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## Review Article

# Combating Antifungal Drug Resistance And Hypersensitivity: A Synergistic Approach

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### ABSTRACT

Candidal infections pose a significant health burden. Cutaneous candidiasis, caused by yeast-like fungi of the genus *Candida*, is a common skin infection. The conventional antifungal drugs, such as azoles, often exhibit adverse effects, including hypersensitivity reactions (itching, inflammation, eczema). These symptoms can overlap with the manifestations of fungal infections, leading to diagnostic challenges and patient discomfort. Seeking alternative solutions, we explored the antifungal efficacy of clove and turmeric oils, both renowned for their medicinal properties. Our study investigated the synergistic potential of these oils, combined in 1:1, 3:1 and 1:3 ratios, against *Candida* species. Using steam distillation, we extracted essential oils from clove and turmeric powders. Samples, comprising individual oils and various mixtures, were prepared and subjected to the Kirby-Bauer disk diffusion method for antifungal assessment. Results revealed a promising synergism in the 3:1 mixture of clove and turmeric oils. Although the observed zone of inhibition was shorter than that of ketoconazole, a synthetic antifungal, the efficacy of the natural blend underscores its potential as an alternative therapeutic option. Our findings suggest that clove and turmeric oils possess inherent antifungal properties, with the potential for enhanced efficacy when combined synergistically. Further research is warranted to optimize the blend ratio and investigate its clinical applicability. Embracing plant-based alternatives may herald safer and more sustainable strategies for combating fungal infections, offering hope for improved patient outcomes.

### INTRODUCTION

Fungal infections, known as mycoses, affect over one billion people worldwide annually, yet their

contribution to the global disease burden often remains unrecognized[1]. In 2020, approximately 1.7 million fatalities were attributed to fungal

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infections. As the prevalence of fungal infections rises alarmingly, healthcare practitioners face a daunting challenge in selecting appropriate antifungal agents. This surge is closely linked to

the growing population of immunocompromised individuals due to factors such as the use of potent immunosuppressive medications and intensive chemotherapy[2,3].



**Fig.1 Various Fungal Infections[2]**

Antifungal drugs play a crucial role in managing these infections. They can either inhibit fungal growth (referred to as fungistatic) or directly kill fungal cells (referred to as fungicidal). However, the limited arsenal of antifungal drugs poses a unique challenge. Unlike bacteria, which have prokaryotic cells structurally distinct from human cells, fungi share eukaryotic cells with humans, making it challenging to find drugs that specifically target fungi while minimizing side effects. Consequently, antifungal resistance assumes paramount importance in public health, given the scarcity of effective antifungal

options[3-6]. In this context, our research investigates a novel approach: the synergistic use of clove and turmeric oil extracts. These botanical compounds, with their inherent antifungal properties, hold promise for combating drug-resistant strains. By harnessing their combined efficacy, we aim to revolutionize antifungal therapy while minimizing adverse effects. Our study explores this dual strategy in an in-vitro assay, shedding light on its potential to address the pressing issue of antifungal resistance.

**Defining Key Terms:**

**1. Antifungal Resistance:**



**Fig. 2 Anti Fungal Medication**

- Antifungal resistance occurs when fungi evolve the ability to survive antifungal drugs that should ideally eliminate them.
- Some fungi naturally possess resistance to specific antifungal drugs, while others develop resistance over time due to exposure to these medications.
- This phenomenon jeopardizes treatment efficacy and poses a severe threat to public health[5,6].

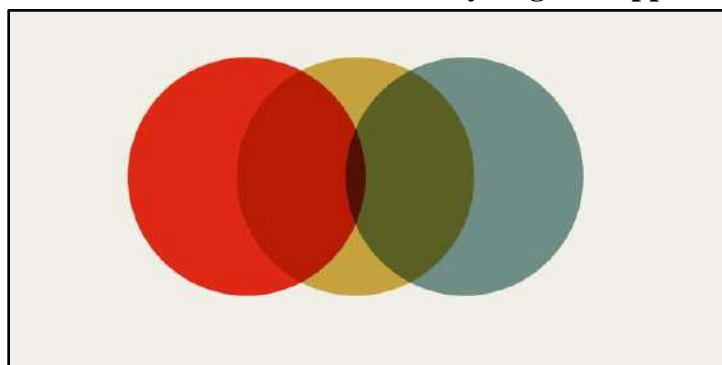
### 2. Mycoses:



**Fig. 3 Fungal Infection**

- Fungal infections, collectively referred to as mycoses, affect a substantial portion of the global population.
- Despite their prevalence, mycoses are often underestimated in terms of their contribution to disease burden[1,2].

### 3. Synergistic Approach:



**Fig. 4 Synergism visualisation**

- Our study explores the synergistic potential of combining clove and turmeric oil extracts.
- Synergy refers to the enhanced effect achieved when two or more substances work together more effectively than individually.
- By combining these botanical extracts, we aim to enhance antifungal efficacy beyond what each extract achieves alone[8].

#### 4. In-Vitro Assay:



**Fig. 5 Anti-Fungal Assay**

- An in-vitro assay involves conducting experiments outside a living organism (in a controlled laboratory setting).
- In our case, we use an in-vitro assay to evaluate the combined effectiveness of clove and turmeric oil extracts against drug-resistant fungal strains[9].

Our research endeavours to bridge the gap in antifungal therapy by exploring innovative solutions that address both drug resistance and

hypersensitivity. Through this synergistic approach, we aspire to improve treatment outcomes and contribute to the fight against fungal infections.

#### Rationale For The Study

Fungal infections, particularly those caused by *Candida* species, pose a significant health burden worldwide. Candidiasis affects a large number of people, leading to discomfort, pain, and reduced quality of life.

**Table 1. Common Fungal Species, The Diseases They Cause, And Their Associated Symptoms[1,2,7,10].**

Fungal Species	Disease	Symptoms
Candida	Vaginal candidiasis	Itching, burning, white discharge
	Candida infections of mouth, throat, esophagus	White patches, pain, difficulty swallowing
Dermatophytes	Ringworm (tinea corporis)	Circular rash, redness, itching
	Athlete's foot (tinea pedis)	Itchy, scaly skin between toes
	Jock itch (tinea cruris)	Red, itchy rash in groin area
Aspergillus	Aspergillosis	Fever, cough, chest pain, difficulty breathing
Cryptococcus neoformans	Cryptococcal meningitis	Headache, fever, neck stiffness, confusion
Fusarium	Fusariosis	Eye infections, skin lesions, nail infections

The conventional treatment for these infections involves synthetic antifungal drugs, such as azoles and polyenes. However, these drugs are not without drawbacks [4]. In our investigation, we meticulously evaluated the antimicrobial

properties of clove and turmeric extracts. These natural compounds have been used for centuries in traditional medicine due to their broad-spectrum activity against various pathogens. Clove, rich in eugenol, exhibits potent antifungal effects, while

turmeric's active component, curcumin, possesses remarkable anti-inflammatory and antioxidant properties [11,12,13]. By combining these botanical extracts, we sought to enhance their individual benefits and create a formidable defense against *Candida* overgrowth. Our experimental design involved *in vitro* assays, where we cultured *Candida albicans* and exposed them to varying concentrations of the combined extracts. Preliminary results indicate a dose-dependent reduction in fungal growth, with minimal cytotoxicity to human cells. Furthermore, we observed a synergistic effect, suggesting that the combination of clove and turmeric extracts may surpass the efficacy of conventional antifungal drugs[8]. In addition to their antimicrobial activity, these plant-based alternatives offer several advantages. They are cost-effective, sustainable, and pose minimal risk of adverse effects. Moreover, they align with the growing interest in natural remedies and eco-friendly solutions[8,29]. As we continue our investigations, we aim to elucidate the underlying mechanisms of action, optimize dosage regimens, and explore potential formulations for topical application. Our ultimate goal is to provide clinicians with evidence-based recommendations for managing cutaneous candidiasis, ensuring patient well-being while minimizing side effects[10,12,13]. Through this research, we hope to bridge the gap between traditional wisdom and modern science, fostering a holistic approach to healthcare.

#### **AIMS & OBJECTIVES (SCOPE OF STUDY)**

**Aim:** To Study Synergistic Anti-Fungal activity of Clove and Turmeric Oil extracts on *Candida albicans*.

#### **Objectives:**

##### **1. Hypersensitivity Reactions:**

Synthetic antifungals can trigger hypersensitivity reactions, including itching, urticaria (hives), and even anaphylaxis. These adverse effects can be challenging to differentiate from the symptoms of the underlying fungal infection itself. For patients already suffering from itching due to candidiasis, distinguishing between drug-induced itching and infection-related itching becomes problematic[29-31].



**Fig.6 Hypersensitive Reaction on Skin**

##### **2. Drug Resistance:**

*Candida* species are notorious for developing resistance to antifungal agents. Over time, repeated use of synthetic drugs can lead to the emergence of drug-resistant strains. This poses a serious threat to effective treatment[4,5].

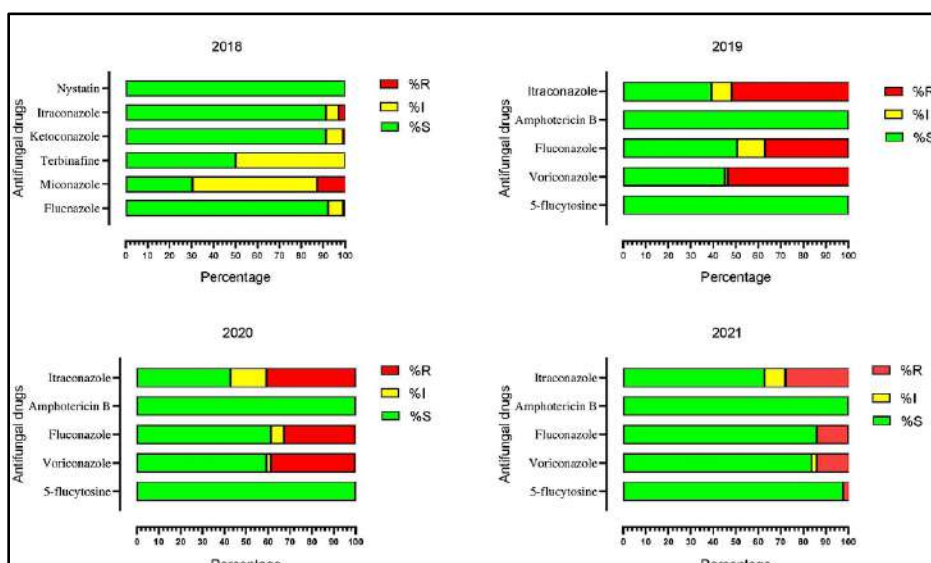


Fig. 7 Antifungal susceptibility pattern of *Candida*[6].

Here,

%R = Resistant (%)

%I = Intermediate Resistant (%) and

%S = Susceptible (%)

### 3. Synergism Hypothesis:

The outburst of drug resistant microbial strains necessitates the studies for synergistic effects of

antibiotics in combination with plant's derivatives to develop the antimicrobial cocktail with a wider spectrum of activity and reduction of adverse side effects of antimicrobial agents. We hypothesize that combining clove and turmeric extracts may enhance their antifungal activity while minimizing adverse effects[8,32,33].

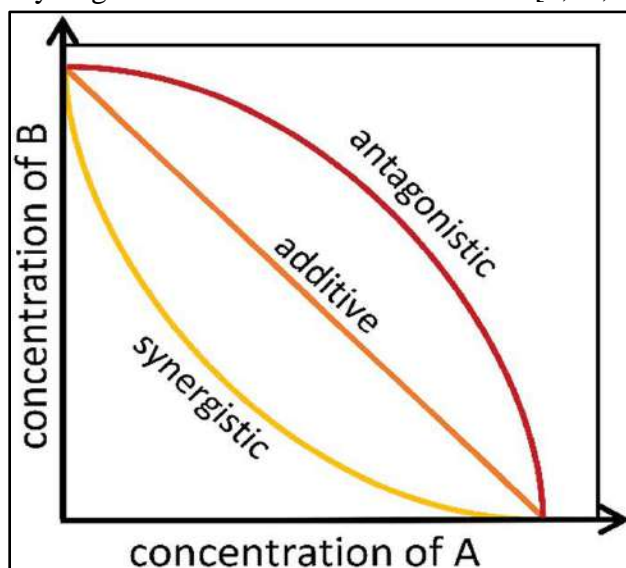


Fig.8 Synergism of Drugs

## Materials & Methods (Research Methodology):

### 1. Collection and Preparation of Plant Materials

#### Turmeric (*Curcuma longa*):

We obtained turmeric powder from a commercially available standardized source. The powdered turmeric was stored in an airtight container to prevent moisture absorption and degradation of active compounds.



Clove (*Syzygium aromaticum*):

Clove buds were procured from a reputable supplier. The buds were sun-dried to reduce

moisture content. The dried clove buds were ground into a fine powder using a grinder.

## 2. Extraction

### Turmeric Extraction:



**Fig. 09 Extraction Using Steam Distillation**

We performed hydro distillation to extract essential oil from the turmeric powder. The powdered turmeric was loaded into a Round bottom flask, and water was added. The mixture was heated, and the volatile components were vaporized. The condensed vapor was collected, and the separated essential oil was stored in amber glass vials[12,45,46].

### Clove Extraction:

Similar to turmeric, we subjected the clove powder to hydro distillation. The clove powder was placed in the RBF, and water was added. The distillation process yielded clove essential oil, which was carefully collected and preserved[13,45,46].

## 3. Phase Separation

### Turmeric Essential Oil:

The hydro distilled turmeric essential oil was subjected to phase separation. We used a separating funnel to separate the oil layer from the aqueous layer. The oil layer, rich in bioactive compounds, was isolated for further analysis[46].



**Fig. 10 Phase Separation using Separating Funnel Clove Essential Oil:**

Similarly, the hydro distilled clove essential oil underwent phase separation. The oil layer was carefully separated from the water layer. The clove oil was retained for subsequent experiments[46].

## 4. Sample Preparation

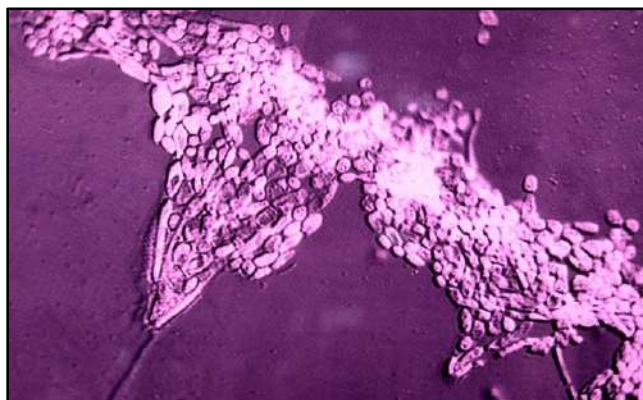
The Clove and Turmeric oils were mixed at predetermined ratios of 1:1, 3:1 And 1:3. We prepared five different samples[43,47]:



**Fig. 11 Samples given for Assay**

1. Turmeric Oil: A sample containing only turmeric oil.
2. Clove Oil: A sample containing only clove oil.
3. 1:1 Mixture: A mixture of turmeric oil and clove oil in a 1:1 ratio.
4. 3:1 Mixture: A mixture of turmeric oil and clove oil in a 3:1 ratio.
5. 1:3 Mixture: A mixture of turmeric oil and clove oil in a 1:3 ratio.

#### **5. Selection of Culture Species**



**Fig. 12 Candida albicans**

Common options include *C. Albicans*, *C. Glabrata*, and *C. Krusei*. We selected *Candida albicans* as our target pathogen for the antifungal activity assay as *Candida albicans* is a common fungal species associated with infections in humans. Which was then incubated on Standard culture media for 48 hrs at 37°C [7,47,48].

#### **6. In-Vitro Assay**

We performed the Kirby-Bauer disk diffusion method to assess the antifungal activity of our oil samples against *Candida albicans*. This method involves placing paper disks impregnated with the essential oils onto agar plates inoculated with the pathogen. The resulting zone of inhibition around the disks indicates the effectiveness of the oils in inhibiting fungal growth [47-49].





**Fig. 13 In Vitro Anti-Fungal Assay on Candida albicans**

## 7. Data Analysis

The data analysis began with the measurement of the diameters of the zones of inhibition. These measurements, taken in mm, quantified the

**Table 2. Zone of Inhibition(in mm)**

Organism	Candida albicans		
	Dilutions	1:1	1:3
Clove oil	14	11	19
Turmeric oil	10	14	16
Control	30	27	32

### Interpretations:

- Sensitive: Zone of inhibition on more than 12mm

The zones of inhibition were measured in millimetres, with larger zones indicating greater antifungal activity. The results were compared to the zone of inhibition for the Ketoconazole control to evaluate the relative effectiveness of the oil samples[33,34]. The individual oils showed significant antifungal activity. This indicates that both turmeric and clove oils have potent antifungal properties. The mixtures of turmeric and clove oils also showed significant antifungal activity. Interestingly, the 3:1 mixture had the largest zone

antifungal activity of each sample. The larger the zone of inhibition, the more potent the antifungal activity. The results were then compared with the zone of inhibition around the Ketoconazole control. The interpretation of the results focused on potential synergism between the turmeric and clove oils. If the zone of inhibition for a mixture was greater than the sum of the zones for the individual oils, this indicated a synergistic effect. In other words, the mixture was more effective than the individual oils alone[49].

### OBSERVATIONS / RESULTS:

The antifungal activity of turmeric oil, clove oil, and their mixtures was evaluated against *Candida albicans* using the disk diffusion method. The results are summarized in the table below:

- Moderately Sensitive: Zone of inhibition between 8-12mm
- Resistant: Zone of inhibition less than 8 mm of inhibition, suggesting a potential synergistic effect between turmeric and clove oils. This synergy was less pronounced in the 1:1 and 1:3 mixtures, indicating that the ratio of the two oils can impact their combined antifungal activity. The results of this analysis provided insights into the antifungal properties of turmeric and clove oils, both individually and in combination. These findings could have implications for the development of new antifungal treatments. Further research is needed to optimize the ratios of the two

oils and to investigate their mechanisms of action

## **DISCUSSION & CONCLUSION:**

### **Discussion:**

Fungal infections, once considered manageable, have become a growing global health concern. The rise in immunosuppressive therapies, increased international travel, and global warming have contributed to the surge in invasive fungal infections. These infections can range from superficial skin conditions to life-threatening systemic diseases. Unfortunately, the available antifungal arsenal is limited, and resistance is on the rise. Conventional antifungal agents, including polyenes, azoles, echinocandins, and flucytosine, have limitations such as toxicity, drug interactions, and the development of resistance. As super yeasts like *Candida auris* emerge, even the strongest antifungal drugs face challenges. Therefore, the development of novel antifungal drugs is crucial. Seeking alternative solutions, we investigated the antifungal efficacy of clove and turmeric oils, both known for their medicinal properties. We extracted clove and turmeric oil samples Using steam distillation, we extracted essential oils from clove and turmeric powders. Our study investigated the synergistic potential of these oils, combined in 1:1, 3:1 and 1:3 ratios, against *Candida* species. Samples, comprising individual oils and various mixtures, were prepared and subjected to the Kirby-Bauer disk diffusion method for antifungal assessment. Our in vitro assays revealed promising synergism in the 3:1 mixture of clove and turmeric oils. Although the observed zone of inhibition was shorter than that of synthetic antifungal ketoconazole, the natural blend demonstrated efficacy. Further research is warranted to optimize the blend ratio and explore its clinical applicability. Clinical Applicability: Further research is warranted to optimize the blend

ratio and explore its clinical applicability. Our findings contribute to the field of plant-based medicine and offer hope for improved patient outcomes

### **CONCLUSION**

The emergence of antifungal resistance poses a significant challenge to global health. To combat this threat effectively, investments are necessary to develop novel antifungal drugs with innovative mechanisms of action. Additionally, diagnostic tools capable of identifying antifungal resistance and instances of hypersensitivity need to be accessible worldwide. By addressing these aspects, we can improve our ability to manage invasive fungal infections and reduce associated morbidity and mortality. Our study emphasizes the importance of exploring herbal alternatives to synthetic antifungal drugs. Specifically, we investigated the combination of clove oil and turmeric oil, which demonstrated synergistic effects against *Candida* species. Clove oil and turmeric oil, when combined in a 3:1 ratio, demonstrated synergistic effects against *Candida* species. However, their efficacy fell short of ketoconazole. To make herbal alternatives viable, additional investigations are warranted. By harnessing the power of natural compounds, we can potentially develop safer and more effective treatments for fungal infections. Future research should focus on refining the formulation and understanding the mechanisms underlying this synergism. In conclusion, our findings contribute to the growing field of plant-based medicine and offer hope for improved antifungal therapies with fewer side effects and more efficacy.

### **AUTHOR CONTRIBUTIONS:**

N. S. Pamnani: developed the theory and performed the experiment. S. Sahu and K.



Deshmukh: performed the extractions. A. Kale: wrote the original draft and verified the analytical findings. P. H. Chaudhary: supervised the findings of this work. P. Burange: provided critical feedback. All authors discussed the results and contributed to the final manuscript.

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