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 (Nunez 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
similar environmental conditions (Bonthond et al., 2021). In addition, host-associated microbiota 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; Lutzu 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 (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 | *Enteromorpha sp.*          |                            | Zoospores settled on submerge surfaces formed by bacteria                | Thomas and Allsopp (1983)                                                 |
|                   | *Enteromorpha sp.*          | Naturally attached microflora | Increasing zoospores settlement on mixed bacterial biofilm              | Dillon et al. (1989)                                                     |
|                   | *Enteromorpha sp.*          | Naturally attached microflora | Positive correlation between bacteria to zoospores settlement           | Joint et al. (2000)                                                      |
|                   | *Enteromorpha sp.*          | *Vibrio anguillarum*        | Secreting AHLs increasing zoospores settlement                          | Joint et al. (2002)                                                      |
|                   | *Enteromorpha sp.*          | *Vibrio and Shewanella*     | Single-species biofilms affect zoospores settlement                      | Patel et al. (2003)                                                     |
| *Ulva fasciata*   | Naturally attached microflora |                            | Increasing zoospores settlement on mixed bacterial biofilm              | Shin (2008)                                                              |
| *Ulva sp.*        | *Vibrio anguillarum NB10*   | AHLs with longer (> 6 carbons) N-acyl chains, such as N-(3-oxodecanoyl)-L-homoserine lactone | Diffusion rates of AHLs, stability in seawater affect zoospores settlement | Tait et al. (2005)                                                      |
| *Ulva intestinalis* | *Vibrio anguillarum*        | AHLs with N-(3-oxodecanoyl)-L-homoserine lactone (3O-C12-HSL) as side chain | Increasing zoospores settlement                                         | Wheeler et al. (2006)                                                   |
| *Ulva sp.*        | *Rhodobacteraceae family,* | AHLs                       | Interaction of microbes affect zoospores settlement                      | Tait et al. (2009)                                                      |
|                   | *and the Bacteroidetes*     |                            |                                                                          |                                                                           |
|                   | *Flavobacteriaceae*         |                            |                                                                          |                                                                           |
|                   | *Rhodobacteraceae family,* |                            |                                                                          |                                                                           |
|                   | *and the Bacteroidetes*     |                            |                                                                          |                                                                           |
|                   | *Flavobacteriaceae*         |                            |                                                                          |                                                                           |
|                   | *Rhodobacteraceae, and*    |                            |                                                                          |                                                                           |
| *Ulva fasciata*   | *Marinomonas sp.*           | Physical association       | Zoospores released                                                       | Singh et al. (2011a,b,c)                                                 |
| Morphogenesis     | naturally attached microflora |                            |                                                                          |                                                                           |
| *Ulva lactuca*    | Naturally attached microflora |                            | Many strains of marine and associated bacteria-induced growth, such as *Enteromorpha* | Provasoli and Pintner (1980)                                             |
| *Monostroma*     | Naturally attached microflora |                            | Culture filtrate of bacteria and extracts of brown and red alga were also capable of morphogenesis | Tatewaki et al. (1983)                                                  |
| *oxyspermum*     |                             |                            |                                                                          |                                                                           |
| *Ulva pertusa*    | *Flavobacterium and*        | Thallusin                  | Direct physical attachment needed for morphogenesis                      | Nakanishi et al. (1996)                                                 |
| *Monostroma*     | *Vibrio*                    |                            | Secreting thallusin hormone affect morphogenesis                        | Matsuo et al. (2003)                                                    |
| *oxyspermum*     | *Zobellia sp.*              |                            | Affect tubular extensions                                               | Marshall et al. (2006)                                                   |
| *Ulva linza*      | *Bacteroidetes*              |                            | Affect the growth of fronds                                             | Singh et al. (2011a)                                                    |
| *Ulva fasciata*   | *Firmicutes*                | Roseobacter, *Sulfitobacter* and *Halomonas* | Affect the development of the *Ulva* gametes into thalli               |                                                                           |
| *Ulva mutabilis* |                             |                            |                                                                          |                                                                           |
| Spoerner et al. (2012) |                             |                            |                                                                          |                                                                           |
| Macroalgal growth | *Ulva lactuca*              | Indigenous microflora       | Nitrate, phosphate, growth factors (IAA, adenine and kinetin) and trace metals | Growth-promoting                                                        | Bradley (1991)                                                          |
| *Caulerpa taxifolia* | *Vibrio*                    | Cytokinin                  | Growth-promoting                                                        | Maruyama et al. (1988)                                                   |
| *Nitrogen*        | *Agrobacterium–*            | Nitrogen                   | Fix N2 in the rhizoids                                                  | Chisholm et al. (1996)                                                   |

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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 biosorants, 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 (Tsekov et al., 2010) and Chondracanthus chaminssoi (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 14000 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

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| Seaweed | Microbe | Mediators | Function | Reference |
|---------|---------|-----------|----------|-----------|
| Codium fragile ssp. tomentosoides | Azotobacter | Nitrogen | N₂ fixation | Head and Carpenter (1975) |
| Ulva fasciata | Marinomonas sp. | | | |
| Laminaria japonica | Pseudoalteromonas porphyrae | Catalase | Induced cell size and growth | Dimitrieva et al. (2006) |
| Pronitis lanceolata | Roseobacter | | Growth-promoting | |
| Gracilaria dura | Bacillus licheniformis | Indole-3-acetic acid (IAA) | Formation of bacterial galls | Ashen et al. (1999) |
| Gracilaria dura | Exiguobacterium homienae and endophytic Bacillus pumilus, Bacillus licheniformis | EPS, Indole-3-acetic acid (IAA) | Bud regeneration | Singh et al. (2011a), (2011c) |

Table 1. (Continued)
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 (Smil, 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 (Raghunandan 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 (Raghunandan 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 (Raghunandan 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 phytorelceptor activity, phytohormonal responses and changes in plant and soil microbiomes while decreasing dependency on chemical fertilizers (Chiaiese et al., 2018; Ali et al., 2021).
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 *Ascophyllum 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

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**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. 3β,11α-dihydroxy ergosta-8,24(28)-dien-7-one; 7. Cytoglobosins C and D; 8. Chaetopyranin; 9. Penicitide 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-methylasidioploidin; 16. asporyzin C; 17. Scleroderolide; 18. brevianamide M; 19. 6-O-methylaverufin; 20. Z-roquefortine C; 21. Penijanthine A; 22. 5,7-dihydroxy-2-{3-(4-methoxy-6-oxo-6H-pyran-2-yl)-2-phenylethylamino; 23. Penicimonoterpeine; 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.

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changes and numerous microorganisms and herbivorous insects, because of secondary metabolites (Busetti et al., 2017; Sarasan et al., 2017; Teixeira et al., 2019; Menaa 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 leukemia 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 ochratophyllum* from the seaweed *Sargassum kjellmanianum* produces a rare anticancer steroid compound, 7-nor-ergosteroide and a newly recognized steroid derivative, 3β,11α-dihydroxyergosta-8,24(28)-diene-7-one (Schulz et al., 1998; Erbert et al., 2012). A cytotoxicity study showed that 7-nor-ergosteroide had anticancer effects on human cancer cell lines, such as NCI-H460, SMMC7721 and SW1990; however, 3β,11α-dihydroxy ergosta-8,24(28)-diene-7-one had a weak inhibitory effect on SMMC-7721 cell growth (Cui et al., 2009a,b). Tricholocystis 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 alga, that can synthesize penicidite 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 gladiate* (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-methyloxanthone 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 fabeilformis*, 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 (lasiolide, de-O-methylasiodiplodin and 5-hydroxy-de-O-methylasiodiplodin) were isolated from an unidentified fungus of *Sargassum* 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 asporyzin 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 alga, and produces novel naphthenic tetracyclic diterpenes (coniogenone 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 aerugi- nosa* (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. gladiate* 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 penijanthine 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. gladiate 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-pyridine showed significant inhibitory activity against C. albicans. In addition, the tetranorditerpenoid derivatives of penicimonoterpen and penicillide 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 µg 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 alga Cladophoropsis spongios 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 µg ml⁻¹ DPPH free radical and inhibited peroxidation of 37.0 µg ml⁻¹ linoleic 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 (Hasselstrøm 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).
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Conflict of interest

None declared.

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