

Antifungal Activity of The Combination of Cinnamon Bark (*Cinnamomum burmannii*) and Turmeric Rhizome (*Curcuma longa*) Ethanolic Extracts against *Candida albicans*

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Abstract

Background: Recurrent aphthous stomatitis is a common and painful multifactorial inflammatory condition of the oral mucosa, with a global prevalence of 20% and of 8% in Indonesia. The resulting open mucosal ulcerations facilitate opportunistic *Candida albicans* infection. The current increase in antifungal resistance of up to 40% has prompted research for alternative natural ingredients for safer and more effective treatments.

Objective: This study aimed to evaluate the antifungal activity of ethanolic extracts of cinnamon bark and turmeric, both individually and in combination, against *C. albicans*.

Methods: The extracts were obtained through a maceration method with 96% ethanol, and their phytochemical content was analyzed using LC-MS/MS. For the antifungal assay, the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values were determined using a microdilution test, while the effect of the extract combination was evaluated using a checkerboard microdilution method.

Results: LC-MS/MS analysis tentatively identified *ar*-turmerone, bisdemethoxycurcumin, and curcumin in turmeric extract, while cinnamon bark extract contained nitrogen-containing compounds. Turmeric extract showed stronger antifungal activity, with MIC and MFC values of 1,000 µg/mL, while cinnamon bark extract showed MIC and MFC values of 2,000 and >8,000 µg/mL, respectively. The combination of the two extracts led to a stronger inhibitory activity than each extract, resulting in an FICI of 0.14, indicating a synergistic effect.

Conclusions: These findings suggested that the combined treatment suppressed fungal growth at much lower concentrations, indicating a strong synergistic interaction between turmeric and cinnamon bark extracts with potential as a natural antifungal agent against *C. albicans*.

INTRODUCTION

Recurrent Aphthous Stomatitis (RAS), commonly known as canker sores, is a multifactorial inflammatory condition marked by the recurrence of painful ulceration on the oral mucosa. The global prevalence of RAS is diverse, between 5% and 66%, averaging around 20%.¹ According to data from the Indonesian Health Survey (SKI) 2023, the prevalence of dental and oral diseases in Indonesia was 57.6%, with RAS being one of the most prevalent conditions at 8.0%.² Women were more frequently affected by recurrent oral ulcers than men (59.7%), with the highest prevalence observed among individuals aged 18-24 years (56.9%). Recurrent aphthous stomatitis (RAS), the most common type of recurrent oral ulceration, may cause significant pain and discomfort, thereby impairing essential oral functions such as eating and speaking.³ Although RAS is characterized as an idiopathic inflammatory condition driven by the immune system, the resulting open mucosal ulcerations serve as a portal of entry for opportunistic microorganisms. A primary complication in RAS cases is secondary infection by *C. albicans*. The colonization of this fungus within RAS lesions not

only exacerbates pain during mastication and speech but also significantly impedes the physiological process of tissue healing.¹ Several antifungal agents are widely used to treat *Candida* infections. Some antifungal drugs, such as nystatin, fluconazole, clotrimazole, and ketoconazole, can cause unpleasant side effects.⁴ The increasing cases of infections caused by *C. albicans* have led to an increase in the use of antifungal agents, which in turn has contributed to the development of resistance. As many as 40% of patients exhibited resistance to the current antifungal drugs.⁵ This has prompted researchers to investigate various natural ingredients and find natural substances that can prevent the growth of pathogenic fungi, including *C. albicans*.

The use of natural antifungal agents has been gaining increasing interest due to their low side effects compared to synthetic antifungal drugs.⁴ Cinnamon (*Cinnamomum burmannii*) and turmeric (*Curcuma longa*) are among the medicinal plants that are widely used in traditional medicine to treat various infection-related symptoms, such as sore throat, stomatitis, cough, and skin disorder.^{6,7} A previous study revealed that ethanolic extract of cinnamon bark could inhibit the growth of *C. albicans* at a minimum inhibitory concentration (MIC) of 25%. Phytochemical screening showed that the ethanol extract of cinnamon bark contains alkaloids, flavonoids, and saponins.⁸ Alkaloids exerted antifungal effects mainly by interacting with the structural components of the fungal cell wall and genetic material. This specific interaction triggers alterations in the cellular amino acid composition and disrupts DNA stability. This disturbance undermines membrane stability and disrupts cellular homeostasis by altering osmotic pressure, ultimately leading to cell lysis and inhibiting fungal growth.⁹

In line with the antifungal potential of cinnamon, another natural ingredient that also showed inhibitory activity against *C. albicans* is turmeric. Previous research by Mubarak et al.¹⁰ showed that ethanolic extract of turmeric could inhibit the growth of *C. albicans* with an MIC value of 12.5%. The Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) analysis of ethanolic extract of turmeric rhizome showed curcumin as the major secondary metabolite with the concentration of 7.80%, followed by methoxy curcumin (4.12%), and bisdemethoxy curcumin (2.28%).¹¹ These curcuminoid compounds inhibit the growth of *C. albicans* by causing direct damage to the fungal cell membrane and inducing denaturation of essential cellular proteins.¹² Furthermore, curcumin exhibits antifungal activity against fungal pathogens, including *C. albicans*, through multiple mechanisms, such as impairment of cellular stress responses and inhibition of efflux pump activity. In addition, curcumin possesses antioxidant and anti-inflammatory properties that may reduce ulcer-associated inflammation, modulate oxidative stress, promote tissue repair, and thereby accelerate ulcer healing.^{13,14} Even though the antifungal effect of cinnamon bark and turmeric rhizome has been reported earlier, no reports so far on the effect of the combined extracts.

The use of a single plant extract often requires high concentration to achieve the desired clinical efficacy, while the increasing prevalence of antifungal resistance may render single-agent therapies inadequate. Therefore, combining plant extracts with different mechanisms of action may provide synergistic antifungal effects and reduce the concentrations required for therapy.¹⁵ In traditional medicine, both herbs are commonly used in combination. Therefore, based on the previously reported antifungal potential of turmeric and cinnamon bark extracts, the present study aimed to evaluate the antifungal activity of each extract as well as the combination of both extracts against *C. albicans*. The secondary metabolite profile of the extracts was analyzed by LC-MS/MS.

RESEARCH METHODS

Instruments and Materials

Instruments. The instruments used in this study included a UV-Vis spectrophotometer (Thermo Scientific®, USA), a rotary evaporator set (Heidolph®, Germany), and LC-MS/MS instruments (Waters, USA).

Materials. The plant materials used in this study, such as cinnamon bark powder and turmeric rhizome powder obtained from the Ministry of Health's Sardjito Hospital. Identification and authentication of plant materials were done at the same institution (document no. T1.02.04/D.XI.6/19537.6/2025) and confirmed the plant species as *Cinnamomum burmannii* and *Curcuma longa*. Chemicals and other materials used in this study include 96% ethanol (technical grade), Sabouraud Dextrose Agar (Oxoid®, France), Sabouraud Dextrose Broth (Himedia®, India), DMSO (Merck®, Germany), nystatin (Taisho®, Japan), and *C. albicans* ATCC 10231.

Determination of the Loss on Drying of Cinnamon Bark and Turmeric Rhizome Powders

The gravimetric method was used to determine the loss on drying of cinnamon bark and turmeric powders, referencing the Indonesian Herbal Pharmacopoeia, 2nd Edition.¹⁶ The cinnamon bark and turmeric powders (1–2 g) were accurately weighed into a weighing bottle that had been previously dried in an oven at 105°C for 30 minutes and tared to a constant weight. The weighing bottle containing the sample powder was then placed in an oven with the lid open and dried at 105°C for 30 minutes. After drying, the bottle was cooled in a desiccator to room temperature and then weighed. The loss on drying was calculated using this Equation (1) as follows:

$$\text{Loss on drying (\% w/w)} = \frac{a-b}{a} \times 100\% \dots\dots\dots (1)$$

where *a* is the weight before heating (g), and *b* is the weight after heating (g).

Extraction

The cinnamon bark powder (50 g) and turmeric rhizome powder (50 g) were extracted separately using the maceration method with 500 mL 96% ethanol (1:10 ratio) for 4 hours with agitation on a shaker at 150 rpm. After the maceration process was completed, the extract was filtered to obtain the filtrate and residue. The residue was then remacerated with 500 mL of 96% ethanol, followed by filtration to obtain the second filtrate. All filtrates from the maceration process were combined and concentrated using a vacuum rotary evaporator at a temperature of 50°C until a thick extract of turmeric and cinnamon bark was obtained. The yield of the thick extract (% w/w) was calculated using the following Equation (2):

$$\text{Yield of extract (\% w/w)} = \frac{\text{Weight of extract (g)}}{\text{Weight of cinnamon bark or turmeric powder (g)}} \times 100\% \dots\dots\dots (2)$$

Determination of the Water Content of Extracts

The determination of the water content of the extract was carried out using the azeotropic distillation method with water-saturated toluene, following the procedure described in the Indonesian Herbal Pharmacopoeia, 2nd Edition.¹⁶ A sample containing an estimated 1–4 mL of water was accurately weighed and placed into a dry flask. Then, 200 mL of water-saturated toluene was added to the flask, the distillation apparatus was assembled, and the neck of the flask was sealed with plastic wrap. An additional 10 mL of water-saturated toluene was introduced into the receiving tube through the condenser. The flask was gently heated on a hot plate until the toluene began to boil, and the distillation rate was adjusted to 2–4 drops per second until all the water was completely distilled. After the process was finished, the apparatus was cooled to room temperature, and the volume of water was measured after complete separation between the water and toluene layers. The water content was then calculated as a percentage (% v/w) using the following Equation (3):

$$\text{Water content (\%v/b)} = \frac{\text{Volume of water (mL)}}{\text{Weight of extract (g)}} \times 100\% \dots\dots\dots (3)$$

Identification of Secondary Metabolites by LC–MS/MS

The identification of secondary metabolites of the ethanolic extracts of cinnamon bark and turmeric rhizome was carried out using the Liquid Chromatography–Mass Spectrometry/Mass Spectrometry (LC-MS/MS) instrument with the ACQUITY UPLC® H-Class system (Waters, USA), equipped with a C₁₈ column (particle size 1.8 µm, length 100 mm). The analysis was continued using an Xevo G2-S QTOF mass spectrometer (Waters, USA) at a column temperature of 50°C. The mobile phase consisted of water containing 5 mM ammonium formate (phase A) and acetonitrile containing 0.05% formic acid (phase B), operated in a stepwise gradient at a flow rate of 0.2 mL/min for 23 minutes. The mass spectra were obtained using electrospray ionization (ESI) in positive ion mode with a mass range of 50–1,200 m/z. Data were acquired and processed using MassLynx software version 4.1.

Antifungal Activity Test of Cinnamon Bark and Turmeric Rhizome Extracts

Antifungal activity was tested with the microdilution method in a 96-well microplate. The *C. albicans* suspension was first standardized using a spectrophotometer at a wavelength of 530 nm until an absorbance value of 0.12–0.15 was obtained. If the absorbance value did not fall within this range, the suspension was diluted using SDB medium. According to CLSI (2008), the prepared fungal suspension was then diluted 1:100 from the stock suspension and further diluted 1:20 to obtain a fungal colony count of 5 × 10² to 5 × 10³ cells/mL for antifungal activity testing. The

SDB medium is used as the negative control, while nystatin with a stock concentration of 128 µg/mL is used as the positive control. Stock solution concentrations were prepared for 32,000 µg/mL of ethanolic turmeric extract and 16,000 µg/mL of ethanolic cinnamon bark extract. To each well, 100 µL of SDB medium was added. The first column contained only SDB medium as the media control, while the second column contained SDB medium with a *C. albicans* suspension to observe fungal growth. Next, 100 µL of extract solution was added to the 96-well microplate containing 100 µL of SDB medium. Two-fold serial dilutions were done by transferring 100 µL from the first well to the next well, subsequently, to reach the tested extract concentration ranging from 15.625 to 8,000 µg/mL for the ethanol extract of cinnamon bark and 31.25 to 16,000 µg/mL for the ethanol extract of turmeric rhizome. Discard the last aliquot to keep equal volumes. Then, 10 µL of *C. albicans* suspension was added to each well. Nystatin (128 µg/mL) served as a reference antifungal agent. The 96-well microplate was then incubated at 37°C for 48 hours. The antifungal assay of each sample was tested in triplicate. The antifungal activity of each extract was indicated by the Minimum Inhibitory Concentration (MIC) value. The MIC value was determined by observing the lowest concentration that indicates the media remains clear without any fungal growth.

Antifungal Activity Test of The Combined Cinnamon and Turmeric Extracts

The antifungal activity test for the combined ethanol extracts of cinnamon bark and turmeric rhizome was evaluated using the checkerboard microdilution method. The stock solution concentrations were prepared four times the MIC of ethanolic turmeric extract and twice the MIC of ethanolic cinnamon bark extract. The ethanol extract of turmeric was diluted inside the microplate well, while the ethanol extract of cinnamon bark was diluted outside the microplate well. The 96-well microplate was then incubated at 37°C for 48 hours. The antifungal assay of each sample was tested in triplicate. The combined MIC value obtained was used to calculate the Fractional Inhibitory Concentration Index (FICI) to determine the effect of the combination of the two extracts.

Data Analysis

All experimental measurements and assays in this study were performed in triplicate to ensure the reliability and reproducibility of the results. Antifungal activity was assessed using the minimum inhibitory concentration (MIC) values obtained from the combination test. These values were then used to calculate the Fractional Inhibitory Concentration Index (FICI), which reveals the type of interaction between the two extracts. The FICI was calculated as using the Equation (4) as follows:

$$FICI = \frac{MIC_{A \text{ in combination}}}{MIC_{A \text{ in alone}}} + \frac{MIC_{B \text{ in combination}}}{MIC_{B \text{ in alone}}} \dots\dots\dots (4)$$

where A is the cinnamon bark ethanol extract, and B is the turmeric ethanol extract.

RESULT AND DISCUSSION

Determination of the Loss on Drying of Cinnamon Bark and Turmeric Rhizome Powders

Loss on drying testing is a critical physicochemical parameter used to evaluate moisture and volatile fractions in herbal formulations. Maintaining an appropriate loss on drying value is important because excessive moisture may adversely affect the stability and quality of the extract during storage.¹⁷ The drying loss results for cinnamon bark and turmeric powders are shown in **Table 1**.

Table 1. Loss on Drying Results for Cinnamon Bark and Turmeric Rhizome Powders

Replication	Cinnamon Bark Powder (% w/w)	Turmeric Powder (% w/w)
I	6.89	5.23
II	6.85	5.10
III	6.93	5.12
Mean ± SD	6.89 ± 0.04*	5.15 ± 0.07*

Notes: *±: Standard deviation of triplicate measurements

The loss on drying values for cinnamon bark powder and turmeric powder were 6.89 and 5.15% w/w, respectively. These results comply with the requirements outlined in the Indonesian Herbal Pharmacopoeia, which states that the loss on drying should not exceed 10%.¹⁶ This demonstrated that both powders meet the quality standards regarding volatile matter and moisture content, making them highly stable and suitable for further extraction processes. Furthermore, maintaining the loss-on-drying value below 10% is important to prevent microbial contamination during

storage, as excessive moisture content can serve as a growth medium for bacteria and fungi. Therefore, low loss-on-drying values indicated that both powders possess good storage stability and a lower risk of deterioration due to microbial growth.¹⁸

Extraction of Cinnamon and Turmeric Powder

This study employed the maceration method for extraction, that was chosen to avoid degradation of thermolabile compounds. Ethanol was used as the extraction solvent because it can extract a broad spectrum of secondary metabolites, including polar and non-volatile compounds. Additionally, ethanol was selected for its safety and low toxicity.⁴ The maceration method of cinnamon bark and turmeric powders using 96% ethanol produced extract yields of 11.33% w/w for cinnamon bark and 13.89% w/w for turmeric. Determining the extract yield is crucial because it shows how much extract was successfully obtained during extraction. The extraction yield is often used as a preliminary indicator of extraction efficiency. In phenolic-rich plant materials, a higher yield may reflect greater recovery of bioactive constituents, although the actual content of active compounds must be verified through phytochemical analysis.¹⁹

Determination of the Extract's Water Content

Determining water content is a key parameter that indicates the minimum moisture level in powdered plant materials. For plant materials containing essential oils, such as cinnamon bark and turmeric, the water content analysis was performed using the toluene distillation method. This technique is preferred because it helps prevent the degradation of volatile compounds that are sensitive to heat during analysis. In this method, the water volume is measured after complete phase separation between the water and toluene layers. Assessing water content is vital to ensure extract quality and stability, as maintaining a low water content helps prevent microbial contamination and preserve the quality of the extract during storage.²⁰ The water content analysis results for cinnamon bark and turmeric extracts are shown in **Table 2**.

Table 2. Water Content Analysis Results of the Extracts

Replication	Cinnamon Bark Extract (% w/w)	Turmeric Rhizome Extract (% w/w)
I	10.00	2.94
II	10.00	2.94
III	10.00	2.94
Average ± SD	10.00 ± 0.00*	2.94 ± 0.00*

Notes: *±: Standard deviation of replicated measurements

The water content of the concentrated cinnamon bark extract was 10.00% v/w, which meets the Indonesian Herbal Pharmacopoeia requirement of no more than 16%. Meanwhile, the concentrated turmeric extract showed a water content of 2.94% v/w, also comply with the Indonesian Herbal Pharmacopoeia standard, which specifies a maximum limit of 10%. These results demonstrated that both extracts are within acceptable moisture levels, supporting their stability and quality for further storage.¹⁶

Identification of Secondary Metabolites by LC–MS/MS

The characterization of bioactive constituents in the ethanol extracts of cinnamon bark and turmeric was performed to identify the possible secondary metabolites that may contribute to their pharmacological effects. In this study, Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) was used as an analytical platform. LC-MS/MS is known as a highly sensitive and selective technique capable of resolving complex phytochemical mixtures and providing detailed information about chemical composition, molecular weight, and structural features of analytes. The principle of LC-MS/MS combines liquid chromatography (LC) for separating constituents based on polarity and interaction with the stationary phase, followed by tandem mass spectrometry (MS/MS), which provides accurate mass measurement and fragmentation-based molecular identification. This combined approach enables reliable detection and analysis of diverse secondary metabolites, including those present at trace levels, supporting precise phytochemical profiling of the plant extracts.²¹

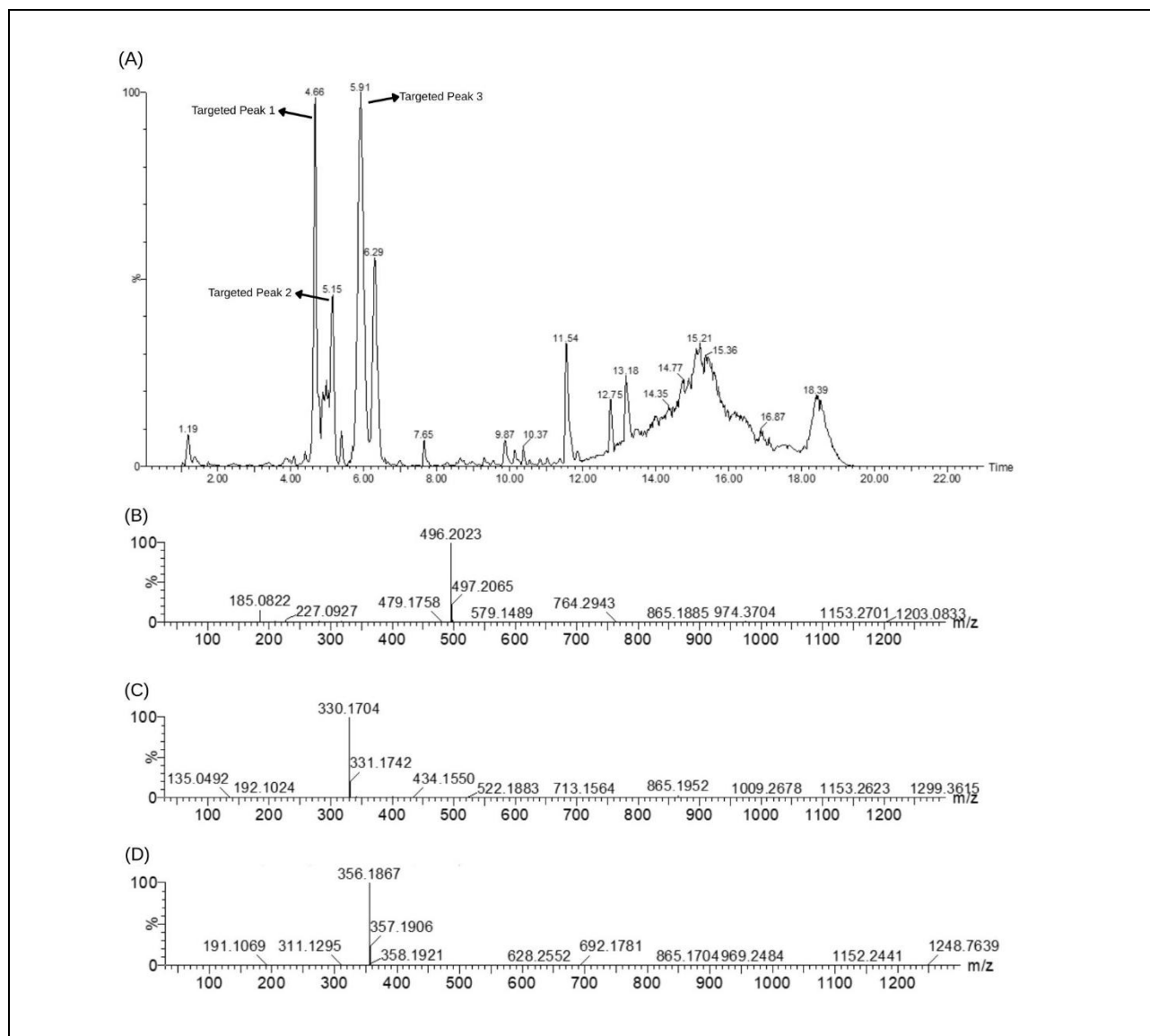


Figure 1. LC-MS/MS data for the ethanolic extract of cinnamon bark (A); include the observed m/z values at targeted peak 1 ($C_{17}H_{26}N_{11}O_7^*$) (B); at targeted peak 2 ($C_{19}H_{24}NO_4^*$) (C); and at targeted peak 3 ($C_{17}H_{22}N_7O_2^*$) (D) using Electrospray Ionization (ESI) in positive mode. *: not identified

The LC-MS/MS analysis was performed to identify the major secondary metabolites in the cinnamon bark extract. The chromatographic profile (**Figure 1A**) showed main secondary metabolite peaks, with the highest intensities at retention times of 4.66 and 5.91 minutes, indicating the dominant metabolites in the extract. Additional dominant peaks appeared at 5.15 and 6.29 minutes. Subsequently, mass spectrometry (MS) analysis was conducted to determine the molecular mass associated with each main chromatographic peak (**Figure 1A**), followed by elemental analysis to establish the molecular formulas of the detected compounds. Electrospray ionization (ESI) in positive mode was used to generate the ion spectra. The mass spectrum at 4.66 minutes (**Figure 1B**) showed the molecular ion peak at m/z 496.2023 $[M+H]^+$, suggesting a molecular weight of approximately 495 g/mol and a predicted molecular formula of $C_{17}H_{26}N_{11}O_7$. The peak at 5.15 minutes (**Figure 1C**) displayed the molecular ion peak at m/z 330.1704 $[M+H]^+$, indicating a molecular weight of 329 g/mol, corresponding to the molecular formula $C_{19}H_{24}NO_4$. Meanwhile, the peak at 5.91 minutes (**Figure 1D**) produced the molecular ion peak at m/z 356.1867 $[M+H]^+$, corresponding to a molecular weight of 355 g/mol and a calculated formula of $C_{17}H_{22}N_7O_2$.

Based on MS characteristics and elemental predictions, the primary constituents detected in the ethanol extract of cinnamon bark are likely nitrogen-containing compounds, indicating the presence of alkaloids and/or peptide-like metabolites. Although alkaloids have been reported in several species within the genus *Cinnamomum*, specific alkaloid structures from *C. burmannii* bark remain largely unreported.^{22,23} Previous studies have generally recognized cinnamaldehyde as a major volatile compound in cinnamon bark extracts; however, it was not found in the extract analyzed in this study.²⁴ These findings suggested the potential existence of previously unreported nitrogenous

metabolites in *C. burmannii* extract, requiring further structural identification and investigation of their biological activity. Additionally, the absence of cinnamaldehyde may be due to the extraction method and LC-MS/MS ionization mode used, which favor the detection of non-volatile and polar compounds. Besides cinnamaldehyde, *C. burmannii* was reported before to produce compounds such as burmannic acid and burmafuranic acid. Burmannic acid is a β -ionone derivative containing a carboxylic acid group attached to C-5 of 3-hydroxy-5,6-epoxy- β -ionone, whereas burmafuranic acid is an apocarotenoid derivative that has been isolated from *C. burmannii*.^{25,26} However, neither burmannic acid nor burmafuranic acid was detected in the present study. The difference in the extraction procedure and the source of plant material may affect the secondary metabolite detected in *C. burmannii* extract that differ from those reported earlier.

Moreover, a study by Farag et al.²⁷ showed that the content of cinnamaldehyde in cinnamon preparations can vary depending on the extraction method and sample preparation. In this study, a maceration extraction method using 96% ethanol as a solvent was employed, which tends to extract polar and semipolar compounds rather than the volatile components of essential oils. Additionally, the prolongation of the maceration process can increase the likelihood of evaporation or degradation of volatile compounds such as cinnamaldehyde, as these compounds are volatile and relatively unstable during the extraction process. Therefore, the cinnamaldehyde content in the extract is likely to be very low, making it undetectable in LC-MS/MS analysis. A study by Yu et al.²⁸ also reported that cinnamaldehyde is best analyzed using the Gas Chromatography-Mass Spectrometry (GC-MS) method due to its characteristic as the primary volatile compound in cinnamon essential oil.

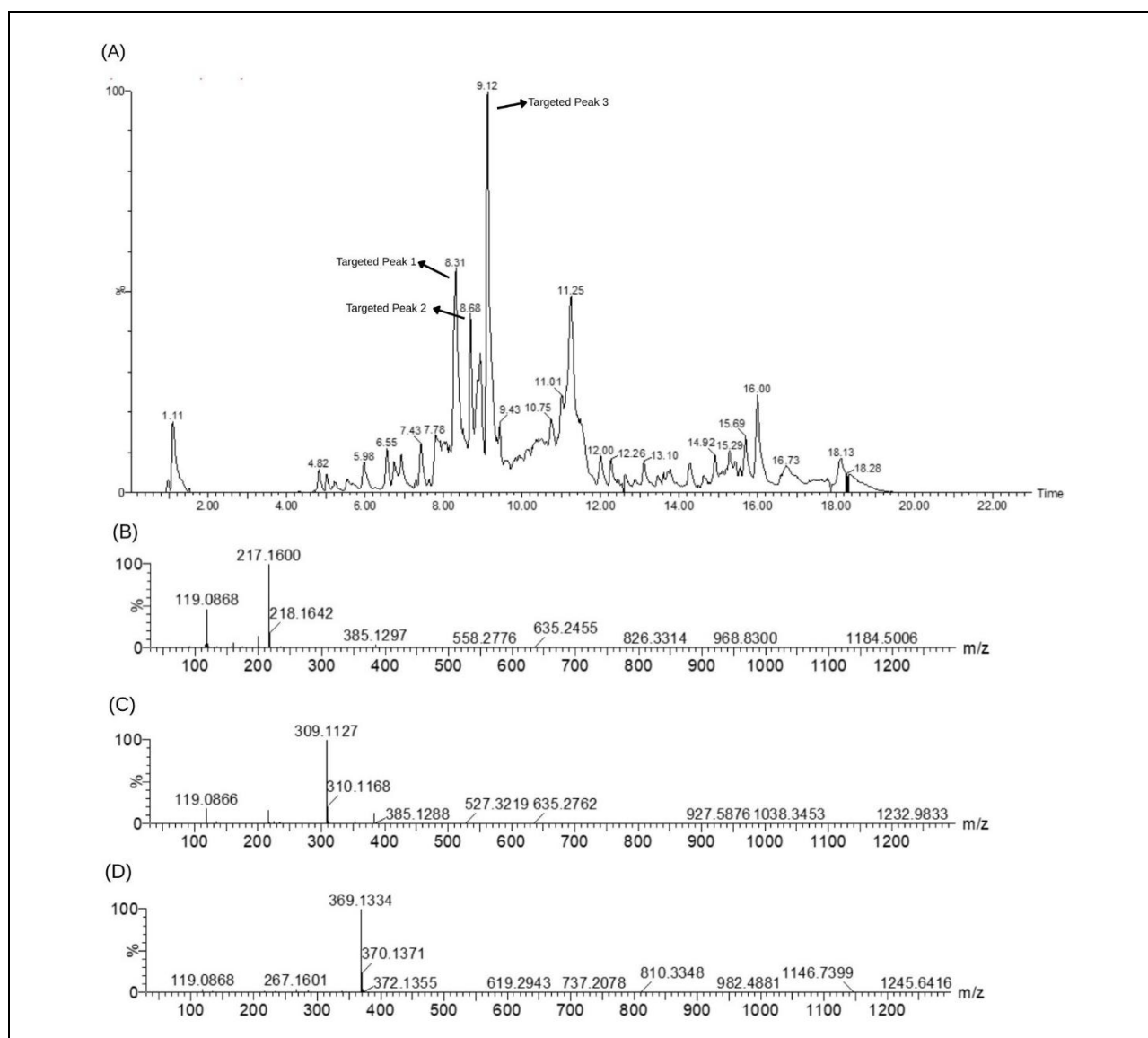


Figure 2. LC-MS/MS data of turmeric ethanol extract (A) and the observed m/z values at targeted peak 1 (*ar*-turmerone) (B), targeted peak 2 (bisdemethoxycurcumin) (C), and targeted peak 3 (curcumin) (D) using Electrospray Ionization (ESI) in positive mode.

The LC-MS/MS analysis was also performed on the turmeric ethanol extract to tentatively identify its secondary metabolites. The chromatogram data from the analysis of the turmeric ethanol extract using LC-MS/MS are shown in **Figure 2**. The chromatogram (**Figure 2A**) displays the highest peak, representing the main secondary metabolite in the extract, with a retention time of 9.12 minutes. Additional prominent peaks corresponding to secondary metabolites were observed at retention times of 8.31, 8.68, and 11.25 minutes. The mass spectrum of the peak at 8.31 minutes (**Figure 2B**) showed m/z of 217.1592 $[M+H]^+$, indicating a molecular weight of 216 g/mol and a molecular formula of $C_{15}H_{20}O$. Based on this data, the compound was tentatively identified as *ar*-turmerone.²⁹ The peak at 8.68 minutes (**Figure 2C**) showed m/z of 309.1127 $[M+H]^+$, suggesting a molecular weight of 308 g/mol and a molecular formula of $C_{19}H_{16}O_4$. Additionally, this compound was tentatively identified as bisdemethoxycurcumin.²⁹ The main peak at 9.12 minutes (**Figure 2D**) exhibited m/z of 369.1334 $[M+H]^+$, indicating a molecular weight of 368 g/mol and a molecular formula of $C_{21}H_{20}O_6$, which was tentatively identified as curcumin.²⁹ All in all, the LC-MS/MS analysis of the turmeric ethanol extract tentatively identified three compounds *i.e.* *ar*-turmerone, curcumin, and bisdemethoxycurcumin (**Figure 3**). The chromatogram profile indicated curcumin as the major metabolite in the extract.

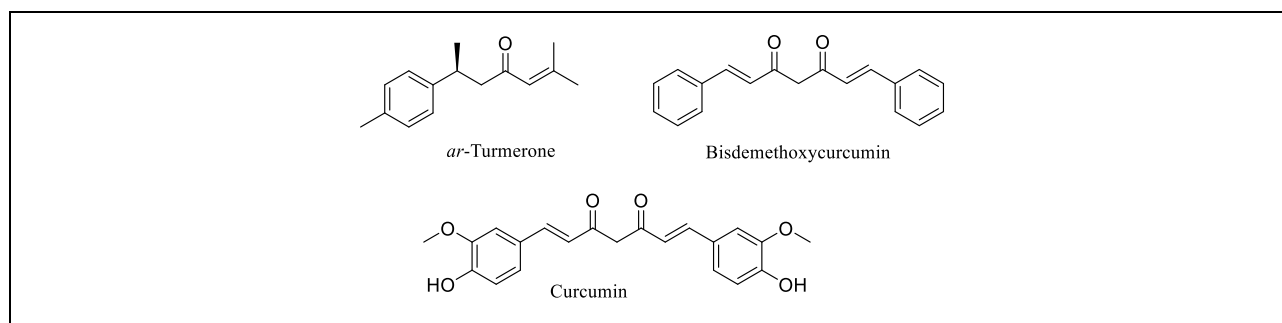


Figure 3. Structures of *ar*-turmerone, curcumin, and bisdemethoxycurcumin tentatively detected in the turmeric ethanol extract based on LC-MS/MS analysis.

Antifungal Activity Test of Cinnamon Bark and Turmeric Rhizome Extracts

The antifungal activity test of the single extract from cinnamon bark and turmeric was carried out using the microdilution method against *C. albicans*. The basic principle of the microdilution method involves preparing a series of extract concentrations, which are then transferred into wells containing growth medium previously inoculated with a standardized fungal suspension. Observation is performed after incubation, and the lowest concentration at which the medium remains clear with no visible fungal growth is determined as the MIC. Subsequently, the solution at the MIC concentration is sub-cultured onto fresh agar medium without the addition of samples or fungal inoculum and incubated again for 48 hours. Media that remain clear without fungal growth are defined as the Minimum Fungicidal Concentration (MFC).³⁰

The results in **Table 3** showed that the ethanol extract of cinnamon bark exhibited an MIC value of 2,000 $\mu\text{g/mL}$, whereas the ethanol extract of turmeric demonstrated a lower MIC value of 1,000 $\mu\text{g/mL}$, indicating that turmeric extract was more effective in inhibiting the growth of *C. albicans* than cinnamon bark extract. As a comparison, the positive control nystatin showed a significantly lower MIC value of 2 $\mu\text{g/mL}$, indicating a much stronger antifungal potency. Antifungal activity is classified as weak when the MIC value obtained from the assay exceeds 1,500 $\mu\text{g/mL}$.³¹ Therefore, the antifungal activity of the ethanol extracts of turmeric and cinnamon bark falls into the moderate-to-weak category, as both require relatively high concentrations to inhibit fungal growth.

Table 3. Antifungal Activity Test Results of Cinnamon and Turmeric Extracts (n=3)

Fungal Strains	Tested Samples	MIC ($\mu\text{g/mL}$)	MFC ($\mu\text{g/mL}$)
<i>C. albicans</i> ATCC 10231	Ethanol Extract of Cinnamon Bark	2,000	>8,000
	Ethanol Extract of Turmeric	1,000	1,000
	Nystatin	2	2

In addition to the MIC results, the fungicidal capacity of the extracts was evaluated through the determination of the Minimum Fungicidal Concentration (MFC). As shown in **Table 3**, the ethanol extract of cinnamon bark had an MFC value higher than 8,000 $\mu\text{g/mL}$, indicating it did not display fungicidal activity within the tested concentration range and primarily acted as a fungistatic agent. In contrast, the ethanol extract of turmeric had an MFC value of 1,000 $\mu\text{g/mL}$, equal to its MIC value, suggesting that turmeric extract was capable of both inhibiting the growth of *C. albicans* and exerting fungicidal activity at the same concentration. These results align with previous studies, where the lowest

concentration resulting in no colony growth after sub-culturing on agar was defined as the MFC. Franconi and Lupetti³² reported that MFC values may correlate with MIC values for some antifungal agents, but these correlations are not always reliable and need more clinical validation. In this context, the MFC/MIC ratio for turmeric indicated a fungicidal effect, while the ratio for cinnamon bark extract exceeded the test's upper limit (MFC/MIC > 4), suggesting its primary action is fungistatic. As a comparison, nystatin, the positive control, showed identical MIC and MFC values (2 µg/mL), confirming its potent fungicidal activity against *C. albicans*.

Antifungal Activity Test of The Combined Extracts

When testing two or more antifungal extracts together, their interaction can result in synergistic, additive, indifferent, or antagonistic effects. In this study, the checkerboard microdilution method was used to evaluate the interaction between ethanol extracts of cinnamon bark and turmeric against *C. albicans*. This technique involves a two-dimensional serial dilution in a 96-well microplate, allowing each extract to be tested alone and in combination. The interaction is then quantitatively assessed using the fractional inhibitory concentration index (FICI), which determines whether the combination improves antifungal effectiveness.³³ A FICI value of ≤ 0.50 indicates synergism, $0.50 - 1.00$ suggests an additive effect, $1.00 - 2.00$ is considered indifferent, and above 2.00 is classified as antagonistic.³⁴

The combination of cinnamon bark and turmeric ethanol extracts showed significantly improved antifungal activity against *C. albicans* compared to each extract used alone, as shown in **Table 4**. The combined treatment suppressed fungal growth at only 1/64 of the MIC of cinnamon bark extract and 1/8 of the MIC of turmeric extract, resulting in an FICI value of 0.14, which indicates a strong synergistic interaction.³⁴ This synergy demonstrates that both extracts enhance each other's antifungal effects, allowing effective inhibition of *C. albicans* at much lower concentrations. This increased activity may result from the complementary mechanisms of action of alkaloid-rich cinnamon extract and curcuminoid-containing turmeric extract, which disrupt fungal cell structures and inhibit fungal metabolic pathways. These findings are consistent with previous studies demonstrating that combinations of plant-derived antifungal agents may exhibit greater antifungal activity than individual extracts, likely due to synergistic interactions among their bioactive constituents.³⁵

A study by Cho et al.³⁶ also reported that combinations of plant extracts exhibited stronger antifungal activity against *C. albicans* than individual extracts alone, as indicated by lower MIC values and synergistic FICI scores. The study suggested that synergistic interactions may occur because different bioactive compounds act through complementary mechanisms, such as disrupting fungal cell membranes, inhibiting intracellular enzymes, inducing oxidative stress, and interfering with fungal metabolic pathways. In addition, the use of combined plant extracts may enhance antifungal potency at lower concentrations and potentially reduce the risk of antifungal resistance development. Similar findings were reported by Tsopmene et al.,³⁷ who demonstrated that the combination of curcumin and nystatin exhibited synergistic effects against *C. albicans* isolates and strains including ATCC 9002, Ca13, and Ca14, with FIC values of 0.5, 0.26, and 0.5, respectively. These results indicated that the addition of curcumin improved the antifungal efficacy of nystatin, allowing fungal inhibition at lower concentrations compared with the use of nystatin alone. Furthermore, a study by Shahina et al.³⁸ reported that the combination of cinnamon leaf oil (CNL) from *Cinnamomum zeylanicum* and clove flower bud oil (CLV) from *Eugenia caryophyllus* exhibited additive and synergistic effects against *C. albicans*, with FICI values of 0.72 ± 0.16 and 0.5 ± 0.0 against strains RSY150 and ATCC 10231, respectively. The synergistic interaction observed against ATCC 10231 resulted in a 2.2-fold reduction in MIC values compared with the individual oils. These findings emphasized the potential of plant-derived natural product combinations as an approach to improve antifungal efficacy by maximizing synergistic effects between their bioactive constituents.

Table 4. Antifungal Activity Test Results of the Combined Cinnamon and Turmeric Extracts (n=3)

Tested Samples	MIC Single Extract (µg/mL)	MIC Combined Extracts (µg/mL)	FICI Index
Ethanol Extract of Cinnamon Bark	2,000	31.25	0.14
Ethanol Extract of Turmeric	1,000	125	(Synergistic Effect)*

*FICI interpretation: ≤ 0.5 = Synergistic; $> 0.5 - 1$ = Additive; $> 1 - 4$ = Indifferent; > 4 = Antagonistic (Nikolic et al., 2022)³⁴

Based on the LC-MS/MS analysis, cinnamon bark ethanol extract was detected to contain nitrogen-containing compounds, possibly as alkaloids or other N-containing natural products. In particular, alkaloids are known secondary metabolites with antimicrobial properties,³⁹ that also might contribute to the antifungal activity of *C. burmannii* extract in this study against *C. albicans*. In general, alkaloids, which are basic and contain nitrogen, can interact with the amino acid components of the cell walls and genetic material of microbes, including fungi. This interaction can trigger changes

in the structure and composition of these amino acids, disrupting the stability and balance of DNA. This imbalance then damages the DNA chain and triggers damage to the membrane or cell wall, ultimately leading to lysis and death of the microbial cell.⁸ Furthermore, turmeric ethanol extract showed significant antifungal activity against *C. albicans*, consistent with its phytochemical profile and known pharmacological properties. The LC-MS/MS analysis tentatively identified the presence of curcumin and its derivatives, which are recognized as the main bioactive compounds responsible for turmeric's antifungal effects. Curcumin is widely documented to exhibit antifungal activity through various mechanisms, giving it a broad spectrum of effectiveness. Previous studies indicate that curcumin targets multiple cellular pathways in fungi. Notably, it modulates the TUP1 regulatory gene, which is critical for fungal virulence and morphological changes. Blocking TUP1 disrupts hyphal formation, reducing *C. albicans* virulence. Additionally, curcumin induces apoptosis-like death in fungal cells and enhances reactive oxygen species (ROS) production, triggering oxidative stress and cellular damage.⁴⁰ These multimodal mechanisms demonstrate the strong antifungal effects of curcumin and underline its promise as a natural alternative with fewer side effects than many traditional synthetic antifungal drugs.

Combining bioactive extracts that work together offers a promising treatment approach, as it lowers the needed concentration of each extract compared to using a single extract, while still maintaining or even boosting antifungal effectiveness. This method is especially important with the rise of antifungal resistance, where natural extract combinations could be good alternatives for improved antifungal treatments.¹⁵ Overall, the synergy observed between cinnamon bark and turmeric rhizome extracts highlighted their potential to be developed into effective herbal antifungal formulations, particularly for applications that require enhanced activity at lower concentrations.

Limitation

While this study provides important findings regarding the antifungal potential of the combination of turmeric rhizome and cinnamon bark ethanolic extracts against *C. albicans*, several limitations should be considered. The phytochemical identification in this study was limited to tentative compound identification based on LC-MS/MS analysis, and the detected compounds were not further isolated or structurally confirmed using more comprehensive analytical methods such as LC-HRMS/MS or NMR analysis. In addition, cinnamaldehyde, which is widely reported as one of the major bioactive compounds of cinnamon, was not detected in this study, possibly due to the maceration extraction method and the LC-MS/MS ionization mode that were more suitable for non-volatile and polar compounds. Furthermore, the antifungal activity evaluation was restricted to in vitro assays against a single fungal strain of *C. albicans* ATCC 10231; thus, the effectiveness of the extracts against other *Candida* species or clinical isolates remains unknown. Therefore, further studies are required to isolate and identify the active compounds responsible for the antifungal activity, evaluate their mechanism of action and toxicity profile, and confirm their antifungal potential through broader microbiological and pharmacological studies.

CONCLUSION

This study found that both ethanol extracts of turmeric rhizome and cinnamon bark exhibited antifungal effects against *C. albicans*. The turmeric extract showed stronger activity with MIC and MFC values of 1,000 µg/mL, indicating fungicidal activity, whereas cinnamon bark extract showed a MIC of 2,000 µg/mL and an MFC >8,000 µg/mL, indicating mainly fungistatic activity. The LC-MS/MS analysis tentatively identified curcuminoids in the turmeric extract and nitrogen-containing compounds, such as alkaloids and related N-containing compounds, in the cinnamon bark extract, which may contribute to their antifungal effects. When used together, the two extracts showed enhanced antifungal activity, as demonstrated by a Fractional Inhibitory Concentration Index (FICI) value of 0.14. This strong synergistic effect suggested that combining these extracts allows for effective inhibition of *C. albicans* at significantly lower and safer concentrations.

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GENERATIVE AI DISCLOSURE STATEMENT

Grammarly was used for grammar correction and language improvement during the writing process of this manuscript. The authors have verified the accuracy and originality of all content. No AI tools were used to generate or modify images.

AUTHOR CONTRIBUTION STATEMENT

Ni Komang Ayu Cintia Dewi: Investigation, Data curation, Data analysis, Writing original draft. **Andreas Gangsar Bayu Waskito:** Investigation, Data curation. **I Komang Yodi Premanadinata:** Investigation, Data curation. **Gusti Ayu Indah Pradnya Apsari Dewi:** Investigation, Data curation, Writing original draft. **Dhea Amanda Avrillya:** Investigation, Data curation. **Anak Agung Ayu Vivi Trysbiantari Kusuma:** Investigation, Data curation, Data analysis. **Cokorda Istri Diah Ari Suci Prabandari Susila:** Investigation, Data curation. **Nonye Treasure Ujam:** Methodology, Review, and editing of the manuscript. **Ni Putu Eka Leliqia:** Methodology, Supervision, Review, and editing of the manuscript. **Ni Putu Ariantari:** Conceptualization, Methodology, Resources, Supervision, Review and editing of the manuscript.

CONFLICT OF INTEREST

The authors state that there are no conflicts of interest to disclose.

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