



## *Atuna racemosa* Raf. Plants: A Novel Source of Antibacterial and Antibiofilm Agents

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### ABSTRACT

Antibiotic resistance has become a global issue and has had a disastrous impact, increasing patients' morbidity and mortality. Biofilm formation is one of the factors contributing to bacterial resistance against many antibiotics. As one of the world's richest sources of plant biodiversity, Indonesia has the potential to develop its natural resources as raw material for medicine. *Atuna racemosa* Raf. is a native Indonesian plant, that belongs to the Chrysobalanaceae family and grows abundantly in the Maluku Islands. It is widely used in Ambon as cooking spice and massage oil, as well as to treat inflammation including fever, leg inflammation, and diarrhea. Many recent studies have conducted botanical investigations regarding the potential of *Atuna racemosa* Raf. as a potent antibacterial agent. Many active compounds are found in *Atuna racemosa* Raf., such as 4'-O-methyl-ent-galocatechin and (+)-galocatechin, which are known to be effective against antibiotic-resistant bacteria, namely Methicillin-resistant *Staphylococcus aureus* (MRSA). Atun plants also contain several types of phytochemical components in which additional antibacterial activity was discovered. Accordingly, Atun has the potential to be developed as an alternative antibacterial and antibiofilm source. This narrative review aimed to identify the potential of the *Atuna racemosa* Raf. Plant as a source of antibacterial and antibiofilm agents, the phytochemical components, and its various extracts, as well as its active compounds. This review is expected to contribute to the discovery of a novel antibacterial and antibiofilm source which is safe and effective, in the context of utilizing Indonesia's biodiversity.



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### INTRODUCTION

Infections due to antibacterial resistance are one of the major health problems in the world, especially in underdeveloped countries (Nii-Trebi, 2017). In 2016, the number of deaths due to antibiotic resistance reached 700 thousand cases (World Health Organization, 2017). The significant impacts of antibiotic resistance are the increase in patient morbidity and mortality, length of hospital stay, and the cost of healthcare (Basak et al., 2016). The aggravating factors of the mechanism of resistance are the inappropriate use of antibiotics and the mechanism

of biofilm formation (Taylor *et al.*, 2014). Microbes that have formed biofilm colonies are very difficult to be treated with conventional antibiotics, which will lead to persistent infection, especially when patients use medical implants or experience chronic ulcers, such as diabetic ulcers and burns (Römling and Balsalobre, 2012; Kostakioti *et al.*, 2013).

One of the ways to deal with antibiotic resistance in bacteria is to seek for antibacterial alternatives by utilizing natural ingredients. *Atuna racemosa* Raf. is a native Indonesian plant that grows in many parts of Eastern Indonesia, especially the Maluku Islands (Wahyono *et al.*, 2017). Atun fruit (Figure 1) was used previously as a cooking spice and massage oil, as well as for treating diarrhea, leg inflammation, and fever. These applications might explain the discovery of the Atun fruit's antibacterial activity, which shared the same features with current conventional antibiotics, namely chloramphenicol (Prance, 2004; Buenz *et al.*, 2007b). Atun fruit is also shown to have inhibitory activity against the growth of Methicillin-resistant *Staphylococcus aureus* (MRSA) strains (Salasia *et al.*, 2017) and other bacterias. This antibacterial activity was also found in several other parts of the plant. Apart from an antibacterial agency, the phytochemical components contained in the Atun plant have various activities such as anti-inflammatory, antioxidant, and anti-ulcer (Pacaña and Galarpe, 2017).

This narrative review is focused on the antibacterial and antibiofilm activity, phytochemical components and types of extracts, as well as the active compounds which play a role in those activities. This review is expected to provide a deeper and more comprehensive understanding of the potential of the Atun plants as an alternative source of antibacterial and antibiofilm agents. This review is also hoped to add insights in exploring the potential of Indonesia's biological wealth in the form of herbal plants, which can provide alternative therapies from sources that are easily found and obtained at an affordable price (Pacaña and Galarpe, 2017).

### Phytochemical Components and Kinds of Extracts

The phytochemical components of *Atuna racemosa* Raf. can be obtained by analyzing various kinds of extracts from the inner bark, seeds, shells, fruit, and kernels of *Atuna racemosa* Raf. (Pacaña and Galarpe, 2017). The solvent used for the extraction of plant biomolecules is selected based on the polarity of the solution. A solvent with a similar polarity to the solution will dissolve efficiently. Based on the level of polarity, ethyl acetate is the most non-polar solvent, then methanol and water is the most polar sol-

vent. However, the activity of methanol is more efficient in degrading the cell wall, causing polyphenols to leave the cell more easily. In addition, the components in plants that are active in inhibiting microorganisms are aromatic organic compounds that are often obtained using methanol extract (Altemimi *et al.*, 2017). Various kinds of extracts and phytochemical components, as well as their activities, are listed in Table 1.

### Active Compounds

According to a research conducted by (Buenz *et al.*, 2007b), the active compounds in Atun fruit can be utilized as anti-inflammatory agents for fever, sore throat, ulcers, as well as mouth and throat infections. In addition, in the same study, other active components such as  $\alpha$ -parinic acid,  $\alpha$ -oleostearic acid, catechins, glycerides triparinarin, and elaestearoparinarin were also discovered (Buenz *et al.*, 2007a). Other compounds found in Atun extract are 4'-O-methyl-ent-gallocatechin and (+)-gallocatechin which are derivatives of the flavan-3-ol compound (Salasia *et al.*, 2017). The structures of the active chemical compounds from Atun extract are shown in Figures 2 and 3.



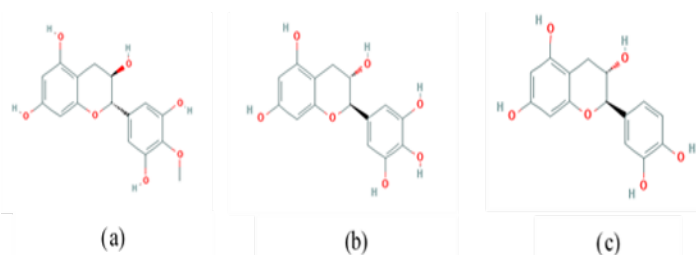
Figure 1: Atun Fruit

### Antibacterial Activity

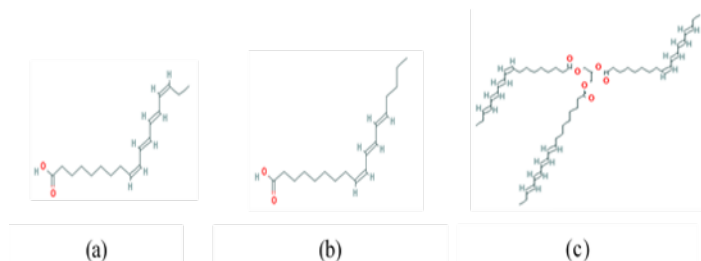
Fatty acids and glycerides have anti-inflammatory effects that can inhibit COX-1 and catalyze prostaglandin biosynthesis *in vitro* (Smith and Malkowski, 2019). The flavanol derivatives identified in Atun fruit, 4'-O-methyl-ent-gallocatechin and (+)-gallocatechin, to have potent anti-inflammatory and antibacterial effects. The antibacterial activity of these flavanol derivatives is explained by the production of hydrogen peroxide. The hydrogen peroxide will damage the pathogenic cell membrane by disrupting the phospholipid bilayers. Hence the function of the pathogenic membrane will be disrupted (Nikoo *et al.*, 2018).

**Table 1: Phytochemical components and kinds of extracts from different parts of *Atuna racemosa* Raf. plant with their activities**

Phytochemical Component	Kind of extracts	Activity	Reference
Alkaloid	Aqueous and methanol extract of seed, ethyl acetate extract of seed and shell, ethanol extract of inner bark	Antimicrobe, antibacteria, analgesic, antispasmodic	Mujeeb <i>et al.</i> (2014); Pacaña and Galarpe (2017); Nadayag <i>et al.</i> (2019)
Flavonoid	Decocted extract of a shell, ethyl acetate and methanol extract of seed and shell, ethanol extract of inner bark	Antimicrobe, antibacteria, anti-ulcer, antioxidant, antidiabetic, antitumor, antispasmodic	Mujeeb <i>et al.</i> (2014); Pacaña and Galarpe (2017); Wang <i>et al.</i> (2018); Nadayag <i>et al.</i> (2019)
Saponin	Aqueous and methanol extract of seed, ethyl acetate extract of seed and shell, ethanol extract of inner bark and kernel	Antimicrobe, antioxidant, immunomodulator, anticancer, antidiabetic, anti-obesity, coagulant	Mujeeb <i>et al.</i> (2014); Pacaña and Galarpe (2017); Nadayag <i>et al.</i> (2019); R.P. Gentallan Jr. <i>et al.</i> (2019)
Anthraquinone	Methanol and decocted extract of seed	Antioxidant, anti-fungi, antiviral, antimicrobe	Pacaña and Galarpe (2017); Bouarab-Chibane <i>et al.</i> (2019)
Tanin	Aqueous, methanol, and decocted extract of seed and shell, ethanol extract of inner bark and kernel	Antimicrobe, anti-diarrhea, antioxidant	Pacaña and Galarpe (2017); Nadayag <i>et al.</i> (2019); R.P. Gentallan Jr. <i>et al.</i> (2019)
Coumarin	Aqueous and methanol extract of seed	Bacteriostatic, antitumor, anticoagulant, anti-inflammation	Jain and Joshi (2012); Pacaña and Galarpe (2017)
Terpenoids	Aqueous, methanol, and decocted extract of seed and shell	Antioxidant, anti-fungi, antiviral, antimicrobe	Dave and Ledwani (2012); Pacaña and Galarpe (2017); Nadayag <i>et al.</i> (2019)
Steroid	Ethanol extract of inner bark	Antibacteria, anti-inflammation, antioxidant hepatoprotective, anti-fungi, anti-diarrhea	Patel and Savjani (2015); Nadayag <i>et al.</i> (2019)
Cardiac glycoside	Ethanol extract of kernel	Antiviral, antibacteria, anti-inflammation, antioxidant, immunomodulator	R.P. Gentallan Jr. <i>et al.</i> (2019)



**Figure 2: Structures of flavanol, isolated from *A. racemosa*, consisted of a) 4'-O-methyl-ent-gallocatechin, b) (+)-gallocatechin, c) catechins**



**Figure 3: Structures of fatty acid and glycerides, isolated from *A. racemosa*, consisted of a)  $\alpha$ -parinic acid, b)  $\alpha$ -oleostearic acid, c) triparinarin**

**Table 2: Antibacterial activity seen indifferent parts of *A. racemosa* plant**

Bacteria	Antibacterial Activity		Part of plants	Reference
	Diffusion method (Zone of inhibition - mm)	Dilution method (mg/mL)		
Methicillin-resistant Staphylococcus aureus (MRSA)	16	70, 0.016-0.032	Fruit	Salasia <i>et al.</i> (2017); Buenz <i>et al.</i> (2007b)
Escherichia coli	15.7, 7.3-10, 9.3-13	0.11375, 8.57	Inner bark, Shell, Kernel	Nadayag <i>et al.</i> (2019); Pacaña and Galarpe (2017)
Pseudomonas aeruginosa	16, 18.33		Inner bark, Kernel	Nadayag <i>et al.</i> (2019); R.P. Gentallan Jr. <i>et al.</i> (2019)
Salmonella typhimurium	16		Inner bark	Nadayag <i>et al.</i> (2019)
Klebsiella pneumoniae	14		Inner bark	Nadayag <i>et al.</i> (2019)
Staphylococcus aureus	20.7, 28.92, 10-13.7, 20-40, 7.3-9.7	2.138, 0.11375, 0.016-0.032	Inner bark, Kernel, Shell, Fruit	Bouarab-Chibane <i>et al.</i> (2019); R.P. Gentallan Jr. <i>et al.</i> (2019); Pacaña and Galarpe (2017); Buenz <i>et al.</i> (2007a)
Bacillus subtilis	21.7		Inner bark	Nadayag <i>et al.</i> (2019)
Bacillus cereus	15.5		Kernel	R.P. Gentallan Jr. <i>et al.</i> (2019)

In previous studies, the antibacterial activity of Atun fruit extracts was also proven to be effective against Methicillin-Resistant *Staphylococcus aureus* (MRSA) through *in vitro* tests and have passed phase I human trials (Buenz *et al.*, 2007b). Moreover, *A. racemosa* also contains alpha-parinaric acid, which has strong antibacterial activities, especially in MRSA infections (Salasia *et al.*, 2017).

Another study also mentioned that catechin in the form of epigallocatechin gallate may overcome methicillin resistance by inhibiting the synthesis of Penicillin Binding Protein 2a (PBP2a). The protein encoded by the *mecA* gene is crucial for the survival of *S. aureus* bacteria and cannot be inhibited properly by beta-lactam antibiotics (Fishovitz *et al.*, 2015). The inhibition of PBP2a synthesis will increase the activity of beta-lactam in inhibiting cell wall biosynthesis (Radji *et al.*, 2013). Flavonols are demonstrated to have anti-MRSA abilities by inhibiting beta-lactamases, inactivating the efflux pump, disrupting the stability of the bacterial plasma membrane, and inhibiting topoisomerase (Sangeetha *et al.*, 2020).

Other phytochemical components, such as flavonoids and anthraquinones, can bind and interact with bacterial cell walls. Tannins also interact with bacteria in inhibiting enzymes, disrupting the uptake of substrates, membranes, and metal ion complexation, and inducing modulation in essential ribosomal pathways. This mechanism causes the declining of the translation process, thereby inhibiting protein synthesis and bacterial growth (Huang *et al.*, 2018). Terpenoids will trigger membrane disruption, while alkaloids can interfere with cell walls and DNA (Bouarab-Chibane *et al.*, 2019). Steroids are antibacterial, especially against gram-negative bacteria by inducing liposome leakage (Epanand *et al.*, 2007).

The antibacterial activity of *A. racemosa* extract was determined by diffusion and dilution methods. These tests were done on various types of bacteria, ranging from resistant strains to wild-type strains (WHO, 2017). According to the World Health Organization (World Health Organization, 2017), the current list of resistant strains of bacteria that urgently require the discovery of novel antibiotics includes MRSA which is placed in the high priority list of antibiotic-resistant bacteria. Several studies have also proven that Atun extract has the potential to provide a source of antibacterial agents for resistant strains. Results of studies showing the zone of inhibition and minimum inhibitory concentration (MIC) from different parts of Atun plant extracts are presented in Table 2.

### Antibiofilm Activity

Catechins present in the active compound of *A. racemosa* also exerted an antibiofilm effect (Hengge, 2019). Biofilms are collections of bacterial cells that attach to tissues and form glycoproteins and extracellular matrix. Biofilms will protect bacteria from host cell immunity and antibiotics (Taylor *et al.*, 2014). The epigallocatechin-3-gallate (EGCG) catechin is reported to have an inhibition effect toward biofilm formation, particularly against *Pseudomonas aeruginosa* (*P. aeruginosa*), (Nikoo *et al.*, 2018). The extracellular polymers in the biofilm will be eliminated by EGCG by inhibiting the formation of amyloid fibers (Hengge, 2019). Bacteria with a high ability to form biofilms tend to be more resistant (Wahyudi *et al.*, 2019). This inhibitory effect does not only apply for *P. aeruginosa*, but also against other biofilm-forming bacteria such as *Streptococcus pneumoniae* (*S. pneumoniae*) and *Staphylococcus aureus* (*S. aureus*) (Song *et al.*, 2017). Biofilms are also a major cause of several chronic infections, such as infections in diabetic ulcers (Banu *et al.*, 2015). Against this condition, the catechins found in Atun have a dual function, namely as antibiofilm and anti-ulcer agents. The study conducted by Rashidi *et al.* (2017) proved that catechins have a significant role in wound healing, angiogenesis, increasing collagen deposition, and preventing other complications such as the entry of resistant pathogens such as *P. aeruginosa* and *S. aureus*. In another study, catechins also increased the deposition of hydroxyproline, fibronectin, and nitric oxide levels. This fibronectin plays an important role in hemostasis, infection control, and increasing epithelialization degree of the skin tissue (Hajiaghaalipour *et al.*, 2013).

### Future Prospects and Strategies

Atun extracts have a bioactive composition which was observed to be a potential source of antibacterial and antibiofilm agents, namely catechin and alpha-parinaric acid. To optimize the application, these active compounds can be dereplicated and elucidated, hence resulting in new compounds with a more potent and safe antibacterial agency (Hubert *et al.*, 2017). Furthermore, these compounds can be applied either as a single drug or in combination with existing antibiotics. A synergistic combination provides benefits since it is possible to give a lesser dose of each drug; thus, the side effects are also minimized (Bhardwaj *et al.*, 2016). As an antibiofilm agent, the active compound in Atun can be made into slow-release nanoparticle preparations so that it can provide a longer and more effective effect. Furthermore, the use of Atun extract as

a sustained release for coating materials on medical devices, such as prostheses and catheters can be considered as an effort to prevent biofilm formation implementing the so-called “*smart devices*” strategy (Ramasamy and Lee, 2016).

## CONCLUSIONS

This scientific review concludes that *Atuna racemosa* Raf. Contains phytochemical components and active compounds which are potential sources for antibacterial and antibiofilm agents. However, further research is needed in order to determine the exact molecular target of the active compounds contained therein. This review is expected to provide new insights in developing innovative antibacterial and antibiofilm agents.

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## Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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