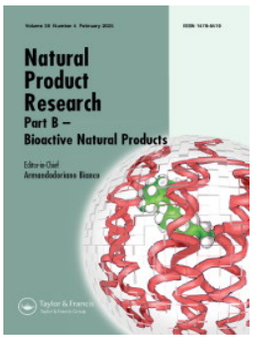


Taylor & Francis
Taylor & Francis Group

Natural Product Research

Formerly Natural Product Letters

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/gnpl20

Semisynthesis and biological activities of derivatives of cyclocommunol from *Artocarpus altilis* fruit peel

Syamsurizal, Arash Samadi, Samuel Tanoeyadi, Muhammad Amin, Leigh E. Skala & Taifo Mahmud

To cite this article: Syamsurizal, Arash Samadi, Samuel Tanoeyadi, Muhammad Amin, Leigh E. Skala & Taifo Mahmud (27 Feb 2025): Semisynthesis and biological activities of derivatives of cyclocommunol from *Artocarpus altilis* fruit peel, Natural Product Research, DOI: 10.1080/14786419.2025.2472277

To link to this article: https://doi.org/10.1080/14786419.2025.2472277

NATURAL PRODUCT RESEARCH
https://doi.org/10.1080/14786419.2025.2472277

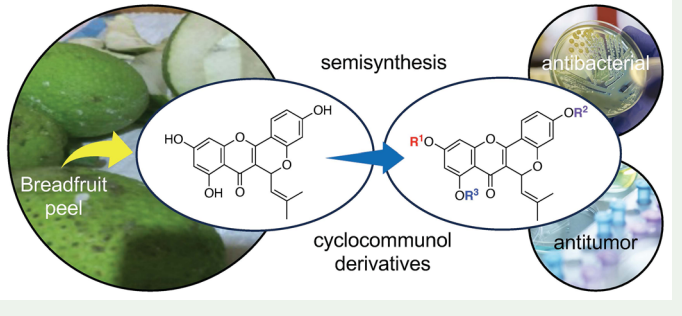
Semisynthesis and biological activities of derivatives of cyclocommunol from *Artocarpus altilis* fruit peel

Syamsurizal[a,b], Arash Samadi[b], Samuel Tanoeyadi[b], Muhammad Amin[b], Leigh E. Skala[b] and Taifo Mahmud[b]

[a]Department of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi, Indonesia; [b]Department of Pharmaceutical Sciences, Oregon State University, Corvallis, OR, USA

ABSTRACT

Artocarpus altilis (breadfruit) is an economically important species of the Moraceae family found throughout the tropics. While breadfruit pulp is widely used and processed into various food products, the peel waste is currently underutilised. Our chemical study of breadfruit peel has led to the isolation of the major constituent cyclocommunol (**1**). Using **1** as the starting material, we synthesised nine cyclocommunol derivatives (**2**–**10**) and tested their antibacterial and antitumor activities. Compounds **1**, **3, 4**, and **9** have weak antibacterial activity against several Gram-(+) and Gram-(–) bacteria. In addition, compounds **7** and **9** showed moderate cytotoxicity against the MCF-7 breast cancer cell line, whereas compound **4** showed comparable cytotoxicity against the NCI-H460 lung cancer cell line. The study showed that the underutilised breadfruit peel waste may be used as a source of compounds with pharmaceutical potential.



ARTICLE HISTORY
Received 5 June 2024
Accepted 20 February 2025

KEYWORDS
Artocarpus altilis; cyclocommunol; semi-synthesis; antibacterial; antitumor

1. Introduction

Artocarpus plants are a group of trees and shrubs belonging to the Moraceae family commonly found in Southeast Asia and the Pacific. They produce many phenolic compounds, such as prenylated flavonoids (Chen et al. 1993; Lan et al. 2013), many

CONTACT Syamsurizal syamsurizal68@gmail.com; Taifo Mahmud taifo.mahmud@oregonstate.edu
Supplemental data for this article can be accessed online at https://doi.org/10.1080/14786419.2025.2472277.

of which were reportedly to have biological activities, including potent antioxidant, anti-inflammatory, antitumor, antifungal, and/or antibacterial activities (Soifoini et al. 2021; Jalal et al. 2022; Dada et al. 2023). In addition, they also produce lectins, steroids and triterpenes (Jagtap and Bapat 2010; Soifoini et al. 2021). One of the widely distributed *Artocarpus* plants is breadfruit (*A. altilis*), which has been used as a food crop for over 3000 years in Oceania, and currently is grown in 90 countries (Turi et al. 2015). The fruit contains high amounts of carbohydrates, phosphorus, and calcium (Mehta et al. 2023); therefore, it is commonly processed into various food products and snacks. The leaf and fruit extracts have been reported to have good antibacterial activities against various bacteria, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus mutans* and *Enterococcus faecalis* (Pradhan et al. 2013). The methanol (MeOH) extract of the pulp, which contains a high amount of quercetin, has been shown to induce apoptosis in several cancer cell lines including human breast cancer MCF-7 cells (Jalal et al. 2019). While breadfruit pulp is widely used and processed into various food products, the peel waste, which contains about 40% starch, is currently underutilised. It is either discarded or used as animal feed (Ragone 2011). To this end, we explored the potential of breadfruit peel as a source of bioactive compounds. Our preliminary study showed that the ethyl acetate (EtOAc) extract of breadfruit peel has moderate antibacterial activities against several bacteria. While the fruit peel has been reported to contain several different types of polyphenols (Soifoini et al. 2021), the active constituents of the peel with antibacterial activity were unknown. Here we report the isolation and identification of the major antibacterial compound in breadfruit peel, as well as the synthesis of nine derivatives of the natural product and the evaluation of their antibacterial and antitumor activities.

2. Results and discussion

To explore the potential of breadfruit peel to be a source of bioactive compounds, we prepared various extracts of the peel and examined their antibacterial activity. Briefly, the breadfruit peel was dried and pulverised, and the powder was extracted with MeOH. The MeOH extract was then partitioned successively with *n*-hexane, dichloromethane (CH_2Cl_2), EtOAc, and water (H_2O) to yield *n*-hexane, CH_2Cl_2, EtOAc, and H_2O extracts. Each extract was evaluated for their antibacterial activity against *Propionibacterium acnes, P. aeruginosa*, and *Staphylococcus epidermidis*. The results showed that only the EtOAc extract had moderate antibacterial activity against all three tested bacteria at a concentration of 20 mg/mL with *S. epidermidis* being the most sensitive and *P. acnes* being the least sensitive strains (Figure 1). The EtOAc extract was then fractionated by SiO_2 vacuum liquid chromatography (VLC) with a gradient eluent of *n*-hexane–EtOAc, EtOAc, and MeOH to afford 5 fractions. The major fraction (EA-4) was subsequently purified by SiO_2 column chromatography with gradient eluent of *n*-hexane–EtOAc to give **1** (174 mg, 0.017% from dried peel).

Compound **1** was isolated as a yellow powder. Its HRESIMS showed a characteristic molecular ion peak $[M+H]^+$ at *m/z* 353.1019 (calc. *m/z* 353.1018) representing a molecular formula of $C_{20}H_{17}O_6^+$. The ^{1}H NMR spectrum of **1** (Tables S1 and S2) showed resonances of two methyl groups at δ_H 1.70 (3H, s) and 1.96 (3H, s) and two doublets at δ_H 5.49 (1H, d, J = 9 Hz) and 6.21 (1H, d, J = 9 Hz), suggesting the presence of a

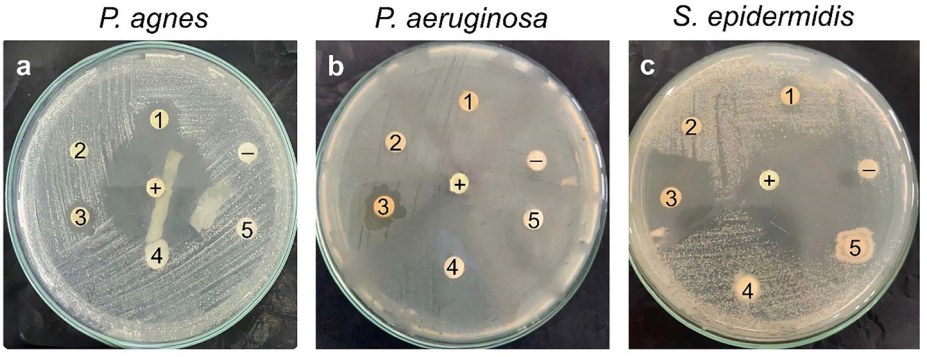


Figure 1. Agar-based disc diffusion assay of breadfruit peel extracts against several bacteria. (a) *Propionibacterium acnes*; (b) *Pseudomonas aeruginosa*; and (c) *Staphylococcus epidermidis*. (1) MeOH extract; (2) *n*-hexane extract; (3) EtOAc extract; (4) CH_2Cl_2 extract; (5) H_2O extract; (+) positive control: tetracycline was used for *P. acnes and P. aeruginosa*, whereas chloramphenicol for *S. epidermidis*; (–) negative control (MeOH).

prenyl group attached to a tertiary carbon. Three aromatic proton resonances were observed at δ_H 6.45 (d, $J = 2$ Hz), 6.65 (dd, $J = 2$ and 8 Hz) and 7.73 (d, $J = 8$ Hz) as well as two singlets at δ_H 6.27 (*s*) and 6.54 (*s*), indicating the presence of a 1,2,4-trisubstituted and a 1,2,3,5-tetrasubstituted benzene moieties. The ^{13}C NMR spectrum of **1** showed resonances of 20 carbons, which based on the chemical shifts and HSQC correlations were predicted to belong to a prenylated flavonoid. Further 2D NMR analysis, including HMBC and NOESY, suggested that **1** is a 4′,5,7-trihydroxy prenylated flavonoid, cyclocommunol (Figure 2). The chemical structure of **1** was subsequently confirmed by comparing the data with those reported in the literature (Tables S1 and S2) (Lin and Sheh 1992; Sengul et al. 2009). Cyclocommunol (**1**) was first isolated from *Artocarpus communis* (Lin and Sheh 1992). It has been reported to have antibacterial and antitumor activities against several cancer cell lines. Cyclocommunol reportedly kills cells *via* a caspase-dependent apoptotic manner, down-regulation of the phosphorylation/expression of Akt/mTOR and Mcl-1, generation of reactive oxygen species, and/or induction of autophagy (Soifoini et al. 2021). To explore the therapeutic potential of its derivatives, we synthesised nine cyclocommunol derivatives (**2**-**10**) (Figure 2) and tested their antibacterial and antitumor activities.

Compound **2** was synthesised from **1** by reacting it with methyl iodide in the presence of K_2CO_3 (Noviany et al. 2021). The trimethyl product (55% yield) was purified chromatographically and the chemical structure was confirmed by NMR and HRESIMS. The HRESIMS of **2** showed a molecular ion peak $[M+H]^+$ at *m/z* 395.1493, which is 42 atomic mass units higher than that of **1**. The ^1H NMR spectrum of **2** (in $CDCl_3$) showed three methoxy proton resonances at δ_H 3.94 (3H, s), 3.92 (3H, s), and 3.84 (3H, s) (Table S3), whereas the ^{13}C NMR spectrum also showed three methoxy carbon resonances at δ_C 56.4, 55.8, and 55.6 (Table S4), consistent with the methylation of all three free hydroxy groups in **1**.

Compounds **3** and **4** were synthesised from **1** by esterification with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP). The reaction gave **3** (7,4′-diacetyl cyclocommunol) (*m/z* 437.1229) and **4** (5,7,4′-triacetyl cyclocommunol) (*m/z* 479.1331) in 35% and 65%, respectively. The products were separated by SiO_2 column

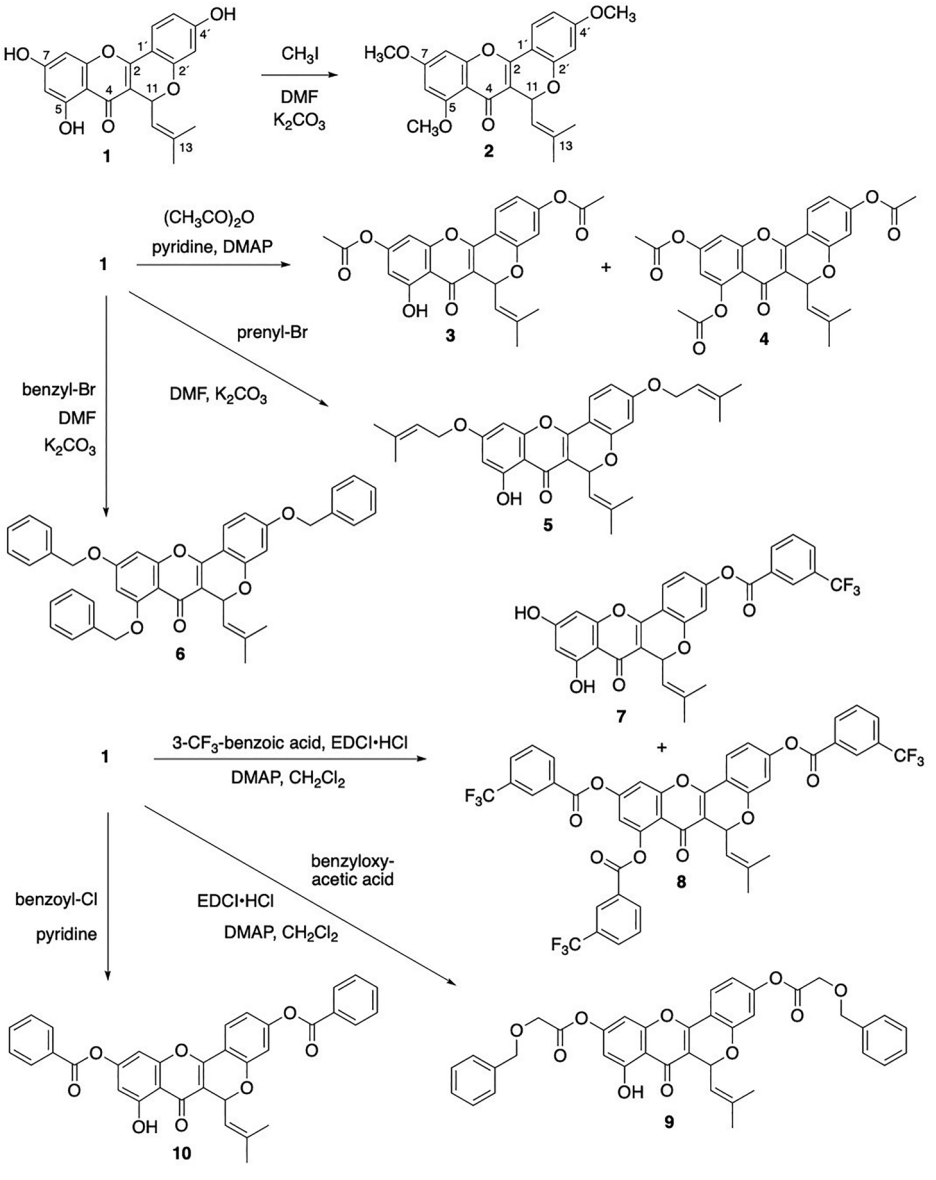


Figure 2. Chemical structure of cyclocommunol and synthetic schemes to derivatives **2**–**10**.

chromatography using hexane-EtOAc (4:1) as a mobile phase. The structures of compounds **3** and **4** were assigned based on comparisons of their ^{1}H and ^{13}C NMR data with those of **1**. The less sterically hindered C-7 and C-4′ hydroxy groups seem to be more susceptible to modifications than the C-5 hydroxy group. In addition, the hydrogen bonding between the C-5 hydroxy group (δ_H ~12.7) and the neighbouring ketone is expected to reduce the reactivity of the hydroxy group.

Compound **5** was prepared by treating **1** with prenyl bromide and K_2CO_3 to give 7,4′-diprenyl cyclocommunol (**5**) (*m/z* 489.2270) in 68% yield. The positions of the substituents at C-7 and C-4′ are consistent with those observed in compound **3**. Compound **6** was synthesised by treating **1** with benzyl bromide in the presence of

K_2CO_3 in 98% yield. The reaction went smoothly, and a fully substituted product (*m/z* 623.2439) was obtained. Our first attempt to derivatize **1** with 3-trifluoromethyl benzoic acid, in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI•HCl) and DMAP, only provided a mono-substituted product **7** (*m/z* 525.1153). While the result was somewhat disappointing, we learned that the C-4′ hydroxy group is more reactive than the C-7 hydroxy group. Nevertheless, upon repeating the reaction under the same condition, we did obtain the fully substituted compound **8** (*m/z* 869.1438) with a reasonable yield of 46%. The reaction of **1** with benzyloxyacetic acid in the presence of EDCI•HCl and DMAP only gave the disubstituted product **9** (*m/z* 649.2077) in 30% yield. Similar to compounds **3** and **5**, the positions of the substituents were determined to be at C-7 and C-4′. Finally, the reaction of **1** with benzoyl chloride in pyridine gave compound **10** (*m/z* 561.1535). All products were purified by SiO_2 column chromatography and/or HPLC and the chemical structures were characterised by ^1H and ^{13}C NMR (Tables S1 to S4) as well as HRESIMS.

Compounds **1**–**10** were evaluated for their antibacterial activity against *S. aureus*, *Escherichia coli*, *P. aeruginosa*, *Salmonella enterica* using an agar diffusion assay (Figure 3). *P. acnes* was not tested as our preliminary study showed that the EtOAc extract of breadfruit peel did not show significant activity against this strain. The results indicated that **1**, **4**, and **9** were found to have low antibacterial activity against the four tested bacterial strains, whereas **3** was active against *E. coli*, *S. aureus*, and *P. aeruginosa*. On the other hand, **7** was only active against *E. coli* and *S. aureus*. However, the synthetic derivatives appear to have lower antibacterial activity than **1**, as judged from their inhibition zones (Figure 3). Conversely, **2**, **5, 6**, **8,** and **10** did not show any antibacterial activity against the tested bacterial strains. Most synthetic derivatives that contain ester side chains at C-7 and/or C-4′ showed antibacterial activity, whereas compounds with ether side chains have no antibacterial activity.

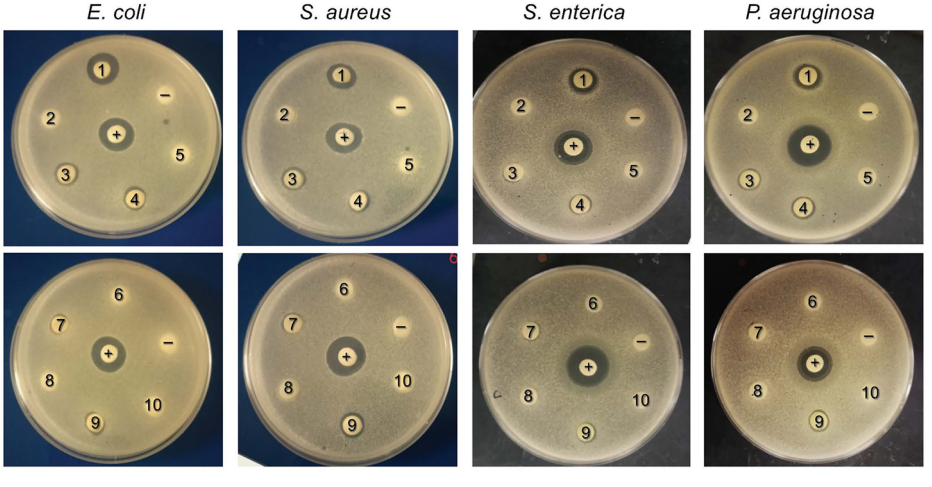


Figure 3. Antibacterial activity test of compounds **1**–**10** on agar-based disc diffusion assay. Each disc was impregnated with 2 µL of compound solution (6 mg/mL). Compounds **1**–**10** are numbered as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, respectively. Apramycin (**+**) (0.5 mg/mL, 2 µL) and DMSO (**–**) (2 µL) were used as positive and negative controls, respectively.

Table 1. *In vitro* cytotoxicity test of compounds **1**-**10** against cancer cell lines.

	IC_{50} (μM)	
Comp.	MCF-7	NCI-H460
1	>100	>100
2	>100	>100
3	>100	>100
4	>100	75.6
5	>100	>100
6	>100	>100
7	76.9	>100
8	>100	>100
9	32.7	>100
10	>100	>100
5-fluorouracil	29.1	63.4

Cytotoxicity evaluation of compounds **1**-**10** against the MCF-7 breast cancer cell line and the NCI-H460 lung cancer cell line showed that only **7** and **9** have moderate cytotoxicity against the MCF-7 cell line, with IC_{50} values of 77 and 33 μM, respectively, whereas **4** showed detectable cytotoxicity against the NCI-H460 cell line with an IC_{50} value of 76 μM (Table 1). Other compounds were considered inactive with IC_{50} value of more than 100 μM. Unfortunately, based on these results alone, it is not immediately clear why only **7** and **9** were active against MCF-7 cell, whereas **4** is more active against NCI-H460 cell. Therefore, further investigations are warranted to obtain more understanding of the structure-activity relationship of cyclocommunol and its derivatives.

3. Experimental section

See supplementary materials.

4. Conclusions

The present study showed that cyclocommunol (**1**) is one of the major bioactive components of breadfruit peel. Using **1** as a precursor, we synthesised nine cyclocommunol derivatives (**2**–**10**) and tested their antibacterial and antitumor activities. Compounds **1**, **4**, and **9** demonstrated weak antibacterial activity against *S. enterica, E. coli, S. aureus*, and *P. aeruginosa*, whereas compound **3** was active against *S. aureus*, *E. coli*, and *P. aeruginosa*. In addition, compounds **7** and **9** showed moderate cytotoxicity against the MCF-7 cell line, with IC_{50} values of 77 and 33 μM, respectively, whereas compound **4** was active against the NCI-H460 lung cancer cell line with an IC_{50} value of 76 μM.

Acknowledgments

The authors thank Tasya Aurellia, Nurunnisa F. Amalia, and Cindy Z. Ulayya for collecting samples and providing technical assistance.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Institute for Research and Community Service, University of Jambi, Indonesia under grant 249/UN21.11/PT.01.05/SPK/2022 and the Oregon State University College of Pharmacy Faculty Development Funds. Arash Samadi and Leigh E. Skala were supported by Grant T32 AT010131 from National Center for Complementary and Integrative Health (NCCIH). The content is solely the responsibility of the authors and does not represent the official views of NCCIH or the National Institutes of Health (NIH).

ORCID

Syamsurizal http://orcid.org/0000-0002-5277-0205
Taifo Mahmud http://orcid.org/0000-0001-9639-526X

References

Chen C-C, Huang Y-L, Ou J-C, Lin C-F, Pan T-M. 1993. Three new prenylflavones from *Artocarpus altilis*. J Nat Prod. 56(9):1594–1597. doi:10.1021/np50099a021.

Dada SO, Ehie GC, Osukoya OA, Anadozie SO, Adewale OB, Kuku A. 2023. In vitro antioxidant and anti-inflammatory properties of *Artocarpus altilis* (Parkinson) Fosberg (seedless breadfruit) fruit pulp protein hydrolysates. Sci Rep. 13(1):1493. doi:10.1038/s41598-023-28684-z.

Jagtap UB, Bapat VA. 2010. *Artocarpus*: a review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol. 129(2):142–166. doi:10.1016/j.jep.2010.03.031.

Jalal T, Natto HA, Wahab RA. 2022. Cytotoxicity and toxicological studies of *Artocarpus altilis* extracts, inducing apoptosis and cell cycle arrest via CASPASE-3 and CASPASE-8 pathways against human breast MCF-7 cells. Comb Chem High Throughput Screen. 25(6):973–985. doi: 10.2174/1386207324666210302095557.

Jalal TK, Khan AYF, Natto HA, Abdull Rasad MSB, Arifin Kaderi M, Mohammad M, Johan MF, Omar MN, Abdul Wahab R. 2019. Identification and quantification of quercetin, a major constituent of *Artocarpus altilis* by targeting related genes of apoptosis and cell cycle: in vitro cytotoxic activity against human lung carcinoma cell lines. Nutr Cancer. 71(5):792–805. doi:10.1080/01635581.2018.1516790.

Lan WC, Tzeng CW, Lin CC, Yen FL, Ko HH. 2013. Prenylated flavonoids from *Artocarpus altilis*: antioxidant activities and inhibitory effects on melanin production. Phytochemistry. 89:78–88. doi:10.1016/j.phytochem.2013.01.011.

Lin CN, Sheh WL. 1992. Pyranoflavonoids from *Artocarpus communis*. Phytochemistry. 31(8):2922–2924.

Mehta KA, Quek YCR, Henry CJ. 2023. Breadfruit (*Artocarpus altilis*): processing, nutritional quality, and food applications. Front Nutr. 10:1156155. doi:10.3389/fnut.2023.1156155.

Noviany N, Samadi A, Carpenter EL, Abugrain ME, Hadi S, Purwitasari N, Indra G, Indra A, Mahmud T. 2021. Structural revision of sesbagrandiflorains A and B, and synthesis and biological evaluation of 6-methoxy-2-arylbenzofuran derivatives. J Nat Med. 75(1):66–75. doi:10.1007/s11418-020-01445-2.

Pradhan C, Mohanty M, Rout A, Das AB, Satapathy KB, Patra HK. 2013. Phytoconstituent screening and comparative assessment of antimicrobial potentiality of *Artocarpus Altilis* fruit extracts. Int J Pharm Pharm Sci. 5(3):840–843.

Ragone D. 2011. Farm and forestry production and marketing profile for breadfruit (*Artocarpus altilis*). In: Elevitch CR, editor. Specialty Crops for Pacific Island Agroforestry. Holualoa, Hawai'i: permanent Agriculture Resources (PAR); p. 1–18.

Sengul M, Yildiz H, Gungor N, Cetin B, Eser Z, Ercisli S. 2009. Total phenolic content, antioxidant and antimicrobial activities of some medicinal plants. Pak J Pharm Sci. 22(1):102–106.

Soifoini T, Donno D, Jeannoda V, Rakoto DD, Msahazi A, Farhat SMM, Oulam MZ, Beccaro GL. 2021. Phytochemical Composition, Antibacterial Activity, and Antioxidant Properties of

the *Artocarpus altilis* Fruits to Promote Their Consumption in the Comoros Islands as Potential Health-Promoting Food or a Source of Bioactive Molecules for the Food Industry. Foods. 10(9):2136. doi:10.3390/foods10092136.

Turi CE, Liu Y, Ragone D, Murch SJ. 2015. Breadfruit (*Artocarpus altilis* and hybrids): a traditional crop with the potential to prevent hunger and mitigate diabetes in Oceania. Trends Food Sci Technol. 45(2):264–272. doi:10.1016/j.tifs.2015.07.014.