J Herbmed Pharmacol. 2025; 14(1): 104-111.

http://www.herbmedpharmacol.com doi: 10.34172/jhp.2025.52806

Journal of Herbmed Pharmacology

Antibacterial efficacy of fruit extracts from three mangrove species: *Rhizophora mucronata, Sonneratia alba,* and *Sonneratia caseolaris* against multidrug-resistant (MDR) isolates derived from clinical specimens

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ARTICLE INFO

Article Type:
Original Article

Article History:
Received: 6 October 2024
Accepted: 11 December 2024
epublished: 25 December 2024

Keywords:
Antibacterial activity
Rhizophora mucronata
Sonneratia alba
Sonneratia caseolaris
Multidrug resistance bacteria

ABSTRACT

Introduction: The emergence of multidrug-resistant (MDR) bacteria poses a significant challenge to public health, necessitating the exploration of alternative antimicrobial agents. This study investigates the antibacterial activity of fruit extracts from *Rhizophora mucronata*, *Sonneratia alba*, and *Sonneratia caseolaris* against MDR isolates derived from clinical specimens.
Methods: Antibacterial activity was assessed against multiple multidrug-resistant bacterial strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA) strain sa1, vancomycin-resistant *Enterococcus* (VRE) strain ef1, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) strain ps1, and extended-spectrum beta-lactamase (ESBL) *Escherichia coli* strain ec1. The antibacterial efficacy was determined using an agar-based well diffusion test to ascertain the zone of inhibition. Microdilution was assessed to ascertain the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values. Standard procedures were used to screen for plant phytochemicals (terpenoid, alkaloid, flavonoid, tannin, and saponin).
Results: An ethanol extract of mangrove fruit exhibited antibacterial activity against MRSA, VRE, CRPA, and ESBL-*Escherichia coli*, producing an inhibitory zone diameter of 3-24 mm at 10 and 20 mg/mL, with MIC and MBC values exceeding 20 mg/mL. Specifically, *Sonneratia alb*a was effective against MRSA and VRE with MIC and MBC values ≥10 mg/mL. *Sonneratia caseolaris* was effective against CRPA and ESBL-*Escherichia coli* with MIC and MBC values ≥5 mg/mL Phytochemical identification results showed the presence of terpenoids, alkaloids, flavonoids, tannins, and saponins in all three extracts.
Conclusion: The fruit extracts examined have antibacterial activity against MDR isolates. Additional studies are required to isolate and characterize the specific bioactive substances that generate these effects.

Implication for health policy/practice/research/medical education:
This in vitro research demonstrated the antibacterial ability of mangrove fruits from *R. mucronata, S. alba,* and *S. caseolaris* against multidrug-resistant (MDR) bacteria derived from clinical specimens. Therefore, they might be good alternative treatments for infectious diseases caused by MDR bacteria. Future studies should investigate the mechanisms behind the observed antibacterial effects of mangrove fruits to enhance their application as natural antimicrobial agents against MDR bacteria. Additionally, exploring the optimal active compounds and dosages could further optimize these compounds' efficacy in clinical settings.
Please cite this paper as: Prastiyanto ME, Wardoyo FA. Antibacterial efficacy of fruit extracts from three mangrove species: *Rhizophora mucronata, Sonneratia alba,* and *Sonneratia caseolaris* against multidrug-resistant (MDR) isolates derived from clinical specimens. J Herbmed Pharmacol. 2025;14(1):104-111. doi: 10.34172/jhp.2025.52806.

Introduction

Since their discovery in the early 1900s, antibiotics have saved countless lives. However, the concerning growth of antibiotic resistance has eclipsed the history of antibiotics (1). In developing countries, including Indonesia, antibiotics can be purchased without a doctor's

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prescription, and excessive use of antibiotics and not according to the rules can cause resistance (2). Antibiotic resistance has become a serious issue not only in Indonesia (3) but also in the world, and each year it causes a large number of deaths. Patients with multidrug-resistant (MDR) bacterial infections have a higher risk of death due to the difficulty of treatment. Infections produced by MDR bacteria incur greater treatment expenses than those initiated by non-resistant bacterial strains (4). It has been claimed that over 2.8 million cases of antibiotic-resistant infections happen across the United States each year, with over 35 000 reported death instances (5). Multi-drug resistant cases in Indonesia are above 50% (2).

Multidrug-resistant is considered when gram-positive and gram-negative bacteria are resistant to three or more classes of antibiotics (6). Some MDR bacteria that commonly infect humans include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum beta-lactamase *Escherichia coli* (ESBL *E. coli*), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) (7). MRSA is a *S. aureus* resistant to methicillin-type antibiotics; this was first described in the 1960s and further discussed in the last decade as a cause of nosocomial infections (8). MRSA can induce several infections, involving pneumonia and osteomyelitis, as well as severe conditions related to sepsis and infective endocarditis (9). The overall global prevalence of MRSA is 14.69% (10). VRE has become a challenge to manage in hospitals. They can cause various infections, most commonly urinary tract infections, intra-abdominal infections, bacteremia, or endocarditis (11).

Another bacterium that has become resistant to antibiotics is CRPA. CRPA refers specifically to strains of *P. aeruginosa* that are resistant to carbapenems, which poses significant challenges in treatment due to the limited effectiveness of available antibiotics against these strains (12). ESBL *E. coli*, an enzyme produced by *E. coli* bacteria has caused problems in healthcare systems. The rising numbers of ESBL-producing bacteria is due to the enhanced utilization of antibiotics, including penicillin, cephalosporins, and monobactams (13). *β-Lactams* are frequently used antibiotics given to fight against infections, resulting in many resistant bacteria to β-Lactam medicines, including *E. coli* bacteria (14). Therefore, it is essential to develop effective treatment options, including natural antibacterial medicines derived from biological sources. Natural anti-MDR bacterial agents can derived from marine (15,16), mushroom (17), and plants (18,19). One of the natural ingredients that can be used as a source of antibiotics is mangrove fruit. Mangrove fruit comes from the *Sonneratiaceae* family. Mangrove plants, particularly *Rhizophora mucronata*, *Sonneratia alba*, and *Sonneratia caseolaris*, have been recognized for their potential antibacterial properties. However, there remains a notable gap in research specifically focusing on the fruit extracts of these species against MDR bacteria. Various parts of mangrove plants exhibit antibacterial properties. For instance, extracts from *Avicennia marina* have shown effectiveness against several bacterial strains, including *E. coli* and *S. aureus* (20). Similarly, the bark extracts of *S. caseolaris* have been noted for their antimicrobial efficacy against both Gram-positive and Gram-negative bacteria (21). This research examines the antibacterial efficacy of fruit extracts from three mangrove species (*R. mucronata, Sonneratia alba,* and *S. caseolaris*) against MDR isolates found in clinical specimens.

Materials and Methods

Collection of mangrove fruit

The subjects in this study were three species of mangrove fruit (*R. mucronata*, *S. alba*, and *S. caseolaris*) (Figure 1). *R. mucronata* mangrove fruits were obtained from the Grand Maerakaca area, Semarang, Central Java, Indonesia, and *S. alba* and *S. caseolaris* mangrove fruits were obtained from the Morosari Demak Mangrove Forest, Central Java, Indonesia. The three types of samples collected were mangroves with scientific names identified by the government as protected mangrove forest areas. The trees had fresh, not mushy, and not rotten fruits.

Mangrove fruit extraction

The extracting process of mangrove fruits was conducted utilizing the maceration technique with 96% ethanol. The three types of fresh mangrove fruits were washed, cut into small pieces, and dried in the sun (22). After that, dried fruits were ground using a blender to produce a fine powder. The mangrove fruit powder was put into 96% ethanol solvent for 3 × 24 hours (every 24 hours a new solvent was replaced), filtered using Whatman filter paper number 1, concentrated using a rotatory evaporator at a temperature below 40 °C, and then using a water bath to obtain a thick extract. The extract obtained was then collected and stored at room temperature (23)

Preparation of test bacteria

MDR bacteria were obtained from the patients of Dr. Kariadi Hospital, Semarang City, Indonesia. Wound swabs and urine specimens were collected according to known protocols, inoculated onto blood agar and MacConkey agar (both from Merck, Darmstadt, Germany), and incubated overnight at 37 ± 2 °C. The bacterial colonies were identified through colony type, margin, elevation, size, shape, and color. Using the VITEK®2 Compact (bioMérieux, Craponne, France) equipment, all isolates were identified, and the resistance pattern was assessed. The MDR bacteria used in this study are shown in Table 1.

Wound swabs and urine specimens were collected according to known protocols, inoculated onto blood agar and MacConkey agar (both from Merck, Darmstadt, Germany), and incubated overnight at 37±2 °C. Then, they were scratched on oblique HIA media, incubated at 37 °C for 24 hours, and stored in the refrigerator as a

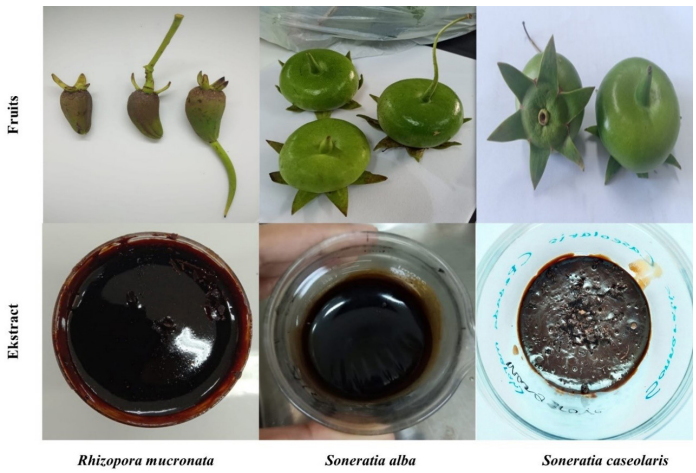

Figure 1. Mangrove fruits and extracts of *Rhizophora mucronata*, *Sonneratia alba*, and *Sonneratia caseolaris*.

stock of bacteria. The colonies were suspended in a test tube containing 0.95% NaCl (physiological), using an inoculating needle and then homogenized. The turbidity of the suspension was equated with standard McFarland 0.5 solution (1.5×10^8 cells/mL).

Antibacterial activity tests

The activities of mangrove ethanol extracts antibacterial agents were evaluated by two methods of diffusion and microdilution tests (19,24).

Diffusion method

MRSA, VRE, CRPA, and ESBL *E. coli* bacteria were cultivated on blood agar plates for 24 hours at 35 ± 2 °C. All MDR bacteria were standardized to a 0.5 McFarland standard (1.5×10^8 colony-forming units [CFU]/mL). Each one of the MDR bacteria was grown on MHA media by using a sterile cotton swab. After 5 minutes, the medium was punctured with a cork borer (0.5 cm in diameter). Two concentration variations were made, namely 10 mg/mL and 20 mg/mL. The resulting extract was solubilized in dimethyl sulfoxide (DMSO). Each well received 100 µL of the extract at varying concentrations, followed by incubation at 35±2 °C for 16-20 hours. Positive controls included vancomycin and oxacillin for MRSA bacteria, vancomycin, and ampicillin for VRE-*E. faecalis*, meropenem and ceftriaxone for CRPA, and meropenem and ampicillin for ESBL-*E. coli* bacteria. The incubation results were observed for the presence of an inhibition zone formed and measured using a caliper.

Dilution method

Determination of minimum inhibitory concentration (MIC)

Mueller-Hinton broth (MHB) was employed to ascertain the MIC. In this test, 100 µL of MHB was added to each well on a microwell plate. 100 µL of mangrove fruit extract was added to the first well, followed by a series of dilutions until it reached the 12th well. After diluting the three mangrove fruit extracts, 10 µL (0.5 McFarland; 1.5 × 108 CFU/mL) was added to each well, except for the negative control, and incubated at 35±2 °C for 18-20 hours. After incubation, the MIC value was determined by observing the color change on the microwell plates and compared with the controls.

Determination of minimum bactericidal concentration (MBC)

Determination of MBC value was carried out by

Table 1. The organisms used for in vitro antibacterial screening in this study

Species and strain	Common name of MDR bacteria	Source	Antibiotic resistance
Staphylococcus aureus sa1	MRSA	Wound	Ciprofloxacin, benzylpenicillin, gentamicin, oxacillin, levofloxacin, nitrofurantoin, moxifloxacin, sulfamethoxazole
Enterococcus faecalis ef1	VRE	Urine	Ciprofloxacin, gentamicin, levofloxacin, streptomycin, vancomycin, erythromycin, tetracycline,
Pseudomonas aeruginosa pa1	CRPA	Wound	Cefazolin, ampicillin, sulbactam, ceftazidime, tazobactam, gentamicin, aztreonam, meropenem, cefepime, tigecycline, nitrofurantoin, amikacin, ciprofloxacin, sulfamethoxazole
Escherichia coli ec1	ESBL *Escherichia coli*	Urine	Ciprofloxacin, ampicillin, tazobactam, sulbactam, cefepime, ceftazidime, cefazolin, gentamicin, ceftriaxone, sulfamethoxazole

MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL, Extended-spectrum beta-lactamase.

subculturing each well on blood agar plate media for 16-20 hours at a temperature of 35 ± 2 °C. The MBC value was determined by observing the growth of bacterial colonies on blood agar plate media. The lowest concentration of mangrove fruit extract showing MDR bacteria unable to grow was the MBC value of the extract.

Phytochemical screening of the extract

The analysis for terpenoid, alkaloid, flavonoid, tannin, and saponin of the crude extracts of *R. mucronata*, *S. alba*, and *S. caseolaris* fruits was carried out using the previously described methods (25). To assess the presence of flavonoids, 1.0 mL of 10% lead acetate was introduced to 1.0 mL of the extract in a test tube. The occurrence of a yellow precipitate was considered indicative of flavonoids. To assess the presence of tannins, 5.0 g of extract was combined with 10 mL of distilled water. The mixture was filtered and the ferric chloride reagent was introduced to the filtrate. A blue-black precipitate was judged positive for tannins. Saponin levels were determined by shaking 0.5 g of dry extract with water in a test tube. Frothing that remained during heat was utilized to detect the presence of saponins. Terpenoids were tested by evaporating 0.5 mL of the dried extract in a water bath and then heating it with 3 mL of concentrated sulfuric acid in a water bath for ten minutes. The creation of a grey color indicated the presence of terpenoids.

Results

The results of the study on the antibacterial activity of the ethanol extract of mangrove fruits on the growth of MRSA, VRE, CRPA, and ESBL *E. coli* bacteria indicated that the zones of inhibition ranged from 3 to 24 mm at concentrations of 10 and 20 mg/mL (Table 2). These results showed that the extracts of the three mangrove fruits had anti-MDR bacterial activity.

The result of microdilution concentrations for each of the three extracts remained ≤20 mg/mL for all tested MDR bacteria (Table 3). The fruit extract of S. alba showed superior efficacy compared to the other two extracts against gram-positive MDR bacteria (MRSA and VRE) (Figure 2), with MIC and MBC values of 5 and 10 mg/mL for MRSA. Meanwhile, in VRE bacteria, the MIC and MBC value was 5 mg/mL. The fruit extract of S. caseolaris showed superior efficacy compared to the remaining two extracts against gram-negative MDR bacteria (CRPA and ESBL-*E. coli*) (Table 3 and Figure 2), with the MIC and MBC values of 5 mg/mL against CRPA and ESBL-*E. coli*.

Table 2. The diameters of the inhibitory zones of the mangrove fruit extract

Mangrove extract and antibiotic	Concentration (mg/mL)	Average inhibition zone diameter (mm)			
		Gram-positive		Gram-negative	
		MRSA	VRE-*E. faecalis*	CRPA	ESBL-*E. coli*
Rhizophora mucronata	10	13	12	13	13
	20	14	17	15.5	14
Sonneratia alba	10	8	11	3	7
	20	10	19	7	10
Sonneratia caseolaris	10	17	14	16	15
	20	19	24	17	16
Vancomycin 30 µg		25	0	-	-
Oxacillin 1 µg		0	-	-	-
Meropenem 10 µg		-	-	0.6	20
Ceftriaxone 30 µg		-	-	0	-
Ampicillin 10 µg		-	14	-	0
DMSO		0	0	0	0

MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE-*E. faecalis* Vancomycin-resistant Enterococcus strain; CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-*E coli*: Extended-spectrum beta-lactamase *Escherichia coli*; DMSO: Dimethyl sulfoxide.
Vancomycin, oxacillin, meropenem, ceftriaxone, and ampicillin were used as positive controls.

Table 3. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) for the ethanol extracts from mangrove fruits (mg/mL)

	MRSA		VRE		CRPA		ESBL-*E. coli*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
Rhizophora mucronata	20	20	20	20	5	10	5	20
Sonneratia alba	5	10	5	5	10	10	10	20
Sonneratia caseolaris	10	10	20	10	5	5	5	5
DMSO	0	0	0	0	0	0	0	0

MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE-*E. faecalis* Vancomycin-resistant Enterococcus strain; CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-*E coli*: Extended-spectrum beta-lactamase *Escherichia coli*; DMSO: Dimethyl sulfoxide.

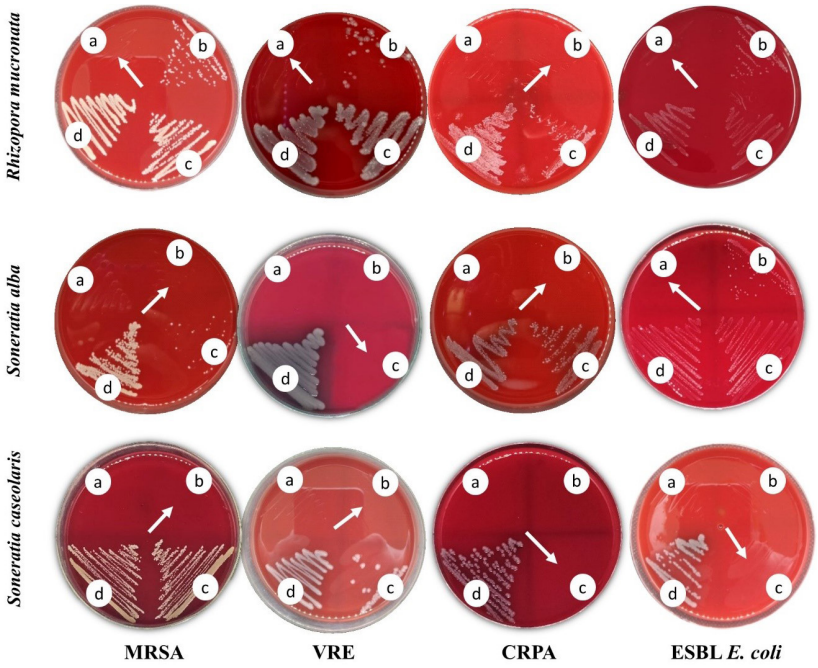

Figure 2. Minimum bactericidal concentration (MBC) of the ethanol extracts from three mangrove fruits against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant (VRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and extended-spectrum beta-lactamase *Escherichia coli* (ESBL-*E coli*). Concentrations: (a) 20 mg/mL, (b) 10 mg/mL, (c) 5 mg/mL, (d) 2.5 mg/mL. White arrow: MBC value; Blue box: Mangrove fruit extract with the smallest MBC value against multidrug-resistant (MDR) bacteria.

The phytochemical test of mangrove extract showed that the three extracts contained bioactive compounds like flavonoids, terpenoids, tannins, alkaloids, and saponins (Table 4).

Discussion

The extracts of the three mangrove fruits had anti-MDR bacterial activity. Previous studies have shown that 50 mg/mL of methanol extract from *S. caseolaris* fruits had the strong antibacterial activity on *E. coli, S. aureus,* and *B. subtilis* (26). Our study used MDR bacteria while previous studies used standard bacteria. In addition, the inhibition zone in this study showed a better diameter, namely at a concentration of 20 mg/mL, showing an inhibition zone between 7 and 24 mm against the tested MDR bacteria. This study used ethanol solvent while the previous study used methanol solvent. The ethanol solvent is more semi-polar than the methanol solvent, allowing the active compounds in mangrove fruits to dissolve more. This is in line with previous studies that bilimbi fruit extract with ethanol solvent resulted in a wider diameter of inhibition zone against MDR bacteria than methanol solvent (7)

Our study showed that the concentration of microdilution assay of the three mangrove fruit extracts was ≥20 mg/mL against all MDR bacteria tested. Previous studies reported that the ethanolic extract of *S. alba* leaves produced a MIC value of 3.26 µg/mL against *S. aureus* (non-MDR) bacteria (27). The results of previous studies yielded better scores. This was possible because the test bacteria used were non-MDR strains of bacteria (non-MDR *S. aureus*).

Sonneratiaceae plants are rich in tannins, which are known to play a role in antimicrobial activity (28). Several secondary metabolites were also found in mangroves, including alkaloids, phenolics, steroids, and terpenoids. These compounds were identified from several parts of parts, such as stems, fruits, leaves, and roots (29). According to research by Wonggo et al (30), mangrove leaves contain bioactive compounds, namely flavonoids, tannins, saponins, and steroids. Tannins have been discovered to inhibit bacterial growth through a variety of mechanisms, such as iron chelation, disruption of the cell membrane, inhibition of fatty acid biosynthetic pathways, and inhibition of cell wall synthesis (31). Flavonoids

Table 4. The outcomes of the phytochemical investigation of fruit extracts

Fruit extract	Phytochemicals content				
	Terpenoids	Alkaloids	Flavonoids	Tannins	Saponins
Rhizophora mucronata	+	+	+	+	+
Sonneratia alba	+	+	+	+	+
Sonneratia caseolaris	+	+	+	+	+

exhibit antimicrobial properties against various pathogens, including bacteria, through mechanisms that bind to DNA, inhibiting replication processes and ultimately leading to cell death (32). Saponins can engage with lipids. Proteus lipopolysaccharides contribute to the increased permeability of the bacterial cell wall due to their detergent-like qualities, which damage the outer membrane of bacteria (33). It has been demonstrated that natural alkaloids can disrupt the bacterial cell membrane (33), influence the DNA function, and inhibit protein synthesis (34) in studies on the antibacterial mechanism. Thus, natural alkaloids are potentially active against various bacteria.

The findings from this study underscore the potential of mangrove fruit extracts as effective alternatives to conventional antibiotics in treating infections caused by MDR bacteria. The significant antibacterial activity observed, particularly against MRSA, VRE, CRPA, and ESBL-*E.coli*, indicates that these natural compounds could be crucial in addressing the growing issue of antibiotic resistance in clinical settings. This research contributes to the broader understanding of plant-based antimicrobials and their potential integration into treatment protocols for resistant infections. It is particularly relevant in regions like Indonesia where antibiotic resistance is a pressing public health concern.

Despite the promising results, there are several limitations to consider. The study primarily focused on ethanolic extracts; thus, other extraction methods or solvents may yield different antibacterial profiles. Furthermore, this research was conducted under laboratory conditions; therefore, further studies are needed to evaluate the effectiveness of these extracts in vivo. The specific bioactive compounds responsible for the observed antibacterial effects were not isolated or characterized in this study, which limits understanding of their mechanisms of action.

Future research should aim to isolate and characterize the specific bioactive compounds in the mangrove fruit extracts that contribute to their antibacterial properties. Investigating these compounds' mechanisms of action against MDROs could provide insights into their therapeutic potential. Additionally, conducting in vivo studies will be essential to assess the efficacy and safety of these extracts in clinical applications. Expanding research to include other mangrove species and different parts of the plants may also reveal a broader spectrum of antimicrobial activity.

Conclusion

This study highlights the significant antibacterial activity of ethanol extracts from mangrove fruits against various MDR bacterial strains. The results indicate that species such as *S. alba* and *S. caseolaris* may serve as valuable sources for developing new antimicrobial agents to combat antibiotic resistance. Given the urgent need for alternative treatment options in light of rising MDRO prevalence, further exploration into mangrove-derived compounds is warranted to harness their full potential in clinical applications.

Acknowledgment

The authors would like to thank Universitas Muhammadiyah Semarang for funding the research through the Institutional Research Grant for completing this study. The authors would also like to congratulate Julianita Luria Pongmakamba, Meishella Ratna Amelia, and Nur Afnun Febrikayanti from the Department of Medical Laboratory Technology, Universitas Muhammadiyah Semarang, Indonesia, for their assistance in collecting mangrove samples.

Authors' contribution

Conceptualization: Fandhi Adi Wardoyo.
Data curation: Muhammad Evy Prastiyanto.
Formal analysis: Muhammad Evy Prastiyanto.
Funding acquisition: Fandhi Adi Wardoyo.
Investigation: Fandhi Adi Wardoyo.
Methodology: Muhammad Evy Prastiyanto.
Project administration: Fandhi Adi Wardoyo.
Resources: Muhammad Evy Prastiyanto.
Software: Muhammad Evy Prastiyanto.
Supervision: Fandhi Adi Wardoyo.
Validation: Fandhi Adi Wardoyo.
Visualization: Muhammad Evy Prastiyanto.
Writing–original draft: Muhammad Evy Prastiyanto.
Writing–review & editing: Fandhi Adi Wardoyo.

Conflict of interests

The contributors assert the absence of any conflict of interest.

Ethical considerations

The contributors have fully committed to ethical standards, including the avoidance of plagiarism, data manipulation, and multiple publications.

Funding/Support

This research was funded by the University of Muhmmadiyah Semarang, Indonesia. However, no grant number was provided.

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