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Mechanistic Elucidation of the Antifungal Activity of *Persea americana* Seeds Against Multidrug-Resistant *Candida auris* and *Candida albicans*

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ABSTRACT

Introduction: The increasing prevalence of multidrug-resistant fungal pathogens, particularly *Candida auris* and *Candida albicans*, represents a significant global health challenge. Plant-derived bioactive compounds provide promising alternatives for antifungal therapy. This study aimed to evaluate the antifungal killing kinetics of *Persea americana* seed extracts against multidrug-resistant *C. auris* and *C. albicans*.

Methods: Time-kill assays were performed at minimum inhibitory concentration (MIC), 2×MIC, 4×MIC, and 8×MIC. Log_{10} viable counts were determined over 42 hours. Phytochemical profiling of the extract was conducted using High Performance Liquid Chromatography (HPLC).

Results: The extract exhibited dose- and time-dependent antifungal activity, producing significant reductions in viable counts compared to controls. At higher concentrations (4×MIC and 8×MIC), rapid killing was observed, with near-complete clearance by 42 hours. HPLC analysis identified flavonoids (quercetin, kaempferol, apigenin, catechin), phenolic acids (p-coumaric acid, quinic acid), and phytosterols (campesterol), which likely contributed to the antifungal activity.

Conclusion: These results indicate that *P. americana* seed extracts possess potent antifungal properties, exhibiting both fungistatic and fungicidal effects depending on dose and exposure time. The findings highlight the potential of *P. americana* seeds as a source of novel antifungal agents.

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Introduction

Invasive candidiasis is a leading cause of fungal morbidity and mortality worldwide, particularly among hospitalized and immunocompromised patients (Lass-Flörl et al., 2024). Globally, an estimated 1.57 million people develop Candida bloodstream infection or invasive candidiasis each year, resulting in nearly 995,000 deaths (63.6%) (Denning, 2024). Even with antifungal therapy, mortality remains high, reflecting both the severity of infection and the limitations of current treatments (Boakye-Yiadom et al., 2024).

Epidemiological patterns have shifted over recent decades, with infections increasingly caused by non-albicans Candida (NAC) species such as *C. glabrata, C. tropicalis, C. parapsilosis,* and *C. krusei.* These species often display reduced susceptibility or intrinsic resistance to commonly used antifungals (Makanjuola et al., 2018; Oluyele et al., 2023; Figueroa-Ramos et al., 2024). Of particular concern is Candida auris, an emerging multidrug-resistant (MDR) pathogen capable of nosocomial outbreaks, persistence on healthcare surfaces, and resistance to multiple antifungal classes (Mishra et al., 2023; Kim et al., 2024). Recognizing this threat, the World Health Organization has listed Candida spp., including C. auris and C. albicans, among its fungal priority pathogens (Casalini et al., 2024).

Resistance mechanisms in Candida species include overexpression of efflux pumps, mutations in target enzymes (e.g., ERG11), alterations in ergosterol biosynthesis, and glucan synthase modifications often occurring in combination in MDR isolates (Navarro-Mendoza et al., 2024). With only a few antifungal drug classes available, therapeutic options are increasingly constrained, especially in low-resource settings where availability and cost are limiting (Oluyele et al., 2023; de Souza et al., 2025). The narrow antifungal pipeline further underscores the urgency of identifying new therapeutic agents with novel modes of action.

Natural products represent a promising avenue in antifungal drug discovery. Plants are reservoirs of diverse secondary metabolites with demonstrated antimicrobial activity (Oluyele et al., 2025). *Persea americana* (avocado), a tropical evergreen widely cultivated worldwide, has long been used in ethnomedicine for its antimicrobial properties (Oluyele and Akinyeke, 2025). It is particularly rich in phytochemicals such as phenolics, flavonoids, and terpenoids (Bhuyan et al., 2019; Sarmah et al., 2024). Extracts of *P. americana* have demonstrated antifungal activity against Candida spp. and other pathogenic fungi, with effects on both planktonic cells and biofilms (Idris et al., 2009; Jesus et al., 2015; Akpomie et al., 2021).

However, while inhibitory activity of *P. americana* against Candida species has been reported, little is known about its pharmacodynamics specifically, its time–kill kinetics against MDR isolates. Minimum inhibitory concentration (MIC) values provide static endpoints but do not capture the rate, magnitude, or sustainability of microbial killing (Kadeřábková et al., 2024). Time–kill assays, which measure changes in viable counts over time, can distinguish fungicidal from fungistatic effects and reveal post-antifungal activity or regrowth dynamics (Klepser et al., 1998; Öz et al., 2016; Oluyele et al., 2025b). Such data are essential for predicting therapeutic potential and informing dosing strategies, yet remain underexplored in studies of plant-derived antifungals.

Therefore, this study investigates the time–kill kinetics of *P. americana* extracts against multidrug-resistant Candida species. By assessing the rate and extent of fungal killing, this work aims to determine whether *P. americana* exhibits rapid and sustained fungicidal activity, thereby contributing to the development of novel, plant-based antifungal strategies in the face of rising MDR fungal infections.

Materials and Methods

Test Organisms and Preparation of Inoculum

The test organisms used in this study were multidrug resistant strains of Candida albicans and Candida auris obtained from the stock culture of previously identified isolates at the Microbiology Laboratory, in our institution. The organisms were reconfirmed through standard mycological tests (Oluyele et al., 2023). The test organisms were maintained on Sabauraud dextrose agar (SDA) agar slant and stored in the refrigerator at 40C for further studies. McFarland standard (0.5) was prepared by combining 0.05ml of 1% barium chloride Dihydrate (BaCl2.2H2O) with 9.95ml of 1% Sulfuric acid (H2SO4) to yield 1.0%w/v barium sulphate suspension. The accuracy of the density of a prepared McFarland standard was checked by using a spectrophotometer at 625 nm. The McFarland standard was vigorously agitated on a vortex mixer before use. Inoculum of each test organism was prepared by picking five distinct colonies of approximately 1 mm in diameter from a 24-hour-old culture. Colonies were suspended in 5 mL of

sterile 0.85% saline. The resulting suspension was vortexed for 15 seconds and its turbidity was adjusted to 0.5 McFarland standard. This procedure yielded a yeast stock suspension of 1-5 x 106 cells per mL (Oluyele et al., 2023).

Collection of Plant Materials and Preparation of Extracts

Mature fruits of *P. americana* (avocado pear) were collected from the Akungba-Akoko community in Ondo State, Nigeria (Latitude 7°47′40″N). The plant material was authenticated at the Department of Plant Science and Biotechnology, Adekunle Ajasin University, Akungba-Akoko, and a voucher specimen (No. PSBHT-283) was deposited in the departmental herbarium for reference. The seeds were separated from the fruits, air-dried, and ground into fine powder. Extraction was carried out using a modified procedure described by Oluyele and Oladunmoye (2017). A total of 650 g of the powdered seeds was soaked in 3.5 L of ethanol inside an airtight container for 72 hours, with intermittent shaking to facilitate the release of phytochemicals. After maceration, the mixture was first sieved through muslin cloth and then filtered using Whatman No. 1 filter paper to obtain a clear extract. The filtrate was concentrated under reduced pressure using a rotary evaporator, after which the crude extract was weighed, transferred into a clean container, and stored under refrigeration at 4 °C until required for further analysis.

Determination of Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) of the extract were determined using standard tube-dilution and plating methods, respectively (Oluyele et al., 2025). For MIC determination, a series of extract concentrations (200 to 3.125 mg/mL) were prepared in sterile Sabouraud Dextrose Broth (SDB). To each tube, 0.1 mL of standardized fungal inoculum (adjusted to 0.5 McFarland standard) was added. Control tubes consisted of SDB only (negative control) and SDB with inoculum but without extract (positive control). All tubes were incubated at 35 °C for 48 hours. Following incubation, fungal growth was assessed both visually (turbidity) and spectrophotometrically using a Beckman Model 35 spectrophotometer at 600 nm. The percentage inhibition of growth at each concentration was calculated using the formulae:

OD test, corr = OD test – OD extract blank

% Inhibition = (OD pos – OD test, corr) x 100 (OD pos – OD neg)

OD test, corr = Corrected test optical density

OD test = Optical density of the broth containing both inoculum and extract at a given concentration (SDB + inoculum + extract)

OD extract blank = Optical density of the broth containing extract only without inoculum (SDB + extract)

OD pos = Optical density of the broth containing test inoculum without extract (SDB + inoculum)

OD neg = Optical density of the broth containing only sterile medium (SDB) without inoculum or extract (SDB only)

The MIC was defined as the lowest extract concentration that produced ≥90% growth inhibition compared with the control.

Time-Kill Kinetics Assay

Time–kill kinetics of the extract against the test *Candida* isolates were assessed using standard procedures (Oluyele, 2025b). Standardized inocula (~1×106 CFU/mL) prepared from overnight cultures were exposed to the extract at 1×MIC, 2×MIC, 4×MIC, 8×MIC and 16×MIC concentrations in Sabouraud Dextrose Broth (SDB). Control sets included growth control (SDB with inoculum only), sterility control (SDB only), solvent control, and extract blank. All inoculated tubes were incubated at 35 °C with gentle shaking, and aliquots were withdrawn at 6, 18, 22, 26, 30 and 42 h. Each sample was serially diluted in sterile phosphate-buffered saline, plated on Sabouraud Dextrose Agar (SDA), and incubated at 35°C for 24–48 h. Colonies from plates yielding 30–300 colonies were counted to determine viable counts (CFU/mL), which were converted to log10 values and plotted against exposure time to generate time–kill curves. Fungicidal activity was defined as a ≥3 log10 CFU/mL (≥99.9%) reduction from the starting inoculum, while a reduction of <3 log10 indicated fungistatic activity.

High Performance Liquid Chromatography (HPLC) Analysis of Extract

About 2 g of sample was extracted in 20 mL acetonitrile–methanol (1:1 v/v) with 30 min agitation, and the organic phase was collected into a 25 mL standard flask. Analysis was performed on an Agilent 1200 HPLC system using reversed-phase chromatography with a Hypersil BDS C18 column (250 mm × 4.0 mm). The mobile phase consisted of 0.1% formic acid and acetonitrile

under gradient elution, with an injection volume of 20 µL, flow rate of 0.6 mL/min, and detection at 280 nm. Reference analyte standards were first injected to generate retention time and peak profiles, which were then used to identify test sample peaks by comparison of chromatographic patterns and UV spectra (Oluyele, 2025a).

Results

Killing Kinetics of *Persea americana* Seed Extract Against MDR *Candida* spp

The killing kinetics data showed that *P. americana* seed extracts suppressed growth of both *C. auris* and *C. albicans* in a concentration- and time-dependent manner (Figure 1 and 2). Against *Candida auris*, at MIC and 2×MIC, viable counts gradually declined from ~1.8 log10 cfu/mL at 6 h to 0.7–0.6 log10 cfu/mL at 42 h. At 4×MIC and 8×MIC, the extract produced faster killing, reducing counts to ≤0.48 log10 cfu/mL by 42 h. In contrast, the negative control-maintained growth above 2.3 log10 cfu/mL.

Against *C. albicans*, a similar pattern was observed, with counts reducing from ~1.83 log10 cfu/mL at 6 h to 0.48–0.6 log10 cfu/mL at 42 h at higher concentrations. The negative control-maintained growth (≥2.3 log10 cfu/mL), while the positive control (standard antifungal) achieved near-complete clearance by 42 h.

Phytochemical profile

HPLC analysis of *P. americana* seed extract identified eleven bioactive compounds including flavonoids (vitexin, orientin, catechin, quercitrin, quercetin, kaempferol, apigenin), phenolic acids (p-coumaric acid, quinic acid), tocopherol, and campesterol (Table 1 and Figure 3).

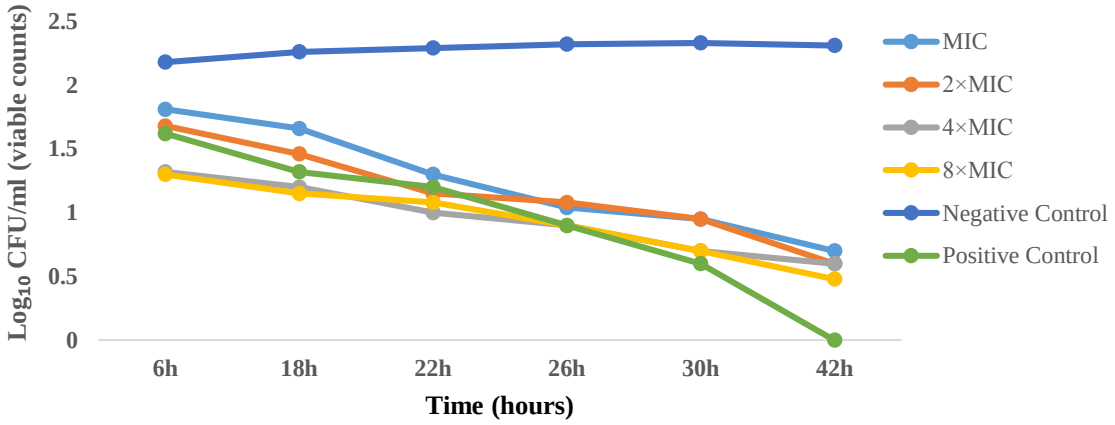

Figure 1: Kill kinetics of *Persea americana* against *Candida auris*

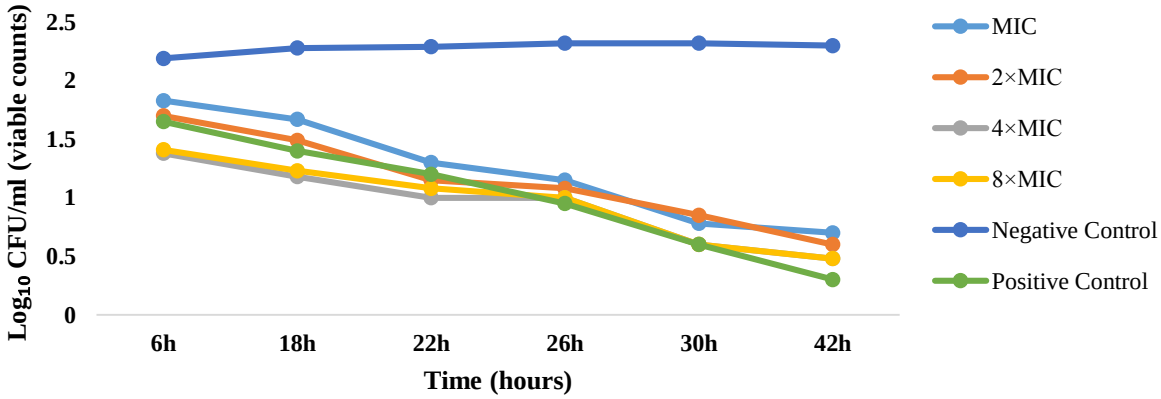

Figure 2: Kill kinetics of *Persea americana* against *Candida albicans*

Table 1: HPLC identified compounds of *Persea americana* seeds extract

Components	Retention time (Minute)	Area (AU)	Height (AU)
Vitexin	1.263	1341.6490	44.821
Orientin	2.641	396.9422	11.941
Catechin	6.312	482.9291	14.552
Quercitrin	7.950	352.2841	12.846
Camposterol	12.213	93.5455	6.892
Tocopherol	13.814	110.4321	8.282
P-Coumaric	14.653	182.4131	9.123
Quinic acid	15.349	178.6413	9.014
Apigenin	16.342	180.1426	9.970
Kaempferol	9.050	991.8246	25.814
Quercetin	11.050	150.2411	8.842

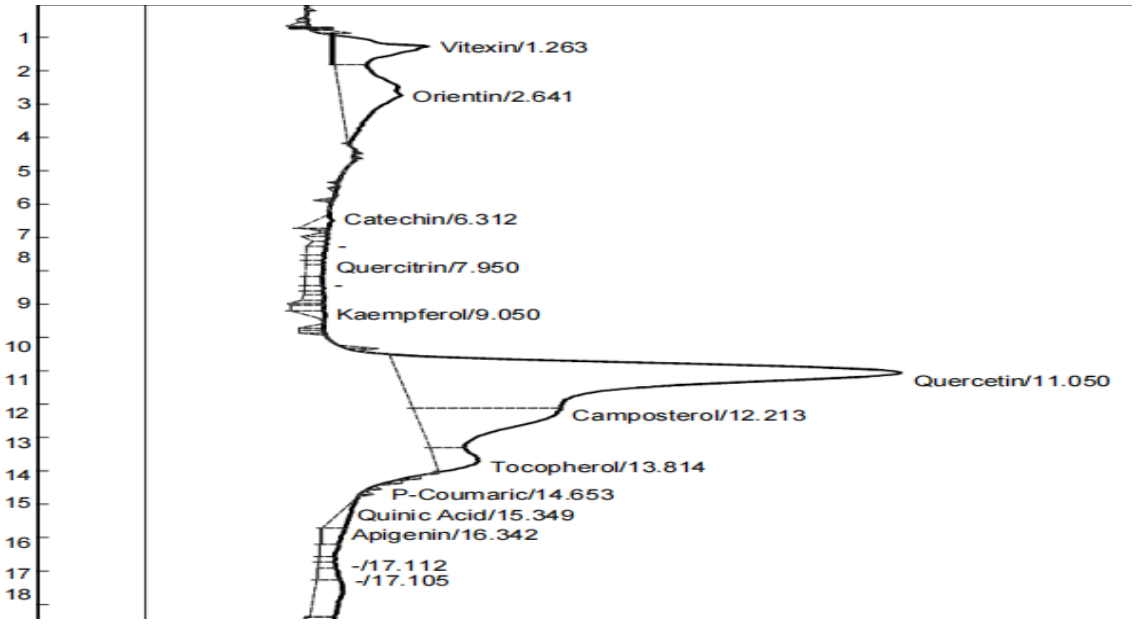

Figure 3: Chromatograph of *Persea americana* seed extract
Peaks corresponding to identified bioactive compounds are labeled with their respective retention times. Key compounds detected include, phenolic acids, and phytosterols, alongside tocopherol.

Discussion

Fungal infections caused by *Candida* species remain a major global health concern, particularly in immunocompromised patients (Oluyele et al., 2023), and the emergence of multidrug-resistant Candida spp has intensified the need for new therapeutic options (Murphy and Bicanic, 2021; Mallick et al., 2025; Oluyele, 2025a; Oluyele, 2025b). Plant-derived bioactive compounds represent a valuable reservoir of antifungal agents due to their chemical diversity and potential to act through multiple mechanisms (Nasim et al., 2022; Oluyele et al., 2025). The present study evaluated the antifungal activity of *P. americana* seed extracts against MDR *C. auris* and *C. albicans*, focusing on time–kill kinetics.

The results from this study revealed a concentration- and time-dependent inhibition of both pathogens. At MIC and 2×MIC, the extract exerted a fungistatic effect by slowing fungal growth without achieving complete clearance, while at 4×MIC and 8×MIC, it produced near-total killing within 42 hours, confirming fungicidal activity. Although both fungi were susceptible, *C. albicans* showed slightly faster clearance, with viable counts reduced to 0.48 log10 cfu/mL at 42 hours compared with 0.6 log10 cfu/mL for *C. auris*.

The gradual reduction in viable counts at lower concentrations can be explained by partial inhibition of cellular pathways, which slows replication but permits temporary survival through stress response mechanisms such as efflux pump activation and antioxidant defenses

(Guimarães et al., 2023). At higher concentrations, however, these protective mechanisms are overwhelmed, leading to irreversible damage and cell death (Oluyele, 2025b). The slightly slower clearance of *C. auris* relative to *C. albicans* highlights the resilience of this emerging multidrug-resistant pathogen and stresses the importance of natural antifungal agents capable of suppressing its growth.

The antifungal activity observed is likely mediated by the synergistic action of phytochemicals detected in the extract. Flavonoids such as quercetin, catechin, kaempferol, and apigenin have been widely reported to disrupt fungal membranes, inhibit ergosterol biosynthesis, induce oxidative stress, and interfere with biofilm formation (Hirasawa and Takada, 2004; Aboody and Mickymaray, 2020; Jan et al., 2022; Mahmud et al., 2023; Li et al., 2018). Phenolic acids such as p-coumaric and quinic acid contribute to antifungal activity by altering membrane permeability and inhibiting fungal metabolic enzymes (Ansari et al., 2013; Ma et al., 2015; Simonetti et al., 2020; Rossatto et al., 2021; Sharma et al., 2021), while phytosterols including campesterol and tocopherol may destabilize membrane fluidity and compromise ion transport (Burčová et al., 2018; Wang et al., 2025). The combination of these metabolites likely accounts for the observed transition from fungistatic to fungicidal action across different concentrations.

These findings are consistent with earlier reports on the antimicrobial properties of *P. americana*. Akpomie et al. (2021) reported that ethanolic seed extracts inhibited most urinary tract isolates, although aqueous extracts were inactive. Idris et al. (2009) observed broad-spectrum activity of methanolic, ethyl acetate, and chloroform extracts, with methanol extract producing strong inhibition against *C. albicans*. Hernández-Martínez et al. (2022) identified and recombinantly expressed a cysteine-rich antimicrobial peptide from avocado seeds, which showed potent antifungal activity against *C. albicans* and *C. glabrata*. More recently, Oluyele and Akinyeke (2025) demonstrated the anti-Salmonella activity of a P. americana seed peptide (PASP), which produced inhibition zones of 15–22 mm, with pharmacodynamic data confirming concentration- and time-dependent killing. The similarity between the present study and these earlier reports reinforces the view that avocado seeds are a valuable source of antifungal and antimicrobial agents.

The results of this study confirm that *P. americana* seeds possess broad-spectrum antifungal potential, attributable to their diverse phytochemical profile. The extract was able to exert both fungistatic and fungicidal effects depending on concentration, and its activity against *C. auris* a major drug-resistant pathogen further accentuate its therapeutic relevance.

Conclusion

P. americana seed extracts demonstrated significant antifungal activity against both *C. auris* and *C. albicans* in a concentration- and time-dependent manner. The extract displayed fungistatic activity at MIC and 2×MIC, but fungicidal activity at higher concentrations (4×MIC and 8×MIC). While both fungi were susceptible, *C. albicans* was slightly more responsive than *C. auris*. The antifungal activity is likely due to the synergistic presence of flavonoids, phenolic acids, and phytosterols identified via HPLC.

Given the demonstrated antifungal efficacy of *P. americana* seed extracts against both *C. albicans* and *C. auris*, further investigations are warranted to isolate and characterize the specific bioactive compounds responsible for the observed activity. Future studies should also explore the underlying mechanisms of action, assess cytotoxicity and safety profiles, and evaluate the pharmacokinetics of these extracts in relevant in vivo models. In addition, the potential for synergistic application with existing antifungal drugs should be examined to determine whether *P. americana* can enhance therapeutic outcomes or reduce resistance development. Such efforts will provide critical insights into the translational potential of this plant as a source of novel antifungal agents.

Declarations

Conflict of Interest

Authors declare no conflict of interest

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Consent for Publications

The authors gave approval for the publication of the manuscript.

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Software: Not applicable
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Visualization: Not applicable
Writing – original draft: Olumide Oluyele
Writing – review & editing: Olumide Oluyele

Ethical Considerations

The authors have fully adhered to ethical standards, ensuring no issues related to plagiarism, misconduct, data fabrication, falsification, duplicate publication or submission, or redundancy. The authors declare that no artificial intelligence tools were used in the preparation, writing, analysis, or editing of this manuscript. All sections of the work were entirely developed, written, and reviewed by the authors without the assistance of AI-based technologies.

AI Use Disclosure

During the preparation of this work, the authors used a generative AI tool (ChatGPT) solely for language editing, grammar correction, and formatting assistance. The AI tool was not used for data analysis, interpretation, or generation of scientific conclusions. After utilizing the tool, the authors reviewed, revised, and verified all content and take full responsibility for the accuracy and integrity of the final manuscript.

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