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"Recent Advances in Herbal Azo Compounds as Promising Antifungal Agents: A Comprehensive Review of Design, Synthesis, In Vitro and In Vivo Evaluations, and Future Prospects"

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ABSTRACT:
Fungal infections pose a significant public health concern, demanding the development of innovative and effective antifungal agents. Herbal compounds, specifically Azo derivatives, have emerged as promising candidates for combating topical fungal infections. This comprehensive review synthesizes recent advancements in the field of herbal Azo compounds, shedding light on their potential as antifungal agents. The review encompasses a wide array of topics, including the design and synthesis of novel herbal Azo conjugates, there in vitro antifungal activities, and in vivo evaluations for their efficacy and safety. Furthermore, this review outlines the future prospects of herbal Azo compounds in the realm of antifungal therapy. By discussing ongoing research, challenges, and opportunities, it provides valuable insights into the direction of future studies and the potential translation of herbal Azo compounds from the laboratory to clinical practice.

1. Introduction

Topical fungal infections present a persistent challenge to global healthcare, necessitating continuous innovation in therapeutic interventions. In the pursuit of novel and effective strategies for combating these infections, The current investigation centers on creating, producing, and assessing innovative Azo botanical compounds with the primary goal of addressing superficial fungal infections. The fundamental aspect of this study revolves around the advancement of nanoparticles. The cornerstone of this research lies in the development of nanoparticles, a cutting-edge approach that integrates the unique antifungal properties of selected plant extracts. The Neem tree, also known as *Azadirachta Indica*, has gained global recognition due to its extensive medicinal qualities[3]. Research has shown that Neem leaf and its components possess a variety of beneficial effects, including modulation of the immune system, reduction of inflammation, regulation of blood sugar levels, prevention of ulcers, treatment of malaria, combating fungal and bacterial infections, protection against oxidative stress, and prevention of mutations and cancer development.[1]Neem has been widely employed in traditional medicinal systems such as Ayurveda, Unani, and Homeopathy, and has garnered considerable attention from contemporary medicine. It boasts a wide range of biologically active compounds that exhibit chemical diversity and structural complexity[1]. Several triterpenoids derived from limonoids have been obtained from the seeds and seed oil of the Indian neem tree and their antifungal properties remain unexplored. Neem oil and neem leaf (*Azadirachta indica*) extracts are known for their Antifungal properties, suitable for topical application in treating skin fungal infections, Although the use of crude extracts from Neem seeds to combat plant pathogenic fungi is well-documented, there is limited information available regarding their specific antifungal activities[2]. Experiments examining the impact of

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different levels of Neem leaf extracts on the development of mycelia from Crinipellis and Phytophthora, as well as on the sprouting of Crinipellis spores, which results in decrease in the growth of Phytophthora mycelia when cultivated in neem leaf extract medium[3]. The current research examines how the aqueous leaf extract obtained from Azadirachta indica (Neem) affects adhesion, cell surface hydrophobicity, and biofilm formation, potentially influencing the colonization process of *Albicans*[4]. Antifungal activity of Herbal extracts antifungal effects of Azadirachta indica (Neem) leaf extracts were assessed against various dermatophytes, including Trichophyton and Epidermophyton occosum, demonstrating significant inhibitory properties. An analysis of methanol extracts from dried fruits of Terminalia chebula (T. chebula) identified flavonoids, alkaloids, glycosides, saponins, tannins, terpenoids, and steroids. Among the four tested extracts, methanol extracts from T. chebula dried fruits displayed the highest antifungal activity. Azadirachta indica (Neem) leaf and its constituents have garnered global attention for their diverse medicinal properties, including immunomodulatory, anti-inflammatory, antihyperglycemic, antiulcer, antimalarial, antifungal, antibacterial, antioxidant, antimutagenic, and anticarcinogenic effects. Neem produces a wide range of biologically active compounds, exhibiting chemical diversity and structural variability, with over 140 compounds isolated from different parts of the tree. Each of these botanical sources harbors bioactive compounds known for their antimicrobial attributes, making them promising candidates for the synthesis of therapeutic agents against fungal pathogens. The incorporation of nanotechnology into this novel approach adds a layer of sophistication, with the aim of enhancing drug delivery and optimizing therapeutic efficacy. By screening and evaluating the selected plant extracts, this research endeavors to contribute to the development of advanced and efficacious treatment modalities for topical fungal infections. As we embark on this exploration at the intersection of herbal medicine and nanotechnology, the potential impact of our findings on the field of antifungal therapy is significant. Through a comprehensive investigation, encompassing both in vitro and in vivo evaluations, we aspire to lay the groundwork for the emergence of a new class of antifungal agents that can address the challenges posed by topical fungal infections in a manner that is both innovative and effective. Tea tree oil (*Melaleuca alternifolia*) is a widely recognized antifungal agent suitable for topical application in treating fungal skin infections such as athlete's foot and nail fungus[6]. Prior to use, it is advisable to dilute it with carrier oil. Garlic (*Allium Sativum*) contains allicin, a compound with antifungal properties, and its consumption in raw form or as supplements may contribute to combating fungal infections[7].Oregano oil (*Origanum vulgare*), containing compounds like carvacrol and thymol with potent antifungal properties, can be administered internally in minimal amounts or applied topically[8].Clove oil (*Syzygium Aromatium*) contains eugenol, an antifungal agent suitable for topical use in treating fungal infections, but it should be diluted with a carrier oil[9]. Turmeric (*Curcuma longa*) and its active compound, curcumin, have demonstrated antifungal properties in studies and can be incorporated into the diet or taken as a supplement [9].Grapefruit seed extract is believed to possess Gastro-protective activity, including antifungal effects, and can be administered orally or topically[10]. It has also demonstrated antibacterial, antiviral, and antifungal effects. Studies have investigated the safety of turmeric and curcumin, indicating that the compound is relatively harmless when orally administered at doses of 6 g/day for 4–7 weeks. Furthermore, curcumin has been associated with nephroprotective, hepatoprotective, and immunomodulatory effects. As a result, curcumin presents a viable alternative to existing antifungal therapies[11].Curcumin, the primary polyphenolic compound found in the rhizome of *Curcuma longa* L. (commonly known as turmeric), has garnered significant attention for its numerous health benefits[11]. Currently, there is rapid advancement in the pharmaceutical application of nanoparticle technology. Substances with nano-sized particles show considerable potential for effectively delivering drugs and antigens via mucosal routes.[12] Recent advancements in delivery systems utilizing nanoparticles and microparticles are transforming the food industry's delivery mechanisms. These breakthroughs hold promise in addressing numerous technical hurdles related to encapsulating, safeguarding, and delivering active components like colors and flavors[13].The natural world offers a wealth of novel antifungal compounds, and the medicinal

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properties of plants are widely utilized in traditional medicine. Given the diverse array of chemicals found in plants, many researchers have focused on assessing the antifungal properties of extracts and essential oils derived from medicinal plants. This compound exhibits anti-inflammatory, anti-mutagenic, and anticancer properties.Infections caused by invasive Candida present notable health risks, especially for patients in hospital settings, those with compromised immune systems, or those in critical condition, and the available antifungal treatment options are limited. Resistance, whether inherent or acquired, can arise due to the selection pressure of antifungal agents within individual patients or through the transfer of resistant strains between patients, leading to an increasing incidence of multidrug resistance in Candida strains such as *Candida glabrata* and *Candida auris*. Swift identification of Candida infections resistant to antifungal treatment is crucial for effective patient care, underscoring the necessity of implementing antifungal stewardship programs to minimize unnecessary use and mitigate the emergence of multidrug resistance[14]. Utilizing plants for medicinal purposes dates back to ancient times, offering a cost-effective and purportedly safe alternative treatment method. Additionally, plants serve as a viable source for developing novel synthetic compounds. This review highlights recent advancements in utilizing specific plants for treating skin ailments over the past 17 years, showcasing the evolving technical landscape in this field.[15]*Candida albicans* is the most commonly isolated yeast strain in cases of bloodstream infections. Despite significant advancements in diagnostic and therapeutic methods, these infections remain a substantial challenge in intensive care units worldwide. The economic burden and mortality associated with bloodstream fungal infections, particularly in vulnerable patients, are excessively high. *Candida albicans* demonstrates high adaptability, capable of developing resistance following prolonged exposure to antifungal agents. Factors contributing to antifungal tolerance and resistance include biofilm formation, which reduces antifungal accessibility, selection of spontaneous mutations enhancing target expression or reducing susceptibility, chromosomal abnormalities, heightened expression of multidrug efflux pumps, and evasion of host immune defenses. Comprehending these resilience mechanisms may aid in crafting alternative therapeutic approaches to regulate or overturn resistance. This analysis concentrates on the fundamental elements associated with antifungal resistance and tolerance in individuals afflicted by bloodstream infections caused by Candida albicans.[16,17]

The leaf extracts of *Azadirachta indica*(Neem) were evaluated for their antifungal effects against various dermatophytes, including Trichophyton and Epidermophyton occosum. The results indicated a signicant inhibitory capability against these organisms.[17,18] Neem contains a wide range of biologically active substances that vary in chemical composition and structure, with over 140 compounds identified from various parts of the tree. The first polyphenolic flavonoids, Quercetin and ß-sitosterol, were isolated from fresh Neem leaves, known for their antibacterial and antifungal properties. Researchers subsequently purified active fractions from Neem organic extracts using HPLC, revealing significant levels of major compounds such as 6-deacetylnimbin, azadiradione, nimbin, salannin, and epoxy-Azadiradione, which exhibited notable activity against various pathogenic fungi during bioassays. Research has explored the antimicrobial properties of Neem leaves, bark, and seeds separately, but there is a gap in studies comparing the effectiveness of aqueous extracts from these parts. Therefore, this study was undertaken to compare the antimicrobial effects of neem leaf, bark, and seed aqueous extracts against pathogenic bacteria and fungi[19].Various factors affecting the accuracy and reproducibility of the agar diffusion method, such as gel thickness and uniformity, inoculum size, temperature, and pH, were carefully considered to ensure reliable results. Neem leaves contain several compounds including chlorogenic acid, cinnamic acid, ferulic acid, naringenin, taxifolin, kaempferol, and vanillin. These compounds contribute to various biological activities associated with Neem leaf extracts. The ancient healing practice of Ayurveda from India relies on a diverse range of natural plant and fruit extracts to address various health issues. These botanical remedies, including culinary fruits, herbs, and spices, are widely regarded as safe by regulatory bodies such as the US Food and Drug Act, EU Standards, and the Food Safety and Standards Authority of India. Incorporating these ingredients into one's diet is believed to support overall well-being, and it's notable that the rich array of spices

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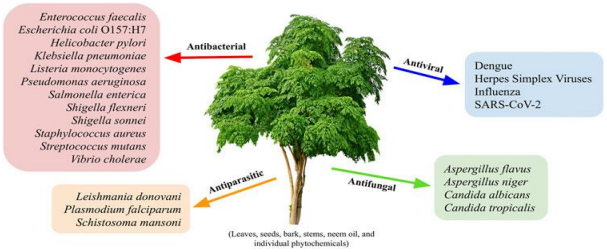
in Indian cuisine is deeply rooted in Ayurvedic principles.[20,21] Neem leaf (*Azadirachta indica*), Turmeric (*Curcuma longa*) Curcumin, *Terminalia chebuka*, and *Terminalia bellerica* are selected for screening based on their potential to accelerate antifungal activity[23].

***Fig 1**:* Represents "The medicinal properties of Neem, including its potent Antifungal, Antibacterial, and antiviral effects, Antiparasitic effects to make it a valuable natural remedy in combating ailments caused by organisms such as bacteria, fungi, and viruses."



Curcumin	Neem	Haritaki	Baheda
Kingdom: Plantae	Kingdom: Plantae	kingdom: Plantae	Kingdom Plantae
Phylum: Tracheophyta	Phylum: Spermatophyta	Phylum: Tracheophyta	Phylum Tracheophyta
Class: Liliopsida	Subphylum: Angiospermae	Class: Magnoliopsida	Class Magnoliopsida
Order: Zingiberales	Class: Dicotyledonae	Order: Myrtales	Order Myrtales
Family: Zingiberaceae	Order: Rutales	Family: Combretaceae	Family Combretaceae
Genus: *Curcuma* L.	Family: Meliaceae	Genus: Terminalia	Genus *Terminalia*
Species: *Curcuma longa*	Genus: *Azadirachta*	Species:	Species *Terminalia*
	Species: *Azadirachta indica*		

Table 1 : Taxonomical classification of herbal extracts

2. Materials and Discussion

The synthesis and evaluation of these compounds, including in vitro and in vivo studies, are discussed, shedding light on their mechanisms of action and future prospects in antifungal therapy. The review aims to be a valuable resource for researchers, clinicians, and stakeholders involved in the development of novel antifungal agents, with the goal of inspiring further exploration and innovation in the held of herbal Azo compounds for treating topical fungal infections. The primary natural products include peptides and lectins with antifungal properties, along with plants and secondary metabolites from fungi. Various proteins, enzymes, and metabolic pathways are potential targets for developing effective inhibitor compounds. Recent research has focused on investigating heat shock proteins, calcineurin, salinomycin, the trehalose biosynthetic pathway, and the glyoxylate cycle across different fungal species.[24] It also outlines a novel approach to address topical fungal infections by developing nanoparticles with enhanced antifungal properties using herbal extracts[25]. The selected herbal extracts, including Neem leaf, Turmeric Curcumin, *Terminalia chebula*, and *Terminalia bellerica*, are incorporated into Azo herbal conjugates. Turmeric (*Curcuma longa*) and its active compound, curcumin, have demonstrated antifungal properties in studies and can be incorporated into the diet or taken as a supplement[26] . *Terminalia bellerica* Seeds are reported to contain a new cardenolide, cannogenol 3-O-D-galactopyranosyl14-O-L-rhamnopyranoside and phospholipids.[27] curcumin has been shown to offer benefits through its anti-inflammatory and antioxidant properties, a significant challenge associated with its consumption is its low bioavailability, mainly stemming

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from inadequate absorption, quick metabolism, and rapid elimination. Various approaches have been explored to enhance the bioavailability of curcumin by addressing these underlying mechanisms[28,29].The study involves in vitro evaluation of the synthesized nanoparticles for their efficacy in inhibiting fungal growth and extends to in vivo studies to explore therapeutic potential and safety. Curcumin has the potential to inhibit the immunostimulatory functions of macrophages[30]. Alcoholic extracts from medicinal herbs like *C. Asiatica*, *T.Arjuna*, and *R. serpentina* showed superior antimicrobial effects compared to the chemical preservative sodium benzoate. Consequently, these plant extracts could be promising for prolonging the shelf life of fruit juices or serving as natural preservatives.[31] The utilization of plant extracts for the synthesis of metal nanoparticles is a burgeoning technique due to its simplicity and effectiveness compared to alternative methods[32].This innovative approach combines the antimicrobial properties of herbal extracts with the advantages of nanoparticle technology, potentially leading to the development of a new class of antifungal agents with improved drug delivery and efficacy for the treatment of topical fungal infections. The antifungal properties of Herbal extracts A chemical examination of methanol extracts derived from desiccated fruits of Terminalia chebula (T. chebula) unveiled the existence of flavonoids, alkaloids, glycosides, saponins, tannins, terpenoids, and steroids. Among the quartet of examined extracts, the methanol extracts from desiccated fruits of T. chebula demonstrated the most substantial antifungal efficacy. Tea tree oil (*Melaleuca alternifolia*) is a widely recognized antifungal agent suitable for topical application in treating fungal skin infections such as athlete's foot and nail fungus. Prior to use, it is advisable to dilute it with a carrier oil.[33] Garlic (*Allium Sativum*) contains Allicin, a compound with antifungal properties, and its consumption in raw form or as supplements may contribute to combating fungal infections.[34] Oregano oil(*Origanum vulgare*), containing compounds like carvacrol and thymol with potent antifungal properties, can be administered internally in minimal amounts or applied topically.[35] Clove oil (*Syzygium Aromatium*) contains eugenol, an antifungal agent suitable for topical use in treating fungal infections, but it should be diluted with a carrier oil.[36] Grapefruit seed extract is believed to possess broad-spectrum antimicrobial properties, including antifungal effects, and can be administered orally or topically[37]. Neem oil and Neem leaf(*Azadirachta indica*) extracts are known for their antifungal properties, suitable for topical application in treating skin fungal infections.[37]

3. Conclusions

In conclusion, this review serves as a valuable resource for stakeholders interested in developing novel antifungal agents, emphasizing the exploration of herbal azo compounds for topical fungal infection treatment. The study proposes a novel approach involving the synthesis of nanoparticles with enhanced antifungal properties using herbal extracts, aiming to harness their inherent antimicrobial effects. Through comprehensive in vitro and in vivo evaluations, this approach integrates the benefits of herbal remedies with nanoparticle technology for improved drug delivery and efficacy. These findings highlight the potential for developing a new class of antifungal agents, offering promising alternatives for combating topical fungal infections and revolutionizing current therapeutic strategies.

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