Mini-review on potential antifouling compounds from the red algae *Kappaphycus alvarezii*: Can we use bacterial endophytes as an alternative eco-friendly antifouling agent?

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Abstract. Biofouling is a process of unwanted organism attachment, which may cause a significant problem in the shipping and aquaculture industries. Until today, tributyltin (TBT), a harmful chemical substance, is commonly used to treat biofouling despite its adverse effect on aquatic life. Therefore, eco-friendly and sustainable antifouling active compounds attract more attention. Among marine resources, macroalgae have a variety of compounds that could be used as an antifouling agent. Among macroalgae species, *Kappaphycus alvarezii* is Indonesia's most abundant macroalgae species, yet other industries also need this species for other purposes. Thus, an alternative solution is required to tackle this conflict of interest in using similar natural resources. Endophytic bacteria from macroalgae produce compounds similar to their hosts. Therefore, they can be a sustainable source of antifouling. This mini-review aims to examine and discuss the potential use of endophytic bacteria from *K. alvarezii* as an antifouling coating. Data mining was carried out online from various sources, and then selected based on the data's relevancy. Based on the results, various compounds from *K. alvarezii* have broad bioactivity that could be applied to an antifouling coating.

Key Words: antifouling, biofouling, endophytic bacteria, *Kappaphycus alvarezii*, macroalgae, sustainability.

Introduction. Biofouling is the attachment of unwanted organisms to a surface (Callow & Callow 2002; Maki & Mitchell 2003; Yan & Yan 2003). The phenomenon of biofouling in water-submerged objects causes massive aquaculture losses (Cao et al 2011). For instance, biofouling causes bad circulation in floating net cages (Gansel et al 2017). Each year, more than 5.7 billion USD is used for biofouling control in the marine industry (Rajitha et al 2020). In addition, 5-10% of operational costs are dedicated to controlling biofouling (Fitridge et al 2012; Bannister et al 2019). From the data above, it can be concluded that handling biofouling is still tricky and costs a fortune.

Tributyltin (TBT) is often used to overcome biofouling problems (Sánchez-Lozano et al 2019). However, since 2008, the International Maritime Organization (IMO) has banned TBT as an antifouling agent (Rumampuk et al 2018; Harrison et al 2020). This restriction is mainly based on the adverse effects of TBT on the environment, such as imposex (sterility) in several types of mollusks and morphological abnormalities in Pacific oysters *Crassostrea gigas* (Harrison et al 2020). Nevertheless, TBT is still commonly used in Indonesia. Thus, it harms aquatic life such as gastropods, mollusks, and other organisms in many regions (Rumampuk et al 2018). In addition, TBT can settle on the sediment and be accumulated by benthic organisms (Cao et al 2011; Frouin et al 2011; Gadhi et al 2019). This is not in line with United Nations Sustainable Development Goals

(SDGs) point number 14 on life below water (Sturesson et al 2018). Therefore, an environmentally friendly source of antifouling is needed to support SDGs 14.

One of the eco-friendly antifouling sources is macroalgae (Hellio et al 2001, 2001b; Plouguerné et al 2012, 2010). For instance, most macroalgae from the genera *Sargassum* and *Ulva* have antifouling compounds, such as chromanol and polyphenols (Plouguerné et al 2012). Former *Eucheuma cottonii*, recently known as *Kappaphycus alvarezii*, is an abundant macroalga in Indonesia, and has a relatively clean surface, without any adhering organisms (Tan et al 2013). Therefore, *K. alvarezii* is thought to have potential as a source of antifouling compounds. However, its status as a food and export commodity becomes a challenge to developing antifouling compounds at an industrial scale (Jumaidin et al 2017). To face this challenge, the utilization of endophytic bacteria can be an alternative because they can produce compounds similar to their host and are relatively flexible and easier to produce (Busetti et al 2017; Lane & Kubanek 2008; Tiwari & Bae 2020). Hopefully, this strategy will impact the sustainability of underwater life, as stated in SDG-14, by paying attention to marine pollution, protecting marine ecosystems, and enhancing a sustainable aquatic economy (Sturesson et al 2018). This mini-review aims to discuss the antifouling activity of compounds on *K. alvarezii* and its endophytic bacteria, along with its potential application as an antifouling coating.

The Symbiosis between Macroalgae and Bacteria. Bacterial symbionts in macroalgae can be grouped in two types, epiphytic and endophytic bacteria (Goecke et al 2010). Endophytic bacteria live inside their host, while epiphytes outside the host. Both are known to produce compounds similar to or even the same as their host (Tiwari & Bae 2020). The similarity occurs due to the transmission of genetic material between species, called horizontal gene transfer (HGT) (Gao et al 2014). Interestingly, the community structure of symbiotic bacteria can be specific to a species, regardless of habitat differences (Goecke et al 2010). The close relationship between bacteria and macroalgae can be seen in the ability of bacteria to ward off the invasion of pathogenic microorganisms that attack macroalgae, making bacteria a form of macroalgae defense (Goecke et al 2010). On the other hand, macroalgae produce sugar as a nutrient for bacteria, while bacteria supply CO_2 and nitrogen (de Oliveira et al 2012). The involvement of bacteria in the nutrient supply and defense of macroalgae makes macroalgae without bacteria to experience growth defects such as failure of germination, stunting and difficulties in reproducing (Campbell et al 2011; Egan et al 2013). To date, a total of 63 isolates of symbiotic bacteria were obtained from *K. alvarezii* in the Philippines (Butardo et al 2003; Sugrani et al 2019). The genera of endophytic bacteria known to exist in *K. alvarezii* are *Brevibacillus, Pseudomonas, Pseudoalteromonas, Halomonas, Streptomyces, Nocardiopsis, Brevibacterium, Brachybacterium, Micrococcus, Klebsiella, Aeromonas,* and *Kocuria* (Santhi et al 2014; Nur et al 2019).

Biofouling Mechanisms. The biofouling process is divided into four main phases: the formation of the primary layer, the formation of biofilms by prokaryotes, the sticking of eukaryotic microorganisms, and the attachment of higher-order organisms (Maki & Mitchell 2003). The primary layer is formed from the adsorption of organic and inorganic macromolecules in the seconds to the first minute of a submerged surface (Amara et al 2018). This changes the physiochemistry of surface material, thus inviting bacteria to stick and obtain nutrients (Dunne 2002). Bacteria benefit from the help of proteins, lipids, extracellular DNA, as well as organelles such as pili or flagella to stick to the surface material (Berne et al 2015). In addition, the attachment of bacteria is also influenced by charge, hydrophobicity, and the presence or absence of organic and inorganic layers on a surface (Geng & Henry 2011). Furthermore, eukaryotic organisms such as diatoms and protozoans attach to biofilms using polysaccharides or proteins (Amara et al 2018). The microfouling process can occur for days, accompanied by the attachment of invertebrate larvae as macrofoulers for weeks (Yebra et al 2004).

New Generation of Renewable Antifouling Agent. Macroalgae vary both morphologically and functionally. They are generally divided into three types based on their pigmentation: red algae (Rhodophyta), green algae (Chlorophyta), and brown algae (Phaeophyceae, Heterokontophyta) (Busetti et al 2017). High biodiversity of macroalgae opens the great potential of natural compound discovery, each with its own unique capabilities (Anyanwu et al 2018). These days, macroalgae are used as a source of many active ingredients in various sectors, such as pharmaceuticals, cosmetics, agriculture, bioenergy, and nutrition (Weinberger 2007; Tierney et al 2010; de Almeida et al 2011; De Jesus Raposo et al 2015; Gaysinski et al 2015; Anyanwu et al 2018; Sari et al 2019). In addition to being a source of active ingredients, macroalgae are also the source of basic materials in the manufacture of various products in numerous industrial sectors, one of which is in the maritime sector as an antifouling coating material (Nylund & Pavia 2005; Plouguerné et al 2010; Wang et al 2018 Gadhi et al 2019).

Table 1 presents several compounds from macroalgae that are known to be used as natural antifouling sources. Specifically, red algae (Rhodophyta) contain many specific biochemical compounds compared to other types of algae, such as nucleotides (glutamate, citrulline, and ornithine), fatty acids (eicosenoate, and dihomolinoleic), and secondary metabolites (12-HEPE, and 5-HEPE) (Plouguerné et al 2010; Wang et al 2018; Bannister et al 2019; Gadhi et al 2019; Sugrani et al 2019; Pinteus et al 2021). Taxonomically, macroalgae *E. cottonii* and *K. alvarezii* are the same species (Sugrani et al 2019). One of the red algae, *Delisea pulchra* produces halogenated furanones, which is the most effective natural compound against fouling organisms such as barnacles (Lalegerie et al 2020).

Table 1

Potential antifouling activity of various compounds from macroalgae

Organisms	*Compounds*	*Activity*	*Antifouling activity*	*Source*
Delisea pulchra	(5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone	Quorum Sensing Inhibition	Inhibiting AI-2 to interact with LuxR receptors	(Brameyer & Heermann 2015)
	4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5*H*)-furanone		Disrupting 3-oxo-C6-HSL thus inhibiting carbapenem production for carABCDEFGH operon expression	(Manefield et al 2001)
Sphaerococcus coronopifolius	*Bromosphaerone*	Antibacterial against *Staphlococcus aureus*	Disrupting bacterial cell membranes due to polar clusters of alcohol, and non-polar clusters of aliphatic carbon with bromine	(Etahiri et al 2001; Hughes & Fenical 2010)
	12S-hydroxybromosphaerodiol			
	Bromoditerpene-sphaerodactylomelol	Antimicrobial against *E. coli, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Candida albicans*	Alpha and beta unsaturated ketones can inhibit nucleophiles	(Smyrniotopoulos et al 2008; Rodrigues et al 2015)
Callophycus serratus	Diterpene-benzoate macrolides	Antibacterials against resistant pathogens	Hydrophobic and due to rigidity of tetrahydropyran structure	(Lane et al 2009)

Table 1

Potential antifouling activity of various compounds from macroalgae (continuation)

Organisms	*Compounds*	*Activity*	*Antifouling activity*	*Source*
Solieria filiformis	Lectin	Antibacterials against *P. aeruginosa, Enterobacter aerogenes, Serratiamarcescens, Salmonella typhii, Klebsiella penumoniae,* and *Proteus*	Lectin can specifically bind to polysaccharides, beta-glucans, and peptidoglicans.	(Holanda et al 2005; Cheung et al 2015)
Delisea carnosa	Gelatine	Prevent epibiont attachment	Gelatin coating prevents direct sticking to the macroalgae surface	(Nylund & Pavia 2005; Wang et al 2018)
Ceramium tenuicorne	DCM extract	Disrupting microfouler cell wall	Polar compounds create cytoplasmic leakage	(Wang et al 2018)
Gracillaria vermiculophylla	Hexane extract	Disrupting microfouler cell wall	Non-polar compounds break down cell walls	(Wang et al 2018)
Gracillaria conferta	H_2O_2 and other oxidizers	Prevents bacterial attachment and disrupting bacterial cell wall	Prevents bacterial oligomer attachment and destroying bacterial cell walls	(Weinberger & Friedlander 2000)
Grateloupia turuturu	Cholesteryl formate	Prevents biofouling attachment	Prevents attachment and growth of epiphytes on the macroalgae surface;	(Plouguerné et al 2008, 2010; Bazes et al 2009; Pinteus et al 2021)
Sargassum muticum	Glycolipid, palmitic acid			

In addition to halogenated furanones, red algae also produce terpenes with antifouling activity (Lalegerie et al 2020). A red macroalgae commonly found in Indonesia is *K. alvarezii*. This species has various compounds with various bioactivities as presented in Table 2. Based on previous studies, it is still difficult to determine whether the compounds obtained have an antifouling activity or not. Thus, the chemical structure and bioactivity data from the search results are used as clues to determine the potential of the antifouling compound. Based on its potential, the application of the compound to antifouling coating is estimated. For a more comprehensible purpose, compounds in Table 2 will be indicated by the number assigned to each compound; the letters accompanying the numbers are further identifiers related to Figure 1.

Table 2

Potential antifouling activity of various known compounds in *Kappaphycus alvarezii*

Organisms	*Compound*	*Known bioactivity*	*Antifouling activity*	*Mechanism of action*	*Source*
Kappaphycus alvarezii	2-butyl-7-4-(chloromethyl) cyclooct-1-enyl) hept-5-en-1-ol [a.1]	Antioxidant	Anti-adhesive and antibiofilm	The antioxidant properties of adhesin reducing, minimizing bonding of barnacles to the surface. Chlorine is bactericidal.	(Del Grosso et al 2016; Makkar & Chakraborty 2018)
	4- (2-chloroethyl) -5-7- (methoxymethyl) undec-3- enyl) cyclooct-4-enone [a.2]				
	Phytochemicals: saponins, phenols, alkaloids, flavonoids, steroids, triterpenoids, phytosterols, and tannins.	Anti-inflammatory and antibacterial	Anti larvae, antibiofilms, anti-adhesives	Prevents attachment and metamorphosis of larvae/spores and lysis of bacterial cell membranes.	(Ranganayaki et al 2014; Wen et al 2014; Charway et al 2018)

Table 2

Potential antifouling activity of various known compounds in *Kappaphycus alvarezii* (continuation)

Organisms	*Compound*	*Known bioactivity*	*Antifouling activity*	*Mechanism of action*	*Source*
Kappaphycus alvarezii	Catechol [3] [a.8]	-	Antiadhesive and antibacterial	Double bonds act to reduce adhesiveness. Alcohol and aldehydeas are antibacterials.	Al-Juhni & Newby 2006; Qian et al 2013; Baskararaj et al 2019
	Gallic acid [4] [c.1]	-	Anticorrosion antiadhesive antibiofilm, and basic ingredients for coating	Hydrolyzable tannins prevent corrosion and rust. Antioxidants prevent clams and bacteria from sticking together by reducing negative charges.	Rahim et al 2007; Borges et al 2013; Wen et al 2014; Baskararaj et al 2019
	Cinnamic acid [5] [a.3]	-	Antibiofilm	Aldehyde and alcohol inhibit bacterial growth.	Borges et al 2013; Baskararaj et al 2019
	Chlorogenic acid [6] [a.4]	-	Antibiofilm	Aldehyde and alcohol inhibit bacterial growth.	Wu et al 2014; Baskararaj et al 2019
	Levoglucosenone [7] [a.5]	Antitumor	Anti macrofouling and antibiofilm	Cytotoxic characteristics.	Arsianti et al 2018; Bhuyar et al 2020
	4-Pyridinemethanol [8] [a.6]	-	Anti macrofouling and antibiofilm	Inhibition of CCP (cytochrome) which is tasked to neutralize hydrogen peroxide.	Atack & Kelly 2006; Brenk et al 2006; Martins et al 2013; Bhuyar et al 2020
	1,2,5- Thiadiazole-3-carboxamide [9] [a.7]	Antibacterial	Antibiofilm	Lysis of bacteria and inhibition of the production of beta-tubulin in fungi.	Bhuyar et al 2020
	hexamethylcyclotrisiloxane [10] [b.1]	-	Fouling release (FR)	Material for antifouling coatings that are easy to clean.	Kim & Klages 2009; Bhuyar et al 2020
	kappa-carrageenan [11] [a.9]	Antibacterial and antioxidant	Antibiofilm and antiadhesive	Reducing bonds. Alcohol and aldehyde are antibacterial.	Kamenarska et al 2007; Madruga et al 2020
	2-acetylfuran [12] [a.10] and 5-methyl-2 (5H) -furanone [13] [a.11]	-	Quorum-Sensing Inhibitors	Antibiofilm on bacteria, and inhibits adhesion biofilm bacteria.	Gule et al 2012; Gautam et al 2019

Table 2

Potential antifouling activity of various known compounds in *Kappaphycus alvarezii* (continuation)

Organisms	*Compound*	*Known bioactivity*	*Antifouling activity*	*Mechanism of action*	*Source*
Endophytic fungi of K. alvarezii					
Xylaria psidii	Extracellular serine protease [14]	Antibacterial	Antibiofilm and antiadhesive	Proteolyticthat break down proteins for adhesion.	Hangler et al 2009; Tarman et al 2011; Indarmawan et al 2016
Mycelium sterillium	2-carboxy-8-methoxy-naphthalene-1-ol [15]	Cytotoxic	Anti larvae and antiadhesive	Cytotoxic and inhibits adhesion by reducing compounds.	Tarman et al 2011; Del Grosso et al 2016
Bacteria from K. alvarezii					
Endophytic Bacteria	- [16]	Antibacterial	Antibiofilm	Actively inhibits gram-positive and gram-negative bacteria.	Wen et al 2014; Sugrani et al 2019
Pseudoaltero monas	Exopolysaccharides (EPS): galactosamine [17]	-	Quorum-Sensing Inhibitors	Antibiofilm by inhibiting AI-2 (autoinducer-2) signaling.	Bernbom et al 2011; Nur et al 2019

According to Leonardi & Ober (2019), the bottom part of the antifouling coating is the adhesive layer. This layer is has compounds with a strong ionic bond, such as compounds [4], tannins, and phenols with anti-corrosion and antibiofilm bioactivity. Furthermore, to facilitate the propagation of antifouling additive, a siloxane compound such as compound [10] is used to act as a matrix, thereby adding more control to the antifouling compound arrangement (Leonardi & Ober 2019). Compound [10] has hydrophobic properties that make the antifouling coating easy to clean (Lejars et al 2011). The top layer of the antifouling coating is an additive layer that gives the coating its character. The main role that coatings have as antifouling agents is the prevention of the formation of bacteria biofilm (Rajitha et al 2020). Alkaloid compounds can inhibit Ca^{2+} in the ion channels of cell membranes, preventing bacteria from sticking to the surface (Qian et al 2013). The properties of bactericidal compounds [1], [2], [3], [5], [6], [9], [11], [16], and saponins can inhibit biofilm bacteria (Saha et al 2018). Compounds [12], [13], and [17] can inhibit quorum sensing signals based on autoinducer-2 (AI-2) molecules similar to halogenated-furanone compounds found in macroalgae *Delisea pulchra* (Rasmussen et al 2000; Brameyer & Heermann 2015).

The restriction of the protein cytochrome C peroxidase by compound [8] stops the conversion of H_2O_2, which is toxic to cells (Atack & Kelly 2006). Moreover, compound [9] can inhibit fungal metabolism through the restriction of β-tubulin protein production (Plouguerné et al 2012; Martins et al 2013). Inhibition of barnacle larvae and algal spores can be performed by using compounds [1], [2], [3], [11], [14], and [15] that reduce adhesive substances or break down proteins responsible for surface attachment. This is in line with the findings of Del Grosso et al (2016), who noted that antioxidants can reduce the sticking ability of macrofouler organisms. Furthermore, compounds [7] and [14] are cytotoxic, deadly to larvae or spores of marine organisms (Arsianti et al 2018). The above compounds are then arranged on a siloxane matrix (bulk) based on the hydrophobicity character of the coating. The additive arrangement is based on the need for amphiphilic properties to prevent the adhesion of biofoulers, but still considering the ease of cleaning (Leonardi & Ober 2019). Therefore, it is proposed to leave a gap between predominantly hydrophilic additive compounds and the matrix (bulk), which is hydrophobic, as presented in Figure 1. Additionally, the topographical shape of the nanostructure can affect amphiphilic properties on the surface, thus preventing the attachment of barnacles or other fouling organisms (Wen et al 2014; Leonardi & Ober 2019).

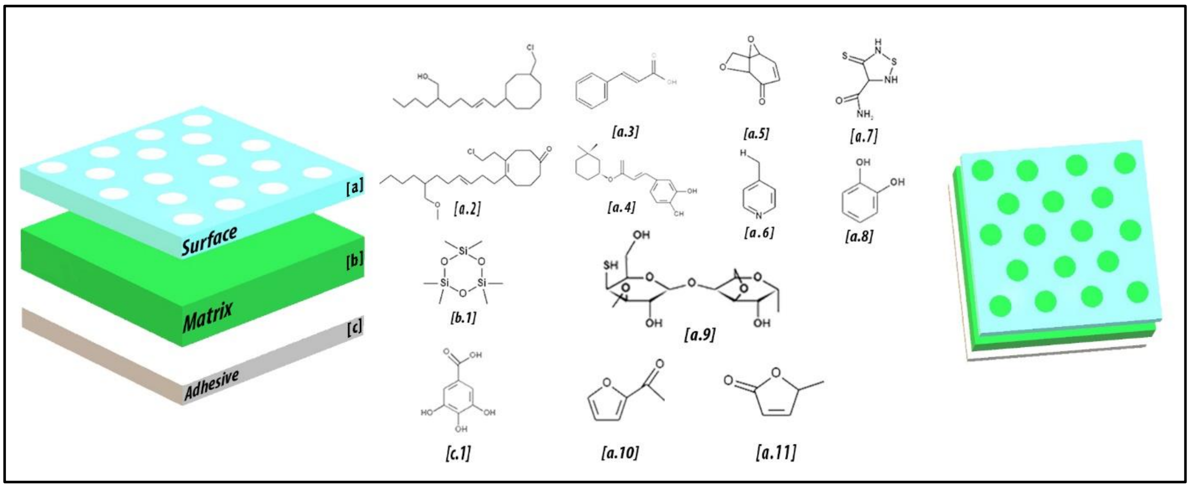

Figure 1. Schematic design of antifouling coating from compounds obtained from *K. alvarezii* and its endophytes. (2-butyl-7-4- (chloromethyl) cyclooct-1-enyl) hept-5-en-1-ol [a.1], 4- (2-chloroethyl) -5-7- (methoxymethyl) undec-3- enyl) cyclooct-4-enone [a.2], Cinnamic acid [a.3], Chlorogenic acid [a.4], Levoglucosenone [a.5], 4-Pyridinemethanol [a.6], 1,2,5- Thiadiazole-3-carboxamide [a.7], Catechol [a.8], kappa-carrageenan [a.9], 2-acetylfuran [a.10], methyl-2 (5H) -furanone [a.11], hexamethylcyclotrisiloxane [b.1], Gallic acid [c.1]).

Although studies related to the application of endophytes from *K. alvarezii* as an antifouling agent are still scarce, it is suspected that bacteria from the species can produce similar compounds as their host through HGT mechanism (Busetti et al 2017). A previous study on prokaryotic endophytes showed that 81% of 181 prokaryotic genes are similar to their host through the HGT processes (Tiwari & Bae 2020). Indeed, the lifespan of endophytic microorganisms is relatively short compared to their host, thus providing a more flexible adaptation space for endophytes (Campbell et al 2011). According to Gao et al (2014), prokaryotic bacteria are more susceptible to HGT than other organisms using transformation, conjugation, and transduction mechanisms. Eukaryotes are less susceptible to HGT because of their need vectors. Therefore, the use of endophytic bacteria from *K. alvarezii* can be an alternative source of compounds, giving the flexibility to produce such compounds without having to depend heavily on the stock of *K. alvarezii* from nature.

Isolation Method of Endophytic Bacteria from Macroalgae. The endophytic bacteria from the macroalgae could be obtained from the surface of a splice of macroalgae. This is needed to be sterilized with sterile seawater and then dried prior to immersion in 5% NaOCl for 5 min. Afterward, the splice must be rinsed four times with sterile distilled water (Kaaria et al 2015; Sugrani et al 2019). Sterilized macroalgae are then crushed and diluted with sterile seawater to a dilution level of 10^5, and the diluted homogenate is then grown on sodium agar (NA) medium (Etminani & Harighi 2018). The grown bacteria are then characterized by determining the endophytic bacteria obtained from macroalgae (Kaaria et al 2015).

Conclusions. Based on the present review, compounds produced by the bacterial endophytes of *K. alvarezii* have a potential use as a natural antifouling coating. Our analysis suggests a further study to confirm the antifouling abilities of compounds extracted from *K. alvarezii* bacterial endophytes.

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Conflict of Interest. The authors declare that there is no conflict of interest.

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