

Minireview

The seaweed holobiont: from microecology to biotechnological applications

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Summary

In the ocean, seaweed and microorganisms have coexisted since the earliest stages of evolution and formed an inextricable relationship. Recently, seaweed has attracted extensive attention worldwide for ecological and industrial purposes, but the function of its closely related microbes is often ignored. Microbes play an indispensable role in different stages of seaweed growth, development and maturity. A very diverse group of seaweed-associated microbes have important functions and are dynamically reconstructed as the marine environment fluctuates, forming an inseparable ‘holobiont’ with their host. To further understand the function and significance of holobionts, this review first reports on recent advances in revealing seaweed-associated microbe spatial and temporal distribution. Then, this review discusses the microbe and seaweed interactions and their ecological significance, and summarizes the current applications of the

seaweed–microbe relationship in various environmental and biological technologies. Sustainable industries based on seaweed holobionts could become an integral part of the future bioeconomy because they can provide more resource-efficient food, high-value chemicals and medical materials. Moreover, holobionts may provide a new approach to marine environment restoration.

Introduction

Seaweed, or macroalgae, is one of the most important organisms in the ocean. These abundant, diverse sessile multicellular photosynthetic eukaryotes provide important ecosystem services in coastal ecosystems; for example, they are ecosystem engineers that provide food, shelter and habitat for other organisms, and are responsible for a large amount of total primary productivity of temperate, arctic and tropical systems worldwide (Egan *et al.*, 2013; van der Loos *et al.*, 2019). Seaweeds, which include brown, red and green algae, produce numerous structural molecules, such as proteins, lipids, carbohydrates and other bioactive compounds that have various applications (e.g., agricultural, cosmeceutical, pharmaceutical and biotechnological) (Soria-Mercado *et al.*, 2012; Hay *et al.*, 2013; Romano *et al.*, 2017; Urtuvia *et al.*, 2017; García-Poza *et al.*, 2020; Leandro *et al.*, 2020a). Moreover, although seaweed has historically been an important part of Asian cuisine, seaweed aquaculture has only recently expanded because of increasing interest in using seaweed for biofuel production and global food security (Neori, 2007; Borines *et al.*, 2011; Kim *et al.*, 2017).

Seaweed functioning, and thus the ecological services and commercial applications it provides, is strongly controlled by interaction with its microbiome. This interplay can affect seaweed in various ways, such as their nutrient exchange, defense mechanisms, biologically active metabolite production, morphology, reproduction and settlement (Brock and Clyne, 1984; Goecke *et al.*, 2010; Bengtsson *et al.*, 2011; van der Loos *et al.*, 2019). Therefore, seaweed functioning in industrial and ecological settings can only be understood by considering interactions with its microbiome (Egan *et al.*, 2013).

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The microbial communities of seaweed contain an abundant, diverse assembly of organisms (including archaea, bacteria, fungi, microalgae, protozoa and viruses) on their surface and tissues. These microorganisms often perform various functions related to host growth and development or stress defense, but can also yield detrimental effects, such as disease (van der Loos *et al.*, 2019). Some microbiota can also contribute to seaweed survival by enabling the host to resist stress caused by rapid or extreme environmental changes (Rosenberg *et al.*, 2010). Consequently, seaweed and associated microbial groups form a 'holobiont' (the host and its symbiont), which represents a single ecological unit with highly specialized symbiotic interactions that are important for the functioning of both the host and the symbiont (van der Loos *et al.*, 2019). Therefore, holobionts may act as a unit of selection that is subject to natural selection and represent a unit to target for the development of seaweed ecological and industrial applications.

The surface of seaweed is a highly active interface for material exchange in nutrient absorption, and waste and secondary metabolite release with the surrounding seawater (Wahl *et al.*, 2012). Therefore, the surface environment of the thallus both provides suitable attachments for specific microorganism taxa and secretes various metabolites that affect microorganism growth, reproduction and group composition (Steinberg *et al.*, 2002; Singh and Reddy, 2014). Hosts can also produce compounds that attract or deter bacteria, inhibit quorum sensing, stimulate the activity of specific bacteria or change nutrient concentrations to promote the proliferation of specific taxa (as reviewed in Bonthond *et al.*, 2021). Such control over their own microbial community is directly linked to seaweed performance (Nuñez *et al.*, 2009). However, the symbiotic relationship formed between seaweed and associated microorganisms is closely related to aspects of the surrounding environment, such as the inorganic salt level and seawater temperature change (Bengtsson *et al.*, 2012). Environmental stressors can alter the microbial communities and shift symbiotic relationships from negative to positive interactions (Menge and Sutherland, 1987), which supports the stress gradient hypothesis because there is increased resilience of the holobiont to changing conditions (Maestre *et al.*, 2009).

Although the rich diversity of microbial communities is important for host growth and development, there is limited information on the composition of these microbial communities and how they vary over space and time; such information is valuable for the management of seaweeds in natural and aquaculture settings (Wahl *et al.*, 2012; Egan *et al.*, 2013; Goecke *et al.*, 2013). In the past decade, molecular identification of the seaweed-

associated microbiome (SAM) using next-generation sequencing technology has gradually revealed the composition and spatiotemporal variation of microbial communities on the seaweed thallus surface (Aires *et al.*, 2013; Michelou *et al.*, 2013; Marzinelli *et al.*, 2015). Although microbial assemblages often vary over time and space, significant host specificity has been observed (Lachnit *et al.*, 2009). However, host promiscuity has also been observed and was determined to be important for facilitating invasions of the red algae *Agarophyton vermiculophyllum* (Bonthond *et al.*, 2021). There have also been reports that stress caused by human activity may damage SAMs. For example, the symbiotic microbiome of a brown algae *Ecklonia radiata* was significantly affected by changes in the morphology of the coastal matrix as a result of coastal urbanization (Aires *et al.*, 2016).

To date, despite growing interest in microbial associations with seaweed to promote commercial applications and ecological stability, the functional relationships of microorganisms and seaweed that form holobionts have remained largely unknown. To summarize the role of this symbiosis from ecological to industrial perspectives, we reviewed the spatiotemporal distribution and function of SAMs; how the specific types and mechanisms of holobiont interactions affect their maintenance, stabilization and establishment; the role of secondary metabolites in seaweed-microbe interactions; and the development and application of products from seaweed and related microorganisms. By clarifying the microbial associations with seaweed, we can better understand the health and functional outcomes for holobionts (Lachnit *et al.*, 2016), which have practical implications for the ecological and industrial management of seaweed.

SAM temporal and spatial distributions

SAM structure and composition are known to vary over time and with the host's internal state and external environment (Tujula *et al.*, 2010; Lachnit *et al.*, 2011; Martin *et al.*, 2014; Campbell *et al.*, 2015). Therefore, understanding SAM composition and dynamics will enable researchers to reveal the unknown mechanisms underlying seaweed responses to environmental changes across time and space, which can help promote seaweed management in ecological and industrial settings (Egan *et al.*, 2013).

SAM composition can be affected by the internal state of the host, such as differing between healthy and stressed individuals (Marzinelli *et al.*, 2015), and based on the external environment, such as differing between organisms from different locations (Longford *et al.*, 2007; Burke *et al.*, 2011) or being more similar between organisms from different populations that are exposed to

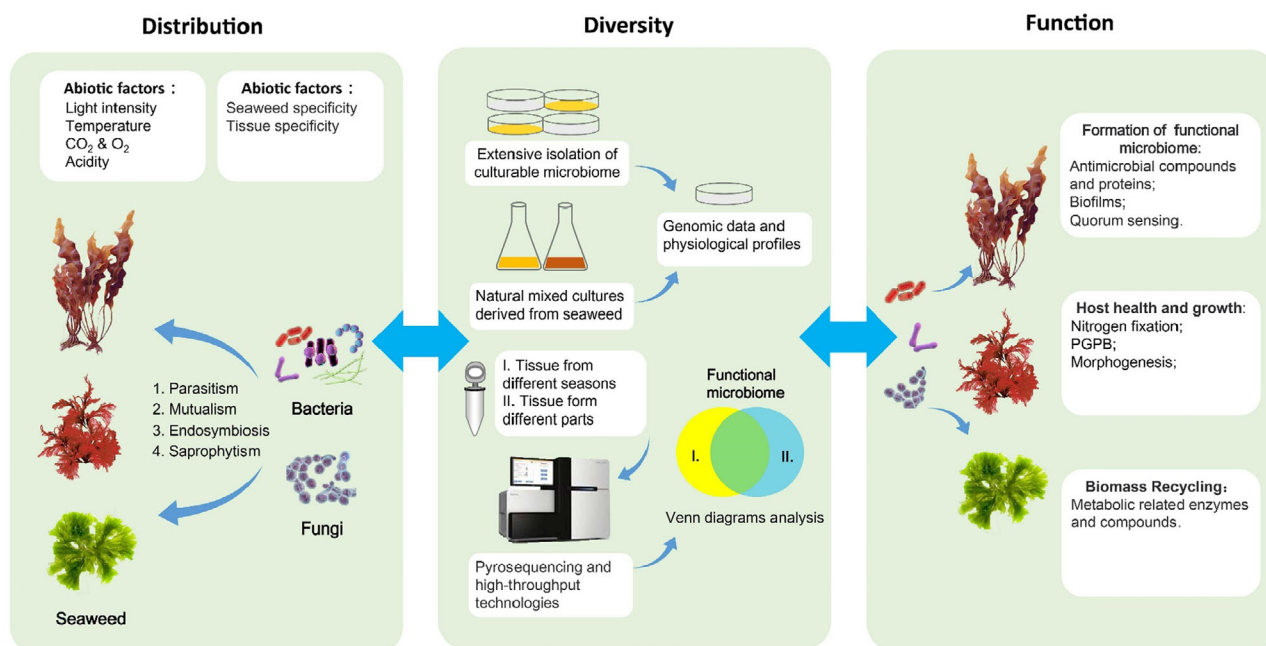


Fig. 1. Schematic diagram for elucidating the diversity and function of seaweed-associated microorganisms.

similar environmental conditions (Bonthond *et al.*, 2021). In addition, host-associated microflora can be tissue-specific; for example, specific microbial species are concentrated in newly growing *Laminaria saccharina* tissues, and this specificity is not affected by season or other environmental factors (Staufenberger *et al.*, 2008). However, many microbial communities do change over time, from less than a day to a whole year; these changes are usually related to seasonal changes and preferences (Tujula *et al.*, 2010; Fuhrman *et al.*, 2015). For example, such changes have been found to be associated with an altered abundance of pathogenic microorganisms and thallus disintegration in *Cystoseira compressa* (Mancuso *et al.*, 2016).

SAM seasonal succession is controlled by various biological and abiotic factors (Fig. 1). Biological factors include seaweed growth cycle and maturation (Bengtsson *et al.*, 2010), and interactions between microbial groups, both among those living on seaweed and between those living on seaweed and in the surrounding seawater (Morris *et al.*, 2012). Microbial community composition is also significantly influenced by abiotic factors that are affected by seasonal changes, such as a rise in summer water temperature (Matsuo *et al.*, 2003; Bengtsson *et al.*, 2010). However, there have been some conflicting findings of how water temperature changes affect seaweed and their microorganisms. For example, seaweed ooze increases in *Laminaria hyperborea* during the summer, which is thought to be favorable for the flourishing of the associated microbes. However, some *L.*

hyperborea-related microorganisms tend to be present in seawater below 10°C (Bengtsson *et al.*, 2010). This indicates that the inherent characteristics of microorganisms also determine SAM composition.

Based on what is known about SAM composition in response to varying environments, it is reasonable to expect that global warming and ocean acidification significantly affect SAM composition (O'Brien *et al.*, 2016). Moreover, although the stress gradient hypothesis proposes that environmental stressors may result in increased resilience of the holobiont to changing conditions (Maestre *et al.*, 2009), it has also been argued that environmental stress, such as temperature changes or eutrophication, can destabilize holobionts and make them more susceptible to pathogen infection (Largo *et al.*, 1995) and increase the frequency or intensity of diseases (Harvell *et al.*, 1999). Therefore, additional research is needed to more definitively determine how environmental changes affect holobionts and, therefore, their ecological and industrial applications.

Interactions between seaweed and related microorganisms

Seaweed–microbe interactions can greatly impact the growth and persistence of the seaweed and have strong effects on the surrounding environment. Therefore, knowledge regarding these interactions can be used to establish approaches to help control the excessive proliferation of harmful algae and develop low-cost ecological

seaweed cultivation techniques to obtain greater biomass for industrial applications (Ramanan *et al.*, 2016; Lutz and Dunford, 2018).

Microorganism colonization of the seaweed surface is very complex and dynamic. Rich and diverse SAMs occur because seaweed is a good habitat for aerobic and photoautotrophic epiphytic microorganisms, which live on the surface, and endophytic microorganisms, which live within or on the interstitial tissues (Wahl *et al.*, 2012; Egan *et al.*, 2013). To further understand the interaction between the seaweed host and microorganisms, researchers have recently paid increasing attention to the classification, identification and functional analysis of various epiphytic and endophytic SAM communities. These microorganisms play direct or indirect roles in seaweed morphogenesis and growth (Veijo *et al.*, 2001; Egan *et al.*, 2013; Singh and Reddy, 2014), and the interaction types between seaweed and microorganisms can be divided into nutrient exchange, signal transduction and gene transfer (de Oliveira *et al.*, 2012). Moreover, specific SAM functions include the production of molecules (such as vitamins and other nutrients) that affect seaweed morphology, development and growth; converting organic matter and nitrate nitrogen to facilitate nutrient uptake of seaweed and helping seaweed defend themselves by quorum sensing and secreting antifouling substances (Table 1) (Veijo *et al.*, 2001; Steinberg *et al.*, 2011; Ihua *et al.*, 2019).

Moreover, even though seaweed-associated microorganisms include bacteria, fungi, archaea, protozoans and viruses, the majority of research to date has been conducted on bacteria (Egan *et al.*, 2013). However, understanding the known interactions between seaweed and all types of related microorganisms can help provide insight into holobiont function and persistence. For example, viruses are the most abundant entities in marine ecosystems (Suttle, 2005) and can even control phytoplankton blooms (Suttle *et al.*, 1990), but the total diversity of viruses in seaweed has yet to be characterized even though viruses can have severe pathogenic effects on their hosts (Lachnit *et al.*, 2016).

Furthermore, interaction types between seaweed and microorganisms cover the whole range of symbiotic relationships: mutualism, symbiosis and parasitism (Fig. 1) (Fuentes *et al.*, 2016; Ramanan *et al.*, 2016). The algal host growth stage and health status, and environmental factors (e.g., nitrogen:phosphorus ratio, light intensity, temperature, pH and salinity) may convert this interaction from one type to another, such as from mutualism to parasitism (Fuentes *et al.*, 2016). For example, the presence of carbon-rich components in seaweed cell walls (e.g., carrageenan, alginate, cellulose and pectin) is essential for microbial colonization (Ruocco *et al.*, 2016; Jönsson *et al.*, 2020). However, parasitic

microorganisms may also use seaweed polysaccharides for nutritional purposes by secreting cell wall-degrading enzymes (Veijo *et al.*, 2001). It is also believed that microorganisms capable of degrading seaweed polysaccharides flourish on aging or dead seaweed, which contributes to seaweed biomass recycling (Martin *et al.*, 2015). Consequently, these relationships affect nutrient recycling and seaweed biomass, and understanding these dynamics may therefore be beneficial for seaweed holobiont use for ecosystem services and ecologically friendly industrial applications (Neveux *et al.*, 2018).

Ecological applications

Seaweeds have substantial impacts on ecosystems because they act as environmental engineers; they substantially contribute to global primary production and provide food and shelter for aquatic life. Macroalgae and their epiphytic bacteria interact as a functional entity, and their interactions can improve seaweed health, growth, disease suppression and adaptation to environmental stressors (Egan *et al.*, 2013; Schmidt and Saha, 2021). Chemical 'gardening' of protective microbes by seaweed has even been demonstrated, which in turn enhances the sustainable production of seaweeds (Saha and Weinberger, 2019; Saha *et al.*, 2020). Consequently, the associated increased seaweed biomass in the environment can be used for feeds, biofuels and fertilizers. Moreover, the holobiont relationship can help facilitate the bioremediation of organic pollutants and heavy metals.

Some seaweed-related microbial strains have been reported to play roles in stress tolerance of seaweed and bioremediation of contaminants, including hydrocarbons and chemical fertilizers (Head *et al.*, 2006; Aires *et al.*, 2013, 2015). Microalgal-microbial interactions have been widely reported to degrade organic pollutants, including black oil, acetonitrile, phenol, naphthalene, benzopyrene, dibenzofuran and azo compounds (Mahdavi *et al.*, 2015); however, there are relatively few studies on the application of seaweed and their related microorganisms in organic pollutant remediation. The symbiotic and epiphytic microorganisms on the surface of seaweed likely play important roles in organic pollutant degradation because microorganisms carry out biodegradation by mineralizing organic pollutants into water, carbon dioxide and fewer toxic compounds; in particular, numerous marine microorganisms have been successfully used in organic pollutant biodegradation (Fig. 3) (Nikolaivits *et al.*, 2017; Khalid *et al.*, 2021).

Despite the potential benefits of holobionts, the role of seaweed and microorganism interactions in organic pollutant bioremediation has not been extensively examined. The most likely reason is that, compared with

Table 1. Examples of seaweed-associated microbe's metabolites having positive effects on seaweed growth and development.

Seaweed	Microbe	Mediators	Function	Reference
Zoospores settlement				
<i>Enteromorpha</i> sp.			Zoospores settled on submerge surfaces formed by bacteria	Thomas and Allsopp (1983)
<i>Enteromorpha</i> sp.	Naturally attached microflora	Biofilm	Increasing zoospores settlement on mixed bacterial biofilm	Dillon <i>et al.</i> (1989)
<i>Enteromorpha</i> sp.	Naturally attached microflora	Biofilm	Positive correlation between bacteria to zoospores settlement	Joint <i>et al.</i> (2000)
<i>Enteromorpha</i> sp.	<i>Vibrio anguillarum</i>	AHLs	Secreting AHLs increasing zoospores settlement	Joint <i>et al.</i> (2002)
<i>Enteromorpha</i> sp.	<i>Vibrio</i> and <i>Shewanella</i>		Single-species biofilms affect zoospores settlement	Patel <i>et al.</i> (2003)
<i>Ulva fasciata</i>	Naturally attached microflora		Increasing zoospores settlement on mixed bacterial biofilm	Shin (2008)
<i>Ulva</i> sp.	<i>Vibrio anguillarum</i> NB10	AHLs with longer (> 6 carbons) N-acyl chains, such as <i>N</i> -(3-oxodecanoyl)-L-homoserine lactone	Diffusion rates of AHLs, stability in seawater affect zoospores settlement	Tait <i>et al.</i> (2005)
<i>Ulva intestinalis</i>	<i>Vibrio anguillarum</i>	AHLs with <i>N</i> -(3-oxododecanoyl)-homoserine lactone (3O-C12-HSL) as side chain	Increasing zoospores settlement	Wheeler <i>et al.</i> (2006)
<i>Ulva</i> sp.	<i>Rhodobacteraceae</i> family, and the <i>Bacteroidetes</i> family <i>Flavobacteriaceae</i> <i>Rhodobacteraceae</i> family, and the <i>Bacteroidetes</i> family <i>Flavobacteriaceae</i> <i>Rhodobacteraceae</i> , and <i>Bacteroidetes</i>	AHLs	Interaction of microbes affect zoospores settlement	Tait <i>et al.</i> (2009)
<i>Ulva fasciata</i>	<i>Marinomonas</i> sp.	Physical association	Zoospores released	Singh <i>et al.</i> (2011a,b,c)
Morphogenesis				
<i>Ulva lactuca</i> and <i>Monostroma oxyspermum</i>	Naturally attached microflora		Many strains of marine and associated bacteria-induced growth, such as <i>Enteromorpha</i>	Provasoli and Pintner (1980)
<i>Monostroma oxyspermum</i>	Naturally attached microflora		Culture filtrate of bacteria and extracts of brown and red alga were also capable of morphogenesis	Tatewaki <i>et al.</i> (1983)
<i>Ulva pertusa</i>	<i>Flavobacterium</i> and <i>Vibrio</i>		Direct physical attachment needed for morphogenesis	Nakanishi <i>et al.</i> (1996)
<i>Monostroma oxyspermum</i>	<i>Zobellia</i> sp.	Thalassin	Secreting thalassin hormone affect morphogenesis	Matsuo <i>et al.</i> (2003)
<i>Ulva linza</i>	<i>Bacteroidetes</i>		Affect tubular extensions	Marshall <i>et al.</i> (2006)
<i>Ulva fasciata</i>	<i>Firmicutes</i>		Affect the growth of fronds	Singh <i>et al.</i> (2011a)
<i>Ulva mutabilis</i>		<i>Roseobacter</i> , <i>Sulfitobacter</i> and <i>Halomonas</i>		Induced the development of the <i>Ulva</i> gametes into thalli
Spoerner <i>et al.</i> (2012)				
Macroalgal growth				
<i>Ulva lactuca</i>	Indigenous microflora	Nitrate, phosphate, growth factors (IAA, adenine and kinetin) and trace metals	Growth-promoting	Bradley (1991)
Marine macroalga <i>Caulerpa taxifolia</i>	<i>Vibrio</i> Agrobacterium–rhizobium	Cytokinin Nitrogen	Growth-promoting Fix N ₂ in the rhizoids	Maruyama <i>et al.</i> (1988) Chisholm <i>et al.</i> (1996)

Table 1. (Continued)

Seaweed	Microbe	Mediators	Function	Reference
<i>Codium fragile</i> ssp. <i>tomentosoides</i>	<i>Azotobacter</i>	Nitrogen	N ₂ fixation	Head and Carpenter (1975)
<i>Ulva fasciata</i>	<i>Marinomonas</i> sp.		Induced cell size and growth	Singh <i>et al.</i> (2011a)
<i>Laminaria japonica</i>	<i>Pseudoalteromonas porphyrae</i>	Catalase	Growth-promoting	Dimitrieva <i>et al.</i> (2006)
<i>Prionitis lanceolata</i>	<i>Roseobacter</i>	Indole-3-acetic acid (IAA)	Formation of bacterial galls	Ashen <i>et al.</i> (1999)
<i>Gracilaria dura</i>	<i>Bacillus licheniformis</i>	EPS		Singh <i>et al.</i> (2011c)
<i>Gracilaria dura</i>	Epiphytic <i>Exiguobacterium homiense</i> and endophytic <i>Bacillus pumilus</i> , <i>Bacillus licheniformis</i>	Indole-3-acetic acid (IAA)	Bud regeneration	Singh <i>et al.</i> (2011b)

seaweed, the cultivation of microalgae is easier. However, because of the great remediation potential of seaweed and related microorganisms, additional exploration of their use in organic pollutant bioremediation is urgently needed.

Moreover, seaweeds have the potential to provide an efficient, eco-friendly and low-cost remediation method to reduce or remove toxic heavy metals from the environment (He and Chen, 2014; Ahmed *et al.*, 2021), particularly because the properties of the cell wall constituents alginate and fucoidan facilitate heavy metal chelation (Davis *et al.*, 2003). Seaweeds, which are among the most promising biosorbents, exhibit efficient metal biosorption capacity because they have several active functional groups (e.g., polysaccharides, proteins, amino, hydroxyl, carboxyl and sulfate) on their cell wall surfaces that serve as binding sites for metal (as reviewed in Ahmed *et al.*, 2021). To date, different kinds of seaweed, including the brown seaweed *Sargassum filipendula* (Verma *et al.*, 2016) and the red seaweeds *Osmundea pinnatifida* (Tsekova *et al.*, 2010) and *Chondracanthus chamissoi* (Yipmantin *et al.*, 2011), have been used to remove heavy metals. However, the roles of seaweed-related microorganisms in the mechanism of seaweed resistance to heavy metal stress are still unknown.

Coexisting microorganisms, especially bacteria, can also promote algal growth. Therefore, a consortium of microorganisms may be more effective than a single bacterium for promoting growth, as has been observed in plants (Baez-Rogelio *et al.*, 2017), because they perform more diverse tasks than single strains and may thus be better at tolerating stressors such as environmental fluctuations and pathogen invasion (Lian *et al.*, 2018). For example, the use of mixed algal–bacterial populations has been reported to increase wastewater treatment efficiency, system robustness and application

potential of sludge. These mixed populations can increase harvested algal biomass, which can be used for feeds, biofuels and fertilizers; ensure efficient removal of various pollutants and promote CO₂ sequestration. Consequently, using a combination of microbial communities, including seaweed-associated microorganisms, may be able to improve wastewater treatment approaches and promote bioremediation of contaminated soils to help improve agricultural yields (Mhedhbi *et al.*, 2020; Sharma *et al.*, 2020; Qi *et al.*, 2021).

Seaweed holobiont-associated industries

Industrial applications of seaweed

Seaweed has been widely consumed for centuries, with evidence of cooked and partially eaten seaweeds dating back 14 000 years in southern Chile (Dillehay *et al.*, 2008). Similar to microalgae, the unique composition of seaweed enables their use as food, feed and energy (Nakanishi *et al.*, 1996; Matsuo *et al.*, 2003; Marshall *et al.*, 2006; Hollants *et al.*, 2013), including as biopolymers, cosmetics, agri-foods and food supplements that contain various beneficial substances (Fig. 3).

In general, functional foods derived from seaweed can provide health benefits by reducing the risk of chronic disease and improving physical capacity (Alba and Kontogiorgos, 2019), and producing large amounts of seaweeds could help enhance global food security (Bjerregaard *et al.*, 2016). Nevertheless, the potential role of seaweed in global food security has only come to light in recent decades as global population increase and food availability have become an issue (Egan *et al.*, 2008; Kim *et al.*, 2017).

Seaweeds have become appealing as a source of functional foods with increased evidence of several health-related seaweed properties, such as antibacterial activity, antioxidant potential, anti-inflammatory

properties, anti-viral activity and anti-fungal activity (Admassu *et al.*, 2015). Seaweeds have low caloric and high nutrient contents, are rich in nutrients that cannot be obtained from terrestrial plants and provide health benefits against various diseases (Bjerregaard *et al.*, 2016; Leandro *et al.*, 2020b; Pandey *et al.*, 2020; Choudhary *et al.*, 2021). Moreover, seaweeds have a range of applications in food development: they can be used as a stabilizer and emulsifier, and have gelling properties; they are commonly used as ingredients in many foods and for commercial food preparation (Pandey *et al.*, 2020); and they have even been used to provide a source of beneficial bioactive substances in reformulated modified meat products (Cofrades *et al.*, 2017).

Despite the evidence of seaweed benefits as a source of functional foods, there is a limited understanding of the nutritional composition of seaweeds across species, geographic regions and seasons. It is also not entirely clear which components are bioavailable; what factors influence how they are released (such as food preparation and genetic differentiation in the gut microbiome) or how they interact with human metabolism or how harvesting, storage and food processing techniques influence their nutritional value (Wells *et al.*, 2017). Furthermore, there is a lack of technologies available that can process seaweeds for human consumption at an industrial scale (Choudhary *et al.*, 2021), which limits the ability to use seaweed to help mitigate global food security issues.

Additionally, the natural products extracted from seaweed are both new sources of natural compounds and important materials for drug synthesis. Seaweed-based bioactive substances have great potential for pharmaceutical and research applications (Smit, 2004), and bioactive seaweed substances have many medicinal properties, including anti-herpes simplex virus type 1, antibiotic (Fernandes *et al.*, 2014), anti-acne biological (Kok *et al.*, 2016), lipase inhibitory (Chater *et al.*, 2016), anticancer activities (Ermakova *et al.*, 2016) and anti-obesity properties (Awang *et al.*, 2014). Carbohydrates extracted from seaweed also have various benefits for industrial use; for example, alginate was shown to inhibit various cancer cell lines, and anticancer effects were seen *in vivo* (Lowenthal and Fitton, 2015), and fucoscan has also been widely used in healthcare products and has many biological activities, such as antibacterial and anticoagulant activities (Kusaykin *et al.*, 2008; Zhu *et al.*, 2010).

Recently, natural cosmeceuticals have become more popular than synthetic cosmetics. Therefore, research on the newly recognized functional components of seaweed has become a promising field of cosmeceutical research. The chemical components isolated from different

seaweed species have a wide range of nutritional, functional and biological activities, which makes these unique seaweed metabolites important in high-end cosmetics. For example, a range of active components can be extracted from brown algae, including unique secondary metabolites, such as chlorophyll and carotene, many of which have specific biological activities (Jesumani *et al.*, 2019). Specifically, in cosmetics, the active compounds extracted from brown seaweed show many functional properties, such as anti-oxidation, anti-wrinkle, whitening, anti-inflammation and anti-allergy properties (Wijesinghe and Jeon, 2011).

Seaweed-derived materials have also received extensive attention in various biological, biomedical and environmental applications. Alginate hydrogels have gradually played an irreplaceable role in wound healing, drug delivery and tissue engineering applications because they maintain the structural similarity of the extracellular matrix in tissues and can effectively induce them to play a role in self-healing (Abasalizadeh *et al.*, 2020; Aswathy *et al.*, 2020; Raus *et al.*, 2021; Sahoo and Biswal, 2021). Moreover, non-wovens made from alginate fibres form soft hydrogels when in contact with body fluids, a property that is valuable in wound dressings, face masks, absorbent MATS and other healthcare textile materials (Gao and Xiangyu, 2018a,b; Gao *et al.*, 2019).

Seaweed fertilizer has also become a fast-growing industry. The waste material formed after the extraction of other high-value products can be processed through various biological and chemical processes to produce high-quality soil fertilizer. Additionally, seaweed is cost-effective and contains diverse bioactive compounds, such as lipids, proteins, carbohydrates, amino acids, phytohormones, osmoprotectants, mineral nutrients and antimicrobial compounds (Ragunandan *et al.*, 2019).

Seaweed extracts also contain many substances that promote plant growth, such as specific polysaccharides and plant growth-promoting hormones (Ali *et al.*, 2021), or that can be used for seed treatment, and foliar spray and soil application to protect plants (Ragunandan *et al.*, 2019; Mukherjee and Patel, 2020). In terms of soil structure, the volume added by seaweed is not large, but its gelatinous alginate content helps hold soil debris together. Moreover, seaweed contains important soil nutrients, such as various amino acids, nitrogen, phosphorus and potassium (Ragunandan *et al.*, 2019; Mukherjee and Patel, 2020).

Seaweed extracts have important potential as plant biostimulants because they can increase crop yield and stability under stress by evoking phytoelicitor activity, phytohormonal responses and changes in plant and soil microbiomes while decreasing dependency on chemical fertilizers (Chiaiese *et al.*, 2018; Ali *et al.*, 2021).

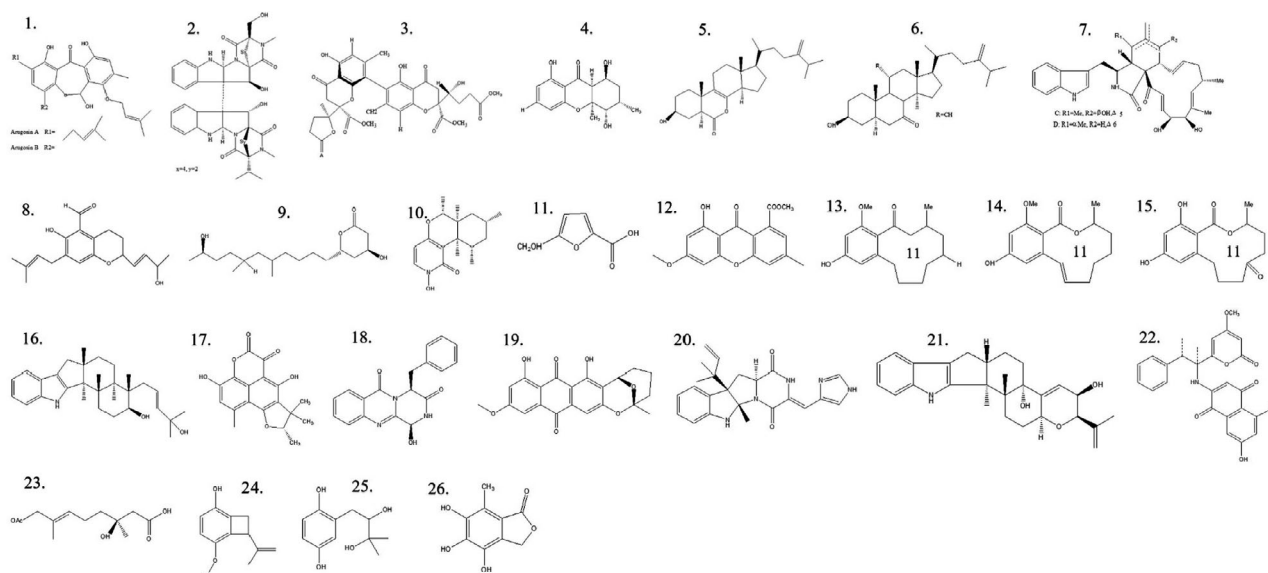


Fig. 2. Bioactive secondary metabolites from seaweed-associated microorganisms. 1. Arugosins A and B; 2. Leptosin A; 3. Noduliprevenone; 4. Monodictysin B; 5. 7-nor-ergosterolide; 6. $3\beta,11\alpha$ -dihydroxy ergosta-8,24(28)-dien-7-one; 7. Cytoglobosins C and D; 8. Chaetopyranin; 9. Penicittide A; 10. N-hydroxy-2-pyridine; 11. 5-(hydroxymethyl)-2-furanocarboxylic acid; 12. Yicathin A; 13. Lasiodiplodin; 14. de-O-methylasiodiplodin; 15. 5-hydroxy-de-O-methylasiodiplodin; 16. aspozynin C; 17. Scleroderolide; 18. brevianamide M; 19. 6-O-methylaverufin; 20. Z-roquefortine C; 21. Penjianthine A; 22. 5,7-dihydroxy-2-[1-(4-methoxy-6-oxo-6H-pyran-2-yl)-2-phenylethylamino]; 23. Penicimonoterpene; 24. 7-isopropenylbicyclo[4.2.0]octa-1,3,5-triene-2,5-diol 25. 2-(3-dihydroxy-3-methylbutyl)benzene-1,4-diol; 26. Epicoccone.

However, the use of seaweed for biostimulant production is limited by factors such as water pollution spread and difficulty standardizing raw material quality because it is harvested from seawater and chemical composition varies by tissue age, environmental conditions, nutrient availability and time of harvest (Chiaiese *et al.*, 2018). Moreover, delivery of seaweed products is mostly limited to foliar and soil application, the latter of which is expensive and requires high levels and multiple applications of extracts (Ali *et al.*, 2021).

Microalgae have been proposed as an alternative source of plant biostimulants because there is potential for increased raw material standardization and cost reduction (Chiaiese *et al.*, 2018). Microalgae are also ubiquitously associated with bacteria in nature, and their interactions, which can be both beneficial or detrimental to microalgae, can greatly affect aquatic ecosystem productivity and stability (Chhun *et al.*, 2021; Lian *et al.*, 2021). Therefore, harnessing these interactions could help improve microalgal yield and thus biostimulant production. However, despite the general belief that there are potential benefits of the interaction between microalgae and crops, there is limited supporting scientific evidence (Chiaiese *et al.*, 2018).

Despite all of the important industrial applications of seaweed, there is a lack of seaweed-microbe symbiosis perspective in the development of seaweed-derived biotechnology. Improving our understanding of holobiont dynamics can help improve seaweed production and

use. Nevertheless, more diverse natural products, especially drugs and their precursors, are more likely to come from seaweed symbionts than from seaweeds themselves.

Seaweed-related microbial bioresources

With the increasing use of seaweed as a source of bioactive substances, seaweed farming and related downstream processing has increasingly become a high-value, sustainable and green industry (Kim *et al.*, 2017; García-Poza *et al.*, 2020). Additionally, the functional application of seaweed-related microorganisms has been increasingly recognized, and numerous seaweed-associated microorganisms are currently considered potential sources of bioactive compounds for drug discovery. For example, the diverse and complex bacterial community associated with *Ascomyllum nodosum* represents a potential source of novel hydrolases for use in biotechnology, such as cosmeceuticals, functional foods, nutrition and biopharmaceuticals (Unnithan *et al.*, 2014; Cheong *et al.*, 2018; Uzair *et al.*, 2018, 2020; Silva *et al.*, 2020). In addition, seaweed and their endophytic symbionts are a good source of bioactive secondary metabolites (Fig. 2), which are described in the subsections below, and can provide stress tolerance to the continuous stresses that macroalgae are exposed to in marine environments, such as prolonged sunlight exposure, moisture and salt concentration variation, tidal

changes and numerous microorganisms and herbivorous insects, because of secondary metabolites (Busetti *et al.*, 2017; Sarasan *et al.*, 2017; Teixeira *et al.*, 2019; Mena *et al.*, 2020).

Anticancer compounds. Some of the compounds produced by seaweed and their endophytic symbionts (Fig. 2) are known to have anticancer properties. For example, leptosins extracted from the endophytic fungus *Leptosphaeria* sp. were isolated from brown algae. Studies showed that these compounds, arugosin A and B (Frenz *et al.*, 2004; Kralj *et al.*, 2006) and leptosin A, can control P-388 leukaemia cell proliferation by inhibiting topoisomerase II (König and Wright, 1996; Pontius *et al.*, 2008). The crude extract of *Apiospora montagnei*, another endophytic fungus isolated from the red algae *Polysiphonia violacea*, produced 50% growth inhibition of different cancer cells (HM02 and HepG2) at microgram concentrations (Klemke *et al.*, 2004). A polyketone, noduliprevenone, from the algal fungus *Nodulisporium* sp. has competitive inhibition of cytochrome P450-1A activity (Pontius *et al.*, 2008). Another study found that monodictysin B, a xanthone derivative from the algal fungus *Monodictys putredinis*, also showed similar activity (Krick *et al.*, 2007). In addition, monodictysins showed moderate activity in cultured mouse cancer cells as inducers of NAD(P)H: quinone reductase, which is a protective enzyme involved in cancer chemoprotection and chemotherapy (Li *et al.*, 1995; Zhu *et al.*, 2009).

Steroids are also a common group of compounds of microbial origin with anticancer activity (Baydoun *et al.*, 2013). For example, the endophytic fungus *Aspergillus ochratoxyllus* from the seaweed *Sargassum kjellmanianum* produces a rare anticancer steroid compound, 7-nor-ergosterolide and a newly recognized steroid derivative, 3 β ,11 α -dihydroxyergosta-8,24(28)-dien-7-one (Schulz *et al.*, 1998; Erbert *et al.*, 2012). A cytotoxicity study showed that 7-nor-ergosterolide had anticancer effects on human cancer cell lines, such as NCI-H460, SMMC7721 and SW1990; however, 3 β ,11 α -dihydroxy ergosta-8,24(28)-dien-7-one had a weak inhibitory effect on SMMC-7721 cell growth (Cui *et al.*, 2010a,b). *Trichocystis* appears to be a representative source of the anticancer drugs cytoglobosins C and D and chaetopyranin (Wang *et al.*, 2006; Cui *et al.*, 2010a,b). Moreover, *Penicillium chrysogenum* QEN 24S is an endophytic fungus isolated from *Laurencia*, an unidentified marine red algae, that can synthesize penicitide A, which has certain cytotoxic activity against human liver cancer cell lines (Gao *et al.*, 2010).

Norditerpenoids have also attracted widespread attention as cytotoxic substances. Studies showed that several novel norditerpenoids from the endophytic fungus *Aspergillus wentii* en-48 of *Sargassum* have cytotoxic effects on several human tumor cell lines. A previous

study found that several novel norditerpenoids (asperolides A and B and wentilactones A and B) from the endophytic fungus *A. wentii* en-48 of *Sargassum* have cytotoxic effects on several human tumor cell lines (Sun *et al.*, 2012). Similar tumor cell inhibition comes from an alkaloid, N-hydroxy-2-pyridine, which is produced by a strain of *Penicillium* sp. isolated from the brown algae *Xiphophora gladiata* (de Silva *et al.*, 2009).

Antimicrobial compounds. Holobionts also have value as producers of antimicrobial compounds (Fig. 2). Researchers identified various new xanthone derivatives with antibacterial ability from *Wardomyces anomalus* that colonized *Enteromorpha* sp., including 2,3,6,8-tetrahydroxy-1-methylxanthone and 5-(hydroxymethyl)-2-furanocarboxylic acid (Abdel-Lateff *et al.*, 2003). Additionally, a newly identified group of xanthone derivatives, yicathins A, B and C, was obtained from the endophytic fungus *A. wentii* of *Gymnogongrus flabelliformis*; it has good inhibitory activity against human pathogenic bacteria such as *Escherichia coli* and *Staphylococcus aureus* (Sun *et al.*, 2013). Additionally, bioactive lactones and three known compounds (lasiodiplodin, de-O-methylasiodiplodin and 5-hydroxyde-O-methylasiodiplodin) were isolated from an unidentified fungus of *Sargasso* from the waters of Zhanjiang, China, and these compounds have significant inhibitory effects on *S. aureus* (Yang *et al.*, 2006).

Macrolides are also known to have antimicrobial activity against gram-positive bacilli and are generally considered to be synthesized by terrestrial plants through secondary metabolic processes; however, endophytic fungi from seaweed can also produce these compounds (Dai *et al.*, 2010). Additionally, it was reported that asporozin C from *Aspergillus oryzae* isolated from *Heterosiphonia japonica* showed good antibacterial and insecticidal activities (Qiao *et al.*, 2010). An endophytic fungus, *P. chrysogenum* QEN-24S, was also identified from *Laurencia*, a red algae, and produces novel naphthenic tetracyclic diterpenes (conidiogenone B and conidiogenol) (Gao *et al.*, 2011). Additionally, these novel compounds also have antimicrobial activity and can effectively inhibit the growth of methicillin-resistant *S. aureus*, *Staphylococcus epidermidis*, *Pseudomonas fluorescens* and *Pseudomonas aeruginosa* (Gao *et al.*, 2011).

Several other compounds have been identified from seaweed and associated microbes that have antimicrobial applications. For example, tryptophan-derived alkaloids are a main compound of antibiotics in medicine, and a strain of *Penicillium* sp. was isolated from the surface-sterilized thallus of *X. gladiata* from New Zealand; it can produce N-hydroxy-2-pyridine alkaloids, which have significant antimicrobial activity against *Bacillus subtilis* (de Silva *et al.*, 2009). Moreover, a series of

antimicrobial compounds have been found in the identification of metabolites of various endophytic bacteria from algae, including scleroderolide (Elsebai *et al.*, 2011), dicerandrol C (Erbert *et al.*, 2012), brevianamide M, 6-O-methylaverufin (Erbert *et al.*, 2012), Z-roquefortine C and penijanthe A (Yang *et al.*, 2016).

Medical antifungal compounds have been in great demand because of their limited variety, and endophytic bacteria from algae are a promising source of antifungal substances. A previous study showed that lasiodiplodins and other bioactive lactones have significant antimicrobial activity against *Fusarium oxysporum* (Yang *et al.*, 2016). A series of antimycotics was also found in research that screened antimycotics from the endophyte *Aspergillus niger* EN-13 of the brown algae *Colpomenia sinuosa*, and included 5,7-dihydroxy-2-[1-(4-methoxy-6-oxo-6H-pyran-2-yl)-2-phenylethylamino] (Strobel and Daisy, 2003) and naphthoquinone (Zhang *et al.*, 2007a, b,c). Additionally, a previous study of algal-derived *Penicillium* sp. of the brown algae *X. gladiata* from New Zealand revealed three alkaloids, the known N-hydroxy-2-pyridone, PF1140, and two new 2-pyridones, 2 and 3, which express notable activity against *Candida albicans* (de Silva *et al.*, 2009). In particular, N-hydroxy-2-pyridone showed significant inhibitory activity against *C. albicans*. In addition, the tetranorditerpenoid derivatives of penicimonoterpene and penicicide A, extracted from the endophytic fungus *A. wentii* en-48 from *Sargassum* sp., have both strong bactericidal activity and anticancer properties, and strong antifungal activity against *C. albicans*, with a minimum inhibitory concentration value of 16 $\mu\text{g ml}^{-1}$ (Sun *et al.*, 2012).

Other bioactive compounds. Some studies have shown that endosymbiotic microorganisms of seaweed also have strong antioxidant potential. It was reported that a strain of *Acremonium* sp. isolated from the brown algae *Cladostephus spongiosus* off the coast of Spain synthesizes the hydroquinone compounds 7-isopropenylbicyclo[4.2.0]octa-1,3,5-triene-2,5-diol and 2-(3-dihydroxy-3-methylbutyl)benzene-1,4-diol, which have antioxidant activity (Abdel-Lateff *et al.*, 2002). These phenolic compounds had obvious scavenging activity against 25.0 $\mu\text{g ml}^{-1}$ DPPH free radical and inhibited peroxidation of 37.0 $\mu\text{g ml}^{-1}$ linolenic acid (Abdel-Lateff *et al.*, 2003). In addition, epicoccone, produced by the fungus *Epicoccum* sp. isolated from the seaweed *Fucus vesiculosus*, was also shown to be an effective antioxidant (Abdel-Lateff *et al.*, 2003).

Concluding remarks and future perspective

The symbiotic system of seaweed and microorganisms plays important roles in marine ecological regulation and

seaweed persistence. SAMs live on the seaweed surface and tissues, have spatiotemporal characteristics and play indispensable roles in regulating seaweed growth and life cycles. Some of these roles include producing vitamins and other nutrients, converting organic matter and nitrate nitrogen to facilitate nutrient uptake and helping seaweed defend themselves by quorum sensing and secreting antifouling substances (Table 1, Fig. 1).

Seaweed farming in China and Indonesia alone contributes approximately 87% of the global supply of seaweed products, of which food production and carrageenan extraction are the two main industries (Dhargalkar and Pereira, 2005; FAO, 2018). Seaweeds have been called the 'promising plant of the millennium' because of its comparative advantages over traditional farming on land (Dhargalkar and Pereira, 2005); it does not require land, freshwater, fertilizers, pests, insects or fungicides to grow and biomass can be used for many purposes, such as food, feed, materials, biofuel or as a gel or stabilizer in a range of applications. In addition, seaweed farming provides positive spin-off effects in terms of ecosystem services, such as creating good breeding habitats for fish and crustaceans (Hasselström *et al.*, 2018). Moreover, some studies showed that large-scale seaweed farming in China has a significant effect on phosphorus absorption and eutrophication mitigation in coastal waters, which are considered a potential carbon sink (Chung *et al.*, 2013; Duarte *et al.*, 2017; Xiao *et al.*, 2017); therefore, seaweed may have great potential for slowing ocean acidification and climate warming. However, despite the increasing importance of seaweed aquaculture, much is still unknown about the interaction between seaweed and microorganisms, from their evolution to their applications.

Currently, the understanding of the ecology and evolution of seaweed–microbial interactions has not been fully utilized in developing seaweed-based technologies (Shurin *et al.*, 2013). In addition, further research in ecological engineering will help promote the use of seaweed and microorganisms as future production platforms for a biorefinery to obtain industrially important chemicals and fuels (Brenner *et al.*, 2008; Cho *et al.*, 2015). As prices of traditional land-grown agricultural foods rise with rapidly growing populations and shrinking land area, alternative foods, such as seaweed-based diets, are likely to become increasingly important (Hafting *et al.*, 2015; Wijesekara and Kim, 2015). Therefore, studying the interaction between seaweed and microorganisms could help future industries that produce high-value products (such as healthcare products, cosmetics, fuels and chemicals) and low-value products (such as aquatic foods and animal feed) (Fig. 3).



Fig. 3. Illustration of the commercial and environmental applications of seaweeds and associated microbes.

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Conflict of interest

None declared.

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