

REVIEW

ANTIBACTERIAL COMPOUNDS FROM RED SEAWEEDS (RHODOPHYTA)

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ABSTRACT

Seaweeds produce great variety of metabolites benefit for human. Red seaweeds (Rhodophyta) are well known as producer of phycocolloids such agar, agarose, carragenan and great variety of secondary metabolites. This review discusses the red algal secondary metabolites with antibacterial activity. The chemical constituents of red algae are steroid, terpenoid, acetogenin and dominated by halogenated compounds mainly brominated compounds. Novel compounds with intriguing skeleton are also reported such as bromophycolides and neurymenolides. In summary, red seaweeds are potential sources for antibacterial agents and can serve as lead in synthesis of new natural medicines.

Keywords: red algae; bioactive compounds; antibacterial

ABSTRAK

Rumput laut menghasilkan berbagai metabolit manfaat bagi manusia. Rumput laut merah (Rhodophyta) dikenal sebagai penghasil phycocolloids seperti agar, agarose, karagenan dan berbagai macam metabolit sekunder. Tulisan ini membahas metabolit sekunder dari alga merah dengan aktivitas antibakteri. Kandungan kimiawi dari alga merah yaitu steroid, terpenoid, acetogenin dan didominasi oleh komponen halogen terutama brominated senyawa. Senyawa baru dengan struktur kimia menarik juga dilaporkan seperti bromophycolides dan neurymenolides. Dari studi ini terbukti bahwa rumput laut merah merupakan sumber potensial untuk agen antibakteri dan dapat berfungsi sebagai senyawa penuntun dalam sintesis obat-obatan alami yang baru.

Kata Kunci: alga merah; senyawa bioaktif; antibakteri

INTRODUCTION

Seaweeds are benthic, macroscopic algae (macroalgae), eukaryotic, multicellular organisms, simplified marine plants that lack of the highly specialized structures (true leaves, stems and roots) and reproductive. Seaweed typically consists of thallus, which is sometime provided with leaf like blade and a root like holdfast. They are able to tolerate salt due to adjustment of the cytoplasm osmolarity and contain photosynthetic pigments (chlorophyll) to produce food and oxygen from carbon dioxide, and the water. Seaweeds are classified based on their pigment. Chlorophytes is green algae that contain pigment chlorophyll as major component. Phaeophyta is brown algae due to the brown pigment called fucoxanthin. Rhodophyta is red algae because of the red pigments called phycoerythrin, phycocyanin, phycobilins, chlorophyll a, β -carotene and unique xanthophyll. Red Algae are essentially marine and important for marine environment in the formation of tropical reefs by contributing to glue the reef structure and resist to wave

[1]. The chemistry of red algae is more diverse than green or brown algae.

Seaweeds have been used since human life in various ways as food, feed, fertilizer and medicine. As a food source seaweed contains low calories, dietary fibers, carbohydrate, minerals, vitamins and essential amino acids. Therefore, seaweeds provide nutritional requirement for human and have beneficial to human health [2-4]. Seaweeds have been one of the richest and most promising sources of bioactive primary and secondary metabolite [5-6]. The primary metabolites called phycocolloid compounds such as carragenan, agar, and alginate are used as gelling, stabilizing and thickening agents in food, cosmetics, and pharmaceutical industries [7]. Thus, seaweeds have contribution to the economic growth. Other primary metabolites are polysulfated polysaccharides such as laminaran, rhamnan sulfate, galactosyl glycerol and fucoidan exhibit bioactivities such as antioxidant, antiallergic, anti-HIV, anticancer and anticoagulant [8-11]. Varieties of secondary metabolites are synthesized by seaweeds such as carotenoids, polyphenols, terpenoids,

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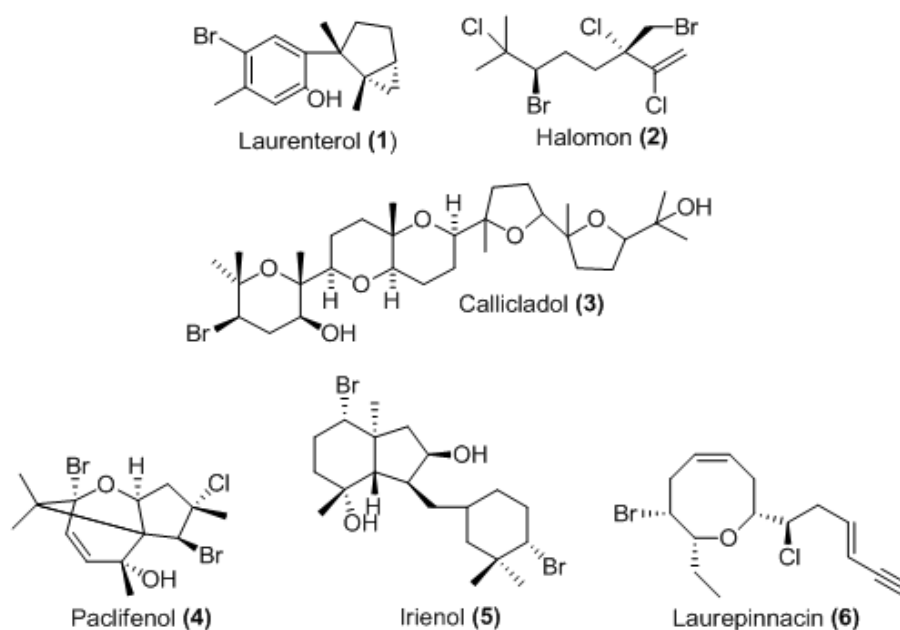


Fig 1. Halogenated compounds from red seaweeds

xanthophylls, chlorophyll, vitamins, alkaloid, saturated and polyunsaturated fatty acid [12-14].

Rhodophyta is rich in diversity of secondary metabolites than brown and green algae. Red algae is the most important source of biologically active metabolites in comparison to other algal. Most of the bioactive substances isolated from marine algae are chemically classified as brominated, aromatics, nitrogen-heterocyclic, nitrosulphuric heterocyclic, sterols, dibutanoids, proteins, peptides and sulphated polysaccharides. The chemistry of Rhodophyta is dominated by compounds from family Rhodomelaceae. Red algae are the main producers of halogenated compounds such as laurenterol (1), halomon (2), callicladol (3) etc as presented in Fig 1 [15-16]. Bromophenols were detected in families Ceramiaceae, Delesseriaceae, Bonnemaisoniaceae, Rhodophyllaceae, Corallinaceae and Rhodomelaceae [17]. The halogenated compounds exhibited diverse biological activities including anti bacterial, antifungal, anti inflammation, ichtiotoxic, cytotoxic and insecticidal activity. In addition, the red algae also produce terpenoid, polyether, and acetogenin along with some amino acid, shikimate, acetate and nucleic acid derivatives [14,18].

Indonesia is a mega biodiversity country and has the highest marine species richness. About 45 percent of world's seaweed species are in Indonesia. Based on the report of Siboga expedition there are approximately 782 species of seaweeds with number of 196 species are green algae, 134 species are brown algae and 452 species are red algae. Potential of seaweed in Indonesia

has contributed to the increase in revenue coastal communities in Riau, Sumatra, Java, Bali, West Nusa Tenggara, East Nusa Tenggara, Sulawesi and Maluku. Eastern Indonesia is called as a barn of seaweed due to high diversity of seaweed species. Various types of seaweed found in Indonesia but few are known to have economic value for food industry and commodity export such as *Gracilaria*, *Gelidium*, *Hypnea*, *Sargasum*, and *Turbinaria*. Production of seaweed Indonesia in 2014 reached 10 million tons. Most of seaweeds in Indonesia are unexplored, unidentified, under development and not fully utilized. According to FAO seaweed is very versatile product and can be diversified to food, cosmetics, pharmaceutical, bioethanol, animal feed, fish feed, integrated aquaculture and wastewater treatment. In Indonesian itself, seaweed production is still limited to the food industry and raw material exports. In efforts to use seaweed as a food industry, cosmetics, pharmaceutical, medicine and agriculture still needs to learn to countries that have experts in seaweed processing. Therefore, future actions still need to study the sustainable utilization of seaweed to improve life and welfare of Indonesian.

Researches on antibacterial activity of Indonesian seaweed were reported but very limited information regarding bioactive compounds. Current research in our group focuses on bioactive of Indonesian red algae. Research has been done on the varied species of red seaweeds collected along South Yogyakarta and East Nusa Tenggara. Research yielded a number of antibacterial compounds such as halogenated

compounds, terpenoid, steroid and long chain fatty acid (unpublished data).

ANTIBACTERIAL ACTIVITY

The incidence of bacterial resistance to antibiotics and other antibacterial agents increase each year. Several ways are available to protect and against infectious diseases such as using vaccine and antibiotics. Each approach has advantages and disadvantages. Some infectious diseases cannot be prevented by vaccine and antibiotics are still a drug of choice [19]. New antibiotics or antibacterial agents could be discovered from traditional and nontraditional resources. There is an urgently need for novel antimicrobial agents from different sources to combat emergence and reemergence infectious diseases [20-21]. The biodiversity of marine environment provides chemical diversity as source of bioactive compounds which promising to have potential and therapeutic applications [22-26]. Marine algae represent a great source of tremendous diversity of complex natural products and could be a promising source of novel bioactive compounds. Compounds with cytostatic, antioxidant, antiviral, antihelminthic, antifungal and antibacterial activities have been detected in green, brown and red algae [27-31]. It has been reported that seaweeds possess potent and broad spectrum of biological activities against the pathogenic microbes of medical, agricultural, aquaculture and environmental importance [32-34].

Several works have been reported in the searching for broad spectrum activity of seaweed extracts. This review only focuses on the antibacterial activity. Numerous extracts of seaweeds have been examined for antibacterial activity against pathogen in human, agriculture and fish. Extracts of seaweeds *Codium decortatum*, *Caulerpa scalpelliformis*, *Gracilaria crassa*, *Acanthophora spicifera*, *Sargassum wightii* and *Turbinaria conoides* from Gulf of Mannar exhibited antibacterial activity against *Vibrio parahaemolyticus*, *Salmonella* sp, *Shewanella* sp, *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Proteus mirabilis* [35].

Screening of 44 species seaweed extracts from Gran Canary, Canary Island, yielded 28 species showed antibacterial activity with *Asparagopsis taxiformis* and *Cymopola barbata* were the strongest activity [36].

The antibacterial activity of *Codium adhaerens* Anderson, *Sargassum wightii* Greville and *Acanthophora spicifera* (Vahl.) Boergs collected from intertidal region of the Mandapam coastal water showed weak activity against human pathogenic bacteria *S. aureus*, *V. cholerae*, *S. dysenteriae*, *S. bodii*, *S. paratyphi*,

P. aeuroginosa and *Klebsiella pneumonia* [37]. Ethanolic extract of *Gracilaria edulis*, *Calorpha peltada*, *Hydrocolthres* sp were tested against bacteria isolated from fish *Escherichia coli*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus faecalis* and *Bacillus cereus*. Results showed that ethanolic extract of *Gracilaria edulis* inhibited the growth of all test organisms except *Bacillus cereus* and *Enterobacter aerogenes*. Ethanolic extracts of *Calorpha peltada* was active against *Escherichia coli*, *Staphylococcus aureus* and *Streptococcus faecalis*, while extract of *Hydrocolthres* sp. only inhibited the growth of *Pseudomonas aeruginosa* [38].

Dichloromethane, methanol and water extracts of 26 species of cultivated seaweeds were screened for their antibacterial activities against five fish pathogenic bacteria strains *Aeromonas salmonicida* ssp. *salmonicida*, *Aeromonas hydrophila* ssp. *hydrophila*, *Pseudomonas anguilliseptica*, *Vibrio anguillarum*, *Yersinia ruckeri*. The dichloromethane extracts of *Asparagopsis armata*, *Ceramium rubrum*, *Drachiella minuta*, *Falkenbergia rufolanosa*, *Gracilaria cornea* and *Halopitys incurvus* showed strong antibacterial activities. *V. anguillarum* and *P. anguilliseptica* were the two most susceptible bacteria strains. The screening results confirmed that seaweeds as a potential source of antimicrobial compounds or as a health-promoting food for aquaculture [33].

All those studies are preliminary for searching antibacterial agents from algae. They screened extract to look at the activity and none of reports were determined the constituent of bioactive compounds. There numerous research in Indonesia as well that done on screen antibacterial activity of seaweed and limited compounds were reported as antibacterial agents.

ANTIBACTERIAL COMPOUNDS FROM RED ALGAE

Numerous bioactive compounds have been isolated and identified from seaweeds. This review focus on antibacterial compounds isolated from Red Algae (Rhodopytha) such as *Laurencia* spp., *Gracillaria* spp., *Acanthophora* spp and other rare species.

Laurencia spp.

Red algae of the genus *Laurencia* (Rhodomelaceae, Ceramiales) mainly found in tropical, subtropical and temperate coastal waters are known to be prolific sources of a wide variety of halogenated secondary metabolites, such as C₁₅-acetogenins, C₁₅-, C₂₀-, and C₃₀-terpenoids. A series of compound C₁₅ acetogenin en-yne were isolated from *Laurencia*

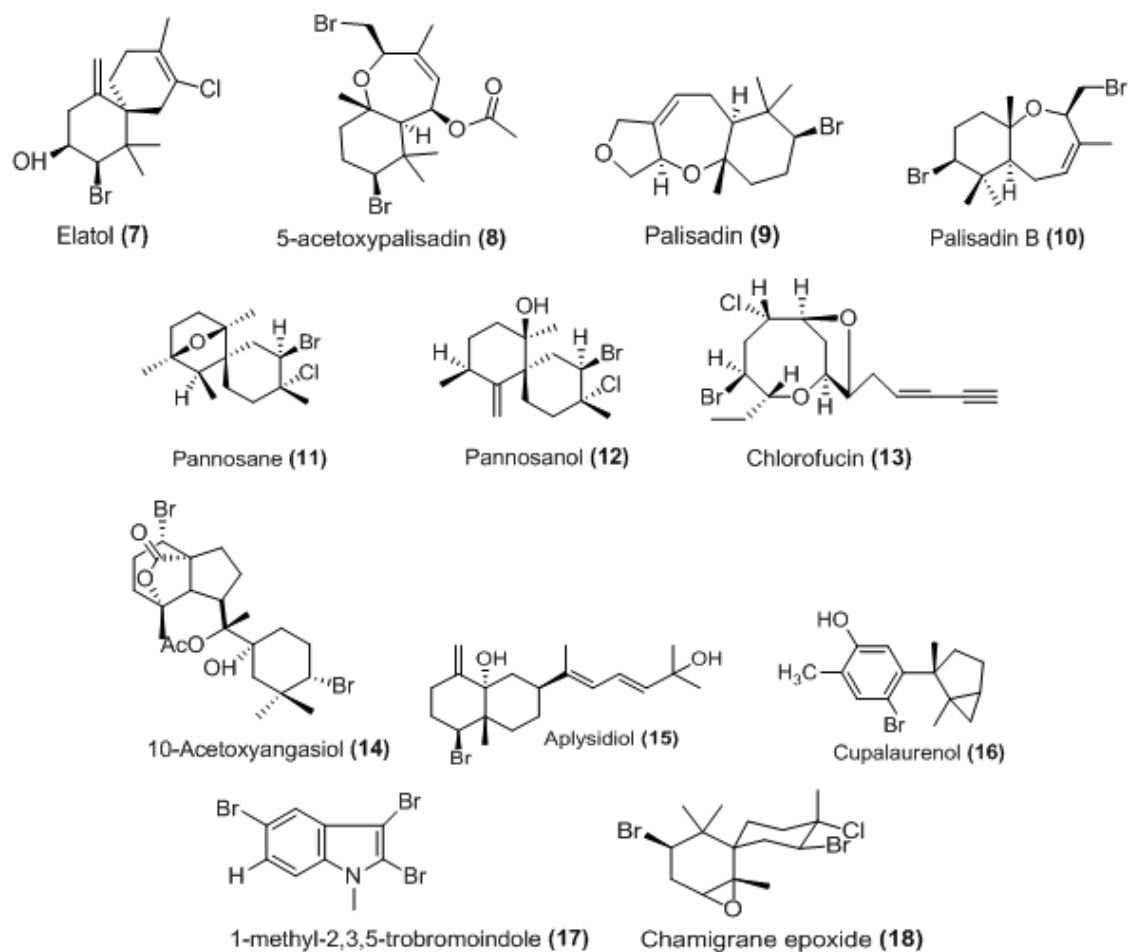


Fig 2. Antibacterial compounds from *Laurencia* spp.

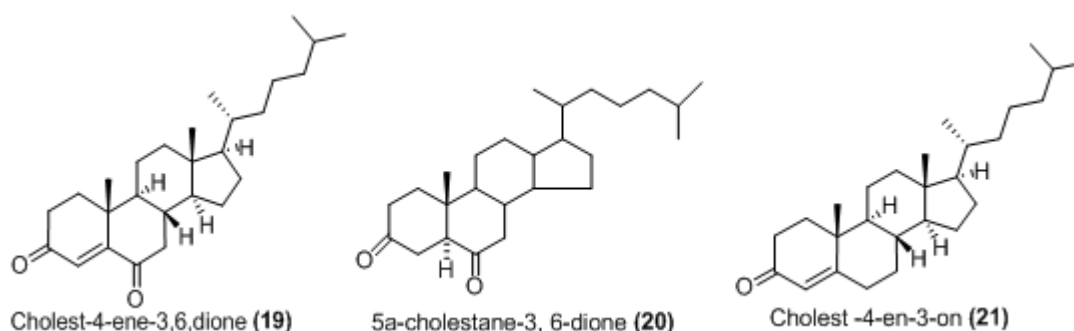
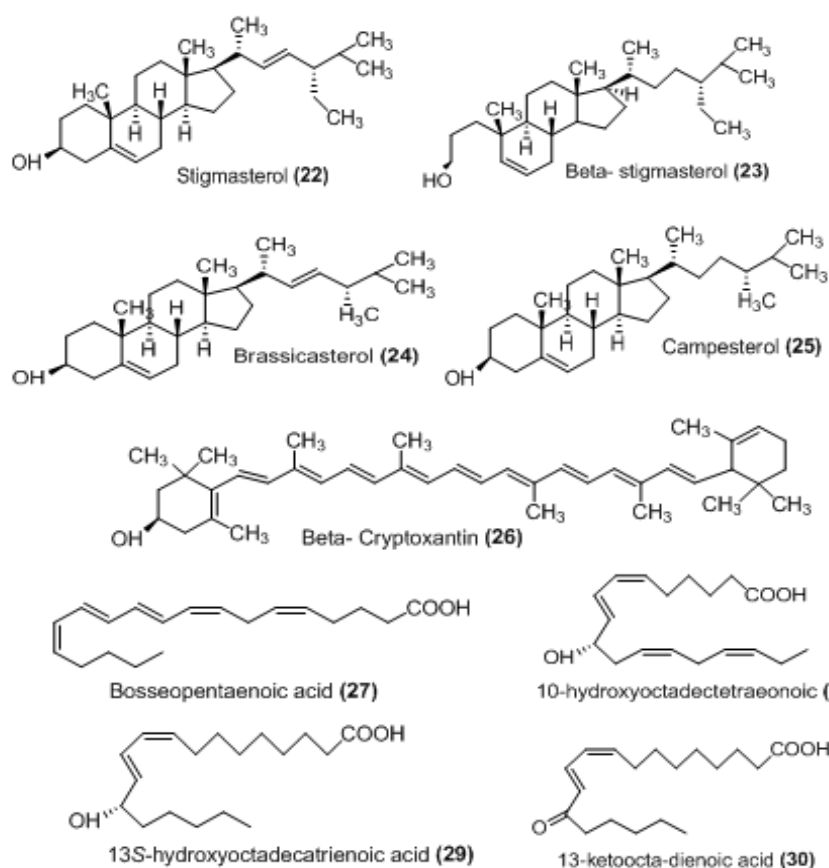
glandulifera collected from the island of Crete and showed activity as antistaphylococcal with MIC 8-256 mg/mL [39].

A halogenated sesquiterpene alcohol, elatol (7) is commonly found in many species of *Laurencia*, and known for its potent antibacterial activity. The compound was isolated for the first time in *L. microcladia*, collected in the Southern Brazilian coast. Studies showed that elatol has ecological roles as antiherbivore activity and potential defense against infection by microorganisms [40]. Antimicrobial compounds 5-acetoxypalisadin B (8), palisadin A (9) and palisadin B (10) were isolated from *L. saitoi* [41].

Antibacterial activity of Malaysian *L. pannosa* was tested against three species marine bacteria *Chromobacterium violaceum*, *Proteus mirabilis*, and *Vibrio cholerae*. Three halogenated sesquiterpene metabolites were identified as compounds responsible for antibacterial activity pannosanol (11), pannosane (12) and 3(Z) Chlorofucin (13). Pannosanol and pannosane are novel metabolites with camigrane framework. Pannosanol showed MIC 60 μ g/disk against

Proteus mirabilis and 100 μ g/disk against *Chromobacterium violaceum* and *Vibrio cholerae*. Pannosane and (3Z) Chlorofucin showed activity against *Chromobacterium violaceum* with MIC 60 and 100 μ g/disk, respectively [42].

Five antibacterial compounds were isolated from Malaysian species of *Laurencia* sp. were examined for antibacterial activities against clinical bacteria, *Staphylococcus aureus*, *Staphylococcus* sp., *Streptococcus pyogenes*, *Salmonella* sp. and *Vibrio cholerae*. The compounds were identified as 10-acetoxyangasiol (14), aplysidiol (15), cupalaurenol (16), 1-methyl-2,3,5-tribromoindole (17), and chamigrane epoxide (18). 10-acetoxyangasiol, aplysidiol, cupalaurenol exhibited potential activity against all tested isolates. The lowest MIC value was observed for 10-acetoxyangasiol against *Vibrio cholerae* at 100 μ g/mL. Compounds 1-methyl-2,3,5-tribromoindole and chamigrane epoxide showed weak inhibition against *Staphylococcus* sp. at MIC 300 μ g/mL [43].

Fig 3. Antibacterial agents from *Acanthopora spicifera*Fig 4. Antibacterial steroid, terpenoid and eiconosoid from *Gracilaria* spp.***Acanthopora* spp.**

The genus *Acanthopora* is one of the most abundance red algae on reef flat with wide distribution in tropic and subtropics regions, but investigation of this species is very rare. The chemical constituent of *Acanthopora* is rich of non halogenated steroid. Some sterols were isolated and identified from *A. spicifera* as 6-hydroxycholest-4-ene-3-one, cholest-4-ene-3,6-dione (19), cholest-5-ene-3 β -ol, 5 α -cholestane-3,6-dione (20),

β -sitosterol, saringosterol, 5 α -cholestane-3,6-dione, cholest-4-ene-3-one (21), 11 α -hidroxy-5 α -cholestane-3,6-dione, cholest-5-en-3 α -ol and cholest-4-ene-3 α ,6 β -diol [44-45]. It has been reported that some sterol showed activity as antibacterial and cytotoxic as well.

***Gracilaria* spp.**

Genus *Gracilaria* is very abundant with more than 300 species. The *Gracilaria* species is important in

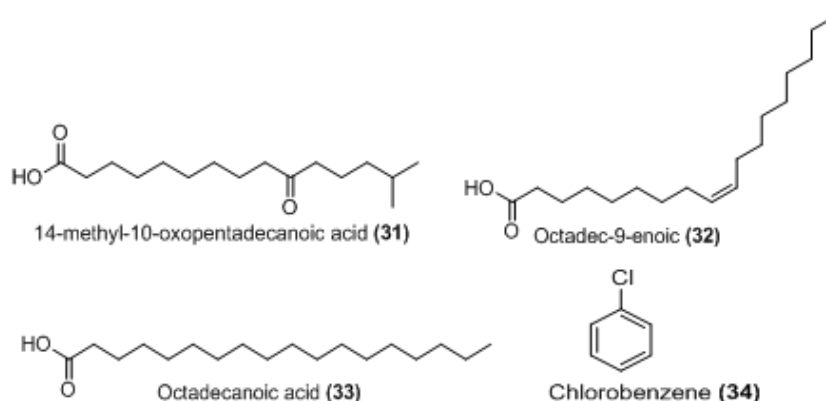


Fig 5. Antibacterial compounds from *Asparagopsis taxiformis*

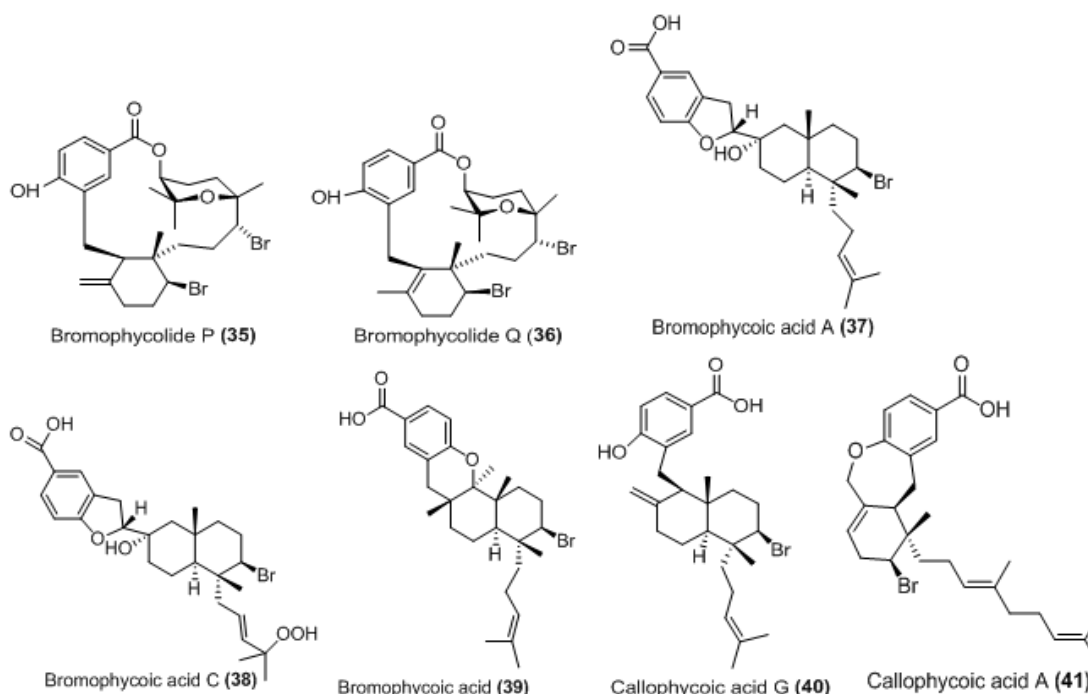


Fig 6. Antibacterial compounds from *C. Serratus*

industrial biotechnology due to the commercially product phycocolloid called agar and agarose widely used in food, pharmaceutical and cosmetic industries [46-49]. In addition *Gracilaria* spp. produces bioactive metabolites such as steroid (22-25), terpenoid (26) and eicosanoid acid (27-30) derivatives and with antibacterial activity [50]. The various bioactivities of genus *Gracilaria* was reviewed comprehensively by deAlmeida et al. [51].

Asparagopsis spp.

The red algae *Asparagopsis taxiformis* collected from the southwestern coast of India was tested for several activities including antibacterial. Chemical constituent were checked by TLC, HPLC and GC-MS

analysis of active fraction yielded compounds 4,5-dimethyl-1H-pyrrole-2-carboxylic acid, 14-methylpentadecanoic acid (31), octadec-9-enoic acid 2,3-dihydroxypropyl ester (32), 9-octadecanoic acid, and octadecanoic acid (33), chlorobenzene (34) [52].

Methanol and dichloromethane extracts of *A. armata* exhibited antibacterial activity against marine bacteria (*Vibrio* spp) and human pathogen (*Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus* spp.) strains. The major metabolites were identified by using GC-MS as bromoform and dibromoacetic acid. Both compounds found to be responsible for the antibacterial activity and is used by *A. armata* as chemical defenses for natural inhibitor and antifoulant of the growth of marine bacteria [53].

Callophycus serratus

Callophycus serratus is a marine red alga found throughout the tropical and subtropical regions in Southeast Asia, Pacific and Africa. Series of novel diterpene-benzoate macrolide (Bromophycolides), diterpene-benzoic acid (callophylic acids) and diterpene phenol (callophycols) were isolated from the Fiji red algae *C. serratus* with varied bioactivities including antifungal, antibacterial, anticancer, antimalarial, antitubercular [54-57]. Bromophycolides P and Q (**34-35**) showed activity as antibacterial against methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant *Enterococcus faecium* (VREF). The tetrahydropyran ring plays an important role in the antibacterial activity [58]. Bromophycoic acid A, C, E and callophycoic acid G (**37-41**) were active against MRSA with bromophycoic acid A and callophycoic acid G were the most potent at MIC 1.6 $\mu\text{g/mL}$. Bromophycoic E, callophycoic acid G and A were active against VREF at MIC 1.6, 3.1 and 0.8 $\mu\text{g/mL}$, respectively [59].

Neurymenia fraxinifolia

The less explored red algae *N. fraxinifolia* from Taveuni, Fiji was screened for antibacterial activity and yielded two novel compounds neurymenolide A and B (**42-43**) were identified having macrocyclic α -pyrones ring and derived from acetogenic pathway. Neurymenolide A exhibited activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF) with IC_{50} of 2.1 μM and 4.5 μM , respectively. The activity of neurymenolide B was less potent than neurymenolide A in any bioassay panel. This suggest that macrocyclic ring and aromatic hydroxy group are restrict and important for bioactivity relationship [60].

***Rhodomella* spp.**

Rhodomella confervoides produce mainly bromophenol compounds with various activities such as citotoxic and antibacterial [61-62] *onfervoides* was investigated for antibacterial activity. Five compounds (**44-48**) were identified by MS and NMR spectroscopic analyses yielded two new brominated compounds (bromophenol) and three known compounds which are 3-bromo-4-[2,3-dibromo-4,5-dihydroxyphenyl] methyl-5-(hydroxymethyl) 1,2-benzenediol and 3-bromo-4-[2,3-dibromo-4,5-dihydroxyphenyl] methyl-5- (ethoxymethyl) 1,2-benzenediol, 3-bromo-4-[2,3-dibromo-4,5dihydroxyphenyl] methyl-5-(methoxymethyl) 1,2-benzenediol, 4,4'- methylenebis [5,6-dibromo-1,2-benzenediol] and bis(2,3-dibromo-4,5-dihydroxybenzyl) ether. Compound bis (2,3-dibromo-4,5-dihydroxybenzyl) ether was the most active against five strains of bacteria with the MIC less than 70 $\mu\text{g/mL}$ [63].

CONCLUSIONS AND FUTURE DIRECTION

The algal chemistry is considered rich of functional group characteristics and broad spectrum of bioactivities. Seaweeds have been used as traditional

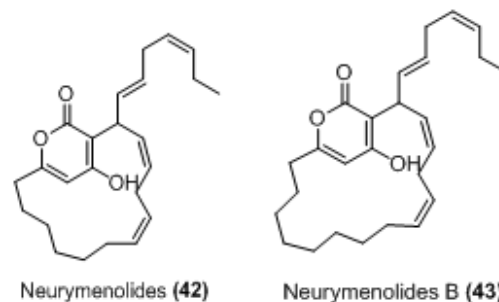


Fig 7. Antibacterial Neurymenolides from *Neurymenia fraxinifolia*

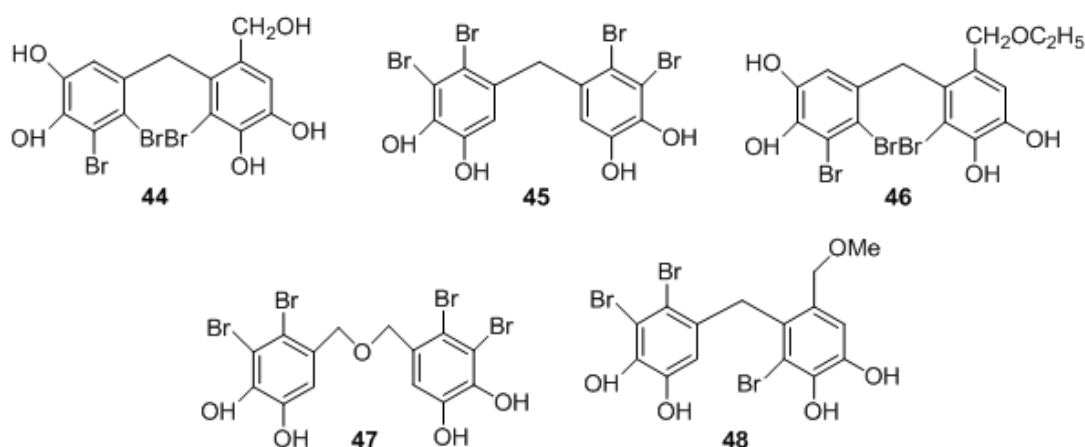


Fig 8. Antibacterial bromophenol from *Rhodomella confervoides*

remedies and potential sources of new antibacterial agents. Research and development continue to drive the study of marine algae and their potential metabolites for human health. Development of seaweed is supported by the facts that seaweeds could be collected, renewable, can be cultivate and fast growing. The investigation data on the chemical constituents and bioactivities showed the potential as antibacterial agents or leads for the synthesis novel antibiotics. Further studies are needed to carry out taxonomically classify and standardize methods for cultivating, harvesting and extracting of potential seaweed. Identifying the active compounds is necessary to gather the pharmacochemical profiles and pharmacologic effects. This review demonstrated that halogenated compounds, steroids, terpenoids and fatty acid possess bioactivity as antibacterial and potential to be developed.

Finally, we conclude that red algae are a potential source for antibacterial agents and can serve as lead in synthesis of new natural medicines. Novel compounds with intriguing chemistry and interesting ring system can be used as template for the design and development of new antibacterial compounds. In addition, interdisciplinary collaboration research in natural products, biology, chemistry, chemical ecology and biomedical sciences is important to deliver products that benefit for human life.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Castro, P., and Huber, M.E., 2013, *Marine Biology*, McGraw-Hill, New York, 102–113.
- Lordan, S., Roos, P.R., and Stanton, C., 2011, *Mar. Drugs*, 9(6), 1056–1100.
- Holdt, S.L., and Kraan, S., 2011, *J. Appl. Phycol.*, 23(3), 543–597.
- Dawczynski, C., Schäfer, U., Leiterer, M., and Jahreis, G., 2007, *J. Agric. Food Chem.*, 55(25), 10470–10475.
- El Gamal, A.A., 2010, *Saudi Pharm. J.*, 18(1), 1–25.
- Bhakuni, D.S., and Rawat, D.S., 2005, *Bioactive Marine Natural Products*, Anamaya Publisher, New Delhi, 1–10.
- Laurienzo, P., 2010, *Mar. Drugs*, 8(9), 2435–2465.
- Jiao, G., Yu, G., Zhang, J., and Ewart, H.S., 2011, *Mar. Drugs*, 9(2), 196–223.
- Pomin, V.H., and Maurão, P.A., 2008, *Glycobiology*, 18(12), 1016–1027.
- Ngo, D.H., and Kim, S.K., 2013, *Int. J. Biol. Macromol.*, 62, 70–75.
- Lee, J.-C., Hou, M.-F., Huang, H.-W., Chang, F.-R., Yeh, C.-C., Tang, J.-Y., and Chang, H.-W., *Cancer Cell Int.*, 13, 1–7.
- Takaichi, S., 2011, *Mar. Drugs*, 9(6), 1101–1118.
- Güven, K.C., Percot, A., and Sezik, E., 2010, *Mar. Drugs*, 8(2), 269–284.
- Maschek, J.A., and Baker, B.J., 2008, "The Chemistry of Algal Secondary Metabolism" in *Algal Chemical Ecology*, Amsler, C.D., Springer-Verlag Berlin Heidelberg, Germany, 1–24.
- Kladi, M., Vagias, C., and Roussis, V., 2003, *Phytochem. Rev.*, 3(3), 337–366.
- Cabrita, M.T., Vale, C., and Rauter, A.P., 2010, *Mar. Drugs*, 8(8), 2301–2317.
- Pedersén, M., Saenger, P., and Fries, L., 1974, *Phytochemistry*, 13(10), 2273–2279.
- Ayyad, S.E., Al-Footy, K.O., Alarif, W.M., Sobahi, T.R., Bassaif, S.A., Makki, M.S., Asiri, A.M., Al Halwani, A.Y., Badria, A.F., and Badria, F.A., 2011, *Chem. Pharm. Bull.*, 59(10), 1294–1298.
- Spížek, J., Novotná, J., Rezanka, T., and Demain, A.L., 2010, *J. Ind. Microbiol. Biotechnol.*, 37(12), 1241–1248.
- Smith, V.J., Desbois, A.P., and Dyrinda, E.A., 2010, *Mar. Drugs*, 8(4), 1213–1262.
- Kasanah, N., and Hamann, M.T., 2004, *Curr. Opin. Invest. Drugs*, 5(8), 827–837.
- Kijjoa, A., and Sawangwong, P., 2004, *Mar. Drugs*, 2(2), 73–82.
- Jha, R.K., and Zi-rong, X., 2004, *Mar. Drugs*, 2(3), 123–146.
- Sashidhara, K.V., White, K.N., and Crews, P.A., 2009, *J. Nat. Prod.*, 72(3), 588–603.
- Newman, D.J., and Cragg, G.M., 2004, *J. Nat. Prod.*, 67(8), 1216–1238.
- Capon, R.J., 2010, *Aust. J. Chem.*, 63, 851–857.
- Kelman, D., Posner, E.K., McDermid, K.J., Tabandera, N.K., Wright, P.R., and Wright, A.D., 2012, *Mar. Drugs*, 10(2), 403–416.
- Boopathy, N.S., and Kathiresan, K., 2010, *J. Oncol.*, 2010, 1–18.
- Liu, M., Hansen, P.E., and Lin, X., 2011, *Mar. Drugs*, 9(7), 1273–1292.
- Vo, T.-S., and Kim, S.-K., 2010, *Mar. Drugs*, 8(12), 2871–2892.

31. Beutler, J.A., McKee, T.C., Fuller, R.W., Tischler, M., Cardellina II, J.H., Snader, K.M., McCloud, T.G., and Boyd, M.R., 1993, *Antiviral Chem. Chemother.*, 4(3), 167–172.
32. Jiménez, E., Dorta, F., Medina, C., Ramírez, A., Ramírez, I., and Peña-Cortés, H., 2011, *Mar. Drugs*, 9(5), 739–756.
33. Bansemir, A., Blume, M., Schröder, S., and Lindequist, U., 2006, *Aquaculture*, 252(1), 79–84.
34. Manilal, A., Sujith, S., Kiran, G.S., Selvin, J., Shakir, C., Gandhimathi, R., and Lipton, A.P., 2009, *Ann. Microbiol.*, 59(2), 207–219.
35. Lavanya, R., and Veerappan, N., 2011, *Adv. Biol. Res.*, 5(1), 38–44.
36. del Val, A.G., Platas, G., Basilio, A., Cabello, A., Gorrochategui, J., Suay, I., Vicente, F., Portillo, E., del Río M.G., Reina, G.G., and Peláez, F., 2001, *Int. Microbiol.*, 4(1), 35–40.
37. Seenivasan, R., Rekha, M., Indu, H., and Geetha, S., 2012, *J. Appl. Pharm. Sci.*, 2(10), 159–169.
38. Kolanjinathan, K., Ganesh, P., and Govindarajan, M., 2009, *Eur. Rev. Med. Pharmacol. Sci.*, 13(3), 173–177.
39. Kladi, M., Vagias, C., Stavri, M., M. Rahman, M.M., Gibbons, S., and Roussisa, V., 2008, *Phytochem. Lett.*, 1(1), 31–36.
40. Dos Santos A.O., Veiga-Santos P., Ueda-Nakamura, T., Filho, B.P., Sudatti, D.B., Bianco, E.M., Pereira, R.C., and Nakamura, C.V., 2010, *Mar. Drugs*, 8(11), 2733–2743.
41. Ji, N-Y., Li, X-M., Li, K., and Wang, B-G., 2009, *Helv. Chim. Acta*, 92(9), 1873–1879.
42. Suzuki, M., Daitoh, M., Vairappan, C.S., Abe, T., and Masuda, M., 2001, *J. Nat. Prod.*, 64(5), 597–602.
43. Vairappan, C.S., Ishii, T., Lee, T.K., Suzuki, M., and Zhaoqi, Z., 2010, *Mar. Drugs*, 8(6), 1743–1749.
44. Wahidulla, S., D'Souza, L., and Govenker, M., 1998, *Phytochemistry*, 48(7), 1203–1206.
45. Lang, K.L., Palermo, J.A., Falkenberg, M., and Schenkel, E.P., 2007, *Biochem. Syst. Ecol.*, 35, 805–808.
46. Prakash, O., Roy, R., and Bhakuni, D.S., 1989, *J. Nat. Prod.*, 52(4), 686–692.
47. Marinho-Sariano, E., 2001, *J. Biotechnol.*, 89(1), 81–84.
48. Francavilla, M., Franchi, M., Monteleone, M., and Caroppo, C., 2013, *Mar. Drugs*, 11(10), 3754–3776.
49. Andriamanatoanina, H., Chambat, G., and Rinaudo, M., 2007, *Carbohydr. Polym.*, 68, 77–88.
50. Gerwick, W.H., and Bernart, M.W., 1993, *Mar. Biotechnol.*, 101–149.
51. de Almeida, C.L.F., Falcão, H.d.F., Lima, G.R.d.M., Montenegro, C.d.A., Lira, N.S., de Athayde-Filho, P.F., Rodrigues, L.C., de Souza, M.d.F.V., Barbosa-Filho, J.M., and Batista, L.M., 2011, *Int. J. Mol. Sci.*, 12(7), 4550–4573.
52. Manilal, A., Sugathan Sujith, S., Sabarathnam, B., Kiran, G.S., Selvin, J., Chippu Shakir, C., and Lipton, A.P., 2010, *Braz. J. Oceanogr.*, 58(2), 93–100.
53. Paul, N.A., de Nys, R., and Steinberg, P.D., 2006, *Mar. Ecol. Prog. Ser.*, 306, 87–101.
54. Lin, A.S., Stout, E.P., Prudhomme, J., Le Roch, K., Fairchild, C.R., Franzblau, S.G., Aalbersberg, W., Hay, M.E., and Kubanek, J., 2010, *J. Nat. Prod.*, 73(2), 275–278.
55. Kubanek, J., Prusak, A.C., Snell, T.W., Giese, R.A., Fairchild, C.R., Aalbersberg, W., and Hay, M.E., 2006, *J. Nat. Prod.*, 69(5), 731–735.
56. Kubanek, J., Prusak, A.C., Snell, T.W., Giese, R.A., Hardcastle, K.I., Fairchild, C.R., Aalbersberg, W., Raventos-Suarez, C., Hay, M.E., 2005, *Org. Lett.*, 7(23), 5261–5264.
57. Lane, A.L., Elizabeth P. Stout, E.P., Hay, M.E., Prusak, A.C., Hardcastle, K., Fairchild, C.R., Franzblau, S.G., Le Roch, K., Prudhomme, J., Aalbersberg, W., and Kubanek, J., 2007, *J. Org. Chem.*, 72(19), 7343–7351.
58. Lane, A.L., E. Stout, E.P., Lin, A-S., Prudhomme, J., Le Roch, K., Fairchild, C.R., Franzblau, S.G., Hay, M.E., Aalbersberg, W., and Kubanek, J., 2009, *J. Org. Chem.*, 74(7), 2736–2742.
59. Teasdale, M.E., Shearer, T.L., Engel, S., Alexander, T.S., Fairchild, C.R., Prudhomme, J., Torres, M., Le Roch, K., Aalbersberg, W., Hay, M.E., and Kubanek, J., 2012, *J. Org. Chem.*, 77(18), 8000–8006.
60. Stout, E.P., Hasemeyer, A.P., Lane, A.L., Davenport, T.M., Engel, S., Hay, M.E., Fairchild, C.R., Prudhomme, J., Le Roch, K., Aalbersberg, W., and Kubanek, J., *Org. Lett.*, 2009, 11(1), 225–228.
61. Ma, M., Zhao, J., Wang, S., Li, S., Yang, Y., Shi, J., Fan, X., and He, L., 2006, *J. Nat. Prod.*, 69(2), 206–210.
62. Ma, M., Zhao, J., Wang, S., Li, S., Yang, Y., Shi, J., Fan, X., and He, L., 2007, *J. Nat. Prod.*, 70(3), 337–341.
63. Xu, N., Fan, X., Yan, X., Li, X., Niu, R., and Tseng, C.K., 2003, *Phytochemistry*, 62(8), 1221–1224.