to disinfectants, making infection control difficult. *Candida auris* is resistant to multiple antifungal drugs, including azoles, echinocandins, and amphotericin B, limiting treatment options[7].

Phytoconstituents as antifungal agents:

Phytochemicals are naturally occurring bioactive compounds derived from plants [8].

Table 2: Classification of Phytochemicals:

Phytochemicals	Examples	Mechanism of action
Alkaloids	Berberine, Phenanthridine	Disrupts fungal cell membranes and inhibits enzyme activity [8]
Flavonoids	Quercetin, Catechins	Disrupts fungal cell walls [8]
Coumarins	Osthole, Psoralen, Imperatorin	Disrupts fungal cell walls, inhibits spore germination, and interferes with oxidative metabolism [8]
Terpenoids	Thymol, Carvacrol	Disrupts fungal membranes by altering lipid composition, leading to leakage of cell contents [8]
Saponins	Tomatidine, Sapindoside B	Interacts with fungal membrane , causing structural disruption and cell lysis [8]

Table 3: Importance of terpenoids and coumarins as bioactive molecules:

Compound	Pharmacological Importance	Industrial and Agricultural Uses
Terpenoids	Anti-cancer, Anti-inflammatory Antimicrobial, Antioxidant, Neuroprotective [8]	Used as flavouring agents, fragrances, natural pesticides and insect repellents [9]
Coumarins	Anti-cancer, Antimicrobial, Antioxidant, Anti-inflammatory [8] Anticoagulant [22]	Used in perfumes and flavouring agents. Used as pesticides and a plant growth regulators[10]

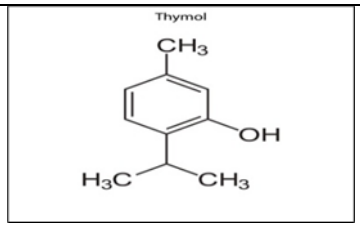
Terpenoids and their antifungal potential:

Definition: Terpenoids are secondary metabolites that can be isolated from natural sources such as plants, microorganisms, animals, insects, marines and endophytes. Terpenoids (also called isoprenoids) are derived from five-carbon isoprene units. Terpenoids compose of more than 40,000 variations to date, which are still being explored [8].

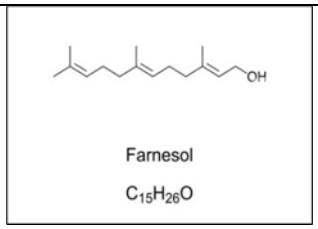
Table 4: Terpenes can be classified into different classes based on the number of isoprene units (n) in the molecule:

Types	Molecular formula	Examples
Monoterpenoids	$C_{10}H_{16}$	Linalool and Geraniol [9]
Sesquiterpenoids	$C_{15}H_{24}$	Bisabolol, Bisabolene, and Farnesene [9]
Diterpenoids	$C_{20}H_{32}$	Gibberellic acid, Carnosolic acid [9]
Triterpenoids	$C_{30}H_{48}$	Betulin, Fusidic [9]

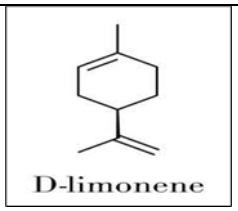
Example of antifungal terpenoids: [11]



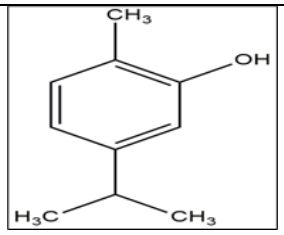
Thymol



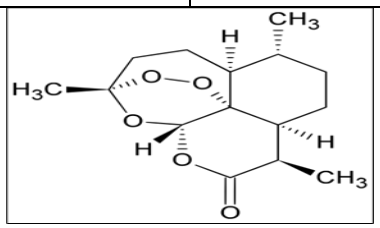
Farnesol



Limonene



Carvacrol

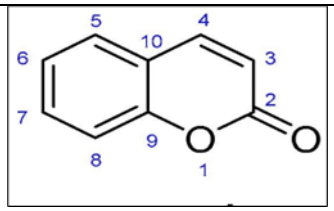


Artemisinin

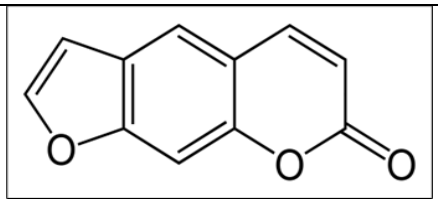
Coumarins and their antifungal potential:

Coumarins are benzopyrone derivatives, primarily found in plants. Present in Tonka beans, cinnamon, and various medicinal plants. They are found in over 150 different species of plants belonging to almost 30 different families. They are mainly secondary metabolites of plants and present in some microbes [8].

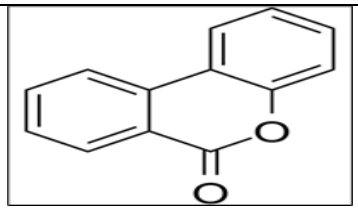
Example of antifungal coumarins: [10]



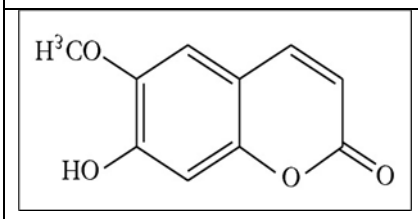
Coumarin



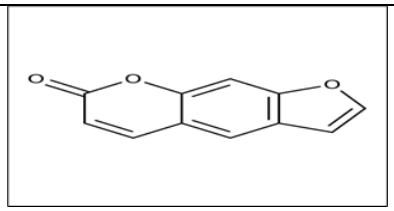
Furanocoumarin



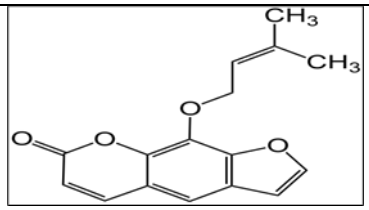
Benzocoumarin



Scopoletin



Psoralen



Imperatorin

Aflatoxins and their antifungal relevance:

Mycotoxins, low molecular weight compounds, naturally originate from different species of filamentous fungi. Aflatoxins are toxic substances made by fungi, mainly *Aspergillus flavus* and *Aspergillus parasiticus*. They contaminate food and animal feed, especially in warm and humid conditions, and can cause serious health problems, including liver damage and immune disorders. The most dangerous types are B1, B2, G1, and G2, with B1 being the most toxic. A.

flavus mainly produces B-type aflatoxins, while A. parasiticus produces both B- and G-types. Under UV light, B-types glow blue, and G-types glow yellow-green. While harmful to humans and animals, their role in fungal biology is still being studied [10].

Comparative Analysis of Terpenoids and Coumarins as Antifungal Agents:

Table 5: Mechanism of Action of Terpenoids and Coumarins

Compound	Mechanism of Action	Examples
Terpenoids	Disrupt fungal membrane integrity by targeting ergosterol	Thymol, Carvacrol, Limonene [11]
	Inhibit fungal enzymatic pathways	Farnesol, Artemisinin [11]
	Induce oxidative stress causing fungal cell damage	Carvacrol [12]
Coumarins	Interfere with fungal cell division and wall integrity	Imperatorin, Osthole [8]
	Blocking essential fungal enzymes	Robustic acid [13]
	Modulate oxidative stress responses in fungi	Scopoletin [14]

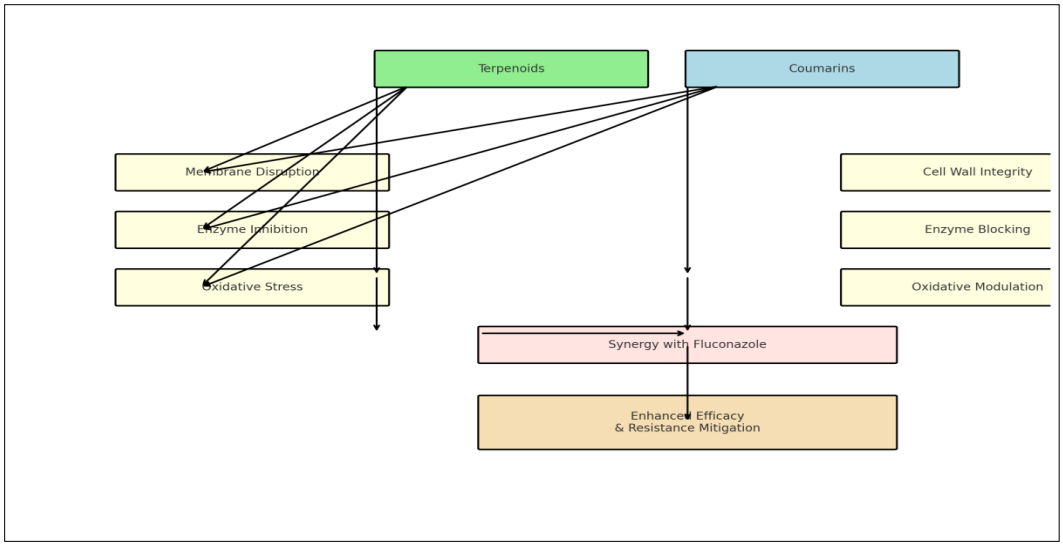


Figure 1.Antifungal Action of Terpenoids and Coumarins

Table 6: Comparative Antifungal Spectrum of Terpenoids and Coumarins

Compound	Effective Against	Example Compounds
Terpenoids	*Candida* spp. (yeasts)	Carvacrol [15], Eugenol, Linalool, Citral[16]
	Aspergillus spp. (molds)	P-cymene, Thymol, Carvacrol [17]
	Trichophyton spp. (dermatophytes)	Linalool, Geraniol, Bisabolol [9]
Coumarins	*Candida* spp. (yeasts)	Scopoletin [18], Robustic acid [13]

	Aspergillus spp. (molds)	Scopolin, Osthenol [19]
	Trichophyton spp. (dermatophytes)	Imperatorin [20]

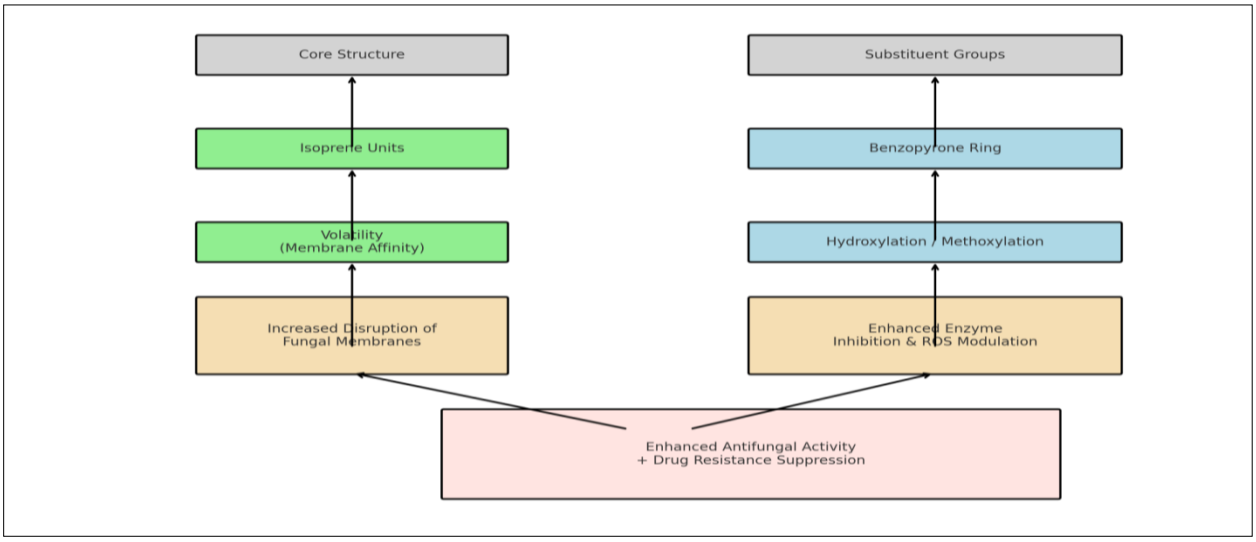


Figure 2. Structure -Activity Relationship (SAR) Flowchart for Terpenoids and Coumarins

Table 7: Synergistic Effects of Terpenoids and Coumarins with Conventional Antifungal Drugs

Natural Compound	Conventional Drug	Synergistic Effect
Scopoletin	Fluconazole	Inhibits fungal efflux pumps, increasing drug retention [18]
Carvacrol, Eugenol and Thymol	Fluconazole	Inhibits biofilm formation and enhances drug efficacy [21]

Table 8: Potential side effects and toxicity considerations.

Compound	Side effects an toxicity
Terpenoids	Cytotoxicity, [11] Local Irritation [22] Neurological Effects [22]
Coumarin	Hepatotoxicity [23]

Table 9: Challenges and Future Perspectives:

Challenge	Proposed Solution
To improve antifungal activity	Structural modifications [14]
Regulatory hurdles	Clinical trials to validate efficacy and safety [11,18]
Fungal resistance to existing drugs	Combination therapy with conventional antifungals [21]
Low bioavailability	Nanotechnology-based drug delivery (nanoemulsions, liposomes) [24]

Discussion:

Terpenoids and coumarins exhibit significant antifungal potential through mechanisms such as membrane disruption, oxidative stress induction, and enzyme inhibition [11, 12, 13, and 14]. Their ability to target drug-resistant fungi makes them promising alternatives to conventional antifungals [21].However, challenges like low bioavailability and limited clinical studies must be addressed. Further research on formulation improvements, structural modifications, and clinical validation is essential for their future application in antifungal therapy [14, 18, 21 and 24].

Conclusion:

Terpenoids and coumarins exhibit strong antifungal properties through multiple mechanisms, including membrane disruption, oxidative stress induction, and inhibition of fungal growth. Their potential synergy with conventional antifungals enhances efficacy and mitigates resistance. Advancements in nanotechnology and structural modifications can improve bioavailability, stability, and therapeutic effectiveness. However, further research is essential to optimize formulations, ensure safety, and validate clinical applications for their successful integration into modern antifungal therapies. Further research is needed to ensure safety, optimize formulations, and validate clinical use for effective antifungal therapy.

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