Seaweed phytochemicals utilization in marine aquaculture

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Abstract. Global aquaculture production has been steadily increasing since early 1990s, while fishery production has been stagnant. It is expected for the aquaculture production to outgrow the fishery production in the next couple of years. Although aquaculture plays an important role in food resilience, this industry still faces difficulties against diseases, from deteriorated environment, and from a lack of nutrients that hinder aquaculture production. Seaweeds produce numerous metabolite compounds with various biological activities, for instance, antioxidant, anti-bacterial and immunomodulator. Bioactive compounds from seaweeds are utilised to ameliorate diseases. Thus, seaweeds become natural resources for the pharmaceutical industry. In the present review, the utilisation of bioactive phytochemicals from seaweeds in the aquaculture industry and their effects on farmed organisms are discussed. This review emphasises the importance of antioxidant, anti-bacterial and immunomodulatory activities and the practical employment of seaweeds inclusion to improve aquaculture production.

Key Words: anti-bacterial, antioxidant, aquaculture, bioactive compound, immunomodulator.

Introduction. A steady increase in global aquaculture production has been reported to take a bigger portion of the global fishery and aquaculture production in 2018 (Føre et al 2018). Global aquaculture production was 82.1 million tonnes in 2018, making up almost 46% of total global fisheries and aquaculture production (FAO 2020). However, aquaculture industries are still facing difficulties that impede its production and threat global food security. Induced stress, high stocking density and high infection rate from pathogenic bacteria can cause diseases that decimate aquaculture industries and massively affect the farmed fish (Føre et al 2018; Culot et al 2019). In addition, uneaten feed waste and sedimentation from the fish farmed can impair the environment (Føre et al 2018; Junior et al 2021). Over time, under certain conditions, this nutrient build-up can induce a red tide and anoxic environment that asphyxiates and wipes out farmed organisms (Risk et al 2021). Meanwhile, fish meal is becoming more limited and expensive due to decreased raw material (Hua et al 2019). Fish feed industries are looking for alternatives that still meet fish nutrition requirements for the optimum growth performance and gonadal maturation of the farmed fish (Arriaga-Hernández et al 2021).

Seaweeds consist of three major groups: green algae, red algae, and brown algae that play an important role in the environment (Hossain et al 2021; Xiao et al 2021). These photosynthetic marine organisms absorb nutrient to grow and biosynthesize various metabolite compounds (Felaco et al 2020; Tanaka et al 2020; Revilla-Lovano et al 2021). Generally, phytochemicals from seaweed consist of carotenoids, polyunsaturated fatty acids, phyco-colloids and sterols (Gnanavel et al 2019) that have numerous biological activities, such as antioxidant (Anjali et al 2019; Pimentel et al

2020), anti-bacterial (Anjali et al 2019; Deepitha et al 2021), anti-obesity (Chin et al 2020), anticancer (Bellan et al 2020) and immunomodulatory (Thépot et al 2021a). Pharmaceutical industries have used seaweed as natural resources to obtain bioactive compounds for its production (Ganesan et al 2019). Meanwhile, aquaculture industries also employ bioactive phytochemicals from seaweed to improve farmed-fish condition and aquaculture production (Thépot et al 2021b). It gives multiple benefits for aquaculture organisms, such as growth performance (Yangthong & Ruensirikul 2020), gonadal maturation (Takagi et al 2020), immunostimulant (Mohan et al 2019) and disease-resistance (Naiel et al 2021; Thépotb et al 2021) as well. Optimizing seaweed utilization in aquaculture industries could ameliorate the detrimental effect of aquaculture problems are previously mentioned (Figure 1).

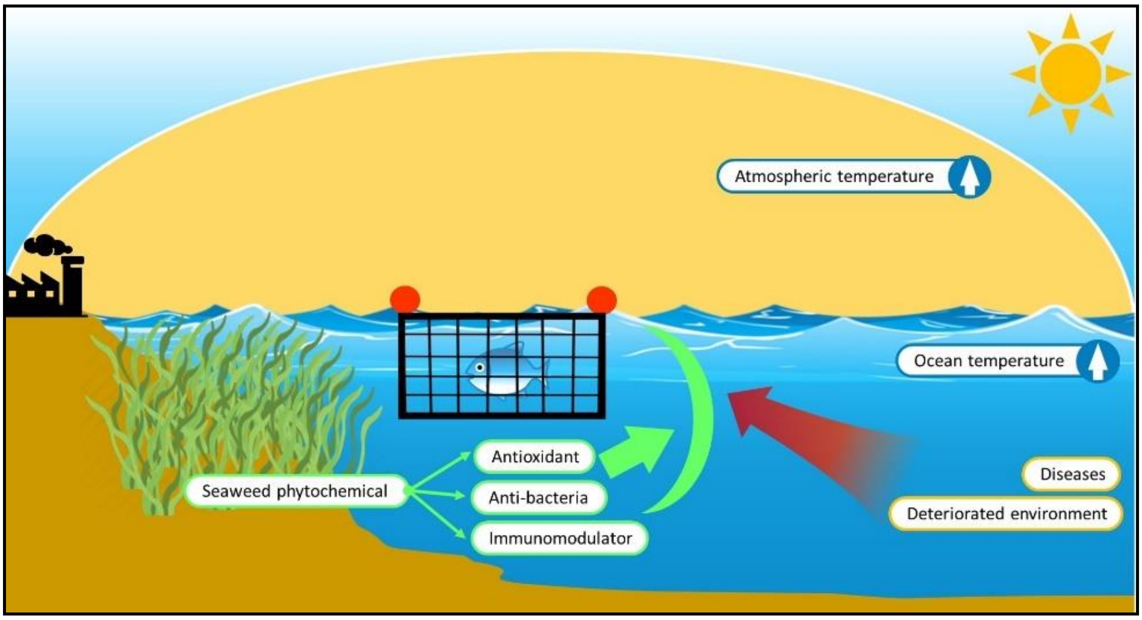

Figure 1. Seaweed phytochemicals protection for aquaculture organisms.

This article reviews seaweed metabolite utilization in aquaculture as an antioxidant, anti-bacterial, therapeutic agent, and additive to improve aquaculture production and resilience (Figure 2).

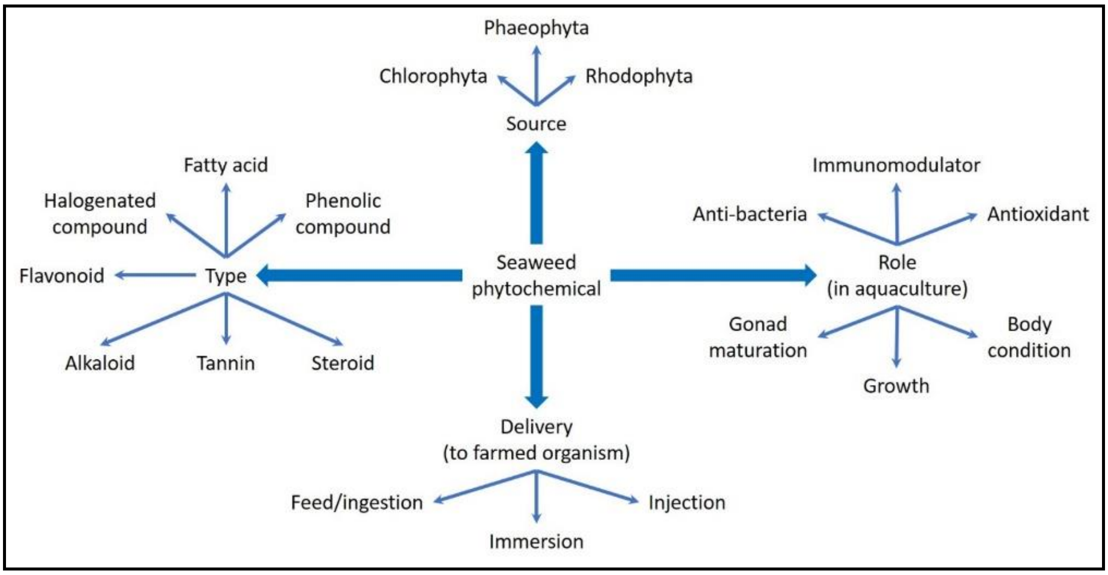

Figure 2. Seaweed phytochemical utilization in aquaculture.

Antioxidant activities of seaweed phytochemicals. An excessive amount of reactive oxygen species (ROS) has been reported to cause lipid peroxidation and lead to cell damage of living organisms. In aquatic organisms, oxygen concentrations are affected by environmental factors such as temperature, salinity, season, and pollutant. Increased temperature heightens oxygen consumption, resulting in increased ROS production (Lushchak 2011). The ROS production may also promote various diseases and toxicity in aquatic organisms exposed to pollutants (Shi et al 2005; Biller & Takahashi 2018). For counteracting the harmful effects of ROS, living organisms have developed a complex antioxidant defense system (Cian et al 2019). The antioxidant defense systems prevent cell damage by delaying the significant accumulation of free radicals in an aquatic environment and improve the innate immunity of aquatic organisms. Moreover, antioxidants protect the developing larvae from oxidative stress (Dandapat et al 2003; Tripathy 2016). Therefore, many studies have reported that dietary natural antioxidant supplements may enhance the antioxidant capacity in aquatic animals (Table 1).

Table 1

Seaweed species and extract with antioxidant benefits as feed diets in aquaculture

Seaweed species	Extracts/ compounds	Marine commodities	Reference
Red seaweeds			
Asparagopsis armata	Extract	Shrimp (*Penaeus vannamei*)	Félix et al 2020
Gracilaria lemaneiformis	-	*Litopenaeus vannamei*	Niu et al 2019
Gracilaria pygmaea	Powder	Rainbow trout (*Oncorhynchus mykiss*)	Sotoudeh & Mardani 2018
Gracilaria sp.	Aqueous extract	European seabass (*Dicentrarchus labrax*)	Peixoto et al 2019
Gracilaria vermiculophylla	-	Rainbow trout (*Oncorhynchus mykiss*)	Valente et al 2015; Araújo et al 2016
Gracilaria vermiculophylla	-	Gilthead seabream (*Sparus aurata*)	Magnoni et al 2017
Gracilariopsis persica	-	Rainbow trout (*Oncorhynchus mykiss*)	Vazirzadeh et al 2020
Hypnea flagelliformis	-	Rainbow trout (*Oncorhynchus mykiss*)	Vazirzadeh et al 2020
Laurencia caspica	Hydroalcoholic extract	Rainbow trout (*Oncorhynchus mykiss*)	Kiadaliri et al 2020
Mix of *Gracilaria* sp, *Fucus* sp, and *Ulva* sp	-	European seabass (*Dicentrarchus labrax*)	Peixoto et al 2016b; Lobo et al 2018
Porphyra haitanensis	-	*Litopenaeus vannamei*	Niu et al 2019
Pyropia columbina	-	Juvenile Pacú (*Piaractus mesopotamicus*)	Cian et al 2019
Green seaweeds			
Enteromorpha sp	Polysaccharides	Banana shrimp (*Fenneropenaeus merguiensis)*	Liu et al 2020
Ulva lactuca	-	Gilthead sea bream (*Sparus aurata*)	Magnoni et al 2017
Ulva lactuca	Powder	European seabass (*Dicentrarchus labrax*)	Peixoto et al 2016a, 2016b
Brown seaweeds			
-	Laminarin	Grouper *(Epinephelus coioides)*	Yin et al 2014
Fucus spp.	Powder	European seabass (*Dicentrarchus labrax*)	Peixoto et al 2016a, 2016b
Laminaria sp.	AquaArom	Atlantic salmon (*Salmo salar*)	Kamunde et al 2019
Saccharina japonica	-	*Litopenaeus vannamei*	Niu et al 2019
Sargassum boveanum	-	Rainbow trout (*Oncorhynchus mykiss*)	Vazirzadeh et al 2020
Sargassum boveanum	Powder	Rainbow trout (*Oncorhynchus mykiss*)	Vazirzadeh et al 2020
Sargassum filipendula	Powder	White-leg shrimp (*Litopenaeus vannamei*)	Schleder et al 2017
Sargassum horneri	-	Juvenile black sea bream (*Acanthopagrus schlegelii)*	Shi et al 2019
Undaria pinnatifida	-	*Litopenaeus vannamei*	Niu et al 2019

Seaweeds are one of the richest and sustainable sources of natural antioxidants, macronutrients, and micronutrients, such as vitamins and trace elements (Bhattacharjee

& Islam 2014; Morais et al 2020). Many studies have reported that seaweed polysaccharides contain anti-inflammatory, antimicrobial, antiviral, immune-enhancing, and efficient antioxidant properties. Those are appropriate to be used as functional feeds that bring health benefits, including in disease management (Susanto et al 2019; Morais et al 2020). Recent work has revealed that *Gelidium pusillum* extracts exhibit a strong antioxidant and anti-bacterial activity against the marine pathogen *Aeromonas caviae*. The infected prawns treated with the ethanolic extract of *G. pusillum* survived even after three weeks compared to untreated ones (Agarwal et al 2021). The antioxidant properties of red seaweed *Halymenia dilate* have been reported to promote a significant growth and a high survival rate of ornamental fish *Poecilia sphenops*. The fish feeds with marine red algae *H. dilate* increased the growth performance and the survival rate of fish up to 99.99%, whereas, in control, it was only 33.32%. This finding suggested that aquatic feeds prepared with red seaweed are nutritionally adequate and a rich source of antioxidants for ornamental fish species *P. sphenops* (black molly) (Azeez et al 2020).

Effects of dietary inclusion of red seaweeds (*Gracilariopsis persica, Hypnea flagelliformis*) and brown seaweeds (*Sargassum boveanum*) on the antioxidant capability of rainbow trout (*Oncorhynchus mykiss*) have been reported (Vazirzadeh et al 2020). Feeding treatments with 5-10% seaweeds up to 83 days increased head-kidney antioxidant enzymes activity of rainbow trout. However, red seaweeds (*G. persica* and *H. flagelliformis*) showed higher superoxide dismutase (SOD) and peroxidase (POD) levels compared to brown seaweeds. Another red seaweed species, *Gracilaria vermiculophylla,* has been reported to enhance POD levels of *O. mykiss* (Araújo et al 2016). It not only induced POD expression, but supplementation with 5% *G. vermiculophylla* also stimulated the expression of the innate immune response of rainbow trout. In another study, supplementation with 5% *G. vermiculophylla* has been reported to increase the sensory panel, intensified the color and produced juicier rainbow trout flesh. In addition, the iodine content of rainbow trout flesh was doubled (Valente et al 2015).

Furthermore, *Gracilaria*-supplemented diet (7.5%) and seaweeds mix (*Gracilaria* sp., *Fucus* sp., and *Ulva* sp.) in European seabass (*Dicentrarchus labrax*) diets have been reported to increased glutathione S-transferase and glutathione reductase, respectively (Peixoto et al 2016b). The effects of dietary supplementation with four different seaweed species (*Porphyra haitanensis, Undaria pinnatifida*, *Saccharina japonica* and *Gracilaria lemaneiformis)* to *Litopenaeus vannamei* have been reported. Seaweed treatments have been shown to improve antioxidant response and immune response in *L. vannamei,* resulting in reduced enterohepatic damage (Niu et al 2019). In addition, seaweed supplementation also regulated intestinal microbiota in *L. vannamei*. Compared to other seaweed species tested in *L. vannamei, G. lemaneiformis* is the most suitable seaweed as the feed ingredient for *L. vannamei*, followed by the brown seaweed *U. pinnatifida*.

Collectively, these studies confirmed seaweed as a natural and effective tool to increase the nutritional value of fish. However, *Gracilaria* sp. supplementations at a concentration above 5% have been reported to reduce fish growth (Araújo et al 2016). It might be correlated with the presence of anti-nutritional factors present in seaweeds, which affect fish digestion processes. Silva et al (2015) studied the effects of the inclusion of three seaweeds (*Gracilaria* sp., *Porphyra* sp., and *Ulva* sp.) in the Nile tilapia (*Oreochromis niloticus*) diet. Notably, compared to other seaweed diets, the *Gracilaria* sp. diet was less ingested by fish and led to evident changes in the fish digestive system morphology with a significant reduction of villi length (Silva et al 2015). These might be related to the anti-nutritional factors (such as lectin, and other bioactive products) present in *Gracilaria* sp. Therefore, even though seaweeds are a potential antioxidant source in aquaculture, further study on anti-nutritional factors and optimal doses of seaweeds in aquaculture feeds are required.

The effects of dietary brown seaweeds (*Sargassum horneri*) on antioxidant status and immune responses of juvenile black seabream (*Acanthopagrus schlegelii*) have been demonstrated (Shi et al 2019). Black sea bream treated with 6% *S. horneri* supplement showed higher total antioxidant capacity, superoxide dismutase, and catalase activities compared to the control group. In addition, the expression levels of immunomodulators genes such as interleukin (IL)-1β, IL-8, and tumor necrosis factor (TNF) in the liver of black sea bream significantly increased with *S. horneri* diets. These results indicated that dietary *S. horneri* supplementation not only improves hepatic antioxidant status, but also enhances the immune ability of the black sea bream.

The antioxidant effect of red seaweed *Pyropia columbina* on juvenile pacú (*Piaractus mesopotamicus*) has been demonstrated (Cian et al 2019). Pacú fish feed added with *P. columbina* (35 g kg^{-1}) showed lower lipid peroxidation and SOD and reduced SOD/CAT ratio in the intestine than the control group. Furthermore, beneficial effects on lipid metabolism were observed in fish fed with added feed with *P. columbina*. The beneficial effects of *P. columbina* as an additive feed are strongly related to their chemical constituents, such as amino acids and phenolic acids. It is known that seaweeds are a rich source of phenolic acids (Cian et al 2019; Pangestuti et al 2019). Phenolic acids showed a strong correlation with high antioxidant activities (Martins et al 2013; Chakraborty et al 2015; Rafiquzzaman et al 2016). The antioxidant activity of phenolic compounds depends on their structural features. The hydroxyl (–OH) group bound to the aromatic ring of phenolic compounds acts as an electron donor, reacts to a free radical or other reactive species, which breaks the cycle of new radicals (Pereira et al 2009; Pangestuti et al 2018). This cycle of new radical breaking activity underlies the antioxidant activity of phenolic compounds. In addition, the attachment of –OH groups at the meta position of benzoic acid increases the H-donating radical scavenging activity of phenolic compounds. However, the carboxyl group negatively affects proton donation due to the electron-withdrawing properties (Fernando et al 2016).

Recently, Kiadaliri et al (2020) reported the effects of hydroalcoholic extract of *Laurencia caspica* on antioxidant defense, innate immune responses, and expression of immune genes in rainbow trout (*O. mykiss*). Rainbow trout were fed with different concentrations of *L. caspica* extracts and then challenged with *Aeromonas hydrophila.* The results showed that the levels of antioxidant enzymes (CAT, glutathione peroxidase, and SOD) were affected by the *L. caspica* supplementation. In addition, *L.* caspica extract supplementation stimulated the immune system and increased rainbow trout resistance to *A. hydrophila*.

Many studies have demonstrated the antioxidant activities of polysaccharides from seaweeds including fucoidan, laminarin and alginates. Antioxidant activity of seaweed polysaccharides have been determined by various methods such as 1,1-diphenyl-2-picryl hydrazil (DPPH) radical scavenging, lipid peroxide inhibition, ferric reducing antioxidant power (FRAP), nitric oxide (NO) scavenging, ABTS radical scavenging, superoxide radical, total antioxidant and hydroxyl radical scavenging assays (Wijesekara et al 2011). In addition, seaweeds polysaccharides have been reported to improve growth rate, immune systems as well as antioxidant levels in fish, shrimps and other marine commodities. The effects of *Enteromorpha* sp. in the banana shrimp (*Fenneropenaeus merguiensis*) aquaculture have been demonstrated. Around 2400 juvenile shrimps (2.18±0.06 g) were fed with diets containing different levels of *Enteromorpha* sp. polysaccharides (1, 2 and 3 g kg^{-1}). Compared to other concentrations, dietary supplementation of 1 g kg^{-1} of *Enteromorpha* sp. polysaccharides showed higher total anti-oxidative capacity (T-AOC) and antioxidant enzymes, including SOD, glutathione peroxidase (GPx), and glutathione S-transferase (Kongsri et al 2013; Liu et al 2020). Laminarin represents storage polysaccharides in brown seaweeds, and it has been isolated from various brown seaweeds species (Pangestuti et al 2018; Pangestuti et al 2021). Structurally, laminarins are composed of (1–3)-β-d-glucan with β-(1–6) branching with different reducing endings, either mannitol or glucose residues. Effects of laminarin as a supplement in the diet of groupers (*E. coioides*) were studied (Yin et al 2014). Supplementation with laminarin for 48 days significantly improved growth rate and antioxidant enzymes levels, including catalase (CAT) and SOD (Yin et al 2014). Therefore, it may be assumed that grouper utilize dietary nutrients more efficiently when fish feed is supplemented with laminarin.

Kamunde et al (2019) reported the effect of the dietary addition of AquaArom, a seaweed meal derived from brown seaweeds *Laminaria* sp., to the antioxidant capacity of Atlantic salmon (*Salmo salar*) for 30 days. The measurement of the antioxidant status revealed that seaweed supplementation dose-dependently increased plasma total antioxidant capacity as well as the level of GSH and activities of CAT and SOD in liver mitochondria.

Seaweed phytochemical as anti-bacterial agent. Antibiotics have been used in fish farming to avoid and eliminate pathogenic bacteria in rearing systems that might cause diseases. Synthetic chemicals are widely employed to oversee and overcome infections in aquaculture (Thanigaivel et al 2015; Nazarudin et al 2020). However, the utilization of synthetic antibiotics is facing several drawbacks. For instance, synthetic antibiotics are non-biodegradable, which means toxic compounds will accumulate in organisms and sediment (Thanigaivel et al 2015; Stabili et al 2019). These conditions will harm not only other organisms and human health but also the environment.

Moreover, repeated uses of synthetic antibiotics develop bacterial resistant strains and, overtime, drug efficacy reduces (Cortés et al 2014; Stabili et al 2019; Jahromi et al 2021). In addition, concerning the growing aquaculture industries, stricter rules from the authority might apply to avoid excessive application of synthetic antibiotics (Cortés et al 2014; Li et al 2018). Thus, a natural and biodegradable antibiotic is preferable in future practices.

Seaweed extract contains various metabolite compounds with various biological activities, for instance, anti-bacterial (Cortés et al 2014). Anti-bacterial agents from seaweed metabolites are considered biodegradable and environmentally friendly (Thanigaivel et al 2015). This type of biological activity can be utilized in aquaculture antibiotics to replace synthetic antibiotics and ameliorate negative effects on other non-targeted organisms and the environment (Li et al 2018; Thépot et al 2021b).

Seaweed extract has been studied as an anti-bacterial agent to reduce pathogenic infection in various mariculture commodities (Table 2). This extract has been delivered to targeted farmed fish through immersion, animal feed, and injection in various life stages. For instance, injection of ethanolic extract of red seaweed *Gracilaria fisheri* to *Penaeus monodon* scaled-down shrimp mortality due to *Vibrio harveyi* infection (Kanjana et al 2011). Similarly, ethanolic extract of red algae *G. fisheri* in shrimp feed reduced mortality of shrimp *P. vannamei* from *Vibrio* infection. Moreover, the extract discouraged attachment and colonization of vibrio in shrimp gut (Karnjana et al 2019). Therefore, ethanolic extract of *G. fisheri* could ameliorate *Vibrio* infection in shrimp. Also, seaweed extract inclusion reduced bacterial load on the fish feed and improved its shelf-life (Castanho et al 2017). Meanwhile, fucoidan inclusion from brown algae *Sargassum wightii* in shrimp feed decreased *Vibrio parahaemolyticus* load in *Penaeus monodon* as well (Sivagnanavelmurugan et al 2014). Similarly, the inclusion of seaweed meal from green algae *Ulva ohnoi* in fish feed lowered the pathogen load of *Photobacterium damselae* in the liver of *Solea senegalensis* (Fumanal et al 2020).

Previous studies revealed that various compounds from seaweed have anti-bacterial activities, for instance, lipophilic halogenated compounds, hexadecane, octadecane, linolenic acid, dimethylamine, alkaloid, flavonoid, tannin, and peptides as well (Table 3). Bioactive compounds can be obtained through solvent extraction using water, methanol, ethanol, butanol or dichloromethane. Seaweed extract has been reported to inhibit bacterial growth of the main pathogenic bacteria in mariculture, for example, *Vibrio*, *Aeromonas*, *Pseudomonas*, and *Streptococcus*. It is suggested that excessive bioactive compounds from seaweed extract, for instance, polyunsaturated fatty acids, produce ROS that interacts and disintegrates bacterial cell membranes leading to cell lysis (Kasanah et al 2019).

Although seaweed extracts show benefits as anti-bacterial agents, utilization of their bioactive compounds is still limited in aquaculture industries. It requires thorough investigation regarding seaweed cultivation, extraction, handling, processing, delivery, and even digestibility in organisms prior to practical use. Seaweed metabolite production is driven by various factors such as season, environment and location. Thus, certain cultivation and extraction methods should be performed to obtain the optimum amount of targeted bioactive compound (Bansemir et al 2006; Maftuch et al 2016). Some fish life stages are sensitive to environmental and nutritional changes. Thus, the delivering method of this anti-bacterial agent that provides maximum efficacy should be considered

(Castanho et al 2017). Moreover, cytotoxic screening should be done prior to phytochemical utilization of the anti-bacterial agent because halogenated compounds from seaweed extracts can cause genetic changes (Bansemir et al 2006). In addition, bioactive compounds from seaweed extracts are biodegradable and easily deteriorated. Thus, precautious processing, handling and storage methods need to be considered (Bansemir et al 2006).

Table 2

Utilization of seaweed extract and its anti-bacterial activities

Seaweed	*Application*	*Mariculture organism*	*Pathogenic bacteria*	*Effect*	*Reference*
Red seaweed					
Asparagopsis armata	Ethanol extract in shrimp fed	*Penaeus vannamei*	*V. parahaemolyticus*	Reduced mortality after pathogenic bacteria challenge; reduced feed contamination.	Félix et al 2020
Gracilaria fisheri	Ethanol extract in shrimp fed	*Penaeus vannamei*	*Vibrio harveyi*, *V. parahaemolyticus*	Reduced biofilm formation in the gut.	Karnjana et al 2019
G. fisheri	Ethanol extract for Artemia enrichment (postlarvae fed)	*Penaeus monodon*	*V. harveyi*	Reduced postlarvae mortality after pathogenic bacteria challenge.	Kanjana et al 2011
G. fisheri	Ethanol extract injection	*Penaeus monodon*	*V. harveyi*	Increased cellular and humoral defence. Reduced mortality after pathogenic bacteria challenge.	Kanjana et al 2011
Green seaweed					
Caulerpa sertularioides	Methanol extract for juvenile immersion	*Litopenaeus vannamei*	*V. parahaemolyticus*, *V. alginolyticus*	Reduced mortality after pathogen injection.	Esquer-Miranda et al 2016
Ulva intestinasis	Hot water crude extract in shrimp fed	*Litopenaeus vannamei*	*V. parahaemolyticus*	Reduced bacterial growth in the hemolymph.	Klongklaew et al 2021
Ulva lactuca	Alga meal in shrimp fed	*Litopenaeus vannamei*	*V. alginolyticus*, *Photobacterium* sp.	Reduced pathogenic bacteria community in hepatopancreas.	Mangott et al 2020
Ulva ohnoi	Alga meal in fish fed	*Solea senegalensis*	*Photobacterium damselae* subsp. *piscicida*	Reduced pathogen loads in liver.	Fumanal et al 2020
Brown seaweed					
Sargassum cristaefolium	Alga meal in shrimp fed	*Litopenaeus vannamei*	*Vibrio* spp.	Reduced pathogen growth in the gut.	Jahromi et al 2021
Sargassum wightii	Fucoidan inclusion in shrimp fed	*Penaeus monodon*	*V. parahaemolyticus*	Reduced pathogen load in the hepatopancreas and muscle tissues	Sivagnanavelmurugan et al 2014

Table 3

Phytochemical composition of seaweed and its anti-bacterial activities

Species	*Solvent extraction*	*Phytochemical composition*	*Mariculture pathogen bacteria*	*Test*	*Reference*
Red seaweed					
Asparagopsis armata	Dichloromethane	Lipophilic halogenated compounds	*Pseudomonas anguilliseptica, Aeromonas salmonicida, Aeromonas hydrophila, Yersinia ruckeri*	In vitro	Bansemir et al 2006
Asparagopsis taxiformis	Water	Bromoform, dibromoacetic acid	*Streptococcus iniae*	In vitro and in vivo (*Lates calcarifer*)	Mata et al 2013
Ceramium rubrum	Ethanol	Fatty acids, fatty acid esters, hydrocarbon and phytol	*Yersinia ruckeri*	In vitro	Cortés et al 2014
C. rubrum	Dichloromethane	Lipophilic halogenated compounds	*Pseudomonas anguilliseptica*	In vitro	Bansemir et al 2006
Drachiella minuta	Dichloromethane	Lipophilic halogenated compounds	*Pseudomonas anguilliseptica*	In vitro	Bansemir et al 2006
Falkenbergia rufolanosa	Dichloromethane	Lipophilic halogenated compounds	*Pseudomonas anguilliseptica, Aeromonas salmonicida, Aeromonas hydrophila, Yersinia ruckeri*	In vitro	Bansemir et al 2006
Gelidium pusillum	Ethanol	Hexadecane, dimethylamine	*Aeromonas caviae*	In vitro and in vivo (prawns)	Agarwal et al 2021
Gracilaria cornea	Dichloromethane	Lipophilic halogenated compounds	*Pseudomonas anguilliseptica*	In vitro	Bansemir et al 2006
Gracilaria edulis	Ethyl acetate	Hexadecanoic acid, 13-octadecenoic acid and 10-octadecenoic acid	*Aeromonas hydrophyla, Vibrio fluvialis, Vibrio compbelii*	In vitro	Kasanah et al 2019
Gracilaria verrucosa	Ethanol/ethyl acetate (16:4)	Alkaloid, flavonoid (quercetin-7-methyl-ether), tannin, phenolic compound	*Aeromonas hydrophila, Pseudomonas aeruginosa, Pseudomonas putida, *Vibrio harveyi, *Vibrio algynoliticus*	In vitro	Maftuch et al 2016
Gracilariopsis lemaneifromis	Ethanol	NA	*Aeromonas hydrophila,* *Vibrio algynoliticus*	In vitro	Li et al 2018
Halopitys incurvus	Dichloromethane	Lipophilic halogenated compounds	*Pseudomonas anguilliseptica, Aeromonas salmonicida, Aeromonas hydrophila, Yersinia ruckeri*	In vitro	Bansemir et al 2006
Green seaweed					
Chaetomorpha linum	Chloroform/methanol (2:1)	Linolenic acid	*Vibrio ordalii,* *Vibrio vulnificus*	In vitro	Stabili et al 2019
Ulva fasciata	Butanol	Amino acids and peptides	*Aeromonas hydrophila, Vibrio algynoliticus*	In vitro	Priyadharshini et al 2011
U. fasciata	Methanol	Amino acids and peptides	*Aeromonas hydrophila*	In vitro	Priyadharshini et al 2011
Ulva prolifera	Ethanol	n.a	*Aeromonas hydrophila,* *Vibrio algynoliticus*	In vitro	Li et al 2018
Brown seaweed					
Sargassum fusiforme	Ethanol	n.a	*Aeromonas hydrophila, Pseudomonas aeruginosa*	In vitro	Li et al 2018

Note: * - weak anti-bacterial activity; n.a - not applicable.

Immunomodulatory functions of seaweed phytochemical. As previously mentioned, phytochemicals are secondary metabolites of the plant. This natural product is crucial for maintaining the plant's health and protecting the plant against pathogen infection and herbivore attack. Secondary metabolites are naturally produced as a response to external stimuli such as climate change, infection, or nutrition (Hurst & Harborne 1967; Brindha 2016; Behl et al 2021). Phytochemicals, which include polysaccharides, glycosides, phenolic compounds, flavonoids, alkaloids, anthocyanins, tannins, saponins, and terpenes, terpenoids and sterols, have immunostimulant activities. Thus, phytochemicals are immunomodulatory agents for combating various types of diseases in aquatic animals (Chakraborty & Hancz 2011; Sharma et al 2019; Behl et al 2021).

Phytochemicals as immunomodulatory agents can modulate, stimulate, and suppress the immune system, and can be categorised into immunostimulants, immunoadjuvants, and immunosuppressants (Yasin et al 2015; Elumalai et al 2020). Immunostimulants aim to stimulate the innate and adaptive immune response to increase the host's disease resistance and enhance the immune system (Kayser et al 2003; Sahoo 2007; Yasin et al 2015). Fish and shellfish, including molluscs and crustaceans, heavily depend on the non-specific immune system's efficacy as their first line of defence mechanism to combat the initial infection or the pathogens spread. Therefore, immunostimulants play a crucial role in the health management strategies of cultured aquatic animals. These reasons encouraged a large portion of the research on immunostimulants to focus on upregulating organisms' non-specific immune response (Barman et al 2013b; Mastan 2015). In recent years, immunostimulants have been widely studied in fish and shellfish. A previous study reported that marine-derived polysaccharides and saponins used as immunostimulants in fish (*Epinephelus fuscoguttatus*, *E. bruneus*, *O. niloticus* and *O. mykiss*) and shrimp could enhance resistance against bacterial pathogens by stimulating β-cells and activating macrophages as well as modifying cell membranes (Barman et al 2013b; Mohan et al 2019).

Immunoadjuvants are employed for enhancing vaccine efficacy and regard a specific antigen. Immunoadjuvants also facilitate immune responses of specific antigens to immune cells and increase phagocytosis. A previous study concerning immunoadjuvant application in aquaculture has been reported to enhance *A. hydrophila* resistance in carp (*Cyprinus carpio*) after bacterial vaccines (the mixture of β-glucan and lipopolysaccharides) inclusion (Selvaraj et al 2006). Immunosuppressants are administered to control the pathological immune response in hypersensitive immune reaction and pathology by decreasing resistance to infections, stress and environmental factors (Arya & Gupta 2011; Chakraborty & Hancz 2011; Srivastava & Pandey 2015). Overdose on immunostimulants might induce immunosuppression (Harikrishnan et al 2011). However, induced immunosuppression of aquatic animals (fish, shrimp, and molluscs) is less affected by this overdose or by prolonged administration of immunostimulants (Misra et al 2006; Koch et al 2021).

A large number of natural polysaccharides extracted from seaweeds have been extensively studied as immunomodulators for aquaculture application, particularly in aquatic animals health management (Table 4) (Barman et al 2013a; Dawood et al 2018), such as carrageenan and galactan from red algae (*Eucheuma*, *Gracilaria* and *Porphyra*), alginate, fucoidan and laminarin from brown algae (*Laminaria*, *Undaria* and *Sargassum*), as well as ulvan from green algae (*Ulva, Codium, Enteromorpha,* and *Caulerpa*) (Mohan et al 2019).

Table 4

Seaweed polysaccharides as immunomodulatory agents on distinctive cultured aquatic animals

Polysaccharide	*Source*	*Aquatic animal*	*Immunological parameters*	*Reference*
Alginate	*Macrocystis pyrifera*	*Epinephelus coioides*	ACH50, SOD, LYZ, PHA, RBA (↑)	Cheng et al 2007
	Macrocystis pyrifera	*Litopenaeus vannamei*	THC, DHC, ProPO, RBA, PHA (↑)	Cheng et al 2004
	Sargassum wightii	*Penaeus monodon*	THC, ProPO, RBA, SOD, PHA (↑)	Kudus et al 2017
	n.a.	*E. fuscoguttatus*	LEU, RBA, PHA, PHI, ACH50, LYZ (↑)	Cheng et al 2008
	n.a.	*E. coioides*	ACH50, RBA, SOD, HA, PHA, LYZ (↑)	Yeh et al 2008
	n.a.	*Salmo salar*	LYZ (↑)	Gabrielsen & Austreng 1998
	n.a.	*Oncorhynchus mykiss*	PRO, LYZ, APA, (↑)	Sheikhzadeh et al 2012
	n.a.	*Dicentrarchus labrax*	C3, LYZ, HSP (↑)	Bagni et al 2005
Fucoidan	*Cladosiphon okamuranus*	*Pagrus major*	PHA, TP (↑)	Sony et al 2019
	Sargassum fusiforme	*Fenneropenaeus chinensis*	THC, ProPO, LYZ (↑), SOD (↔)	Huang et al 2006
	Sargassum horneri	*Litopenaeus vannamei*	THC, PO, LYZ, SOD, (↑)	Lee et al 2020
	Sargassum polycystum	*Marsupenaeus rosenbergii*	THC, ProPO (↑)	Arizo et al 2015
	Sargassum wightii	*Penaeus monodon*	THC, ProPO, RBA, SOD, PHA (↑)	Immanuel et al 2012
	Undaria pinnatifida	*M. japonicus*	THC, ProPO, SBA (↑)	Traifalgar et al 2010
Carrageenan	*Eucheuma cottonii* *Eucheuma spinosa* *Gigartina aciculaire* *G. pistillata*	*L. vannamei*	THC, ProPO, RBA, PHA (↑)	Yeh & Chen 2008
Laminarin	*Laminaria hyperborea*	*Salmo salar*	PHA, ACP, O_2-, Mφ (↑)	Dalmo & Seljelid 1995
	Laminaria digitata	*F. chinensis*	THC, PC (↑)	Yao et al 2005
Ulvan	*Enteromorpha intestinales*	*P. monodon*	THC, RBA, ProPO (↑)	Declarador et al 2014
	E. prolifera	*Apostichopus japonicus*	PHA, RBA, ACP, ALP, CAT, SOD (↑), TCC (↔)	Wei et al 2015
	Ulva rigida	*Mugil cephalus*	LYZ, PHA, RBA, SOD (↑)	Akbary & Aminikhoei 2018
	Ulva rigida	*Psetta maxima*	RBA, IL-1β (↑)	Castro et al 2006
Galactan	*Gracilaria fisheri*	*P. monodon*	THC, ProPO, SOD, O_2- (↑)	Wongprasert et al 2014

Note: n.a - not available; ACP - acid phosphatase; ACH50 - alternative complement pathway; ALP - alkaline phosphate; EOS - eosinophil; Ig - immunoglobulin; IL-1β - interleukin 1 beta; IL-8 - interleukin −8; LEU - leucocytes; LYM - lymphocytes; LYZ - lysozyme activity; Mφ - macrophages; NBT - nitro blue tetrazolium; NEU - neutrophi; NO - nitric oxide activity; O_2– - superoxide anion production; PHA - phagocytic activity; PHI - phagocytic index; RBA - respiratory burst activity; SOD - superoxide dismutase; TLC - total leucocyte count; TLR2 - toll like receptors; TP - total protein; WBC - white blood cells; ACP - acid phosphatase; LYZ - lysozyme activity; ProPO - prophenoloxidase activity; RBA - respiratory burst activity; SBA - serum bactericidal activity; SOD - superoxide dismutase; THC - total haemocyte counts; ACP - acid phosphatase; NOS - nitric acid synthase; PO - phenoloxidase activity; ROS - reactive oxygen species; C3 - complement 3; APA - antiprotease activity; CAT - catalase; TCC - total coelomocyte counts; THC - total haemocyte counts; variation in experimental fish compared to controls: (↑) significant increase; (↔) no significant changes.

Seaweed phytochemical for growth and gonadal maturation. Seaweed is one of the natural sources with high nutritional values. It also contains bioactive compounds such as protein, polyphenols, polysaccharides, pigments, minerals, and polyunsaturated fatty acids that have beneficial effects on aquatic animals by enhancing growth, lipid metabolism, stress response, disease resistance, and physiological activity (Hindu et al 2019; Morais et al 2020). Several studies have been conducted on the application of seaweeds as ingredients for aquatic animal diets. It was reported that dietary supplementation of 1 g kg^{-1} extracted polysaccharides from seaweed *Enteromorpha prolifera* significantly improved growth performance and reduced the feed conversion ratio (FCR) in banana shrimp *Fenneropenaeus merguiensis* (Liu et al 2020). Seaweed polysaccharides can act as prebiotics. It can stimulate the secretion of digestive enzymes, leading to better utilization and digestion of nutrients, followed by exerting growth-promoting and health-improving effects (Mohan et al 2019). Other experimental diets consisted of 4 and 8% of the brown seaweed (mixture powdered of the genera *Macrocystis, Lessoniaceae*, and *Lessonia*) and green seaweed (mixture powdered of genera *Caulerpa, Enteromorpha*, and *Ulva*) and were tested on a growth trial for white leg shrimp *L. vannamei*. The results showed that the inclusion of both green and brown seaweeds in shrimp diets promoted adequate growth and survival rate for juveniles *L. vannamei* (Cárdenas et al 2015). Growth improvement of juvenile *L. vannamei* was found to be also affected by inclusion at low levels (1-3%) of *Ulva lactuca* meal (Elizondo-González et al 2018). According to Nazarudin et al (2020), it was demonstrated that a supplementation of 1.5-3% with brown seaweed *Sargassum polycystum* for Asian sea bass (*Lates calcalifer*) fry led to better survival, increased feed consumption and efficiency, enhanced growth performance and immune function, and produced better quality of the fish carcass. The decline of feed consumption and efficiency, poor FCR, PER, and mortality was found at higher levels of *Sargassum* supplementation. This may be caused by the high Fe content in the treatment, which led to Fe toxicity. Therefore, the authors suggested that using seaweed in supplemented diets should be at moderate levels, since seaweeds could contain toxic heavy metals alongside highly desirable minerals. Rajauria (2015) mentioned that seaweeds also contain dimethyl sulfonyl propionate (DMSP), dimethyl-beta-propionthein (DMTP), and some amino acids that act as attractants for aquatic animals, elevate the feed intake, and improve the FCR and PCR values of feed.

In addition to growth improvement, seaweed-based diets also play an important role in the body coloration, gonad coloration, and gonadal maturation of aquatic animals. This role is due to carotenoids in seaweeds (Rajauria 2015). Cruz-Suárez et al (2009) reported that *L. vannamei* diets containing 3.3% of cultured green seaweed *Ulva clathrata* significantly enhanced growth performance and better body pigmentation compared to *Macrocystis pyrifera* and *Ascophyllum nodosum* diets. This is related to *L. vannamei* capacity to utilize lutein present in *Ulva* more easily than astaxanthin. The increase of astaxanthin was also found in the muscle tissue of marine shrimp *P. monodon* fed with 5% green seaweed *Enteromorpha intestinalis* after 90 days of trial (Mondal et al 2015). The inclusion of *Ulva rigida* meal at a level of 5% in the diet was reported to enhance the surface color of Atlantic salmon fillet due to deposition of *U. rigida* pigments in salmon tissues (yellow/orange color), which is equivalent to fish fed with synthetic astaxanthin (Moroney et al 2017). The enhancement of yellow/orange color was also found in salmon muscle with the inclusion of 10-15% red seaweed *Palmaria palmata* in Atlantic salmon feed (Moroney et al 2015).

The effects of different formulated diets of seaweeds on gonadal enhancement of sea urchin have been investigated. Previous studies reported that the inclusion of 20% *Ulva* in the formulated diet could elevate gonad development of sea urchin *Tripneustes gratilla* and provide commercially acceptable gonads (Cyrus et al 2013; Cyrus et al 2015; Onomu et al 2020). This result is related to the presence of β-carotene found in *Ulva* sp., and carotenoids play an important role in the gonad production and development of sea urchins (Suckling et al 2020).

Conclusions. Seaweeds have numerous secondary metabolites that have biological activities, for instance, antioxidant, anti-bacterial and immunomodulator. These remarkable bioactive properties show that these photosynthetic marine organisms are a valuable natural resource of essential bioactive compounds. Its phytochemical performance and application have been widely studied in aquaculture industries to significantly alleviate pathogen infection and diseases. Bioactive compounds obtained from seaweed can also improve the quantity and quality of aquaculture production. Concerning the stressful conditions in the aquaculture environment for the farmed aquatic animals, seaweed inclusion could ameliorate the detrimental effects of that stress and make aquaculture commodities more resilient to pathogen infections and diseases. Therefore, aquaculture can increase its production and support global food security.

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