Short Communication:

Extraction and Characterization of Phenolic Compounds from the Stem Bark of *Sonneratia caseolaris* (Lythraceae) and Their Potential Antibacterial Activity

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Abstract: *The ethyl acetate fraction separated from the stembark of* Sonneratia caseolaris *retrieved three phenolic compounds, including quercetin-3-O-glucoside (**1**), quercetin (**2**), and 1-O-(2,4-dihydroxybenzoyl)-β-D-glucopyranose (**3**). For the first time, compounds **1** and **3** were discovered from* Sonneratia *genus. Data from various spectroscopic techniques, including mass spectroscopy and one- and two-dimensional NMR, were used to identify their chemical structures. Antibacterial activity has also been assessed for all compounds against* Staphylococcus aureus *ATCC 25175 and* Streptococcus mutans *ATCC 6538. Compounds **1–3** displayed varying levels of antibacterial activity against* S. aureus *and* S. mutans. *However, all compounds exhibited lower efficacy compared to the control, with their minimum inhibitory concentration (MIC) values ranging from 71.25 to greater than 100 μg/mL. This study provides a foundation for optimizing* S. caseolaris *phenolic compounds as antibacterial agents and highlights the need for comparative studies within the* Sonneratia *genus to identify potent bioactive candidates through structural modification or synergistic approaches.*

Keywords: *antibacterial activity; phenolic compounds;* Sonneratia caseolaris*;* Staphylococcus aureus*;* Streptococcus mutans

■ INTRODUCTION

The set of phytochemical groups known as phenolic compounds is commonly isolated from higher plants and is of interest due to its potential medical uses. Numerous bioactivities, including antioxidant, antimutagenic, antibacterial, antiviral, hepatoprotective, anti-inflammatory, anticancer, and antidiabetic properties, have been linked to the phenolic groups [1-3]. Indonesia is one of the mangrove resources that contribute significantly to coastal ecosystems and provide rich biodiversity, including various types of secondary metabolites that have great potential in the field of pharmacology. *Sonneratia* is a genus of mangrove plants that grow in many places in Africa, South Asia, China, Southeast Asia, Indonesia, Australia, Papua New Guinea, and Hawaii. Several plants from this genus were used as traditional medicines to treat various illnesses in South Asia, China, and Southeast Asia [4-7].

Due to its unique metabolic system and biological environment adaption, *Sonneratia* has evolved features such as salt secretion mechanisms, roots, and high

osmotic pressure. *Sonneratia* can generate unique secondary metabolites and endure in a harsh environment [8]. Several extracts of the *Sonneratia* genus have been published and showed a diversity of chemical contents, like terpenoids [8], flavonoids [9-10], lignans [11], alkaloids, and phenolic compounds [12]. This genus also showed various bioactivities, such as antimicrobial, antidiabetic, liver-protective, antioxidant, and antitumor [8,13]. *Sonneratia caseolaris is* one species of the *Sonneratia* genus widely dispersed in Asia mangroves, particularly in Indonesia. Prior study of this species indicates that pyranones and peptides have been identified [14-15]. Reports on the phenolic chemicals found in this species are scarce. To investigate the antibacterial activity of the Indonesian *Sonneratia* plants, we extracted, elucidated, and evaluated the antibacterial activity of three discovered phenolic compounds.

■ EXPERIMENTAL SECTION

Materials

The plant sample used was the stem bark of *S. caseolaris,* which was obtained from the mangrove area in Batu Putih Village, Grabak District, Tuban Regency, East Java, Indonesia, in September 2011. This plant specimen had been recognized in the Biology Department's Plant Taxonomy Laboratory at the Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran. The specimen sample (0808F) was stored in the Laboratory. Various technical solvents were employed, including methylene chloride, *n*-hexane, acetone, methanol, and ethyl acetate. The chromatographic techniques were used for the separation steps, including vacuum liquid chromatography using G_{60} silica gel, column chromatography using 70–230 and 230–400 mesh silica gel, and reversed-phase column chromatography on Fuji Sylisia Chromatorex octadecyl silane (ODS) RP_{18}. GF_{254} and RP-18 silica gel plates (0.25 mm) were utilized for thin-layer chromatography (TLC), while GF_{254} silica gel from Merck was used for preparative TLC. Then, 10% sulfuric acid in ethanol was utilized as the staining reagent. Mutant bacterial species such as *Staphylococcus aureus* ATCC 25175 and *Streptococcus mutans* ATCC 6538 were selected for the antibacterial activity test to explore specific resistance mechanisms that may impact the antibacterial efficacy of phenolic compounds.

Instrumentation

The types of equipment used such as glassware commonly found in organic chemistry labs, a R-200 Buchi rotary evaporator with a Vac V-500 Buchi vacuum pump and a B-490 Buchi water bath, open chromatography columns of varying lengths and diameters, a Vilbert Luomart ultraviolet (UV) lamp (λ 254 and 365 nm). The melting point was determined using A Fisher-John micro melting apparatus. ATAGO AP-300 automatic polarimeter was utilized to determine the optic rotation. JEOL JMS-500 spectrometer was used to record the nuclear magnetic resonance (NMR) spectra with chemical shift (δ) in parts per million (ppm) and tetramethylsilane (TMS) as a standard. The ultra-performance liquid-chromatography mass spectrometry (UP-LC MS/MS) was performed to measure the mass spectrum using a Waters Acuity System, and high-resolution time-of-flight mass spectrometry (HR-TOF ESI-MS) was measured using Waters Xevo QTOF MS. The IR spectra were supported by Fourier transform Infrared Spectroscopy (FTIR) spectrophotometer Spectrum One Perkin Elmer.

Procedure

Extraction and isolation

The stembark powder of *S. caseolaris* (4.9 kg) was successively extracted with *n*-hexane, ethyl acetate, and methanol at room temperature. Each obtained extract was then concentrated under low pressure, resulting in *n*-hexane (145.0 g), ethyl acetate (295.5 g), and methanol extracts (435.5 g). The antibacterial activity of each extract was evaluated against the Gram-positive bacteria *S. aureus* and *S. mutans*. Extracts showing significant antibacterial activity were further separated using chromatography techniques guided by antibacterial tests. Vacuum liquid chromatography (VLC) was used to separate a fraction of the ethyl acetate extract (15.00 g) on a silica gel G_{60} stationary phase and a 10% (v/v) *n*-hexane-ethyl acetate gradient mobile phase, resulting in four main fractions (A-D), combined based on TLC analysis and guided by antibacterial tests. Column

chromatography was used to separate fraction B (1.20 g) further using a stationary phase of silica gel (70–230 mesh) and an *n*-hexane:ethyl acetate mobile phase (9.5:0.5), resulting in three fractions (B1-B3). Fraction B2 (0.32 g) was further separated using column chromatography on a stationary phase of ODS with a mobile phase of methanol:water (8:2), yielding three fractions (B2a-B2c). Fraction B2b (0.12 g) was further separated using RP-18 silica gel, reverse phase, with a mobile phase of methanol: water (1:1), yielding compound **3** (9.50 mg). The separation of compounds from fraction C (1.80 g) was carried out using column chromatography on a stationary phase of silica gel (70–230 mesh) with a mobile phase of *n*-hexane:ethyl acetate (9:1), resulting in three main fractions (C1-C3). Fraction C1 (0.12 g) was further separated using column chromatography on a stationary phase of silica gel GF_{254} with a mobile phase of *n*-hexane: ethyl acetate (9:1), yielding compound **1** (19.50 mg) in the form of a yellow solid. Fraction C2 (0.15 g) was further separated using column chromatography on a stationary phase of silica gel GF_{254} with a mobile phase of *n*-hexane:ethyl acetate (8:2), yielding compound **2** (20.50 mg) in the form of a yellow solid (The flowchart can be seen in Fig. 1).

Compound 1. Yellow solid; UV (MeOH) λ_{max} nm: 260 (ε 5600). FTIR (KBr) ν_{max} cm^{-1}: 3445, 2945, 1645, 1495, 1445, 1385, and 1036. ^{1}H-NMR (acetone-d_6, 500 MHz) δ_H (ppm) and ^{13}C-NMR (acetone-d_6, 125 MHz) δ_C (ppm) data are shown in Table 1, UP-LC MS/MS: *m/z* 463.4243 $[M+Na]^+$, calculation for $C_{21}H_{20}O_{12}$, *m/z* 464.4143.

Compound 2. Yellow solid; UV (MeOH) λ_{max} nm: 254 (ε 6200), 380 (ε 7200). FTIR (KBr) ν_{max} cm^{-1}: 3409, 3210, 1664, 1661 and 1015. ^{1}H-NMR (acetone-d_6, 500 MHz) δ_H (ppm) and ^{13}C-NMR (acetone-d_6, 125 MHz) δ_H (ppm) data are shown Table 1. UP-LC MS/MS: *m/z* 301.0355 $[M-H]^+$ calculation for $C_{15}H_{10}O_7$, *m/z* 302.0415.

Compound 3. Pale yellow solid; UV (MeOH) λ_{max} nm: 203 (ε 3990), 318 (ε 4000) and 332 (ε 3920). UV (MeOH+NaOH) λ_{max} nm (ε): 203 (4490), 334 (3920), FTIR (KBr) ν_{max} cm^{-1}: 3451, 2945, 1752, 1632, 1495, 1425 and 1385 and 1036. ^{1}H-NMR (CD_3OD, 500 MHz) δ_H (ppm) and ^{13}C-NMR (CD_3OD, 125 MHz) δ_C (ppm) data are shown Table 1. HR-ESI TOF-MS: *m/z* 397.1223 $[M+H]^+$, calculation for $C_{13}H_{16}O_9$, *m/z* 396.1123.

Antibacterial activity assay

Antibacterial activity testing of all compounds (**1**–**3**) against *S. aureus* and *S. mutans* was done by dilution method [16-17]. The minimum inhibitory concentration (MIC) was measured by meat water microdilution assay in 96-well microtiter plates. Meat

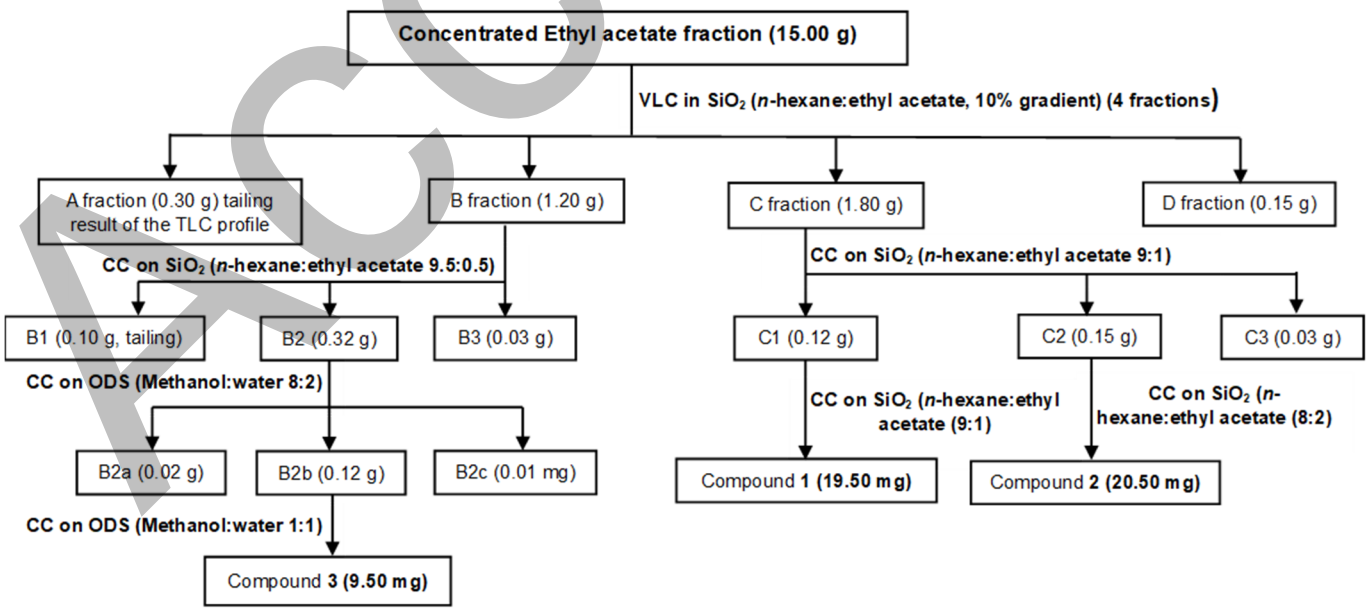

Fig 1. The flowchart of the separation and isolation process of compounds **1**–**3** from the ethyl acetate extract of *Sonneratia caseolaris*

water cultures were kept overnight with each test organism (10 µL) added to each well at decreasing concentrations from 1000–75 µg/L. The plate was incubated for 24 h at 35 ± 1 °C, and 1% chlorhexidine solution was used as an indicator of microbial growth. The MIC value was determined at the lowest concentration of the compound that inhibited the growth of the test organism.

■ RESULTS AND DISCUSSION

Since the ethyl acetate extract of *S. caseolaris* stem bark showed good efficacy against both *S. mutans* and *S. aureus*, it was chosen for further investigation of its secondary metabolite chemicals. Three phenolic compounds were produced using column chromatography to separate and purify this extract. The yellow solid form of compound **1** was afforded, and the molecular formula of compound **1** was specified as $C_{21}H_{20}O_{12}$ based on the UP-LC-MS/MS spectrum of *m/z* 463.4143 $[M+Na]^+$; thus, compound **1** has 12 degrees of unsaturation. The UV spectrum of compound **1** denoted maximum absorption at λ_{max} 260 and 380 nm (ε 5600 and 7200); these absorption peaks are typical for flavonoid compounds with the occurrence of a bathochromic shift due to the addition of sodium hydroxide shear reagent showed the presence of free hydroxyl groups in the flavone skeleton [18]. The IR spectrum (Fig. S1) of compound **1** denoted the presence of absorption bands derived from the hydroxyl group (3445 cm^{-1}), conjugated carbonyl (1640 cm^{-1}), the double bond of the aromatic ring (1390 cm^{-1}) and ether group (1060 cm^{-1}). This prediction was supported by ^{1}H-NMR spectrum (Fig. S2), which denoted the presence of aromatic proton signals located at the *meta*-position at δ_H 6.20 and 6.39 ppm, three ABC-type aromatic protons at δ_H 7.58 and 7.69 and 6.87 ppm, and six oxygenated methine protons of the sugar group at δ_H 5.25, 3.34, 3.47, 3.42, 3.21, 3.71, and 3.57 ppm. The ^{13}C-NMR spectrum showed the appearance of 21 carbon signals detailed by DEPT 135° (Fig. S3) and HMQC (Fig. S4) spectra, as one conjugated carbonyl carbon at δ_C 179.6 one anomeric carbon at δ_C 100.0, five sp^2 CH, nine sp^2 C_q and five oxygenated sp^3 CH. Eight of the twelve degrees of unsaturation were determined to be functionality; the flavonol-glucoside skeleton made up the other four degrees of unsaturation [19-20]. ^{1}H-^{1}H COSY and HMBC tests (Fig. 2) were carried out to ascertain the location of functional groups and partial structure in compound **1**, and the findings were shown in (Fig. S5 and S6). The two aromatic protons at δ_H 6.86 and 7.58 ppm mismatched with each other and correlated with C-4' δ_C 150.0 and C-1' δ_C 123.2 ppm, while the aromatic proton at δ_H 7.69 correlated with carbons δ_C C-3' 146.0 and C-1' 123.2 ppm, suggesting that the two hydroxyl groups on the flavonol skeleton C ring were at positions C-3' and C-4'. The aromatic proton at δ_H 6.19 correlated with carbons δ_C C-5/7/9 163.2/166.3/158.6, suggesting that the other two hydroxyl groups appeared at C-5 and C-7 in ring B. The anomeric proton at δ_H 5.25 correlated with carbons C-3/2", indicating that the sugar group is bound at C-3. The NMR comparison of compound **1** with quercetin-3-*O*-glucoside showed very high agreement. Thus, compound **1** was identified as quercetin-3-*O*-glucoside (Fig. 3, Table 1). The stereochemistry of the sugar group in compound **1** is in accordance with quercetin-3-*O*-glucoside based on the comparison of the value of the matching constant (*J*) in the ^{1}H-NMR spectrum. For the first time, compound **1** was isolated from the *S. caseolaris*.

Compound **2**'s chemical formula, as revealed by the UP-LC-MS/MS spectrum, is $C_{15}H_{10}O_7$ (*m/z* 301.0355); thus, compound **2** has eleven degrees of unsaturation. UV spectrum (methanol) λ_{max} 254 and 380 nm (ε 6200 and 7200), these absorption peaks are typical for flavonoid compounds with flavone skeleton [18]. The IR

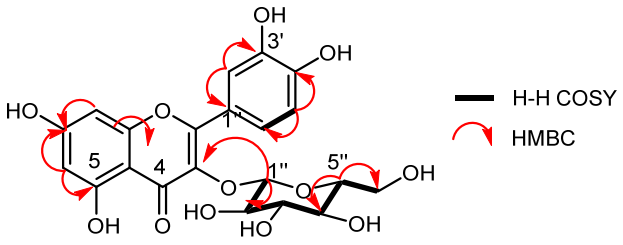

Fig 2. Selected HMBC and ^{1}H-^{1}H-COSY correlations of compound **1,** isolated from *Sonneratia caseolaris* stem bark (acetone-d_6), highlighting structural features that support the compound identification

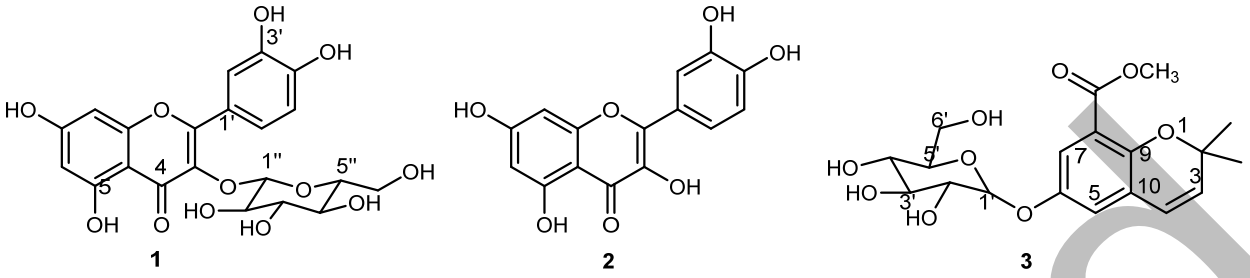

Fig 3. Chemical structures of isolated phenolic compounds **1**–**3** from *S. caseolaris*, displaying key functional groups relevant to their antibacterial properties

Table 1. Detailed NMR data for compounds **1** (quercetin-3-*O*-glucoside), **2** (quercetin), and **3** (1-*O*-(2,4-dihydroxybenzoyl)-β-D-glucopyranose), isolated from ethyl acetate extract of *S. caseolaris* stem bark, acetone-d_6 (for compounds **1** and **2**) and CD_3OD (for compound **3**) at 500 MHz for ^1H and 125 MHz for ^{13}C

Carbon	Compounds				Carbon		
	1		**2**			**3**	
	δ_C (mult.)	δ_H (ΣH, mult., *J*=Hz)	δ_C (mult.)	δ_H (ΣH, mult., *J*=Hz)		δ_C (mult.)	(ΣH, mult., *J*=Hz)
1	-	-	-	-	1	-	-
2	159.1	-	157.8	-	2	77.2	-
3	135.8	-	136.8	-	3	128.4	7.42 (1H, d, 7.2)
4	179.0	-	176.6	-	4	118.0	7.38 (1H, d, 7.0)
5	163.2	-	162.4	-	5	115.8	7.52 (1H, d, 2.5)
6	100.0	6.27 (1H, d, 2.5)	99.2	6.27 (1H, d, 2.5)	6	148.0	-
7	166.3	-	165.0	-	7	114.2	7.74 (1H, dd, 2.5, 6.2)
8	94.8	6.52 (1H, d, 2.5)	94.5	6.52 (1H, d, 2.5)	8	114.3	-
9	158.6	-	148.4	-	9	148.4	-
10	105.8	-	104.2	-	10	115.6	-
1'	123.2	-	121.5	-	11	28.5	1.32 (3H, s)
2'	117.6	7.83 (1H, d, 2.2)	116.2	7.83 (1H, d, 2.2)	12	27.2	1.25 (3H, s)
3'	116.1	-	116.0	-	1"	100.1	4.12 (1H, d, 7.5)
4'	150.0	-	147.0	-	2"	72.7	4.05 (1H, dd, 9.0, 9.5)
5'	146.0	7.00 (1H, d, 8.5)	145.8	7.00 (1H, d, 8.5)	3"	70.1	3.87 (1H, dd, 7.5, 9.5)
6'	123.3	7.69 (1H, dd, 2.2, 8.5)	124.0	7.69 (1H, dd, 2.2, 8.5)	4"	68.4	3.80 (1H, dd, 8.5, 9.5)
1"	104.4	5.25 (1H, d, 7.5)			5"	66.3	3.86 (1H, m)
2"	78.5	3.34 (1H, dd, 9.0, 9.5)			6"	63.2	3.71 (2H, dd, 5.5,12)
3"	75.8	3.47 (1H, dd, 7.5, 9.5)			C=O	167.5	-
4"	71.3	3.42 (1H, dd, 8.5, 9.5)			OCH_3	51.8	3.90 (3H, s)
5"	78.2	3.21 (1H, m)					
6"	62.7	3.71 (1H, d, 12.0), 3.57 (1H, d, 12.0)					

Compounds **1**–**2** (acetone-d_6 at 500 MHz for ^1H and 125 MHz for ^{13}C)
Compound **3** (CD_3OD at 500 MHz for ^1H and 125 MHz for ^{13}C)

spectrum (Fig. S7) of compound **2** denoted the appearance of absorption bands derived from OH (3409 cm^{-1}), C=O conjugated (1664 cm^{-1}), and C=C of the aromatic ring (1611 cm^{-1}), and C–O (1015 cm^{-1}). The proton and carbon DEPT NMR spectra (Fig. S8 and S9) showed that compound **2** was similar to compound **1**. Based on the ^{13}C-NMR spectrum, this compound has 15 carbons consisting of one conjugated carbonyl at δ_C 176.6, five methine sp^2 carbon signals, and nine quaternary sp^2 carbons. Eight of the eleven total degrees of unsaturation are considered occupied by these functional groups; the remaining three degrees of unsaturation are associated with the flavonol skeleton without sugar groups. Based on these spectra and

comparison with the literature, compound **2** was a quercetin compound (Fig. 3, Table 1) [21].

Using the HR-ESI TOF-MS spectrum, compound **3** (9.5 mg) was recovered as a pale yellow solid whose molecular formula was determined to be $C_{19}H_{24}O_9$. As shown in Fig. S10 (*m/z* 397.1223 $[M+H]^+$, the calculation for $C_{19}H_{24}O$, *m/z* 396.1123); thus, compound **3** has eight degrees of unsaturation. The UV spectrum of compound **3** gave absorption at λ_{max} (methanol); 203, 318, and 332 nm (ε 3990, 4000, and 3920), signifying the existence of a conjugated system on the benzene ring [18]. The UV spectrum of compound **3** underwent a bathochromic shift with the addition of sodium hydroxide shifting reagent, indicating an extension of the conjugation caused by the benzenoid system. The FTIR spectrum (Fig. S11) showed the presence of absorption bands derived from hydroxyl groups, carbonyl esters, *gem*-dimethyl, conjugated double bonds, and ethers groups at 3410, 1752, 1632, 1385, 1236, and 1036 cm^{-1}, respectively.

This analysis was utilized using the ^{1}H-NMR spectrum (Fig. S12), which showed a tertiary methyl signal at δ_C 1.59 (2 × CH_3), two olefinic proton signals at δ_H 5.98 and 6.88, two aromatic proton signals at the *meta*-position at δ_H 6.89 and 7.23, one methoxy proton signal at δ_H 3.90 (3H, s), and proton-proton signals of sugar groups at δ_H 4.12, 4.05, 3.87, 3.80, 3.86, 3.79 and 3.54 ppm. Spectra of C and DEPT supported the analysis in which this compound denoted the presence of 19 carbon signals detailed by DEPT experiments 135° (Fig. S13) as a carbonyl ester signal at δ_C 167.5, four methine sp^2 carbon signals at δ_C 111.4, 114.5, 115.8 and 115.2, three quaternary sp^2 carbons at 127.2 and 123.3, two oxy-aryl carbons at 146.9 and 148.0, one methoxy carbon signal at 51.8, two tertiary carbon signals at C 21.2 and 20.2 and six carbon signals derived from sugar groups at 100.1, 72.7, 70.1, 68.4, 66.3, and 63.2 ppm. The functionality was calculated as five out of a total of eight degrees of unsaturation. The remaining three degrees of unsaturation correspond to the skeleton of the benzopyran compound bound with sugar groups [22-23]. Comparison of NMR data of compound **3** with the benzopyran-2,2-dimethyl-6-β-D-glucopyranose-8-carboxylate compound showed very high agreement. Thus, compound **3** was identified as a 1-*O*-(2,4-dihydroxybenzoyl)-β-D-glucopyranose and isolated from this *S. caseolaris* for the first time.

Based on Table 2, compound **2** outperformed compounds **1** and **3** in terms of activity against both *S. aureus* and *S. mutans*, with MIC values of 71.25 and 98.89 µg/mL, respectively, according to the findings of testing the three phenolic compounds. When quercetin-3-*O*-glucoside (**1**) bound sugar groups and quercetin (**2**) did not contain sugar groups, the antibacterial evaluation against *S. aureus* and *S. mutans* revealed that flavonoid compound groupings did not exhibit antibacterial characteristics. On the other hand, 1-*O*-(2,4-dihydroxybenzoyl)-β-D-glucopyranose (**3**) is a phenolic derivative that lacks antibacterial action and has sugar groups. These findings suggested that the appearance of sugar in the structure of flavonoids and phenolic derivatives may lessen their antibacterial effects.

Furthermore, these findings align with previous studies on other *S.* species, which have identified phenolic compounds as the key bioactive components. For example, triterpenoids and flavonoids derived from *S. alba* have exhibited varying antibacterial and anti-inflammatory activity, thereby underscoring the genus's potential as a source of therapeutic compounds [7]. On the other hand, the study's limitation is the moderate

Table 2. The antibacterial activity results of compounds **1**–**3** against *S. aureus* and *S. mutans*

Compounds	MIC (µg/mL)	
	S. aureus	*S. mutans*
Quercetin-3-*O*-glucoside (**1**)	86.50	100>
Quercetin (**2**)	71.25	98.89
1-*O*-(2,4-dihydroxybenzoyl)-β-D-glucopyranose (**3**)	100>	100>
Chlorohexidine (+)	5.00	5.00

antibacterial efficacy observed compared to standard antibiotics. Future studies could focus on structural modifications or the removal of sugar moieties to enhance activity. Testing across a broader range of bacterial strains, including those with varied resistance profiles, could yield more comprehensive insights.

■ CONCLUSION

Three phenolic compounds, quercetin-3-*O*-glucoside (**1**), quercetin (**2**), and 1-*O*-(2,4-dihydroxybenzoyl)-β-D-glucopyranose (**3**) were isolated from ethyl acetate extract of the stem bark of *Sonneratia caseolaris*. Compounds **1** and **3** were reported from this genus for the first time. Compounds **1**–**3** were trailed for their antibacterial activity against *Staphylococcus aureus* and *Streptococcus mutans*. Compound **2** had the highest activity among the phenolic compounds, while compound **3** showed the lowest activity. Because the presence of the sugar group reduced the MIC value, one of the phenolic compounds found has the potential to be a drug that fights bacteria. This can be developed as a target molecule by studying a mechanism that could lead to the discovery of new medicines.

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■ CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

■ AUTHOR CONTRIBUTIONS

Conceptualization, Harizon, Siska Elisahbet Sinaga, Unang Supratman; methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, Harizon, Dikdik Kurnia, Dadan Sumiarsa, Tati Herlina, Siska Elisahbet Sinaga, Yoshihito Shiono, Mohamad Nurul Azmi; visualization, supervision, project administration, Siska Elisahbet Sinaga, Yoshihito Shiono, Mohamad Nurul Azmi, Unang Supratman. All authors have read and agreed to the final version of the manuscript.

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