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Antagonistic Interaction Between Cinnamomum burmanii Bark Extract and Ketoconazole Against Candida albicans: An In Vitro AZDAST Analysis

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ABSTRACT

Background: Pharyngeal candidiasis, driven by *Candida albicans*, poses significant clinical challenges due to rising antifungal resistance. *Cinnamomum burmanii* (cinnamon) bark extract offers potential antifungal properties, prompting interest in combining it with conventional azoles like ketoconazole.
Objective: To evaluate the in vitro antifungal interaction between cinnamon bark extract and ketoconazole against *C. albicans* using the Ameri-Ziaei Double Antibiotic Synergism Test (AZDAST).
Methods: An in vitro experimental study was conducted using *C. albicans* cultures. Antifungal activity was assessed across five groups: cinnamon extract (single doses 1 and 2), ketoconazole (single doses 1 and 2), and their combination. Zone of inhibition was measured and analyzed using Kruskal-Wallis and Mann-Whitney U tests.
Results: Ketoconazole exhibited the highest mean zone of inhibition (38.63 mm). The combination group (21.75 mm) showed no significant difference compared to the lowest cinnamon extract dose (21.73 mm, p=0.825) but was significantly lower than the higher cinnamon dose (27.43 mm, p=0.002) and both ketoconazole doses (p<0.001). AZDAST analysis confirmed an antagonistic interaction.
Conclusion: Combining cinnamon bark extract with ketoconazole results in antagonism, reducing antifungal efficacy. Cinnamaldehyde likely interferes with ketoconazole-ergosterol binding, compromising membrane affinity. These findings underscore the necessity of evaluating herb-drug interactions prior to clinical co-administration.

Key Points (Highlights):

- *Cinnamon extract has antifungal properties against Candida.*
- *Combining cinnamon extract and ketoconazole shows antagonism.*
- *Herb-drug interaction screening is crucial before co-administration.*

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INTRODUCTION

Pharyngeal candidiasis, predominantly caused by *Candida albicans*, constitutes a persistent clinical burden in contemporary otolaryngology practice. Epidemiological data from tertiary referral centers indicate that pharyngitis ranks among the top ten most frequently encountered conditions in ENT outpatient clinics, with acute and chronic forms collectively accounting for over 17% of all patient visits (S. et al., 2026). As an opportunistic commensal organism, *C. albicans* colonizes the oral mucosa in approximately 20–75% of healthy individuals; however, under predisposing conditions such as immunosuppression, prolonged antibiotic use, or metabolic disorders, it transitions into an invasive pathogen capable of causing mucocutaneous lesions that may progress to life-threatening systemic candidiasis (Bollin et al., 2026). Compounding this clinical challenge is the escalating prevalence of antifungal resistance, with approximately 40% of candidiasis cases demonstrating reduced susceptibility to conventional azole derivatives (De Sousa et al., 2025). This resistance phenomenon has progressively undermined the reliability of standard monotherapies, resulting in prolonged treatment courses, recurrent infections, and heightened morbidity, thereby underscoring the urgent need for alternative and adjunctive therapeutic strategies (Dewi et al., 2026).

In response to this therapeutic gap, botanical extracts have attracted considerable research interest owing to their chemically diverse phytoconstituents and multi-targeted mechanisms of action (Augostine & Avery, 2022). *Cinnamomum burmanii* (cinnamon) bark, a widely utilized traditional remedy across Southeast Asia, contains a rich array of bioactive compounds including cinnamaldehyde, eugenol, flavonoids, tannins, and volatile essential oils (Saracino et al., 2022). Preclinical investigations have demonstrated that cinnamaldehyde and eugenol disrupt fungal cell membrane integrity through lipid peroxidation and protein denaturation, while flavonoids and tannins interfere with nucleic acid and protein synthesis (W. Wang et al., 2025). Additionally, the essential oil fraction has been shown to impair fungal metabolic pathways and inhibit biofilm formation (Cho et al., 2026). These mechanistic properties have established cinnamon bark extract as a credible standalone antifungal candidate against *C. albicans*, prompting growing empirical interest in combining it with conventional azole antifungals under the assumption that multi-targeted pharmacological approaches may enhance therapeutic outcomes and circumvent resistance mechanisms (Nedea et al., 2026).

Nevertheless, the empirical co-administration of herbal extracts with synthetic antifungals introduces substantial pharmacodynamic risks that remain insufficiently characterized in clinical settings (Sharma et al., 2026). The biochemical heterogeneity of plant-derived preparations means that their constituent phytochemicals may interact unpredictably with the molecular targets of conventional drugs (Di Vito et al., 2023). Rather than producing additive or synergistic effects, concurrent exposure to specific phenolic compounds may competitively interfere with drug–receptor binding, modify membrane fluidity in ways that impede intracellular drug accumulation, or activate efflux-mediated resistance pathways. Such interactions can paradoxically attenuate the therapeutic potency of the conventional agent, leading to suboptimal clinical responses (Didehdar et al., 2022). Consequently, rigorous preclinical evaluation of herb–drug combinations is essential to delineate their interaction profiles and to prevent inadvertent therapeutic compromise when these agents are used concurrently in patient care (Aliaghazadeh et al., 2025).

Despite the extensive traditional use of cinnamon and its validated in vitro antifungal activity, its specific pharmacodynamic interaction with azole antifungals particularly ketoconazole, a widely prescribed systemic agent for pharyngeal candidiasis remains critically underexplored (Yuan et al., 2024). This study addresses this knowledge gap by systematically evaluating the in vitro interaction between *C. burmanii* bark extract and ketoconazole against *C. albicans* using the Ameri-Ziaei Double Antibiotic Synergism Test (AZDAST), a validated method for classifying antimicrobial interactions as synergistic, additive, or antagonistic (Sethunga et al., 2023). By generating robust, evidence-based data on this combination, the present research aims to inform rational prescribing practices, highlight potential risks of empirical herb–drug co-administration, and provide a methodological framework for future investigations into integrated antifungal therapies (Barbarossa et al., 2024).

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MATERIALS AND METHODS

Reporting Guidelines

To ensure comprehensive and transparent reporting, the methodological framework of this study was structured in accordance with the CARE (CAse REport) guidelines, an EQUATOR network standard. Although originally designed for clinical case reports, its rigorous structural domains encompassing patient presentation, diagnostic assessment, therapeutic intervention, and follow-up were systematically adapted for this in vitro experimental context. In this paradigm, the standardized Candida albicans culture serves as the microbial "patient," facilitating a standardized evaluation of baseline susceptibility, targeted therapeutic interventions, and subsequent microbiological outcomes.

Study Design and Microbial "Patient" Presentation

An in vitro experimental study with a post-test only control group design was executed at the Faculty of Medicine Laboratory, Universitas Islam Malang, from March to May 2025. The microbial "patient," a standardized laboratory strain of Candida albicans, was cultured and inoculated into Mueller-Hinton agar media. To establish a sterile baseline environment analogous to clinical aseptic protocols, all glassware (Erlenmeyer flasks, beakers, Petri dishes, and test tubes) and media were sterilized in an autoclave at 121°C for 120 minutes. Following sterilization, the equipment was cooled to 60°C before handling to prevent thermal degradation of subsequent reagents and ensure optimal aseptic conditions.

Diagnostic Assessment and Therapeutic Interventions

The diagnostic baseline for antifungal susceptibility was established using the Zone of Inhibition (ZOI) assay via the agar well diffusion method. Standardized wells with a diameter of 6 mm were punctured into the inoculated media. The therapeutic interventions were stratified into five distinct experimental groups: Cinnamon extract single dose 1 (K1, 30 µl), Cinnamon extract single dose 2 (K2, 30 µl), Combination of Cinnamon extract and Ketoconazole (KA, 15 µl of each agent), Ketoconazole single dose 1 (A1, 30 µl), and Ketoconazole single dose 2 (A2, 30 µl).

The botanical intervention was prepared by macerating Cinnamomum burmanii bark powder in 96% ethanol at a 1:5 ratio for 24 hours. The mixture was filtered using a Buchner vacuum funnel and subsequently concentrated via a rotary evaporator to yield a 100% thick extract. The synthetic intervention utilized standardized Ketoconazole antifungal disks (15 mcg, 6 mm diameter), stored under optimal conditions to maintain chemical stability.

Therapeutic Focus and AZDAST Application

The core therapeutic evaluation employed the Ameri-Ziaei Double Antibiotic Synergism Test (AZDAST) to classify the pharmacodynamic interaction between the cinnamon extract and ketoconazole. This assay determines whether the combined ZOI is significantly larger (synergism), equal to the sum (additivity), or smaller (antagonism) than the ZOI produced by the individual agents. Following the application of the respective volumes into the wells, the plates were incubated under controlled conditions. The resulting ZOI was measured in millimeters to quantitatively assess the interaction pattern, mirroring the evaluation of therapeutic response in clinical scenarios.

Statistical Follow-up and Data Analysis

Quantitative data derived from the ZOI measurements were processed using SPSS version 26. Initial assumptions were evaluated using the Shapiro-Wilk test for normality and Levene's test for homogeneity of variances. Because the combination group exhibited a non-normal distribution and heterogeneous variances, non-parametric statistical pathways were invoked. The Kruskal-Wallis test was utilized to determine the overall significance of differences across all experimental groups. Subsequently, the Mann-Whitney U test was applied for post-hoc pairwise comparisons to identify specific inter-group variations. Statistical significance was established at $p < 0.05$.

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RESULTS

The antifungal activity, assessed via the Zone of Inhibition (ZOI), revealed distinct efficacy patterns across the experimental groups. Ketoconazole demonstrated the highest inhibitory effect, while the combination of cinnamon extract and ketoconazole exhibited reduced efficacy compared to the individual agents, indicating an antagonistic interaction.

Table 1. Descriptive Statistics, Normality, and Homogeneity of Zone of Inhibition

Group	Treatment	Mean ZOI (mm)	SD	Shapiro-Wilk (Sig)	Normality
K1	Cinnamon Extract - Dose 1	21.73	2.60	0.531	Normal
K2	Cinnamon Extract - Dose 2	27.43	3.79	0.988	Normal
KA	Combination (Cinnamon + Ketoconazole)	21.75	2.12	0.020	Not Normal
A1	Ketoconazole - Dose 1	36.44	0.41	0.150	Normal
A2	Ketoconazole - Dose 2	38.63	1.09	0.392	Normal

Note: *Levene's Test for homogeneity yielded a significance value of 0.0001, indicating heterogeneous variances across groups ($p < 0.05$). The Kruskal-Wallis test confirmed a significant overall effect ($p = 0.000$).*

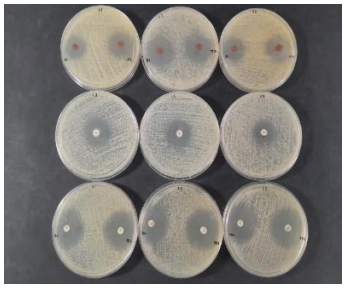

Figure 1

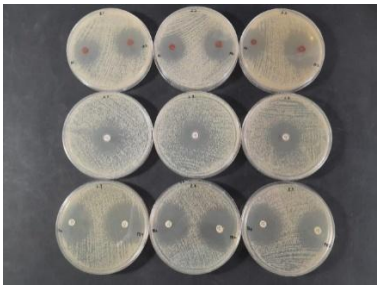

Figure 2

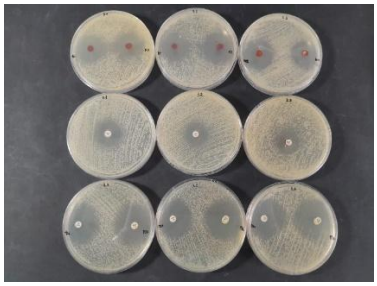

Figure 3

Figure 1. Ameri-Ziaei Double Antibiotic Synergism Test (AZDAST) demonstrating the interaction pattern. The image consolidates the original file's figure 1 (Repetitions 1-3), figure 2 (Repetitions 4-6), and figure 3 3 (Repetitions 7-9). The combination group (KA) exhibits a markedly reduced inhibition zone compared to the individual ketoconazole groups (A1, A2) and the higher dose cinnamon extract (K2), visually confirming an antagonistic interaction against *Candida albicans*.

Table 2. Pairwise Comparisons of Zone of Inhibition (Mann-Whitney U Test)

Comparison	Significance (p-value)	Result
K1 vs K2	0.004	Significant Difference
K1 vs KA	0.825	No Significant Difference
K1 vs A1	0.000	Significant Difference

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Comparison	Significance (p-value)	Result
K1 vs A2	0.000	Significant Difference
K2 vs KA	0.002	Significant Difference
K2 vs A1	0.000	Significant Difference
K2 vs A2	0.000	Significant Difference
KA vs A1	0.000	Significant Difference
KA vs A2	0.000	Significant Difference
A1 vs A2	0.000	Significant Difference

Note: * $p < 0.05$. The combination group (KA) was significantly less effective than both ketoconazole doses and the higher cinnamon extract dose, confirming antagonism.

DISCUSSION

The present study demonstrates that the combination of Cinnamomum burmanii bark extract and ketoconazole exhibits a significant antagonistic interaction against Candida albicans (Tome et al., 2018). While ketoconazole alone produced the most substantial zone of inhibition, the concurrent application of the herbal extract markedly diminished the antifungal efficacy of the azole (Rhimi et al., 2020). This finding challenges the empirical assumption that combining natural botanical extracts with conventional antifungals inherently yields synergistic benefits (Kutsyk et al., 2023). In the clinical context of pharyngeal candidiasis, where patients frequently self-medicate with traditional herbal remedies alongside prescribed systemic azoles, this pharmacodynamic conflict poses a critical risk of suboptimal therapeutic outcomes, prolonged mucosal inflammation, and potential disease progression (Khan, 2024).

The standalone efficacy of cinnamon bark extract is primarily attributed to its rich profile of phenolic compounds, notably cinnamaldehyde, eugenol, flavonoids, and tannins (Zhou et al., 2024). These bioactive agents exert fungitoxic effects through multiple targets: cinnamaldehyde and eugenol disrupt the structural integrity of the fungal cell wall and membrane, inducing cellular leakage, while flavonoids and tannins interfere with nucleic acid and protein synthesis (Mishra et al., 2025). Furthermore, the essential oil fraction impairs fungal metabolic pathways and inhibits glycolysis. The dose-dependent increase in the zone of inhibition observed in the single-agent cinnamon groups corroborates its inherent membrane-disrupting capabilities and confirms its potential as an independent antifungal agent, albeit with a lower potency compared to synthetic azoles (Liu et al., 2024; Shahina et al., 2018).

Conversely, ketoconazole operates through a highly specific and targeted mechanism as the first broad-spectrum systemic antifungal agent with potent fungitoxic properties (Xu et al., 2018). It functions by interacting with cytochrome P-450 dependent enzymes, particularly inhibiting C-14 demethylase, which is crucial for the conversion of lanosterol to ergosterol (Huang et al., 2019). Ergosterol is an indispensable structural component of the fungal cell membrane; its depletion compromises membrane fluidity, increases cellular permeability, and ultimately leads to fungal cell death (H.-X. Wang et al., 2022). The high zone of inhibition values in the ketoconazole groups reflect the potent and targeted nature of this ergosterol biosynthesis inhibition, establishing it as the superior monotherapy in this experimental model (Wei et al., 2020).

The antagonism observed in the combination group likely stems from the competitive and disruptive interaction between the phenolic compounds in cinnamon, particularly cinnamaldehyde, and the

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ketoconazole-ergosterol binding pathway (De Almeida et al., 2019). The free 3-phenyl group of cinnamaldehyde can bind to enzymes on the fungal cell wall and sequester oxygen required for cellular metabolism, while simultaneously inducing protein denaturation and reducing surface tension (D. Wang et al., 2023). These physicochemical alterations modify the baseline fluidity and conformational state of the fungal membrane, thereby reducing the binding affinity of ketoconazole to its target enzymes and impeding its intracellular accumulation (Arteaga-Crespo et al., 2026). Consequently, the herbal extract effectively neutralizes the azole's primary mechanism of action, resulting in a combined inhibition zone that is inferior to the individual agents.

Limitation

A primary limitation of this study is its strictly in vitro design, which does not account for the complex pharmacokinetic parameters, metabolic degradation, or systemic immune responses present in a living organism. The use of a 100% concentrated extract may not accurately reflect the achievable systemic or topical concentrations in clinical practice. Furthermore, the study utilized a specific laboratory strain of C. albicans and a single ethanol extraction method, which may not fully represent the genetic variability of clinical isolates, the presence of azole-resistant strains, or the diverse phytochemical concentrations found in different commercial herbal preparations.

Future research must prioritize in vivo animal models to evaluate the systemic safety, toxicity, and actual therapeutic viability of this combination in complex biological environments, alongside testing against other clinically relevant and resistant fungal strains such as Aspergillus fumigatus, which is highly prevalent in ENT pathologies like rhinosinusitis. From a policy perspective, these findings strongly advocate for the integration of mandatory herb-drug interaction screening in clinical guidelines. Healthcare providers, particularly in otolaryngology, must be educated to routinely inquire about the use of traditional herbal remedies during anamnesis to prevent inadvertent antagonistic interactions, treatment failures, and to optimize patient outcomes.

CONCLUSIONS

The combination of Cinnamomum burmanii bark extract and ketoconazole demonstrates a significant antagonistic interaction against Candida albicans, resulting in markedly reduced antifungal efficacy compared to the individual agents. This antagonism is primarily driven by cinnamaldehyde-induced physicochemical alterations in the fungal membrane, which interfere with ketoconazole-ergosterol binding, compromise membrane affinity, and disrupt cellular permeability. These findings provide critical, evidence-based contraindication against the empirical co-administration of cinnamon bark extract with azole antifungals. Ultimately, this study underscores the imperative for rigorous preclinical herb-drug interaction evaluations and heightened clinical vigilance to ensure safe, effective, and rational pharmacological practices in the management of candidiasis.

DECLARATIONS

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2. Ethical Approval and Informed Consent

Ethical approval and informed consent were not required for this study as it is an in vitro experimental study and does not involve direct human or animal subjects.

3. Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

4. Funding

This work was supported by the internal research grant of Universitas Islam Malang under Grant 2025. The funders had no role in study design, data collection and analysis, decision to publish,

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or preparation of the manuscript.

5. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

6. Authors' Contributions

Conceptualization: F.P.D.; Methodology: F.P.D., R.R.; Formal analysis and investigation: R.R., M.S.F.P., R.C.P.; Writing - original draft preparation: F.P.D., R.R.; Writing - review and editing: S.T.P., F.P.D.; Funding acquisition: F.P.D.; Resources: F.P.D., R.R.; Supervision: F.P.D., S.T.P.

7. AI Disclosure

During the preparation of this work, the authors used AI-assisted language editing tools in order to improve language readability and translate text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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