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Phytochemistry, Toxicity, and Antimalaria Activity of Mangrove Plant from Muara Badak Beach, East Kalimantan, Indonesia

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Abstract

This study aimed to determine the secondary metabolite content, toxicity, and antimalarial activity of methanol extracts of mangrove leaves *Avicennia marina*, *Rhizophora mucronata*, and *Sonneratia caseolaris*. Mangrove leaf extraction by maceration using methanol solvent, then qualitative phytochemical test (color test), toxicity test by BSLT method using *Artemia salina*, and antimalarial activity test using *Plasmodium falciparum* strain 3D7 with Giemsa staining microscopic method. The content of secondary metabolite compounds of methanol extracts of the three mangrove leaf species are alkaloids, flavonoids, saponins, phenolic compounds, steroids, triterpenoids and tannins. The toxicity of methanol extract of *R. mucronata* mangrove leaves against *A. salina* is included in the strong category. Meanwhile, the toxicity of *S. caseolaris* is included in the moderate category and *A. marina* is in the weak category. Mangrove species *R. mucronata* and *S. caseolaris* have good activity against *P. falciparum* 3D7 with IC₅₀ values < 30 μg/ml, while *A. marina* shows poor activity against *P. falciparum* 3D7 with IC₅₀ values > 50 μg/ml. Other tissue parts of these three mangrove species still need further exploration for their bioactivity against *A. salina* and *P. falciparum* 3D7.

Keywords: Mangrove plant; Phytochemical; Toxicity; Antimalarial.

INTRODUCTION

Mangrove forests are plant communities located at the confluence of sea and land in tropical and subtropical regions, especially at latitudes 25°N. Various species of mangrove plants can grow and thrive in areas of high salt content, tides, extreme temperatures, strong winds, anaerobic and muddy, and sandy soils morphological adaptations to their environment (Aljaghthmi et al., 2018; Bibi et al., 2018). Indonesia is one of the countries in Asia with the largest mangrove forest with the highest mangrove species diversity in the world. This condition is supported by the geographical location, geological history and typology of the islands, as well as the unique oceanographic characteristics of Indonesia Mangrove forests function to protect coastal areas from damage due to sea water abrasion, keep the coastline stable, as a breeding ground for marine biota such as fish, crabs, and shrimp. Mangrove plants also have various medicinal properties so that mangrove plants are widely used by people in coastal areas as traditional medicines (Joandani et al., 2019; Tefarani et al., 2019).

People in coastal areas have long known and used mangrove plants as traditional medicines, especially to treat; skin diseases, rheumatism, blisters, arthritis, bleeding, asthma, sore throat, eye problems, stomach pain, infections, diabetes, HIV, hepatitis, smallpox, ulcers, diarrhea, malaria, astringent, aphrodisiac, antiulcer, antitumor, snake bite treatment, anti-aging drugs and anticancer. Mangrove plants are utilized in traditional medicine because they contain active chemical compounds. (Lopez et al., 2018; Lalitha et al., 2021; Syamsul E.S., 2022). Active chemical compounds that are thought to act as drugs to fight various diseases are compounds of the alkaloid group, steroids, triterpenes, phenolics compounds compounds, flavonoids. terpenoids, stilbenes. carotenoids, anthocyanins, anthocyanidins, inositol, saponins, long chain alcohols, tannins, amino acids, benzoquinones, coumarins, quinins, chalcones, lipid compounds, phorbol esters, rotenone, polyphenols, benzofurans, limonoids, sulfur procyanidins, gibberellins and xyloccensins (Kartikaningsih et al., 2024; Usman et al., 2023).

Several Indonesian mangrove species such as *S. caseolaris*, *A. marina*, *R. mucronata*, and *R. apiculata* have pharmacological activity as potent abiomicrobials.

A. marina, has activity as an anticancer. A. corniculatum, A. aureum, A. alba, and R. mucronata showed cytotoxic activity against WiDr cancer cells. A. illicifolius, A. marina and E. agallocha showed signifi cant analgesic activity. Other plant species from the family Meliaceae, Rubiaceae, Piperaceae, Acanthaceae, Myrtaceae, and Myrsinaceae, were shown to have antimalarial activity. Then the study reported that Meliaceae and Rhizophorae

have antimalarial activity (Audah et al., 2022; Arbiastutie et al., 2022).

This means that the content of secondary metabolite compounds of mangrove plants *A. marina*, *R. mucronata*, and *S. caseolaris* originating from the coastal beach of Muara Badak District, Kutai Kartanegara Regency, East Kalimantan, has the potential to find bioactive compounds as natural antimalarial alternative medicinal ingredients.







S. caseolaris

R. mucronata

A. marina

Figure 1. Mangrove plant species A. marina, R. mucronata, and S. Caseolaris.

MATERIALS AND METHODS

Materials

The materials used in this study were the mangrove leaf samples of *A. marina*, *R. mucronata*, and *S. caseolaris* species. Phytochemical test reagents include alkaloids, flavonoids, phenolics compounds compounds, steroids, triterpenoids, saponins, and tannins. Methanol solvent, $H_2SO_{4(p)}$ solution, $HNO_{3(p)}$ solution, $HCl_{(p)}$ solution, and DMSO solution, *Artemia salina* shrimp larvae and *P. falciparum* strain 3D7. The instruments used were glassware generally used in the laboratory, analytical balances, vials, aluminum foil, test tube, micro*pipette, measuring flask, volume pipette, aerator, study lamp, mikroskop, and rotary evaporator.

Preparation of sample

The samples used in this study were mangrove species of A. marina, R. mucronata, and S. caseolaris. Samples were taken from the coastal beach, Muara Badak District, Kutai Kartanegara, East Kalimantan. Then, the sample was washed and dried by air drying without direct sunlight. The dried samples were mashed using a blender until they became powder. After obtaining the sample in powder form, the sample was macerated. The sample powder was weighed as much as 500 g, then put into a beaker and added methanol solvent to cover the entire surface of the sample and then covered with aluminum foil. After 24 h, the results of the first maceration can be taken and then macerated again on the sample dregs up to 3 x 24 h. The methanol extract obtained from the first to third maceration was collected and then concentrated using a rotary evaporator to obtain a concentrated

methanol extract of *A. marina*, *R. mucronata* and *S. caseolaris* mangrove leaves (Mitra et al., 2021).

Phytochemical test

A Phytochemical test is a qualitative test carried out by observing the occurrence of color changes after the extract is added to the reagent. Phytochemical tests are carried out to determine the presence or absence of secondary metabolite compounds contained in a sample. In this study, phytochemical tests were carried out to determine the secondary metabolites contained in *A. marina*, *R. mucronata*, and *S. caseolaris* mangrove leaves (Harahap et al., 2021; Akasia et al., 2021).

Alkaloid test

The alkaloid test was carried out by mixing 10 mL of A. marina, R. mucronata, and S. caseolaris mangrove, which was heated, cooled and then filtered. 2 drops of the filtrate were added to the drip plate, 2 drops of Meyer's reagent, Dragendroff's reagent, and Wagner's reagent were added. Observe the color changes that occur. A positive indicator of the alkaloid test on Mayer's reagent is the formation of a white precipitate. The alkaloid test is said to be positive in the Wagner test if there is a brownish/brick red precipitate, and a positive test on the Dragendrof reagent is said to be positive if there is a brownish/brick red/red-orange precipitate.

Phenolics compound test

The phenolics compounds test was carried out by adding 2 drops of *A. marina*, *R. mucronata*, and *S. caseolaris* mangrove filtrate to a drip plate, adding 1% FeCl₃ solution, then observing the color changes. A positive

indicator of the phenol test is the formation of a blueblack color.

Saponin test

The Saponin test was carried out by mixing 2 drops of *A. marina*, *R. mucronata*, and *S. caseolaris* mangrove filtrate into a drip plate. Then 2 mL of distilled water was added, then shaken until a stable foam was formed, then 1 drop of 2N HCl was added. A positive indicator of the saponin test is the formation of a stable foam.

Flavonoid test

Flavonoid test was carried out by mixing 2 drops of *A. marina*, *R. mucronata*, and *S. caseolaris* mangrove filtrate with 5 mL of methanol, then adding a few drops of concentrated HCl and 1.5 g of magnesium powder. A positive indicator of the flavonoid test is the formation of a red color.

Steroid and terpenoid test

Triterpenoid and Steroid tests were carried out by adding 2 drops of the filtrate to the drip plate, then adding one drop of acetic anhydride and one concentrated sulfuric acid (Liebermann Burchard reagent). A positive indicator of the terpenoid test is the formation of a red or purple color and a positive steroid if the solution is blue or green.

Toxicity test against A. salina

The extracts of A. marina, R. mucronata, and S. caseolaris mangrove were prepared as 1000 mg/L mother liquor by dissolving 3.5 g of sample in 50 mL of methanol. The mother liquor was then made into a solution with various concentrations of 125 mg/L, 250 mg/L and 500 mg/L (Khasanah et al., 2020). The next step in the toxicity test using the BSLT method is hatching shrimp larvae. The hatching of eggs is carried out in an artificial aquarium container in the form of a tube, which is assisted by a 5 W incandescent lamp to stimulate the growth of larvae. The medium used to incubate shrimp larvae is artificial seawater, a mixture of distilled water and pure salt. The oxygen level needed during hatching must be more than 3 mg/L, therefore the artificial seawater media must be aired with an aerator. 0.5 mg/mL of yeast was added as a source of nutrition for A. salina. Within 24-36 h, usually the eggs have hatched into larvae called naupli. Active nauplii aged for 48 h are used as test animals in the experiment. Vials were provided for each group according to the concentration level and were repeated 2 times.

The parent solution of *A. marina, R. mucronata*, and *S. caseolaris* mangrove was added to the vial according to the concentration level. The vial containing the test solution was dried until the solvent had evaporated for several days at room temperature in a desiccator so that only the scale remained from the sample extract and no longer smelled of solvent. Then added 2 drops of 1% DMSO to dissolve the sample. After the sample was

dissolved with DMSO, 1 mL of artificial seawater was added, then 10 *A. salina* L shrimp larvae aged 48 h were added to the vial. One drop of yeast (0.6 mg/mL) was put into each vial as food for *A. salina*, then artificial seawater was added to the volume limit of 10 mL. The standard criterion for assessing the mortality of shrimp larvae is if the shrimp larvae do not show movement for a few seconds of observation. The manual method is to observe the larvae in the vial (Kurniawan et al., 2021).

Antimalarial test

Samples of methanol extract of *A. marina*, *R. mucronata*, and *S. caseolaris* mangrove leaves as much as 10 mg were dissolved in 1000 mL 1 % DMSO solution to make a test solution. The resulting test solution was then made into various concentrations by diluting it, so that the obtained concentrations of 100 µg/mL, 50 µg/mL, 10 µg/mL, 1 µg/mL and 0.1 µg/mL, and 0.01 µg/mL. Prepared test parasites that will be used have been synchronized as a ring stage with parasitemia \pm 1% (hematocrit 5%).

A test well (well 96) was prepared, 2 μL of the test solution was added with various concentrations. After that, 198 µL of the parasite was added at each concentration of each test solution. The test was repeated twice (Duplo). The test well is then put into the chamber and given mixed gas as 5% O2, 5% CO2, and 90% N2. Incubated for 2 x 24 h at 37°C. Then, after 2 x 24 h, the cultures were harvested and a thin blood film was prepared with 20% gymnasia staining. Then, data analysis was performed by counting the number of infected erythrocytes per 1000 normal erythrocytes under a microscope. The data is then used to determine the percent growth and percent inhibition. After obtaining the percent inhibition value, the data were analyzed using the SPSS version 20 probit analysis program to obtain the IC₅₀ value, which is the concentration of the test material that can inhibit the growth of parasites by 50% (Wardani et al., 2020).

RESULTS AND DISCUSSION

Result

Phytochemical of Mangrove Plants

Based on the results of phytochemical tests of methanol extracts of mangrove plant leaves (*A. marina, R. mucronata*, and *S. caseolaris*) is known to contain secondary metabolite compounds such as alkaloids, flavonoids, phenol compounds, steroids, triterpenoids, saponins, and tannins. The complete results of the phytochemical test of methanol extracts of the three mangrove leaf species are presented in Table 1.

Table 1. Phytochemical screening of the third mangrove species.

Secondary Metabolite	Methanol Extract of Mangrove Leaf					
Compounds	A. marina	R. mucronata	S. caseolaris			
Alkalaoids	-	+	+			
Flavonoids	-	+	+			
Saponins	+	+	+			
Fenolic compound	+	+	+			
Steroids	-	+	+			
Triterpenoids	+	-	-			
Tannins	+	+	-			

Toxicity against A. salina

Toxicity tests in this study used the Brine Shrimp Lethality Test (BSLT) method to determine the toxicity of methanol extracts from mangrove leaves (*A. marina, R. mucronata*, and *S. caseolaris*) against *A. salina*. The toxicity of methanol extracts of the three mangrove leaf species was determined by calculating IC₅₀ values using SAS probit analysis. LC₅₀ (Lethal Concentration 50%) value is the dose value of a compound that can kill 50% of test animals. The results of calculating the LC₅₀ value

of the three methanol extracts of mangrove leaves are presented in Table 2.

Table 2. The LC₅₀ value and toxicity level of mangrove species *A. marina*, *R. mucronata* and *S. saseolaris*.

Methanol Extract of Mangrove Leaf	LC ₅₀ Value (ppm)	Category Toxicity
A. marina	256,132	Low
R. mucronata	48,165	Strong
S. caseolaris	104,96	Moderate

Antimalarial Activity

The antimalarial test of methanol extracts of mangrove leaves of A. marina, R. mucronata, and S. caseolaris was carried out in vitro with Giemsa staining test method. This test uses P. falciparum strain 3D7. Antimalarial test data were obtained using SPSS probit analysis to determine the IC₅₀ value of the methanol extract of mangrove leaves of A. marina, R. mucronata, and S. caseolaris. The IC₅₀ values obtained are presented in Table 3 and Figure 2.

Table 3, The IC_{50} values of mangrove A. marina, R. mucronata and S. sasseolaris.

Methanol Extract of Mangrove Leaf	Treatment of Concentration Variation (μg/ml)					IC ₅₀ (μg/ml) (μg/ml)	
	100	50	10	1	0,1	0,01	1C ₅₀ (μg/mi) (μg/mi)
A. marina	52,93	45,93	40,23	22,80	10,91	2,36	57,341
R. mucronate	73,04	52,28	37,13	17,59	12,05	6,76	24,118
S. casseolaris	100	63,76	36,32	14,66	9,85	0,24	21,975

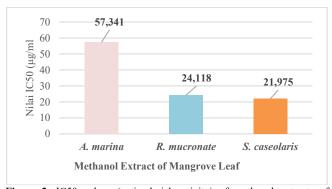


Figure 2. IC50 values (antimalarial activity) of methanol extracts of mangrove leaves of *A. marina, R. mucronata* and *S. caseolaris*.

Discussion Phytochemical

According to Table 1. It is known that the methanol extract of *A. marina* mangrove leaves contains secondary metabolite compounds; saponins, phenolics compounds, triterpenoids, and tannins. *R. mucronata* leaf extract contains compounds; alkaloids, flavonoids, saponins, phenolics compounds, steroids, and tannins. While *S. caseolaris* mangrove leaf extract contains alkaloid compounds, flavonoids-, saponins, phenolics compounds,

and steroids. In the research of Audah et al., (2022) reported that S. caseolaris mangrove leaf extract contains compounds; steroids, flavonoids, and tannins. A. marina leaf extract is; steroids, flavonoids, saponins, and tannins. And R. mucronata leaf extracts are steroids, flavonoids, saponins, and tannins. Then Muhaimin, et al., (2019), stated that the content of secondary metabolite compounds in methanol extracts of S. caseolaris leaves are alkaloids, flavonoids, phenolics compounds, steroids, tannins, quinones, and glycosides. According to Akasia et al., (2021) the secondary metabolite compounds contained in mangrove extracts of S. caseolaris are flavonoids, saponins, phenolics compoundss and steroids. In other studies, it has been reported that the secondary metabolite compounds of R. mucronata are lipids, alkaloids. flavonoids, inositol, triterpene. phenolics compoundss compounds, and tannins (Hardoko et al., 2016; Taniguchi et al., 2018). It was reported that the methanol extract of R. mucronata stem bark has successfully isolated six compounds, including cinchonain Ib, breynioside B, polystachyol, β-sitosterol 3-O-β-D-glucopyranoside, β-sitosterol 3-O-β-D-(6'-Opalmitoyl) glucopyranoside, and β-sitosterol 3-O-β-D-(6'-O-stearoyl) glucopyranoside (Linh et al., 2020).

The difference in the content of phytochemical compounds in the three mangrove plant species may be due to the location of their habitat, where each location of mangrove plant habitat has a different pH value so that it can affect the content of secondary metabolite compounds contained in mangrove plants. Then the solvent used during extraction also affects the content of the compounds obtained (Akasia et al, 2021).

Toxicity

According to the data presented in Table 2, it shows that the methanol extract of *R. mucronata* mangrove leaves has the lowest LC₅₀ value of 48,165 ppm, this shows that the methanol extract of *R. mucronata* mangrove leaves is toxic to *A. salina* with a strong category. While the toxicity of the methanol extract of *S. caseolaris* mangrove leaves has an LC₅₀ value of 104.96 ppm with a moderate category, then the toxicity of the methanol extract of *A. marina* mangrove leaves has an LC₅₀ value of 256.132 ppm with a weak category.

Meyer et al., (1982) stated that the toxicity level of plant extracts can be determined by looking at the LC₅₀ value. If the LC₅₀ value is smaller than 1000 ppm, it is considered toxic, whereas if the LC₅₀ value is higher than 1000 ppm, it is considered non-toxic. Under the Meyer category, it can be declared that the methanol extract of mangrove leaves A. marina, R. mucronata, and S. caseolaris, are toxic to A. salina with an LC₅₀ value of < 1000 ppm. Audah et al. (2022), reported that the water extract of S. caseolaris leaves, ethanol extract of A. marina mangrove leaves, and n-hexane extract of R. mucronata are toxic to A. salina, each with an LC₅₀ value of 229.77 ppm and 160.43 ppm is toxic to A. salina with an LC₅₀ value of 488.93 ppm. Bokshi B. (2020), reported that the ethyl acetate fraction of the stems and the carbon tetrachloride fraction of the leaves of S. caseolaris mangrove showed very strong toxicity properties against A. salina, with LC₅₀ values of 25.0 ± 0.05 and 25.0 ± 0.07 μg/ml, respectively. According to Rozirwan et al. (2022), it was reported that A. marina mangrove leaf extract contains bioactive compounds such as alkaloids, saponins, flavonoids, steroids and steroids which are toxic to A. salina which can be developed for the pharmaceutical field. Based on the Brine Shrimp Lethality Test (BSLT), ethanol, ethyl acetate, and nhexane extracts of R. mucronata mangrove are classified as toxic to A. salina, and the secondary metabolite compounds found in the ethanol extract are terpenoids, alkaloids, ketones, phenols, turpentine oil, essential oils, unsaturated fats, and camphor (Zulfahmi I et al., 2024)

The bioactivity of medicinal plants can be detected by the content of phytochemical compounds in plants. From the results of the phytochemical test, it is known that the methanol extract of *R. mucronata* mangrove leaves contains alkaloids and flavonoids, where the two compounds are known to be toxic because they can work as respiratory tract poisons and even alkaloids can cause stomach poisoning, thus inhibiting the ability of

organisms to eat. At the same time, alkaloid compounds can also block taste receptors in the mouth area of *A. salina* larvae, so that larvae do not get taste stimuli and are unable to recognize their food and as a result *A. salina* larvae die of starvation (Davis et al., 2019).

The three mangrove leaf extracts in this study were positive for saponin compounds. Saponin compounds can affect the life of *A. salina* larvae, because the glycosides contained in saponins can bind oxygen in water, so that the oxygen content in the solution is reduced and as a result the larvae will die from lack of oxygen (Khasanah et al., 2020). While the methanol extract of mangrove leaves *A. marina* does not contain alkaloids and flavonoids, so the level of toxicity is lower than mangrove *R. mucronata* and *S. caseolaris*.

Antimalarial Activity

According to the results obtained (as presented in Table 3 and Figure 3) methanol extracts of mangrove leaves A. marina, R. mucronata, and S. caseolaris can inhibit the growth of P. falciparum strain 3D7 respectively with IC₅₀ values of 57.34; 24.12; and 21.97 μg/mL. According to Gessler, the level of antimalarial activity with in vitro methods can be categorized into 3 groups, namely very good if the IC₅₀ value is $< 10 \mu g/mL$, a fairly good category if the IC₅₀ value is between 10 - 50 μg/mL, and less active of category if the IC₅₀ value is $> 50 \mu g/mL$ (Gessler et al., 1994). Depending on the IC₅₀ value, A. marina mangrove leaf extract has antimalarial activity with less active of category because the IC_{50} value > 50 μg/mL. Meanwhile, methanol extracts of mangrove leaves of R. mucronata and S. caseolaris showed fairly good antimalarial activity with IC50 values between 10- $50 \mu g/mL$.

R. mucronata mangrove plants contain saponin compounds, which can act as an inhibitory mechanism against malaria by forming complexes with cell membranes through hydrogen bonds, thereby damaging the permeability of malaria cell walls and causing death. Saponins are also substances that can hemolyzes blood. Therefore, saponins can hemolyzes malaria cell membranes in the same way as red blood cell membranes (Juniharti et al., 2021; Gunawan*et al., 2018). R. *mucronata* leaf extract also contains alkaloid compounds, where these alkaloid compounds can prevent parasite growth in the blood and prevent the formation of peptidoglycan so as to prevent the formation of cell walls due to cell breakdown. The mechanism of action of alkaloids as antimalarial drugs is to prevent the detoxification of hemiparasites in the food vacuole. Likewise, the leaves of mangrove S. caseolaris also contain saponin compounds, so they act as substances that can hemolyzes blood. The mechanism of flavonoid compounds as antimalarial agents is to block the nutrient channels needed by parasites by forming specific membranes (Uzor P. F, 2020; Variani et al., 2021). However, A. marina mangrove leaf extract does not contain alkaloids and flavonoids, so it does not have

antimalarial activity and has no potential as a malaria herbal medicine.

The accumulation of phytochemical compounds contained in the extracts of mangrove leaves R. mucronata and S. caseolaris can provide antimalarial activity by increasing red blood cell oxidation or inhibiting protein synthesis, thus becoming a factor that influences the antimalarial potential of mangrove plants R. mucronata and S. caseolaris (Ahmed et al., 2010). R. mucronata extract is also known to have antidiabetic, antioxidant, and tissue-enhancing effects that are potentially compared to A. marina (Al-Jaghthmi et al., 2020). In another study it was reported that ethanol extract derived from S. alba leaves showed significant antiplasmodial efficacy in reducing parasitemia levels, inducing significant inhibition percentages, inhibiting Plasmodium growth. Thus, S. alba leaves have the potential to be a promising natural source of antimalarial agents because ethanol extract derived from S. alba leaves has diverse phytochemical constituents that are efficacious as antiplasmodial. (Muhaimin M et al., 2024). Traditional medicine using mangrove skin, bark, fruit, and flowers from the species Lumnitzera littorea. Rhizophora mucronata, Scyphiphora hydrophyllacea, Sonneratia alba, Xylocarpus granatum, and Xylocarpus moluccensis is a popular method used as a malaria drug in people's social life. (Tamalene M.N. et al., 2021).

CONCLUSION

The secondary metabolite compounds contained in the methanol extract of mangrove leaves R. mucronata and S. caseolaris have antimalarial activity against P. falciparum starin 3D7 with a fairly good category including the IC₅₀ value between 10 - 50 µg/ml, hence the two species of mangrove have potential to be developed as a natural antimalarial herbal medicine. The mangrove species A. marina, R. mucronata and S. caseolaris are toxic to A. salina with a strong category (LC₅₀ value < 1000 ppm), Hence that the third species of mangrove can be examined by cancer cells to determine its potential as a natural anticancer medicinal material.

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Conflict of Interest: The authors declare that they have no conflict of interests.

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