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Antimalarial potential of endophytic fungi from *Rhizophora apiculata* roots in Sidodadi village, Lampung: An in vitro study

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ABSTRACT

Malaria remains a major global health threat as Plasmodium parasites transmitted by female Anopheles mosquitoes increasingly develop resistance to frontline drugs. Mangrove plants are rich in terpenoids, alkaloids, and flavonoids with potent antiplasmodial activity, but harvesting large biomass jeopardises fragile coastal ecosystems. Endophytic fungi residing inside plant tissues can synthesise the same metabolites as their hosts, thus offering a sustainable source of new antimalarial leads. This study aimed to isolate and characterise root-derived endophytic fungi from Rhizophora apiculata growing in Sidodadi Village and to evaluate their antimalarial potential. Root segments were surface-sterilised and plated on potato dextrose agar; emerging colonies were sub-cultured until ten pure isolates were obtained. Crude filtrate and mycelial extracts were screened in vitro using the haem-polymerisation inhibition assay. Isolate B.S.CE7 exhibited the highest activity, inhibiting β-haematin formation by 91.4 % and 78.6 % in filtrate and biomass extracts, respectively, with IC_{50} values of 0.24 mg ml^{-1} and 0.70 mg ml^{-1} (chloroquine control 0.14 mg ml^{-1}). Morphological examination placed B.S.CE7 in the genus Aspergillus. Phytochemical tests revealed the presence of alkaloids, flavonoids, saponins, and terpenoids, compounds commonly implicated in antiplasmodial mechanisms such as haem detoxification blockade. These results demonstrate that mangrove-associated Aspergillus sp. is a promising reservoir of antimalarial metabolites comparable in potency to established drugs. The study highlights the value of exploring endophytes to expand the natural-product pipeline while conserving mangrove biodiversity and provides a foundation for compound isolation.

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INTRODUCTION

Malaria remains one of the world's deadliest communicable diseases. The World Malaria Report 2023 recorded 249 million cases and 608,000 deaths in 2022, representing an increase compared with 2021 and marking the fifth consecutive year of global resurgence (WHO, 2023). In Southeast Asia, Indonesia ranks second only to India, contributing nearly one-third of regional cases. Although national incidence declined from 1.8 million cases in 2010 to 811,636 in 2022 (a 55% reduction over a decade), transmission persists in eastern provinces, particularly Papua, Maluku,

and East Nusa Tenggara, where more than 89% of cases occur. (Lubis *et al.*, 2025; Jupp *et al.*, 2024; Istiana *et al.*, 2021).

Malaria is a protozoan parasitic infection caused by Plasmodium spp. and transmitted through the bite of female Anopheles mosquitoes (Malino *et al.*, 2023). In humans, infections are mainly attributed to *P. falciparum, P. malariae, P. vivax*, and *P. ovale* (Mardona *et al.*, 2024). Artemisinin-based combination therapy (ACT) has been the cornerstone of malaria treatment for two decades. However, increasing resistance to partner drugs such as chloroquine and sulfadoxine–pyrimethamine prompted Indonesia to adopt three ACT regimens—artesunate–amodiaquine, artemether–lumefantrine, and dihydroartemisinin–piperaquine—in accordance with WHO guidelines. Despite these measures, mutations in the kelch13 (K13) gene, a molecular marker of artemisinin resistance, have been widely reported in Cambodia, Thailand, and Myanmar, and early signs of ACT failure are emerging in Indonesia. For example, a survey in Pesawaran, Lampung documented treatment failure in 1.6% of *P. falciparum cases*, while K13 mutations have been detected in isolates from Manokwari Health Centre, West Papua (Abubakar *et al.*, 2019; Suwandi, 2014). These findings underscore the urgent need for new antimalarial agents

Historically, many effective antimalarials, including quinine and artemisinin, were derived from plants. This success has encouraged continued exploration of natural products from diverse ecosystems (Mahmiah & Sudjarwo, 2019). Mangrove plants, particularly *Rhizophora spp*., produce various secondary metabolites such as saponins, tannins, flavonoids, phenolics, terpenoids, and steroids, which exhibit antibacterial, antioxidant, and cytotoxic properties (Adisa et al., 2024; Ravikumar & Gnanadesigan, 2012; Aini *et al.*, 2019). Extracts of *Rhizophora mucronata* leaves demonstrate notable antiplasmodial activity (IC_{50} 5.69–4.62 μg mL^{-1}), largely attributed to their terpenoid constituents. The bark extract shows stronger activity (IC_{50} 6.18 μg mL^{-1}), while leaf extracts inhibit chloroquine-sensitive *P. falciparum* strains. Root extracts also display antioxidant effects and may reduce malaria-associated oxidative stress (Hridya *et al.*, 2021; Ravikumar *et al.*, 2011; Clarkson *et al.*, 2004). Collectively, these findings suggest that mangrove-derived metabolites can interfere with Plasmodium growth and development.

However, large-scale harvesting of mangrove plants poses ecological risks. Endophytic microorganisms—fungi or bacteria that live asymptomatically within plant tissues—offer a sustainable alternative source of bioactive metabolites (Harahap & Nurjanah, 2017). These microbes often synthesize the same or structurally similar compounds as their host plants. Endophytic fungi from Jatropha multifida and mangrove species have yielded flavonoids and other metabolites with antibacterial and antiplasmodial properties. For instance, Penicillium species isolated from mangrove roots produce penicoside A and B-resorcylic acid derivatives that exhibit potent activity against *P. falciparum* K1 with low mammalian cytotoxicity (Alhadrami *et al.*, 2021; Kaushik *et al.*, 2014).

A key target for many antimalarial drugs is hem polymerization. During the erythrocytic stage, parasites digest haemoglobin and release toxic free haem, which they detoxify by crystallizing it into haemozoin (Basilico *et al.*, 1998; Hapsari *et al.*, 2022; Muti'ah, 2012). Drugs such as chloroquine inhibit this crystallization, causing toxic haem accumulation and parasite death. Therefore, inhibition of haem polymerization is a widely used strategy for screening novel antimalarial

compounds. Previous studies reported that extracts of endophytic fungi associated with Artemisia annua inhibit haem polymerization (IC_{50} 2.29 mg mL^{-1}) and produce artemisinin derivatives (Septiana *et al.*, 2017). Nevertheless, the antimalarial potential of endophytic fungi from Rhizophora mucronata in Indonesia, particularly through haem polymerization inhibition, remains unexplored. Mangrove ecosystems are chemically unique and represent promising yet underexplored sources of bioactive endophytes. Cultivating endophytic fungi via controlled fermentation provides a sustainable approach to obtaining novel antimalarial compounds without damaging mangrove habitats.

METHOD

Materials and Reagents

Fresh roots of Rhizophora apiculata were collected from Sidodadi Village, Lampung. Distilled water, glacial acetic acid, ethanol (70% and 96%), analytical-grade ethyl acetate, $FeCl_3$, HCl, H_2SO_4, haemin, chloramphenicol, dimethyl sulfoxide (DMSO), and sodium hypochlorite (NaOCl, 1% w/v) were used. Potato Dextrose Agar (PDA) and Potato Dextrose Broth (PDB) were used for fungal isolation and fermentation. Mayer's, Dragendorff's, and Wagner's reagents were employed for qualitative phytochemical screening of alkaloid compounds.

Instrumentation

Standard microbiological and analytical laboratory equipment was used, including an autoclave, centrifuge, rotary evaporator, orbital shaker, incubator, oven, analytical balance, and a 96-well microplate reader.

Experimental Design

The experiment consisted of three main stages: (1) isolation and identification of endophytic fungi from mangrove roots, (2) stepwise fermentation and extraction of fungal metabolites, and (3) evaluation of antimalarial activity using the haem polymerisation inhibition assay, followed by phytochemical screening.

Isolation of Endophytic Fungi

PDA and PDB were prepared by dissolving 39 g and 24 g of the respective media powders in 1,000 mL distilled water. Each medium was supplemented with chloramphenicol (200 mg L^{-1}) to inhibit bacterial contamination, homogenised, sterilised at 121 °C for 15 min, and poured or distributed into sterile containers. Mangrove roots were rinsed under running water, cut into approximately 1 cm segments, and surface-sterilised sequentially in 70% ethanol (1 min), NaOCl (1%, w/v; 1 min), and sterile distilled water (three rinses). Segments were dried on sterile tissue and placed onto PDA plates. Plates were incubated at 28–30 °C for 3–7 days until fungal colonies emerged. Distinct colonies were subcultured repeatedly to obtain pure isolates (Mardina, 2022).

Identification of Fungal Isolates and Growth Curve

Isolates were identified based on macroscopic colony characteristics and microscopic morphology. Mycelia were mounted on slides and observed under 400× magnification. Features including conidiophore branching, phialides, and conidial shape were recorded. Identification

followed the morphological keys of Suryani et al. (2020); molecular confirmation (e.g., ITS sequencing) was not performed. For growth-curve determination, mycelia were inoculated into 10 mL PDB and incubated at 28–30 °C on a rotary shaker (120 rpm) for 14 days. Biomass was harvested every 12 h, dried at 60 °C to constant weight, and dry mass was recorded (Suryani *et al.*, 2020; Rohmah *et al.*, 2018; Hakim *et al.*, 2020).

Fermentation and Extraction

Stepwise fermentation was conducted as follows:

1) Days 0–7: Mycelium from 7-day-old PDA cultures was inoculated into 5 mL PDB.
2) Days 7–14: The entire culture was transferred into 50 mL fresh PDB.
3) Days 14–21: The culture was scaled up into 500 mL PDB and incubated.

After 21 days, broth and biomass were separated by filtration. Both fractions were extracted three times using ethyl acetate at a 1:1 (v/v) solvent-to-sample ratio. Organic layers were combined and concentrated under reduced pressure using a rotary evaporator at 40 °C to obtain crude extracts. Crude extracts were weighed to determine yield and stored in amber vials at 4 °C until analysis (Septiana *et al.*, 2018).

Haem Polymerisation Inhibition Assay

Antimalarial activity was evaluated using the haem polymerisation inhibition method. Each test sample (50 µL) was mixed with 100 µL of 1 mM haemin in 0.1 M NaOH, followed by 50 µL glacial acetic acid to initiate polymerisation. Mixtures were incubated at 37 °C for 24 h. Chloroquine served as the positive control and distilled water as the negative control. After incubation, samples were centrifuged (8,000 rpm, 10 min). Pellets were washed four times with 200 µL DMSO and resuspended in 0.1 M NaOH. Absorbance was measured at 405 nm using a microplate reader (Basilico *et al.*, 1998; Septiana *et al.*, 2018).

Percentage inhibition was calculated as:

$$\text{Inhibition (\%)} = [(A - B) / A] \times 100$$

where A is the negative control absorbance and B is the sample absorbance

IC_{50} Determination and Data Analysis

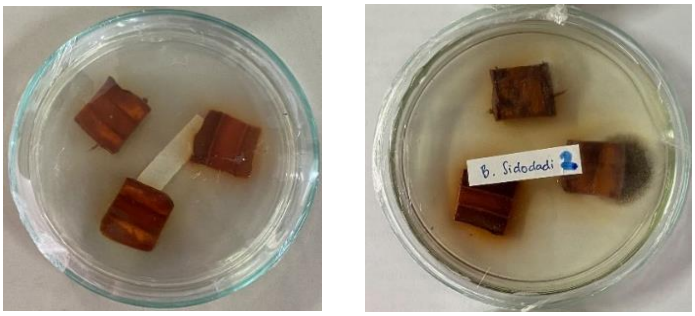
Dose–response data were analysed using linear regression ($y = a + bx$) in Microsoft Excel. IC_{50} values were calculated by setting $y = 50$. Coefficient of determination (R^2) values were recorded to assess model fit (Rahmayani *et al.*, 2013).

Phytochemical Screening

The most active extract was subjected to qualitative phytochemical screening. Alkaloids were detected using Mayer's (creamy precipitate), Wagner's (brown precipitate), and Dragendorff's (orange–red precipitate) reagents. Tannins and phenolics were identified using $FeCl_3$ (blue-black colouration), flavonoids using Mg–HCl reaction (orange/red layer), and saponins by stable foam formation.

RESULTS AND DISCUSSION

The mangrove root material collected in Sidodadi village (Teluk Pandan, Lampung, Indonesia) was authenticated at Herbarium Bogoriense as *Rhizophora apiculata* Blume (Rhizophoraceae). Accurate host identification is critical because endophytic fungal assemblages and their metabolomes are often host-specific, influencing the chemical space available for drug discovery. The surface sterilization process commenced with rinsing mangrove roots under running water to eliminate residual debris such as sand or mud adhering to the root surface. Once cleaned, the roots were cut into approximately 1 cm segments to facilitate the growth of endophytic fungi within the culture medium. The segments were subsequently subjected to sequential immersion in 70% ethanol, sodium hypochlorite (NaOCl) solution, and a final rinse using sterile distilled water. Ethanol acts as a disinfectant by denaturing proteins, thereby compromising the integrity of bacterial cells. Protein denaturation occurs more effectively in water; thus, 70% ethanol is more efficacious than higher concentrations, which tend to denature proteins on the bacterial surface without penetrating the cell membrane to reach intracellular targets (Susatyo, 2016). Sodium hypochlorite (NaOCl), a chlorine-based compound, exerts its antimicrobial effect by irreversibly oxidizing sulfhydryl groups on enzymes, disrupting essential metabolic functions of bacterial cells (Suhartina *et al.*, 2018). Sterile distilled water removes residual disinfectants from the root surface and also functions as a control indicator to assess the success of the surface sterilization procedure (Figure 1). The primary objective of surface sterilization is to eliminate epiphytic microorganisms residing on the plant surface, ensuring that the cultured fungal colonies originate exclusively from endophytes inhabiting internal plant tissues (Ginting *et al.*, 2020). Surface-sterilised root fragments yielded ten morphologically distinct endophytic isolates (B.S.CE1–B.S.CE10) on PDA supplemented with chloramphenicol (Table 1).



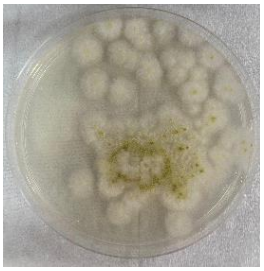
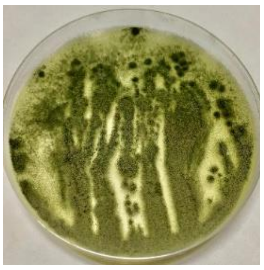
(a) (b)

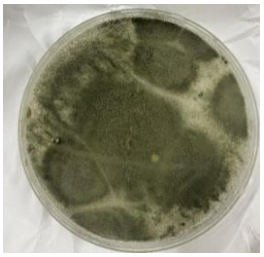
Figure 1. Isolation of endophytic fungi. (a) Sterile sample placed on PDB medium, (b) endophytic fungal isolation after 7 days of incubation.

Endophytic fungal isolates that grew on PDA isolation medium were purified by transferring them onto fresh PDA medium. This purification process aimed to separate the mixed inoculation results, which consisted of multiple morphologically distinct colonies, to obtain pure isolates free from contamination by other microorganisms. Endophytic fungal isolates were purified through macroscopic observation based on colony color and morphology. Colonies exhibiting different shapes and colors were considered distinct isolates, whereas colonies with similar appearances were classified as a single isolate (Putri *et al.*, 2024). If multiple fungal colony types were observed growing in the same Petri dish, they were further subcultured until pure isolates were obtained (Fajrina *et al.*,

2020). Based on the results of isolation and purification of endophytic fungi from mangrove roots (*Rhizophora apiculata* Blume.) through macroscopic characterization, 10 pure isolates were successfully obtained (Table 1). Each isolate was assigned a code (B.S.CE1 to B.S.CE10) to facilitate subsequent screening for antimalarial activity. This purification step is crucial for ensuring the reliability of downstream bioactivity assays, as only axenic fungal cultures can yield consistent and interpretable results. Moreover, accurate identification and classification of isolates based on macromorphological traits serve as the initial basis for exploring their potential secondary metabolites, which may vary significantly among fungal taxa.

Table 1. Results of isolation and purification of endophytic fungal isolates from mangrove roots (*Rhizophora apiculata* Blume.) based on macroscopic characteristics

Isolate Code	Figure	Description			
		Colony COlor	Colony Shape	Colony Distribution	Colony Texture
B.S.CE1		Yellowish white with dark green center	Irregular	Even	Velvety
B.S.CE2		White with light green center	Irregular	Uneven	Velvety
B.S.CE3		Black with yellow edges	Irregular	Uneven	Granular
B.S.CE4		Dark green with light green edges	Irregular	Even	Powdery

Isolate Code	Figure	Description			
		Colony COlor	Colony Shape	Colony Distribution	Colony Texture
B.S.CE5		Yellowish white with a black center	Irregular	Uneven	Velvety (white area), granular (black area)
B.S.CE6		White with dark green center	Irregular	Uneven	Velvety
B.S.CE7		Dark green	Irregular circular	Even	Velvety
B.S.CE8		White	Irregular	Uneven	Cottony
B.S.CE9		White with light green center	Irregular	Even	Velvety (white area), granular (light green area)
B.S.CE10		Yellowish white with black center	Irregular	Even	Velvety (white area), granular (black area)

After obtaining 10 pure isolates successfully isolated from mangrove roots (Rhizophora apiculata Blume.), a subculturing (rejuvenation) step was carried out to ensure that the endophytic fungal isolates were not in the death phase or experiencing excessive nutrient competition due to overly dense cell growth (Fajrina *et al.*, 2020). The isolates were then fermented in Potato Dextrose Broth (PDB) medium on a rotary shaker for 21 days at room temperature (28–30°C). The culture was filtered after fermentation to separate the fungal biomass from the culture filtrate. In the antimalarial activity screening phase, the filtrate was used as the test sample, as most secondary metabolites are released into the fermentation medium (Septiana et al., 2018). The obtained filtrate was subsequently centrifuged to separate the pellet and supernatant. The supernatant was used for the antimalarial activity assay because it contains the fungal secondary metabolites (Rianto et al., 2018). The assay was performed by measuring absorbance using a microplate reader at a wavelength of 405 nm. The percentage of inhibition was then calculated based on the absorbance values, using a standard hematin curve and a negative control previously obtained. Culture filtrates (21 d, PDB, 28–30 °C) were screened with the β-hematin (hemozoin) inhibition assay. Inhibition values ranged from 38.2% (B.S.CE3) to 78.5% (B.S.CE7) at the fixed test concentration, identifying isolate B.S.CE7 as the lead candidate (Table 2). The result is noteworthy because <30% inhibition is often considered inactive at this stage. This suggests several isolated endophytic fungi, particularly B.S.CE7, may produce bioactive metabolites with promising antimalarial potential. The high inhibition activity observed highlights the potential of mangrove-associated endophytes as a valuable source of antiplasmodial agents, which warrants further investigation into their active compounds' chemical nature and mechanism of action.

Table 2. Antimalarial activity screening results of endophytic fungal isolates B.S.CE1 – B.S.CE10

Isolate Code	Absorbance			Inhibition (%)
	Simplo	Duplo	Average ± SD	
B.S.CE1	0,4958	0,5102	0,5030 ± 0,0101	55,7876
B.S.CE2	0,5509	0,5583	0,5546 ± 0,0052	41,2195
B.S.CE3	0,5380	0,5927	0,5653 ± 0,0386	38,1987
B.S.CE4	0,4852	0,4930	0,4891 ± 0,0055	59,7120
B.S.CE5	0,5251	0,5221	0,5236 ± 0,0226	49,9718
B.S.CE6	0,4896	0,4846	0,4871 ± 0,0035	60,2766
B.S.CE7	0,4253	0,4199	0,4226 ± 0,0038	78,4866
B.S.CE8	0,5589	0,5523	0,5556 ± 0,0046	40,9373
B.S.CE9	0,4756	0,5240	0,4998 ± 0,0342	56,6911
B.S.CE10	0,5161	0,5263	0,5212 ± 0,0072	50,6492

Based on the screening data of endophytic fungal isolates B.S.CE1 – B.S.CE10 shown in Table 3, the endophytic fungal isolate B.S.CE7 exhibited the highest hem polymerization inhibition activity at 78.4866%. Therefore, isolate B.S.CE7 was selected for species identification and growth curve analysis. This step was conducted prior to further testing to determine the IC_{50} value of the B.S.CE7 isolate. The superior inhibitory activity demonstrated by B.S.CE7 suggests a strong potential for producing bioactive compounds that are effective against malaria parasites. Endophytic fungi are well-documented as prolific producers of diverse secondary metabolites with pharmaceutical applications, including antimalarial properties (Srikandace, 2007; Azlin *et al.*, 2004). Identifying the

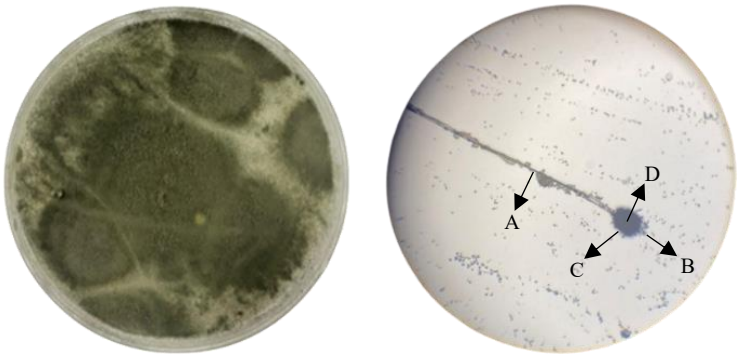
species is crucial to correlate the biological activity with taxonomic classification, which can guide future bioprospecting efforts and facilitate reproducibility in bioactivity studies (Shandhyavitri *et al.*, 2013). Additionally, understanding the growth dynamics through the growth curve analysis ensures optimization of fermentation conditions to maximize metabolite production, which is essential for scaling up potential drug candidates (Baelsmans, 2000).

Species identification of the endophytic fungus was carried out to determine the fungal species used. The identification process was performed using the endophytic fungus at 7 days of growth, followed by macroscopic and microscopic observations. Macroscopic observation included examining the color, shape, texture, and colony distribution. Based on the observations shown in Figure 2 (a), on the seventh day, the endophytic fungal isolate B.S.CE7 formed colonies with a dark green color, irregular round shapes, a smooth velvety texture, and the colony spread evenly across the entire surface of the medium. After macroscopic observation, microscopic identification of the endophytic fungus was conducted using a binocular microscope at 40x magnification by observing the structures of conidiophores, conidia, phialides, and vesicles, which were then compared with the fungal identification guide by Suryani *et al.* (2020). Based on Figure 2 (b) observations, the isolate B.S.CE7 exhibited microscopic characteristics similar to the genus Aspergillus sp. This was evidenced by upright conidiophores with a round structure at the tip.

Additionally, the round structure contained phialides arranged in a circle with single-celled, round conidia, and the vesicle surface was covered by phialides. These findings correspond with the research by Ristiari *et al.* (2019), who reported that endophytic fungi from the genus Aspergillus sp. have macroscopic characteristics of dark green colonies with a smooth velvety texture. Microscopically, they exhibit upright conidiophores, smooth-walled conidia ranging from round to semi-round shapes, and vesicles and phialides.

Accurately identifying endophytic fungal species is a fundamental step for correlating bioactivity profiles with specific taxa, which can influence the selection of fungal strains for pharmaceutical or biotechnological applications (Kaushik *et al.*, 2014). The morphological features observed in isolate B.S.CE7 strongly indicate its affiliation to the genus Aspergillus, a group widely known for its capacity to produce diverse bioactive secondary metabolites, including antifungal, antibacterial, and antimalarial compounds (Vanderesse, 2016; Fajrina *et al.*, 2020). Macroscopic traits such as colony color and texture serve as preliminary but crucial markers for genus-level identification, while microscopic features—especially conidiophore morphology and spore arrangement—allow more precise differentiation between species (Dona *et al.*, 2024). Moreover, studies have shown that endophytic *Aspergillus* species isolated from mangrove ecosystems exhibit unique metabolic profiles, often adapted to the saline and nutrient-variable conditions, which can enhance their potential as sources of novel pharmacologically active substances (Suhartina *et al.*, 2018; Susanti *et al.*, 2021). Thus, identifying B.S.CE7 as *Aspergillus sp*. supports its candidacy for further biochemical characterization and validates its promising antimalarial activity observed in earlier assays. Further molecular identification using ITS sequencing is recommended to confirm species-level taxonomy and to explore genetic markers linked to secondary metabolite biosynthesis (Wulandari *et al.*, 2022; Syamsia *et al.*, 2016). B.S.CE7 displayed dark-green, velvety colonies with radiating wrinkles. Microscopy revealed erect conidiophores terminating in globose vesicles

completely covered by phialides bearing spherical conidia—features diagnostic for the genus *Aspergillus* (Figure 2).



(a) (b)

Figure 2. Endophytic fungal isolate B.S.CE7 (a): macroscopic view, (b): microscopic view, (c): literature

Dry-weight monitoring over 22 days showed classical fungal growth phases (Figure 10). Biomass increased rapidly until day 14 (0.233 g) before declining, placing the stationary phase between days 12–16. Because many secondary metabolites are produced under nutrient-limited, stationary-phase conditions, day 14 was selected for scaled fermentation (Table 3).

Table 3. Biomass weighing results of endophytic fungal isolate B.S.CE7

Days	Weight of Empty Filter Paper (g)	Weight of Filter Paper with Biomass (g)	Biomass Weight Result (g)
2	1.0508	1.1503	0.0995
4	1.0512	1.1691	0.1179
6	1.0509	1.2303	0.1794
8	1.0511	1.2349	0.1838
10	1.0511	1.2395	0.1884
12	1.0513	1.2414	0.1901
14	1.0515	1.2849	0.2334
16	1.0512	1.2334	0.1982
18	1.0507	1.2238	0.1731
20	1.0510	1.2098	0.1588
22	1.0514	1.1863	0.1349

This observation aligns with previous studies indicating that the stationary phase is critical for maximizing secondary metabolite production in fungi, as nutrient limitation triggers biosynthetic pathways associated with bioactive compounds (Dawolo, 2017; Binuni *et al.*, 2020). Selecting the optimal harvest time based on growth table data ensures enhanced yield and efficacy of metabolites, which is essential for subsequent bioactivity assays and potential pharmaceutical applications. Thus, identifying day 14 as the peak biomass and metabolite production point provides a strategic foundation for efficient fermentation scale-up and metabolite extraction (Ginting *et al.*, 2020).

During the growth observation stage of the endophytic fungal isolate B.S.CE7 over 22 days, classical growth phases were observed. On day 2, the endophytic fungus entered the lag phase, where growth began but cell activity was still low. This was caused by the fungus adapting to the new environment and the initial stage of enzyme synthesis to break down substrates as nutrient sources.

On day 4, the fungus entered the acceleration phase, where cells actively began dividing and growing, marking the transition from lag to active growth phase. By day 6, it reached the exponential phase, with optimal cell division activity and a maximum growth rate forming an exponential curve (Sanatang & Purnama, 2023). On day 12, the isolate entered the deceleration phase, marked by decreased cell division activity. By day 14, it reached the stationary phase, with the highest biomass weight due to a balance between live and dead cells caused by nutrient depletion. Under these conditions, the fungal cells produce secondary metabolites to survive (Rahaweman *et al.*, 2016). Biomass increase correlates with increased metabolite production (Hidayatulloh *et al.*, 2019). Therefore, the stationary phase near the onset of the death phase is used as a reference for harvesting secondary metabolites potentially active against malaria, indicated by a slowing growth rate (Annisa *et al.*, 2024). The growth curve declined significantly from day 16 to 21, indicating the fungus had entered the accelerated death phase. These results align with those of Isti'anah *et al.* (2024), which showed that *Aspergillus sp*. endophytic fungi have an exponential phase on day 6 and a stationary phase after day 12.

Endophytic fungal fermentation was carried out using liquid media because it is more optimal for producing biomass and bioactive compounds than solid media (Rianto *et al.*, 2018). This is attributed to the agitation process in liquid fermentation, which helps maintain nutrient homogeneity in the medium, preventing the formation of concentration gradients of products or toxins. Consequently, the endophytic fungi can more efficiently absorb nutrients to support their growth. The agitation also causes continuous movement of the growth medium, facilitating aeration that sustains secondary metabolite production through oxygen availability. Following fermentation, a filtration was performed to separate the biomass and filtrate. The obtained biomass was dried in an oven to remove residual water content, yielding dry biomass. Subsequently, both the filtrate and dry biomass from the B.S.CE7 fungal isolate were subjected to extraction to obtain the filtrate extract and biomass extract.

Extraction was performed using liquid-liquid extraction for the filtrate and solid-liquid extraction for the biomass. Ethyl acetate was used as the solvent at a 1:1 ratio, repeated three times. Extraction was conducted in a separatory funnel, agitated for 10 minutes until two distinct phases formed—the ethyl acetate phase (upper) and the aqueous phase (lower). Ethyl acetate was selected due to its common use as an organic solvent for extracting endophytic fungi and its semi-polar properties that dissolve both polar and non-polar compounds (Ramadhani *et al.*, 2024). This characteristic enables ethyl acetate to extract many active compounds (Isti'anah *et al.*, 2024). Furthermore, ethyl acetate's immiscibility with water simplifies its separation from the polar Potato Dextrose Broth (PDB) medium (Pratama, 2020). A 14-day, aerated PDB fermentation of six-day-old inoculum produced filtrate and mycelial fractions extracted thrice with ethyl acetate (1:1 v/v). Concentration (40 °C, rotary evaporation) gave 244 mg of filtrate extract (yield 0.98 %) and 703 mg biomass extract (yield 2.82 %). Ethyl acetate was preferred because its semipolarity partitions a wide range of fungal metabolites.

The hem polymerization inhibition assay began with determining the hematin standard curve by measuring absorbance at a wavelength of 405 nm (Basillico *et al.*, 1998). The standard curve was established to obtain a linear regression equation quantifying β-hematin concentration. The resulting

hematin standard curve showed the regression equation y = 0.0086x + 0.3454, with a correlation coefficient (r) of 0.9955 and an r^2 value of 0.991. According to the Indonesian Ministry of Health (Depkes RI, 2020), a standard curve has good linearity if the R value exceeds 0.98. Therefore, the hematin standard curve in this study meets the required linearity criteria. This indicates a linear relationship between hematin concentration and absorbance, allowing the regression equation to be used to determine hem polymerization inhibition activity. The β-hematin concentration was determined by substituting the sample absorbance value as 'y ' in the equation y = 0.0086x + 0.3454, where 'x' represents the β-hematin concentration formed. Subsequently, the percentage of hem polymerization inhibition was calculated by comparing the β-hematin concentration of the test sample with that of the negative control. The negative control in this assay was distilled water (aquadest), incubated under the same conditions as the test samples.

Table 3. Antimalarial activity test results of endophytic fungal isolate B.S.CE7

Sample	Concentration (ppm)	Inhibition (%)	IC_{50} ppm
Biomass Extract	250	18,9060	703,0745
	200	15,1471	
	150	13,2679	
	100	8,2186	
	50	5,2799	
Filtrate Extract	250	51,8654	244,4643
	200	41,9635	
	150	36,8302	
	100	27,8541	
	50	22,3561	
Chloroquine	250	80,2805	145,3291
	200	65,4419	
	150	49,8154	
	100	36,9424	
	50	24,0672	

Five-point dose–response curves (50–250 ppm) yielded IC_{50} values of 0.24 mg mL^{1} for the filtrate extract and 0.70 mg mL^{1} for the biomass extract (Table 3). Both fall well below Baelsman's empirical activity threshold of 12 mg mL^{1}, confirming significant β-hematin-blocking capacity. In this assay, the filtrate extract and biomass extract samples were prepared at five concentrations: 250 ppm, 200 ppm, 150 ppm, 100 ppm, and 50 ppm, each replicated twice per concentration. The test samples were then reacted with 1 mM hematin solution inside microtubes. Hematin was used because it can react to form β-hematin crystals, which are analog compounds of hemozoin—the malaria pigment (Basilico *et al.*, 1998). To induce β-hematin crystal formation, glacial acetic acid was added. The addition of glacial acetic acid also aimed to adjust the microtube's acidic environment to mimic the Plasmodium parasite's digestive vacuole. The test samples were then incubated at 37°C for 24 hours. The temperature of 37°C was chosen because after the host's erythrocytes are infected by Plasmodium parasites, β-hematin crystals optimally form at 37°C within 24 hours (Arnida *et al.*, 2021). When benchmarked against recent fungal leads, the filtrate extract is ~30-fold more potent than the ergosteroids reported from *Stemphylium sp*. (IC_{50} 7–9 mg mL^{1}) and approaches the activity

of many semisynthetic aryl-amino-alcohols (IC_{50} 0.12–0.30 mg mL^{1}) that are presently in early development.

Nevertheless, chloroquine in our assay displayed an IC_{50} of 0.14 mg mL^{1}, indicating that the crude filtrate is ~1.7-fold less potent than the reference drug and that purification of the active principle(s) remains essential. Phytochemical screening was conducted qualitatively to identify the secondary metabolite compounds in the endophytic fungal isolate B.S.CE7 that potentially exhibit antimalarial activity (Table 6). Phytochemical screening was performed only on the filtrate extract due to its higher hem polymerization inhibition activity than the biomass extract. Qualitative colour tests showed that the filtrate extract contains alkaloids, flavonoids, terpenoids, and saponins but lacks tannins and phenolics (Table 6). Alkaloids and terpenoids can chelate Fe^{2+} and disrupt haemozoin crystallisation, whereas flavonoids/saponins may potentiate activity via oxidative stress modulation or membrane disruption.

Table 4. Phytochemical screening results of the filtrate extract of endophytic fungal isolate B.S.CE7

Test Parameters	Reagent	Result	Literature (Akasia *et al.*, 2021)	Remaks
Alkaloids	Mayer	Cloudy white precipitate	White precipitate or cloudiness	+
	Wagner	Brown precipitate	Brown precipitate	+
	Dragendoff	Red precipitate	Orange-red precipitate	+
Flavonoids	+ mg +HCl + Amyl alcohol	Orange layer on amyl alcohol	Red, yellow, or orange layer on amyl alcohol	+
Saponins	+ Aquadest + HCL 2N	Stable foam formation (6 cm)	Stable foam formed 1–10 cm high	+
Terpenoids and steroids	+ Acetic anhydride + H_2SO_4	Red	Red or Purple	+
Phenolics	+ $FeCl_3$ 1%	Orange	Dark blue	-
Tanins	+ $FeCl_3$ 1% + H_2SO_4	Orange	Greenish-black or bluish-black	-

Based on the results of phytochemical screening shown in Table 4, the filtrate extract of the endophytic fungus B.S.CE7 contains secondary metabolites such as alkaloids, flavonoids, saponins, and terpenoids. The presumed mechanism of action for the test sample's hem polymerization inhibition activity involves the formation of bonds between the iron ion of heme and the secondary metabolite compounds in the sample that possess hydroxyl groups. The bonding of the iron ion in heme with hydroxyl groups present in flavonoids, saponins, and terpenoids can prevent the conversion of toxic heme molecules into hemozoin, thereby leading to the death of the Plasmodium parasite (Basillico *et al.*, 1998; Purwanto, 2011).

In the alkaloid test of the filtrate extract of the endophytic fungus B.S.CE7, positive results were obtained, indicated by the formation of a cloudy white precipitate with Mayer's reagent, a brown precipitate with Wagner's reagent, and a red precipitate with Dragendorff's reagent. The addition of H_2SO_4 before reaction with the reagents aims to prevent the basic alkaloids from dissolving in the

acidic solution by forming alkaloid salts (Puspa *et al*., 2017). The alkaloid test mechanism involves precipitation due to ligand substitution. The nitrogen atom in alkaloids, which has a free electron pair, can replace the iodide ion present in the reagent to form a coordinate covalent bond with the metal ion (Agustina *et al.,* 2017). Alkaloids are known secondary metabolites with medicinal potential. One type of alkaloid proven to have antimalarial activity is quinine, isolated from the bark of the cinchona tree (*Chinchona succirubra*) (Ernawati *et al*., 2018). Quinine alkaloids inhibit the growth of Plasmodium parasites and have served as a basis for synthesizing antimalarial drugs such as chloroquine and mefloquine (Hafid *et al.,* 2016). Additionally, research by Syafii *et al*. (2016) showed that the ethanol extract of sea buckthorn wood contains the alkaloid strychnine, which is highly active as an antimalarial with an IC_{50} value of 3.09 µg/ml against Plasmodium strain 3D7. Alkaloids act as antimalarials by inhibiting the detoxification process of Plasmodium heme in the food vacuole and function as blood schizonticides and gametocides (Astuti *et al.,* 2022).

In the flavonoid test on the filtrate extract of the endophytic fungus B.S.CE7, positive results were also obtained, indicated by the formation of an orange color in the amyl alcohol layer. The reaction mechanism for flavonoid testing involves HCl and magnesium powder reducing the benzopyran nucleus in the flavonoid structure to form flavylium salts (Effendy *et al*., 2024). Adding amyl alcohol forms colored complexes or precipitates since the color developed after adding HCl and Mg powder fades quickly (Ananta *et al*., 2024). Flavonoids are polyphenolic compounds with antioxidant properties. *Plasmodium* parasites are unable to damage erythrocytes by breaking down hemoglobin into free toxic heme, nor cause lysis of red blood cells, because antioxidants protect the cells against reactive oxygen species (ROS) (Veronika & Chrismayanti, 2020). Antioxidants can reduce the negative effects of oxidative stress, including ROS generated during malaria infection. The pathophysiology of malaria involves free radicals formed through oxidative stress (Laksemi *et al*., 2021). Research by Retnoningtyas *et al*. (2013) demonstrated that the methanol extract of keluwih leaves (*Artocarpus camansi*) has antimalarial activity by inhibiting Plasmodium berghei parasites by 72.83%. This is because flavonoids in keluwih leaves inhibit hemozoin formation, thus restricting Plasmodium parasite growth due to nutrient deficiency. Besides inhibiting parasite growth by preventing oxidative stress, flavonoids exert antimalarial effects by disrupting nutrient transport required by the parasite and inhibiting heme detoxification within the parasite's food vacuole (Astuti *et al*., 2022).

The saponin test on the filtrate extract of the endophytic fungus B.S.CE7 also yielded positive results, characterized by the formation of stable foam. The saponin reaction mechanism involves foam formation due to saponins containing both hydrophobic and hydrophilic groups. When shaken, the hydrophilic groups bind to water while the hydrophobic groups bind to air, producing foam (Sulaeman *et al*., 2022). Adding HCl increases the polarity of hydrophilic groups, resulting in stable foam formation (Karlina & Nasution, 2022). The exact antimalarial mechanism of saponins remains unclear; however, Djamanmona & Anggaraeni (2023) suggested that saponins inhibit parasites by lysing erythrocytes. Moreover, saponins have antioxidant properties as they can scavenge superoxide by forming hyperoxide intermediates, preventing biomolecular damage by free radicals (Putri, 2023). Through their antioxidant activity, saponins can reduce oxidative stress effects, including ROS generated during malaria infection.

In the terpenoid and steroid tests on the filtrate extract of the endophytic fungus B.S.CE7, positive results were obtained for terpenoids, indicated by the formation of a red color, while steroids tested negative. The addition of anhydrous acetic acid aims to form acetyl derivatives of terpenoids or steroids, which then react with H_2SO_4 to hydrolyze water and form colored complexes: reddish-purple for terpenoids and blue-green for steroids (Nurjanah, 2022). The reaction mechanism for terpenoids and steroids involves oxidation by forming conjugated double bonds (Ikalinus *et al.*, 2015). Terpenoids are natural hydrocarbons with biological activities, including antimalarial effects. Artemisinin, a sesquiterpene lactone isolated from *Artemisia annua*, is an example of a terpenoid successfully used as an antimalarial against chloroquine-resistant Plasmodium falciparum (Hafid *et al.*, 2016). Terpenoids exert their antimalarial effects during the erythrocytic stage, where the peroxide bridge in terpenoids is cleaved by Fe^{2+} ions to form reactive free radicals. These terpenoid radicals then inhibit parasite metabolism, leading to *Plasmodium* death (Muti'ah, 2012). Terpenoids can also inhibit sporogony development, disrupting gametogenesis or macrogamete fertilization (Djamanmona & Anggaraeni, 2023). Additionally, terpenoids inhibit protein synthesis in cells responsible for nutrition, thereby restricting Plasmodium parasite growth (Astuti *et al.*, 2022).

The results of this study provide preliminary evidence that the filtrate extract of the mangrove root endophytic fungus B.S.CE7 (*Rhizophora apiculata* Blume.) can inhibit heme polymerization due to the presence of alkaloids, flavonoids, terpenoids, and saponins. These secondary metabolites may act as antimalarial agents by disrupting nutrient transport necessary for the parasite, interfering with heme detoxification, reducing oxidative stress caused by malaria infection, and preventing protein synthesis within the parasite's food vacuole, ultimately causing Plasmodium parasite death. Therefore, considering the potential of the endophytic fungal isolate B.S.CE7 from mangrove roots (*Rhizophora apiculata* Blume), it holds promise for development as an antimalarial drug. *Aspergillus spp*. are prolific producers of indole-diterpenes, polyketides, and meroterpenoids, yet reports of potent β-hematin inhibition from mangrove-derived isolates remain scarce. The IC_{50} of 0.24 mg mL^1 positions B.S.CE7 among the most active crude fungal extracts described to date and underscores the under-explored chemical diversity of Indonesian mangrove endophytes.

CONCLUSION

The following conclusions were drawn from this study: ten endophytic fungal isolates were successfully obtained from the roots of Rhizophora apiculata collected in Sidodadi Village, a coastal mangrove region in Lampung, Indonesia. Among these isolates, B.S.CE7 exhibited the strongest haem polymerisation inhibitory activity, with IC_{50} values of 0.24 mg mL^{-1} for the culture filtrate extract and 0.70 mg mL^{-1} for the biomass extract, compared with 0.14 mg mL^{-1} for the chloroquine control. Morphological characterisation identified this isolate as belonging to the genus Aspergillus. Phytochemical screening indicated the presence of alkaloids, flavonoids, saponins, and terpenoids, which are likely responsible for the observed antimalarial activity. These findings highlight mangrove-associated endophytic fungi, particularly isolate B.S.CE7, as promising and sustainable sources of bioactive metabolites for future antimalarial drug discovery.

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