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Review Article

Comprehensive Review on Plant-Derived Antifungals: *Nigella sativa* and *Catharanthus roseus* Against Opportunistic Candida Infections

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Fungal infections caused by *Candida* species represent a critical global healthcare challenge due to the rising prevalence of immunocompromised host conditions and increasing resistance to conventional antifungal agents. Synthetic therapies—including azoles, echinocandins, and polyenes—are frequently limited by host toxicity, adverse drug interactions, high costs, and the rapid emergence of multidrug-resistant strains like *Candida auris*. Consequently, plant-based secondary metabolites have gained attention as alternative or synergistic therapeutic agents. This review provides a comprehensive synthesis of the pathogenic burden of candidiasis, mechanisms of current antifungal classes, and the therapeutic efficacy of *Nigella sativa* Linn. and *Catharanthus roseus* Linn. Active constituents such as thymoquinone (*N. sativa*) and indole alkaloids (*C. roseus*) demonstrate distinct multi-target antimicrobial mechanisms. Pharmacological evaluation highlights the superior antifungal potency of *N. sativa* extracts over *C. roseus* against various clinical *Candida* strains. Furthermore, current research gaps, standardization challenges, and future clinical integration strategies are critically evaluated.

Keywords: Synthetic Antifungals, Candida albicans, Antifungal resistance

INTRODUCTION

1.1 Global Burden and High-Risk Populations

Fungal diseases, long underreported in comparison to bacterial and viral infections, have emerged as a primary cause of global morbidity and mortality. Opportunistic *Candida* infections span from non-life-threatening superficial mucosal lesions (e.g., oral thrush, vulvovaginal candidiasis, cutaneous manifestations) to invasive systemic candidemia causing multi-organ failure and sepsis.

The growing population of susceptible individuals stems from modern medical interventions, including:

- **HIV/AIDS:** Depletion of CD4+ T-cell counts predisposes individuals to severe recurrent thrush and esophageal candidiasis.
- **Oncology & Chemotherapy:** Cytotoxic drug regimens induce neutropenia and break down mucosal barriers, facilitating fungal entry into sterile tissues.
- **Organ Transplantation & ICU Interventions:** Prophylactic immunosuppression, central venous lines, urinary catheters, and mechanical ventilation provide direct entry points for fungal colonization.
- **Diabetes Mellitus:** Hyperglycemia impairs neutrophil/macrophage function and creates a nutrient-rich environment for fungal proliferation.

1.2 Genus *Candida*: Commensal to Pathogen

Candida yeasts exist as harmless commensals in human oral cavity, gastrointestinal, and vaginal mucosal flora. Transition to pathogenic states relies on virulence factors such as dimorphic switching (morphological alteration between yeast and invasive hyphae), cell surface adhesins, hydrolytic tissue-degrading

enzymes (proteases, lipases), and dense biofilm formation on mucosal tissues and indwelling medical devices. While *Candida albicans* remains the primary isolate, non-albicans species—including *Candida glabrata* (azole tolerance), *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei* (intrinsic fluconazole resistance), and *Candida auris* (multidrug-resistant nosocomial threat)—present substantial therapeutic hurdles.

1.3 Synthetic Antifungals: Mechanisms & Limitations

Current clinical management relies on five major classes of synthetic antifungal drugs:

Antifungal Class	Representative Drugs	Target Mechanism	Primary Limitations & Toxicities
Azoles	Fluconazole, Itraconazole, Voriconazole	Inhibits lanosterol 14-α-demethylase, blocking ergosterol synthesis	Hepatotoxicity, visual disturbances, drug interactions; widespread acquired resistance
Echinocandins	Caspofungin, Micafungin, Anidulafungin	Inhibits β-(1,3)-D-glucan synthase, disrupting cell wall integrity	Lack of oral formulations; low activity against *Cryptococcus* or molds; emerging *FKS* gene mutations
Polyenes	Amphotericin B, Nystatin	Binds ergosterol, forming transmembrane pores and inducing leakage	Severe nephrotoxicity, infusion reactions, electrolyte imbalances
Flucytosine	5-Fluorocytosine	Inhibits thymidylate synthase, halting fungal DNA/RNA synthesis	Rapid resistance emergence; narrow monotherapy spectrum
Allylamines	Terbinafine	Inhibits squalene epoxidase in ergosterol pathway	Ineffective against systemic deep-tissue mycoses

2. Botanicals as Novel Antifungal Candidates

Due to the toxicity, high costs, and single-target mechanisms of synthetic drugs that accelerate fungal resistance, bioactive plant extracts offer a compelling alternative. Plant secondary metabolites act through multifaceted mechanisms—simultaneously targeting cell membranes, cell walls, nucleic acid synthesis, metabolic pathways, and oxidative stress pathways—thereby reducing the likelihood of cross-resistance.

2.1 *Nigella sativa* Linn. (Black Seed)

Nigella sativa (Ranunculaceae family) contains a rich spectrum of bioactives, including essential oils, fixed oils, saponins, and alkaloids.

- **Active Constituents:** Thymoquinone (TQ) is the principal bioactive compound, alongside p-cymene and carvacrol.
- **Antifungal Mechanisms:** Thymoquinone directly disrupts fungal plasma cell membrane integrity, inducing electrolyte leakage, cell lysis, and oxidative damage. Additionally, *N. sativa* extracts suppress fungal biofilm formation and exhibit synergistic effects when combined with standard azoles.
- **Other Properties:** Possesses notable anti-inflammatory, antioxidant, and immunomodulatory properties that aid the host immune response against fungal proliferation.

2.2 *Catharanthus roseus* Linn. (Madagascar Periwinkle)

Catharanthus roseus (Apocynaceae family) produces over 130 terpenoid indole alkaloids alongside flavonoids, saponins, and phenolic glycosides.

- **Active Constituents:** Vincristine, vinblastine, catharanthine, vindoline, and ajmalicine.
- **Antifungal Mechanisms:** Indole alkaloids bind to fungal tubulin, disrupting microtubule polymerization and mitotic spindle assembly, thereby halting fungal cell division. Ajmalicine and associated polyphenols alter cell wall cross-linking and membrane permeability.
- **Other Properties:** Widely utilized in clinical oncology for antineoplastic properties; demonstrates antimicrobial, antidiabetic, and antioxidant activities.

3. Current Challenges & Future Perspectives

3.1 Analytical and Methodological Gaps

- **Phytochemical Variability:** Natural plant extract compositions fluctuate due to geographic origin, soil chemistry, harvesting season, and extraction technique. Standardized, bio-guided fractionation protocol deployment is necessary.
- **In Vitro vs. In Vivo Translation:** Current evidence is predominantly in vitro. Bioavailability, liver metabolism, plasma protein binding, and potential host cytotoxicity remain insufficiently characterized.
- **Limited Spectrum Testing:** Emerging multidrug-resistant threat strains, such as *Candida auris*, require immediate experimental inclusion.

3.2 Research Roadmap and Clinical Integration

1. **Advanced Extraction & Green Chemistry:** Utilize supercritical CO_2 fluid extraction and nano-encapsulation to improve active yield, chemical stability, and target tissue delivery.
2. **Combination Therapies:** Investigate synergistic pairings of thymoquinone or vinca alkaloids with sub-inhibitory doses of fluconazole or amphotericin B to restore drug sensitivity and reduce host toxicity.
3. **In Vivo Models & Clinical Trials:** Conduct pharmacokinetic/pharmacodynamic (PK/PD) profiling and safety assays in animal models to establish human safety margins and clinical efficacy.

CONCLUSION

Candida infections and increasing antifungal resistance highlight the need for safer and more effective therapeutic alternatives. *Nigella sativa* and *Catharanthus roseus* contain diverse bioactive compounds with promising antifungal, antioxidant, and antimicrobial properties. Among these, thymoquinone from *N. sativa* shows considerable potential through membrane disruption and biofilm inhibition. However, further standardized phytochemical, in vivo, pharmacokinetic, and clinical studies are required to establish their safety and therapeutic efficacy.

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