Journal of Tropical Pharmacy and Chemistry

Journal homepage: https://jtpc.jurnalfamul.com

Phytochemical, Toxicity, and Antimalarial Activity Methanol Extracts from Mangrove Coastal Beach Muara Badak, East Kalimantan

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Abstract

The purpose of this study was to determine the content of secondary metabolites, toxicity to *Artemia salina*, and antimalarial activity of methanol extracts of *Avicennia marina*, *Rhizophora mucronata*, and *Sonneratia caseolaris* leaves. Extraction of the third mangrove leaf species was done by maceration using methanol solvent. Then phytochemical test to determine secondary metabolite compounds, then toxicity test against shrimp larvae *A. salina* with BSLT method, and Antimalarial activity test in vitro against *Plasmodium falciparum* strain3D7 (chloroquine sensitive) using Giemsa staining microscopic method. Secondary metabolite compounds contained in methanol extracts of the third species of mangrove leaves are alkaloids, flavonoids, saponins, phenolics compounds, steroids, triterpenoids and tannins. The toxicity of the methanol extract from mangrove leaves of *A. Marina*, *R. mucronata* and *S. caseolaris* against *A. salina* is strong category with a LC_{50} value of 256.132 ± 45.63; 48.165 ± 52.25; and 104.96 ± 9.99 ppm respectively. However, the methanol extract of *R. mucronata* leaves was most toxic to *A. salina* due to its lowest LC_{50} value. Mangrove species *R. mucronata* and *S. caseolaris* showed activity against *P. falciparum* 3D7 in a fairly good category with IC_{50} values < 50 µg/ml, while the activity of mangrove species *A. marina* against *P. falcifarum* 3D7 included unfavorable category with IC_{50} value > 50 µg/ml. The other tissue parts of the third mangrove plant species still need to be further explored regarding their bioactivity against *A. salina* and *P. falciparum* 3D7.

Keywords: Toxicity, and Antimalarial, Mangrove plant, East Kalimantan

Received: 15 August 2023 **Accepted**: 30 June 2025

DOI: https://doi.org/10.25026/jtpc.v9i1.592

How to Cite:

Usman, U., Masruhim, M. A., Rahmadani, A., Aziz, A., 2025. Phytochemical, Toxicity, and Antimalarial Activity Methanol Extracts from Mangrove Coastal Beach Muara Badak, East Kalimantan. *J. Trop. Pharm. Chem.* **9**(1). 24-32. **DOI**: https://doi.org/10.25026/jtpc.v9i1.592

1 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 with morphological adaptations to their environment [1-3]. Indonesia is one of the countries in Asia that has 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 [4-5] 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.

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, and anticancer. The utilization of mangrove plants as traditional medicine is because mangrove plants contain active chemical compounds [6-9]. 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 [10-13].

Several Indonesian mangrove species such as *S. caseolaris*, *A. marina*, *R. mucronata*, and *R. apiculata* have pharmacological activity as potent abiomicrobials. [14]. *A. marina*, has activity as an anticancer [15-16]. *A. corniculatum*, *A. aureum*, *A. alba*, and *R. mucronata* showed cytotoxic activity against WiDr cancer cells [17]. *A. illicifolius*, *A. marina* and *E. agallocha* showed signifi cant analgesic activity [18-19]. Other plant species from the family *Meliaceae*, *Rubiaceae*, *Piperaceae*, *Acanthaceae*, *Myrtaceae*, and *Myrsinaceae*, were shown to have antimalarial activity [20]. Then in the study reported that *Meliaceae* and *Rhizophorae* have antimalarial activity [6].

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.

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

2 Materials and Methods

2.1 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.

2.2 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 [21].

2.3 Phytochemical Test

Phytochemical test is a qualitative test that is 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 of *A. marina, R. mucronata,* and *S. caseolaris* mangrove leaves [22-23].

2.3.1 Alkaloid Test

The alkaloid test was carried out by mixing 10 mL of *A. marina, R. mucronata,* and *S. caseolaris* mangrove which was heated then cooled and then filtered. Added 2 drops of the filtrate into the drip plate and then added 2 drops of Meyer's reagent, Dragendroff's reagent, and Wagner's reagent. 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.

2.3.2 Phenolics compounds 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, then adding 1% $FeCl_3$ solution, then observing the color changes. A positive indicator of the phenol test is the formation of a blue-black color.

2.3.3 Saponin Test

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.

2.3.4 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.

2.3.5 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 [23].

2.4 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 [24]. 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 with the aim of stimulating the growth of larvae. The medium used to incubate shrimp larvae is artificial seawater, which is 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 that have been 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 all of the solvent had evaporated for several days at room temperature in a desiccator so that only 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 [25].

2.5 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 l % 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 are parasites that have been synchronized in the form of a ring stage with parasitemia ± 1% (hematocrit 5%).

A test well (well 96) was prepared, then 2 µL of the test solution was added with various concentrations. After that, 198 µL of 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 mix gas in the form of 5% O_2, 5% CO_2, and 90% N_2. Incubated for 2×24 h at 37°C. Then, after 2×24 h, the cultures were harvested and a thin blood film was prepared with 20% gymnaa 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 by 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% [26].

3 Results and Discussion

3.1 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.

Tabel 1. Phytochemical screening of the third mangrove species

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

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., [14] 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., [27] 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, 23 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 alkaloids, flavonoids, lipids, inositol, triterpene, phenolics compoundss compounds, and tannins [21], [28-29]. 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'-O-palmitoyl) glucopyranoside, and β-sitosterol 3-O-β-D-(6'-O-stearoyl) glucopyranoside [30].

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 at the time of extraction also affects the content of the compounds obtained [23].

3.2 Toksisitas Terhadap 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 from the calculation of IC_{50} values using SAS probit analysis. LC_{50} (Lethl Concentration 50%) value is the dose value of a compound that can kill 50% of test animals. The results of the calculation of the LC_{50} value of the three methanol extracts of mangrove leaves as presented in Table 2.

Table 2. The LC_{50} value and toxicity level of mangrove spesies *A. marina, R. mucronata* and *S. sasseolaris*.

Methanol Extract of Mangrove Leaf	LC_{50} Value (ppm) ± SD	Level of LC_{50} Value
A. marina	256,132 ± 45,63	High
R. mucronata	48,165 ± 52,25	Low
S. caseolaris	104,96 ± 9,99	Moderate

According to the data presented in Table 2, shows that the methanol extract of mangrove leaves *R. mucronata* has a low LC_{50} value of 48,165 ± 52.25 ppm, this means that the methanol extract of mangrove leaves *R. mucronata* is the most toxic to *A. salina* compared to methanol extract of mangrove leaves *S. caseolaris* and *A. marina*, respectively with LC_{50} values of 104.96 ppm and 256.132 ppm.

Meyer et al., [31] stated that the toxicity level of plant extracts can be determined with a look at the LC_{50} value. If the LC_{50} value is smaller than 1000 ppm, it is considered toxic, whereas if the LC_{50} 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 LC_{50} value of < 1000 ppm. Audah et al., [16] 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 LC_{50} value of 229.77 ppm and 160.43 ppm is toxic to *A. salina* with an LC_{50} value of 488.93 ppm.

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. While 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 [32].

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 [24]. 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*.

3.3 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 IC_{50} value of the methanol extract of mangrove leaves of *A. marina, R. mucronata*, and *S. caseolaris*. The IC_{50} values obtained are presented in Table 3.

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)
	100	50	10	1	0,1	0,01	
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

According to the results obtained (as presented in Table 3) methanol extracts of mangrove leaves *A. marina, R. mucronata*, and *S. caseolaris* can inhibit the growth of *P. falciparum* strain 3D7 respectively with IC_{50} 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 IC_{50} value < 10 µg/mL, a fairly good category if the IC_{50} value between 10 - 50 µg/mL, and less active of category if the IC_{50} value > 50 µg/mL [33]. Depending on the IC_{50} 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 a fairly good antimalarial activity with IC_{50} values between 10-50 µg/mL.

R. mucronata mangrove plants contain saponin compounds, where saponin compounds 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 [34-35]. *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 by blocking the nutrient channels needed by parasites by forming specific membranes. 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 [36-38].

The accumulation of phytochemical compounds contained in mangrove leaf extracts of *R. mucronata* and *S. caseolaris* can exert antimalarial activity by increasing red blood cell oxidation or by inhibiting protein synthesis so

that it becomes a factor affecting the antimalarial potential of mangrove plant species *R. mucronata* and *S. caseolaris* [39-40].

4 Conclusions

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 IC_{50} 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 (LC_{50} 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.

5 Declarations

5.1 Acknowledgments

We acknowledge, Institute of Tropical Disease (ITD) Airlangga University, Chemistry Education Laboratory, and Pharmacy Laboratory of Mulawarman University for all the support to carry out work.

5.2 Author Contributions

The names of the authors listed in this journal contributed to this research.

5.3 Conflicts of Interest

The authors declare that they have no conflict of interests.

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