CHAPTER THREE

Challenges to the future domestication of seaweeds as cultivated species: understanding their physiological processes for large-scale production

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Abstract

A detailed understanding of physiological and reproductive processes in seaweeds has repeatedly proven to be an essential pre-requisite in the successful development of a sustainable industry. The prime example of this was the classical discovery of the "conchocelis"-phase of *Pyropia* (*Porphyra*) by Kathleen Mary Drew-Baker in 1949. Such elegant research proved to be pivotal to the development of a globally important "nori" industry which transitioned from the simple provision of the enhanced surface area of the substrata for spore settlement to the sophisticated, mechanized and computerized operations in modern hatcheries supplied by seedling banks of selected

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Advances in Botanical Research, Volume 95
ISSN 0065-2296
https://doi.org/10.1016/bs.abr.2019.11.010

species and their cultivars. All of the pre-requisite knowledge was acquired through intensive applied research. However, not all solutions need to be high-tech; problems caused by epiphytes and contaminants have been achieved by exposing *Pyropia* nets periodically and was found to be effective. This protocol was achieved based on fundamental observations by farmers which were then complemented and refined by laboratory trials. Techniques must be adapted for site-specific differences, as abiotic factors such as water current and movement, surface seawater temperature, light regime and photoperiod, nutrients dispersion and water quality are interrelated, either positively or negatively, influencing seaweed productivity and the end-use of the biomass. Unfortunately, positive techniques that have been shown *in vitro/silica* can prove to be impractical once attempted at large-scale cultivation and/or the return on investment is not justified by the commercial value of the resultant seaweed biomass. This chapter presents a summary of how the judicious application of knowledge based on the eco-physiological processes of common seaweed species from tropical and cold-waters can assist the future development and scale-up of the global seaweed industry.

1. The physiological process associated with seaweeds farmed commercially

One of the most famous species around the world thanks to the popularity of sushi, *Pyropia* (*Porphyra*) is also one example of how the knowledge of reproductive and physiological aspects can promote a whole industry. The classic work of Kathleen Drew Baker (Drew, 1949) showed how researchers were struggling to find out what was the relationship between both the leafy and the filamentous thalli, after germination of some "spores." Clearly, there was some misunderstanding about the role of monospores. The knowledge of the life cycle of various species of the genus *Pyropia*, besides the understanding of the optimal conditions for each phase of the life cycle, allowed for domestication and development of a very valuable industry. Now, it is possible to stimulate or inhibit the sporulation of all phases, controlling nutrient availability, water temperature, and irradiance. For example, to increase the release of conchospores, mechanical stimulation can be used, as with water circulation using compressed air, as well as physical stimulation, such as reducing water temperature from 23°C to 18–20°C (Blouin, Brodie, Grossman, Xu, & Brawley, 2011; Oohusa, 1993). However, differences driven by light, temperature and photoperiod on conchospores release have being reported to be species dependent (López-Vivas, Riosmena-Rodríguez, Llave, Pacheco-Ruíz, & Yarish, 2015).

The reproduction of the main cultivated seaweeds may occurs after some stress stimulus, as well explained in Laminariales by Lüning and Dieck

(1989). One day of low temperature or the absence of light is enough to stimulate spore or gamete release when the seaweeds are cultivated under standard conditions. The authors described that the temperature, photoperiod and internal control systems interacts in the seasonal development of organisms. Even the simple water exchange in cultivation tanks may boost the release of spores/gametes (Kawashima, 1993; Ohno & Matsuoka, 1993). The farming of the red seaweed *Pyropia* and browns seaweeds such as *Saccharina*, and *Undaria*, are based on asexual propagation by using meiospores. The kelps (Laminariales) have a high level of specialization and thallus fragments of sporophytes do not regenerate (Khan & Satam, 2003), so zoospores (i.e. meiospores) are parts of the reproductive cycle. These examples basically reflect that some seaweeds have a hatchery phase easier to manage in their production cycle which has allowed commercial "exploitation" and domestication. However, the biomass production of the most commonly cultivated tropical seaweeds does not necessary require a hatchery phase (in the sense that gametes or spores are rarely involved in mass cultivation); most, e.g.*Gracilaria, Kappaphycus*, and *Eucheuma* are cultivated by vegetative propagation of fragments of thalli. In addition, the maintenance of genotypes of commercial interest by controlling the life cycles would be a factor increasing the success of seaweed production in the long term (Charrier et al., 2017). Thorough knowledge of the physiological processes which regulate productivity in marine farms is therefor essential to the industry.

There is also an increasing need to control the quality of seaweed biomass grown out in sea farms, especially in times of global warming. According to Azanza and Ask (2017), irradiance and Surface Seawater Temperature (SST) are the main factors affecting eucheumatoids (i.e. *Kappaphycus* and *Eucheuma*) production. Specifically for *Kappaphycus alvarezii* and *Eucheuma denticulatum*, the most studied carrageenophyte species, earlier on basic and applied studies of Dawes and Koch (1991) and Dawes, Trono and Lluisma (1993) on the effects of physiological aspects were driven by the necessity to increase the productivity of marine farms. This is also the case for *Gracilaria* cultivation, which has been extensively studied to understand the relationship between abiotic factors and the growth and agar yield and quality. Buschmann, Hernández-González and Varela (2008) reported variations in the productivity of *Gracilaria chilensis,* depending on those area of the coastal shore which were cultivated (i.e. subtidal or intertidal), the region of Chile (i.e. southern or northern) or season (highest growth in spring, declining in the summer and lowest in winter). The authors concluded that several (abiotic) environmental factors were also inter-related to this variation.

2. Optimization of large-scale cultivation: challenges and potential

In order to enhance the production of commercially important seaweeds, it is important to understand and modify the main parameters which influence their cultivation, such as water current and movement, seawater temperature, irradiance and photoperiod, nutrients dispersion and water quality, and understand the relationships of these factors and the intrinsic physiological response.

An understanding of the physiological process made it possible to improve the mass production of biomass in cultivation, for example, of the brown seaweed *Saccharina latissima*. The use of stress conditions, such as thallus dissection and thermal shock, can stimulate the production of meiospores. Also, if the meiospores are maintained under red light it can prevent gametophyte fertilization, while the fertilization and sporophyte development are promoted when cultivated in white light (Kerrison, Stanley, & Hughes, 2018). The hatchery phase is still a challenge if mass cultivation is considered since seeded ropes need to be kept until the young sporophytes achieve 1−2 mm prior to being transferred to open water. This phase can take up to eight months, thereby increasing the costs of operation. To solve that, Kerrison et al. (2018) tested textile sheets as a physical substratum for meiospores, gametophytes, and sporophytes, and observed that these sheets produced twice the biomass, after four months, as compared to the traditional method. In addition, sporophytes grew faster than meiospores and gametophytes, when attached to the sheets with a binder (AT ∼ SEA Technologies, BE). In this new sporophyte seeding technique, the selection of a suitable twine was essential for the sucess of juveniles development (Kerrison et al., 2019). For *Palmaria palmata* cultivation, new hatchery strategies to improve seedling have being develop based on Germination, Maceration and Agitation (GMA) method - from release and handling of tetraspores to produce seedlings (propagules) on cultivation substrate (Schmedes, Nielsen, & Petersen, 2019).

For the production of those seaweeds of mass cultivation by propagules, such as *Gracilaria*, for agar and, *Kappaphycus* and *Eucheuma,* for carrageenan extraction, several methods have been traditionally employed for rapid biomass production. Examples are off-bottom, rafts, and long-line ropes (Hayashi et al., 2017). Basically, the propagules are attached by various tieing methods on to ropes which are then fixed to stakes hammered into soft substrata (off-bottom) or floating, suspended by buoys (rafts and long-lines)

(Buschmann et al., 2008). The use of tubular nets, similar to those used in mollusk farms, replace the ropes, thereby allowing the improvement of productivity of carrageenophyte farms and also increased the possibility of mechanizing the process (Hayashi et al., 2017). Tubular nets works well in cultivations with muddy bottoms and increased sea water movement. This technique could retain the seedlings on the raft, avoiding invasiveness on the environment, and improve the manage of the cultivar by reducing the time spent in comparison with the tie-tie technique (Góes & Reis, 2011; Reis, Pereira, & Goes, 2015). For this, however, it may be extremely efficient in fast-growing species because the terete, side branches grow out through the mesh, before the apertures can be filled with sediments or epiphytic over-growth (depending on the area).

Although many commercial seaweed species are cultivated in slow open water, they are not entirely free from damage caused by natural hazards such as typhoons and storms, which can occur with variable frequency and severity, mainly in tropical regions. This problem is not easy to solve, and according to Kim, Yarish, Hwang, Park and Kim (2017), the only solution is to remove the seaweeds from the sea (as in growing them on land). However, the costs to keep the seedlings in tanks are expensive and laced with difficulties, since they need to acclimate and be further selected for the prevailing conditions in these new conditions which can add further layers of stress.

The first example of intensively managed, on-land seaweed cultivation is the Irish moss (*Chondrus crispus)* aquaculture in Charlesville, Nova Scotia, Canada (Craigie, Cornish, & Deveau, 2019). The growth and photosynthetic rates, zinc contamination, disease control, and clone selection are severe challenges to overcome. Technologies applied included drone monitoring, real-time adjustments of air delivery systems, compressed air-agitation in each tank, regulation of pH by carbon dioxide with carbon recovery up to 90% in the large-scale cultivation tanks. Water issues pipelines were solved by accessing deeper, cooler seawater and providing low incoming particulate matter. The large tanks management use subdivided to facilitate management and harvesting. Prophylactic measures were required in addition to mechanical sorting and handling techniques. This industry is focused on biomass for food production with all requisites to meet the stringent demands of the export market (Japan). The success of this operation was due to the continuous P & D work undertaken a strain selection, biology, engineering and marketing of a high quality product.

There are also other approaches to economically feasible and ecologically sustainable land-based cultivation as in the association of seaweed cultivation with other aquatic organisms in the Integrated Multi-trophic Aquaculture System (IMTA) (Sebök, Herppichb, & Hanelta, 2017). Seaweed-based integrated farms on full scale achieved commercial sucess in some countries, like China, South Africa and Canada, and have being widely studied and reported in Israel (Neori, Guttman, Israel, & Shpigel, 2019; Neori, Sphigel, Guttman, & Israel, 2017). The selection of species depends on economical and logistical factors as well as expertize and equipments required. Suitable models were establish with species of *Gracilaria* and *Ulva*. The seaweed growth works as a function of light intensity, temperature, water motion, plant density and nutrient enrichment, which can be sourced from fertilizers and effluents (Neori, Shpigel, Guttman, & Israel, 2017). For example, Abreu, Pereira, Buschmann, Sousa-Pinto, and Yarish (2011) integrated *Gracilaria vermiculophylla* as a biofilter for fish-effluents rich in nitrogen. The requirements of nutrients for the growth marine seaweed also changes and interact with the season and other factors such as the prevailing light and temperature regimes (Usandizaga et al., 2018). Nobre, Valente, and Neori (2017) elaborated a model to assess water renewal rates and nitrogen limitation (uptake and growth) in commercial seaweed farms based on *Ulva spp*. parameter for the management of the nutrient limitation that occurs when expanding seaweed production and for planning the seaweed integration with other aquaculture products in an IMTA system. According to them, this model helps to support the calculation of the renewals required to expand from a planning stage to a production scale. Shpigel et al. (2018) employed *Ulva lactuca* to reduce nitrogen loads from the effluents of sea urchin tank and fishponds in a semi-commercial land-based IMTA system, and observed that the seaweed assimilated 74% of the dissolved nitrogen and became itself a valuable crop for sea urchin.

Effluents of bioflocs from the farming of marine shrimp were observed by Pedra, Ramlov, Maraschin and Hayashi (2017) to improved not only the growth of *K. alvarezii* in tanks, but also the bioactive content in the biomass, offering the possibility to utilize the raw materials for value-added products, other than carrageenan. Nevertheless, the economic value and long term viability of these systems still needs to be demonstrated before wider adoption will take place. It is claimed that some of the production costs can be off-set, however, monetizing the treatment of (marine) effluents is a very recent area, and it remains to be seen when and where cost-effective operations will be viable.

High productivity of outdoor tank cultivation of several nori species in relation to seeded nets in open sea in Israel, for an entire growth season, were reported by Israel, Levy and Friedlander (2006), suggesting the tank and pond cultivation of the foliose phase as a controlled high yield alternative (50–300% higher than yields indicated for crops grown on seeded nets). However, the known operational costs needed to be highlighted, where the water agitation in the cultivation of seaweeds may be significant. The physical movement and low stocking density are required so as to regulate the temperature and ensure adequate distribution of carbon and nutrients inside the tank, which in turn promote movement facilitating absorption of nutrients by *Pyropia haitanensis*. In high stocking density cultivation, extra carbon supply may be necessary to avoid negative effects on the photosynthesis due to lowered carbon (Jiang, Zou, Lou, & Ye, 2017). Agitation is required as there is a need to break down the laminar barriers on the surface of the seaweed thalli—which affect gaseous exchange (i.e. morphology plays a role here). Energy required for the pumping/agitation is an important consideration: simple movement can be achieved with a paddle wheel. Using compressed air with spargers creates movement (there are physical constraints which determine the shape of tank and where to place spargers), and CO_2 can be added which is both a pH adjustment and a source of carbon. Seaweeds in tanks are stressed, they need to circulate so as to be in the photic zone as much as possible. The amount of agitation determines if they move in a circular cellular motion, or move with laminar flow. In terms of the plants, at the surface of a pond they may well be photo-inhibited. Circulating them from the surface to the bottom means they go through periods of light/dark very rapidly, thereby improving their photosynthetic efficiency.

Development of technologies are required. One example is the closed ring-shaped cultivation model by Sebök et al. (2017). They evaluated growth rates from *P. palmata, C. crispus,* and *U. lactuca* over 7 days in these experimental models. According to these authors, their system reduced the volume of cultivation media required and increased control by separating the supply of CO_2 and nutrients, as well as the temperature control from agitation. To design a new system for optimal growth conditions and efficiency requires an in-depth analysis of every parameter involved in the cultivation process which in many cases has to be established and tested experimentally under laboratory-scale conditions.

Another physiological aspect of seaweeds is that there can be temporal changes in chemical composition of commercial interest, which has an impact on when harvesting should be conducted (Taelman, Champenois, Edwards, De Meester, & Dewulf, 2015). One example is the work of Hayashi et al. (2007), which demonstrated that, depending on the cultivation period, in Brazil, the end-product of carrageenan from *K. alvarezii* could have significant variations in the relative composition of *kappa* and *iota* fractions. The biomass increased according to the duration of the cultivation, giving the highest gel strength, viscosity, and molecular weight values.

One of major challenges to the seaweed industry is the outbreak of diseases, which affect most of the major commercially important species and can cause significant economic losses. Production of the kelp *Saccharina* was far of be affected by many diseases, endo- and epibionts, causing significant economic losses (Wang et al., 2019). *Pyropia* is mainly affected by oomycetes *Olpidiopis* spp. and *Pythium* spp., as well as red rot and chytrid diseases (Gachon, Sime-Ngando, Strittmatter, Chambouvet, & Kim, 2010). Eucheumatoid genera (i.e. *Kappaphycus* and *Eucheuma*) are frequently affected by "ice-ice" disease although there is evidence that bleached thalli are primarily a consequence of physiological stress and not necessarily provoked by pathogens (i.e. they are secondary in nature, Loureiro, Hurtado, & Critchley, 2017). A common point to all of these diseases is that their spread seems to be directly related to intensification of large-scale production (Gachon et al., 2010). There are some short-term solutions to minimize the impacts of these diseases, such as treating the blades of *Pyropia* with regular acid-washing (Gachon et al., 2010), but this is not viable for large-scale production. Hafting et al. (2015) warn of the necessity to develop strains resistant to diseases, which can be supported by the emerging field of phycopathology.

Epiphytes, fouling, and herbivores can be responsible for significant economic losses. Desiccation and pH control can be used in *Pyropia*, and briefly washing the thalli with freshwater works relatively well for tropical species such as *Kappaphycus, Eucheuma* and *Gracilaria* (Kim et al., 2017). Growing seaweeds in high densities can also help minimize the presence of epiphytes since some of these, i.e. *Ulva* and *Ectocarpus* require high irradiances and high densities remove the light. One strategy used in *Saccharina* cultivation is the growth in the laboratory under conditions of short photoperiod, this helps to prevent the growth of epiphytes, activate the basal blade meristem, stimulates continuous growth throughout the year and interrupted the seasonal cycle of growth (Lüning & Pang, 2003). On the other hand, with the increase of the density, space can be limited even for the hosts, so the balance of the epiphytes control and productivity is fundamental. Depending on the situation, the only solution is to change the cultivation site or grow a limited amount of "carry over" biomass, temporarily in tanks (Kim et al., 2017).

The use of biostimulants—extracts of brown seaweeds, i.e., *Ascophyllum nodosum* (AMPEP), or *Ecklonia maxima* (commercially know as Kelpak) could be used in *Kappaphycus* for land-sea-based nursery cultivation operations (Tibubos, Hurtado, & Critchley, 2017) and also to increase carrageenan yield (Loureiro, Reis, Berrogain, & Critchley, 2014). These extracts can also improve the growth of this species and mitigate the damage of epiphytic *Neosiphonia* infestation (Ali, Yasir, Critchley, & Hurtado, 2018; Borlongan, Tibubos, Yunque, Hurtado, & Critchley, 2011; Marroig, Loureiro, & Reis, 2016), and the physiological stress (Borlongan, Gerung, Kawaguchi, Nishihara, & Terada, 2017; Borlongan, Gerung, Nishihara, & Terada, 2017; Borlongan, Luhan, Padilla, & Hurtado, 2016). This concept is interesting if one considers that induction of haloperoxidase seems to be a generic mechanism of brown and red algae against biotic and abiotic stresses (Gachon et al., 2010), and the use of both can help to minimize damage. The treatment with AMPEP induced an oxidative burst response, caused by the interaction between the β-1,3 glucan present in the extract and the β-1,3 glucanase enzyme present in *K. alvarezii,* which stimulated the production of volatile halogenated compounds which were elicited through NADPH oxidase in the cellular membrane. Thus, the β-1,3 glucan, together with betaines and cytokinin-elicitors, also reported to be present in the AMPEP, shielded the treated seaweed seedlings against the effects of constant H_2O_2 exudation and exposure, acting as "vaccine" and growth promoter (Loureiro et al., 2017; Loureiro, Reis, Berrogain, & Critchley, 2012).

Wang et al. (2019) also suggested the use of a specific polysaccharides, the oligoalginate, to prevented and controlled diseases of kelp juveniles in open sea-cultivation. Oligoalginate elicitation was found to decrease the density of endobionts and the number of bacterial cells on the juvenile sporophytes of *S. latissima* and *S. japonica*. However, the same was not true for the adult sporophytes where elicitation increased their susceptibility to epibionts settlement of both species and accelerated the aging of *S. japonica* adults.

3. From the laboratory to the sea: product development

The production of seaweed biomass is predominantly directed to markets and processing for human food, e.g., edible seaweeds—*Laminaria* (kombu), *Porphyra* (nori) and *Undaria* (wakame), or the phycocolloids extracted from *Kappaphycus, Eucheuma,* and *Gracilaria*. However, there are other seaweed-derived products with commercial potential that are emerging and being developed by a diversifying seaweed industry.

New extraction technologies, applications of the biorefinery principle and the discovery of novel bioactive compounds, are stimulating value-added products with applications in several markets such as functional foods, nutraceuticals, cosmeceuticals, pharmaceuticals, dietary feed supplements, fertilizers, biostimulants, bioregulators, bioremediation and nano-particle technologies (e.g., Duan, Critchley, Fu, & Pereira, 2019; Hafting et al., 2015; Martins, Vieira, Gaspar, & Santos, 2014; Michalak & Chojnacka, 2015; Vijayan et al., 2016). There are several studies in the literature about the bioactive compounds, but here we give some examples of the physiology related to bioactive compounds.

Bioactive compounds are chemical products resulting from metabolic processes, such as: proteins, minerals, vitamins, polysaccharides, oils, polyunsaturated fatty acids, plant growth-promoting substances, pigments, and secondary metabolites, which also express biological activity in other organisms, i.e. anti-bacterial, -viral, -fungal, -oxidative, -inflammatory, -diabetic, -hypertensive, -allergic, -tumor properties and -fouling (Admassu, Gasmalla, Yang, & Zhao, 2018; Dahms & Dobretsov, 2017; Hindu, Chandrasekaran, Mukherjee, & Thomas, 2019; Jaswir & Monsur, 2011; Michalak & Chojnacka, 2015; Seca & Pinto, 2018; Vijayan et al., 2016). A wide range of bioactive compounds is reportedly found in marine organisms, as a response to the effect of an exigent, competitive and aggressive aquatic environment (Kolanjinathan, Ganesh, & Saranraj, 2014).

The marine natural products are already a consolidate research field (e.g., *Marine Drugs*) with more than 16,000 products isolated from diverse marine organisms, but screenings are still finding new compounds of interest (Bhakuni & Rawat, 2005). There are at least 3000 bioactive from seaweeds reported (Freile-Pelegrín & Tasdemir, 2019). In a review of the literature for 2017, 89 new compounds from seaweed were reported, in a total of 1490 new compounds from diverse origens (Carroll, Copp, Davis, Keyzers, & Prinsep, 2019).

The popularization of nutraceuticals or functional foods stimulated the commercialization of seaweeds as important ingredients because of the appeal as antihypertensive (mainly polysaccharides, peptides, and phlorotannins) and anti-obesity agents (phlorotannins, carotenoids, fucoxanthin, indole-derivatives, and sterols) found in many edible seaweed (*eg. Pyropia* *yezoensis, Py. columbina, P. palmata, Undaria pinnatifida, C. crispus, Ulva clathrata, Ulva rigida, U. pertusa, Ecklonia cava, E. stolonifera* and *Pelvetia canaliculata*) (Seca & Pinto, 2018). Mouritsen, Rhatigan and Pérez-Lloréns (2019) discuss these resources as human food and highlights the sensory perception and the important role of cookbooks, media-communications, and recipes to ordinary consumer. There are at least 665 species of edible macroalgae with bioactive compounds described (see Pereira, 2016). In this way, bioactive compounds from various seaweeds can occupy new markets. For example, some red seaweeds seems to be a good source of protein for new markets and also a source of ingredients (Cerná, 2011). *Pyropia* is a good source of vitamin B12, and besides their antioxidant activity, they can also have activities against hypertension, preventing cardiovascular disease, and reducing the risk of cancer (Skrovánková, 2011). Besides the diversity of vitamins, all essential minerals are available in dietary seaweeds, and they are a healthy alternative to sodium consumption. The salt made from seaweed has nearly 9%—12% sodium, while normal salt has 98% sodium (Drum, 2013).

Seaweeds can also be used as nutraceuticals in ingredients or as feed additives for other marine organisms. The inclusion of *U. pinnatifida* and *Sargassum filipendula* in the diet of the Pacific white shrimp *Litopenaeus vannamei* was reported to enhance resistance against White Spot Syndrome Virus (WSSV), besides improving digestive physiology, acting in the nutrient absorption and morphology of digestive tract. The addition of only 4% *U. pinnatifida* dry biomass to the feed reduced the cumulative mortality of shrimp at 72 h after WSSV infection (Schleder et al., 2018). *U. pinnatifida* was also reported to improve hemato-immunological parameters and reduce the quantity of *Vibrio* sp., an important group of pathogenic bacteria for shrimp farming. A feed with 0.5% and 2% of *S. filipendula* helped with thermal shock resistance, as indicated higher survival rates in treated animals. The higher content of total phenolic compounds, flavonoids, fucoxanthin, and lutein of the brown seaweeds (*S. filipendula* and *U. pinnatifida*) were reported (Schleder et al., 2017).

New ranges of products with active seaweed-derived ingredients are emerging in multiple markets. In the cosmeceutical industry, the potential applications were well-reviewed by Wijesinghe and Jeon (2011) (*eg. Ecklonia spp., Fucus spp., Ishige okamurae, Hizikia fusiformis, Laminaria japonica, Sargassum spp., Stocheospermum marginatum, Turbinaria spp.*, and *U. pinnatifida*) and Thomas and Kim (2013) (*eg. Dermatophagoides farina, Ecklonia* spp., *Eisenia* spp., *L. japonica, Laurencia* spp.). They are highlighted as promising as brown seaweed polyphenols and phloroglucinol derivatives (e.g. phlorotannins), have emerging applications as cancer chemo-preventive agents against photo-carcinogenesis and other adverse effects of UV-B exposure, photo-aging, inflammatory skin disorder, anti-oxidants, antiallergic and skin whitening, or protective agents. Sulfated polysaccharides (e.g., fucoidans and carrageenan) can also act against degradation and skin photo-aging, helping elasticity by increasing hydration, while carotenoids (e.g. fucoxanthin) can protect against oxidative stress-induced by UV-B radiation. Seaweed-based cosmeceuticals have been produced on a large-scale in the form of bioactive algae-based ingredients (Martins et al., 2014).

As for pharmaceutical applicability, there are several investigations on new drug delivery systems or in direct effect against diseases. An example of these new mechanisms are the food bioactive peptides. These peptide-based therapeutics demonstrated a similar mechanism of drug action, but when incorporated into foods it transports the substances through cell membranes for applications of medical diagnostics, nutraceutical, antimicrobial or cosmetic uses. The development of large-scale production (e.g. from *P. palmata, Porphyra yezoensis, Porphyra columbina, Pyropia columbina, U. pinnatifida, and A. nodosum*), optimization of protein extraction methods, and peptide isolation processes are important to be invested (Admassu et al., 2018).

As effective drugs, at the moment, there is only one seaweed-based product being commercialized, the innovative antiviral nasal spray made of iota-carrageenan (Carragelose®) by the Marinomed Biotech AG. It was demonstrated to be clinically effective against early symptoms of common cold due a protective physical antiviral barrier in the nasal cavity (Martins et al., 2014). This sulfated polysaccharide is cited for having biological effect preventing virus due to the structure in the surface that inhibit target cell binding (Chen et al., 1997). Other seaweed-based products have been sold but without proceed in all clinical test phases. *Laminaria* and *Sargassum* species have been used for the treatment of cancer in China, capsule forms of *Undaria* are used as anti-viral to inhibit the *Herpes simplex* virus, *Asparagopsis taxiformis* and *Sarconema* sp. are used to control and cure goiter (Khan & Satam, 2003). Natural products are preferred over non-natural because of the biochemical specificity, binding efficiency, high chemical diversity, and propensity to interact with biological targets (Martins et al., 2014).

Different medical applications are being studied, it ranges from bioactive against human immunodeficiency virus (HIV) (Besednova et al., 2019) until neglected tropical diseases (Freile-Pelegrín & Tasdemir, 2019). There are many metabolites such as sulfated polysaccharides (e.g. fucoidans and carrageenans), lectins and phenolic compounds with anti-HIV activity. This interest concerns the relatively low cost, high antiviral activity, low or absence of toxicity, the formation of pathogens resistance, good solubility and the possibility of cultivation of seaweed. However, currently there are no seaweed-based drugs on the pharmaceutical market for treating and preventing HIV infection (Besednova et al., 2019). Against several neglected tropical diseases, one of the substances of interest is elatol, the major component of the Brazilian red seaweed *Laurencia dendroidea* (Freile-Pelegrín & Tasdemir, 2019). The natural products can be stimulated depending on the seaweed; this was tested to produce the compound elatol as a rapid response to inducible chemical defenses to herbivory with *L. dendroidea* (Sudatti, Fujii, Rodrigues, Turra, & Pereira, 2018). Special vesicles called *corps en cerise* were described to be responsible for stored halogenated compounds such aselatol, which is transported to the seaweed thallus surface by exocytosis, in higher or lower concentrations depending on the cellular activities (Salgado et al., 2008). Although this species has been extensively studied, the ecological roles and production dynamics of such bioactive are still under investigation (Sudatti et al., 2018).

Another good example is the interactions of various components of seaweeds and bacteria (not just as a prebiotic), such has been highlighted in the recent years—not only by pathogenicity but also the promotion of beneficial or mutualistic interactions, which reflected on the production of primary and secondary metabolites. However the understanding of these relations is still in the beginning and needs further studies (Charrier et al., 2017).

The production of secondary metabolites in *K. alvarezii* and its growth by land-based aquaculture can be modified by treatments with Ascophyllum Marine Extract Powder (AMPEP), a commercial, biostimulant based on the brown seaweed *A. nodosum*. An extensive review of the AMPEP effects on cultivation of *K. alvarezii* and its selected cultivars was made by Hurtado and Critchley (2018). The AMPEP can be applied in the seaweed cultivation fertilized with effluents from shrimp cultivation in a biofloc system (BFT). The combined treatment of extracts of the BFT and AMPEP enhanced by a factor of two the concentration of some carotenoids (e.g. trans-β-carotene, cis-β-carotene, α-carotene, zeaxanthin, lutein, and others). Significantly higher content of total phenolics and flavonoids were found in treatments using the BFT effluents, thereby suggesting that the re-use of aquaculture effluents, in an IMTA for the benefits seaweed (Pedra et al., 2017).

In the context of IMTA, certain seaweeds may play fundamental roles, once the by-products from one species become inputs for another—in a sequential, bio-refinery approach, and the constituents of the algal biomass become feed resources for various extractive processes or for another organism. Such an approach not only mitigates effluents but can also assist economic viability due to product diversification and better management practices (Chopin & Sawhney, 2009). Seaweed aquaculture along affected coasts may also work as a biofilter and used as one treatment to mitigate the effects of marine eutrophication (Lüning & Pang, 2003).

The intensive cultivation of seaweeds also provides opportunities to remediate nitrogen and carbon wastes from wastewater producing biochar once the biomass can sequester carbon, nitrogen, and phosphorous. Biochar offers an interesting commercial solution because there is an increasing necessity to mitigate carbon production in industries. In addition, there is a search for the use of various biomass sources of seaweeds as natural animal feed/supplements, bio-fertilizers, soil conditioners, and feedstock - instead of (or in synergistic combinations) with synthetic chemicals and mineral fertilizers, so minimizing the environmental impacts of these products (Michalak & Chojnacka, 2015). Changes in the pre-treatment and temperature parameters of biochar production can guide its use for enhanced crop productivity and health, amelioration of soils and their microbial communities (i.e. as prebiotics), application to acidic soils (pH control) and carbon sequestration, and also maximize the benefits this seaweed feedstock (Bird, Wurster, Silva, Bass, & De Nys, 2011; Roberts & De Nys, 2016).

The bioremediation properties of selected seaweeds and their biomass has many applications, including the removal of certain metals from solutions. In a biomedical view, sodium alginate has reported the ability to remove strontium 85 and strontium 87 from living beings without seriously affecting their metabolism (Bhakuni & Rawat, 2005). The effective metal-reducing capacity of phytochemicals such as hydroxyl, carboxyl, and amino-functional groups raises the potential applications of certain seaweeds as an efficient, cost-effective and eco-friendly mediated synthesis of metal nanoparticles in the biotechnology industry. In this industry, the use is diverse, for example for application of polysaccharides greatly used as thickening agent in microbiology (agar) and in development of bioplastic (agar and alginate) or for development of coating materials on the surfaces of aquaculture installations and other marine systems to prevent fouling (Vijayan et al., 2016).

Some of the barriers, bottlenecks and limitations facing the global seaweed industry to further innovation and rapid development are suggested here to include the necessary product registrations due to their seasonal and geographic variation of chemical composition, product viability, generation of new markets, design of production systems, selection of efficient cultivars, the difference in the scale studies and technologies (Michalak & Chojnacka, 2015). The variability in chemical composition can be individual, caused by environment variations, and populational, due to genetic differentiation into locally adapted strains or phenotypically acclimated individuals (Martin et al., 2014). Innovative solutions need to be built from the academic knowledge along with the awareness and business expertise, and to bring it to the market, standardization, efficacy, traceability and clinical tests are needed (Hafting et al., 2015; Martin et al., 2014).

Industrial-scale, extensive biomass production of value-added products depends on net growth and the seaweed capacity to grow in specific structures and compositions. Since the hatchery phase needs parameters adjusted for the directional demands of the juveniles, investments in impacts of the surrounding physical and chemical environment (light, nutrients, salinity, and water movement) are required (Charrier et al., 2017). The search is to maximize the benefits of the sustainable seaweed raw materials and the potential for even larger volumes of cultivated biomass (Duan et al., 2019). Intensive, land-based cultivation enables crop manipulation, and management focused on genetic selection and control of parameters that directly act in the seaweed physiology and bioactive production. However, viability depends on the value of the product within various markets, in part as production and capital infrastructure costs must be covered by the value of the end product. A major challenge for savvy producers will be to activate and maintain the profiles of bioactive compounds in cultivated seaweed biomass (Hafting et al., 2015). The manufacturing process, technology, and cost in relation to yields of the product and market cost per kilogram are crucial to define the viability of the product (Martin et al., 2014). Technological advances in extraction process of bioactive compounds from various seaweeds can be driven by innovation and market demand (Michalak & Chojnacka, 2015).

Another challenge would be to bring the extension and application of the results from the laboratory to industrial scales since the new technologies and techniques require re-sizing up to a given scale of production; this is sometimes where enterprises fail (Michalak & Chojnacka, 2015). Besides, laws and regulations can have limited support in cases of new pharmaceuticals and food derived from seaweed (Hafting et al., 2015; Michalak & Chojnacka, 2015).

4. Climate change challenges

As with other sustainable, commercial activities developed in coastal areas, seaweed farming is also seen to be negatively impacted by the effects of climate change. Storm surge/raising sea levels/tsunamis, warming oceans, changes in CO_2/pH, earthquakes, prolonged rainy periods, typhoons and strong currents are being noted with greater frequencies, causing significant production losses (Largo, Chung, Phang, Gerung, & Sondak, 2017).

The higher frequency and intensity of storms in Canada may cause a large loss of rockweed (*A. nodosum*) biomass during the winter each year and with permanent loss in exposed areas that are not able to recover during the summer (Ugarte, Craigie, & Critchley, 2010). The North Atlantic relic kelps forests (such as *Alaria esculenta, Laminaria digitata, L. hyperborea, L. ochroleuca, L. solidungula, S. latissima, Saccorhiza polyschides* and *Saccorhiza dermatodea*) are estimated by niche modeling to be in threat of disappearing due to ongoing climate changes (Assis, Araújo, & Serrão, 2018). Migration of marine species has been noted, modifying ecosystems and seasonal activities, and affecting the seaweed crops. The increasing grazing and herbivorous fish and competition with other species can maximize the sedimentation in coastal, damaging the farms (Kronen, 2013; Largo et al., 2017).

In the coastal environments, seaweed aquaculture beds provide many ecosystem services associated with natural seaweed communities like CO_2 sequestration, food provision, and the supply of chemicals (Chung, Sondak, & Beardall, 2017). Thus, seaweeds acts directly in CO_2 sequestration by photosynthesis, accumulating biomass through nitrogen assimilation (Chen, Xia, Zou, & Zhang, 2019). Even though according to Largo et al. (2017) the idea of seaweed as a carbon sink may seem unrealistic because their life history is short and the accumulation of carbon in their thalli may not last long periods, the farms can contribute to minimizing the effects of ocean acidification.

Kim et al. (2017) made an interesting quantification of nitrogen and carbon removed from seawater in marine, macroalgal farms, considering the most cultivated genera: *Pyropia, Gracilaria, Kappaphycus/Eucheuma,* kelps, and *Sargassum*. According to these authors, these groups can remove approximately 65,000 tons of nitrogen and 760,000 tons of carbon *per* year.

Bjerregaard et al. (2016) calculated that the assimilation of nitrogen by marine farms, considering the production of 500,000 tons of seaweed and assuming nitrogen content of 3% for dry seaweed, could be 10 million tons from seawater or 30% of nitrogen inputs in to the ocean, in wastewater from agriculture, for example. These last authors also calculated that the same 500,000 tons of the seaweed could absorb 135 million tons of carbon or 3.2% of all carbon added in seawater from greenhouse gas emission.

Jiang, Zou, Lou, Deng and Zeng (2018) evaluated the effects of intensive production of *P. haitanensis* in large-scale and high density under conditions of seawater acidification. They verified that the increase in density caused by the growth of biomass and high photosynthetic range helped to reduce acidification of seawater. However, as density increased, the photosynthetic performance reduced. In another work, Jiang et al. (2017) observed that the maintenance of a high stocking density demonstrated a negative effect on the farms once the carbon supply was reduced and compromise photosynthesis of the same species. Intense photosynthesis can deplete dissolved inorganic carbon (DIC) in the water, which makes seaweed cultivation beds subject to low carbon.

Chen et al. (2019) tried to simulate the effects of aspects of climate change, incubating *P. haitanensis* for 10 days at elevated CO_2 levels, and changing diurnal temperature conditions. They observed that in an acid condition and suitable diurnal temperature, the carbon fixation and nitrogen assimilation were enhanced and consequently, the growth of the seaweed thalli. Several authors observed that high concentrations of dissolved inorganic carbon (DIC) in acidified seawater could change the content of soluble proteins, soluble carbohydrates, photosynthetic pigments and other biochemicals in *P. haitanensis* (Chen et al., 2019; Zou & Gao, 2004). This happens because commercial seaweed species can utilize increased DIC efficiently in photosynthesis, in an environment rich in CO_2, since the enhancement of photosynthesis was attributed to the increased activity of intra- and extra-cellular carbonic anhydrase (CA), thereby helping assimilation of carbon and nitrogen, when nutrients were in a sufficient supply (Chen et al., 2019; Zou & Gao, 2004). However, increased carbon and nitrogen metabolic rates were not in parallel and can also be influenced by temperature. Temperature fluctuations in the sea surface would be conducive to carbon fixation and nitrogen assimilation by the enhancement of photosynthesis and nitrate reductase activity in acidified seawater.

In excessively high seawater temperatures, photosynthesis, and energy consumption can negatively affect the cultivated species (Chen et al., 2019). Although, under high-temperature conditions rather than low-temperature, *Gracilaria lemaneiformis* exhibited higher growth rates, regardless of CO_2 levels. In high temperatures, enhanced nitrogen accumulation resulted in an increased content of nitrogen and amino acids as the ratios of C:N was reduced, while at lower temperatures no significant effects on the carbon and nitrogen acquisition were observed. Seasonal temperature changes during the culture period associated with an increase in CO_2 levels might be effective for the growth and nutritional accumulation of *G. lemaneiformis*—if the nutrients in seawater were sufficient (Chen, Zou, Du, & Ji, 2018).

An understanding of the responses to the temperature inside the context of ocean acidification of commercially important seaweeds is an important issue for the management of seaweed aquaculture into the future. Productivity may suffer intensively from the elevation of surface seawater temperature and CO_2 as also their interactions with other environmental factors (Chung et al., 2017). Therefore, the industry may be prepared for the effects of climate change through the development of thermo-tolerant strains (Kim et al., 2017).

Further efforts to identify species for use in seaweed aquaculture in the future will need to take into account their physiological tolerance to environmental changes and to ocean acidification and warming (Chung et al., 2017). This is particularly true for cold temperate species, such as kelps. Efforts to develop fast-growing, disease-resistant, and higher temperature tolerant strains are needed—urgently.

Carrageenophytes, in general, are well-adapted to the tropical seawater temperatures variation in their cultivation site. Temperature experiments revealed that while they exhibit maximum photosynthesis at 17–33°C, they are likely close to their threshold temperatures for thermal inhibition. This knowledge is essential for the improvement of seaweed cultivation practices to ensure sustainable production and supply, specially in the midst of increasing seawater temperatures brought about by global climate change (Borlongan, Gerung, Nishihara, & Terada, 2017). In relation to the most cultivated genera of sub-tropical red seaweeds *Eucheuma/Kappaphycus,* a generally warming ocean facilitated its successful introduction to sub-tropical regions (e.g., Brazil and Japan), and it seems that the increase in atmospheric CO_2 was favorable for their growth with no direct evidence of the impact of the associated lower pH in the field (not the case for coralline algae); Although experiments under laboratory conditions showed that lower pH could result in lower growth rates and a change in protein profile

(Largo et al., 2017). For coralline algae, water chemistry parameters with positive calcification regulatory, control of surface pH and light-independent carbon fixation are important to the maintenance in future ocean conditions (Schoenrock et al., 2018).

One of the main concerns is the production using vegetative propagation, resulting in a reduction of productivity and weak strains, susceptible to disease and epiphyte/pathogen attacks, besides variation in environmental conditions. Attempts to solve this problem have been made for several researchers around the world, raising new crops from spores or improving techniques of micropropagation and tissue culture (e.g., Jong, Thien, Yong, Rodrigues, & Yong, 2015; Luhan & Sollesta, 2010; Tibubos et al., 2017).

Risk assessment of expansion of seaweed farm to larges scale that brings drivers of environmental change (light, nutrients, carbon, kinetic energy, artificial material, noise, dissolved and particulate matter, etc), such as Campbell et al. (2019) for operations in Europe, needs to be made worldwide.

For mitigation, the climate changes impacts on seaweeds modeling approaches with physiological and ecological insights, integrated with genetic, epigenetic, and microbiome levels of intra-specific variation can help to predict a more the scenario (Duarte et al., 2018).

5. Future investigations

The necessary phyconomical developments required for the large-scale production of seaweeds for economic and industrial purposes, needs the interaction of academia, private sector, and government agencies for sharing the learning lessons and to strengthening the field (Hurtado, Neish, & Critchley, 2019). One goal for the development of sustainable cultivation of multiple species of seaweeds is to ensure that commercial aquaculture has minimal adverse effects on the environment and vice-versa. One way to achieve this goal is through the development of improved methods of waste management for land-based and coastal aquaculture (Kim et al., 2017). Carrageenophyte farming can have positive effects on the environment because it demonstrably improves the benthic ecosystem and sequesters carbon, thereby offering the potential for carbon credits (Valderrama, Cai, Hishamunda, & Ridler, 2013). Cultivation of various seaweeds can provide a low footprint for the environment so as to reduce pressure on land, freshwater and other resources, since *S. latissima* production was estimated to have an equivalent footprint as the microalgal production and farmed food (such as sugar beets, maize and potatoes) (Taelman et al., 2015).

Intensification of activities in seaweed cultivation can be achieved in certain locations, particularly in areas where production is seasonal. However, intensification carries the risk of bringing imbalances for farming areas that have reached the limits of their carrying capacity. In particular, the integrated multi-trophic aquaculture (IMTA), provides ecological benefits on overall production and enable the production of two or more cultivated species (Neori et al., 2019).

The aquaculture of some species still uses propagules/plantlets originally derived from natural populations and needs legislation and regulations so as to avoid their overexploitation (Kim et al., 2017), although the seaweed farming already contributed against the overexploitation of fishery resources (Hurtado, 2013). New technologies such as remote sensing data from high-resolution drones and satellites can make estimative of natural stocks of seaweed and identify potential areas for seaweed collection and cultivation (Setyawidati et al., 2018). Ensuring the biodiversity is a necessity for further value of seaweeds in the environment and their applications (Critchley et al., 2019).

A thorough understanding of the commercial species physiology is increasingly important to all forms of seaweed exploitation. The end-user industries and environmental concerns demand more control, quality, and greater utilization of the by-products, something even more difficult if marine farms due to effects of climate changes are considered. New technologies and processes need to be developed to address market needs and promote environmental sustainability.

In spite of the foregoing, there remains a tremendous need for continues research, development, innovation and refinement so as to find and improve on “new” applications for seaweeds and their bioactives, this includes “disruptive technologies” which provide things the industry “does not yet know it needs”. By no means is everything we need to know about seaweeds and their properties fully known. However, we “need to know what we do not know”. We need to recognize “seaweeds” as a polyphyletic “rag bag” of some very desperately associated genera of marine photosynthetic organisms. There is no “one size fits all” category for seaweeds and their bioactivities. We will only get the most benefits from their goods and services if we understand more about their fundamental biology - but then also have the skills and knowledge to take that information and apply it to beneficial services and products which provide the "greatest bang for the buck" for human society and the sustained existence of this planet.

A serious analysis must be undertaken related to biomass production and the viability of the production and value chain. Land-based, intensive cultivation has high costs, and biomass selection and maintenance is not easy. Back to basics, fundamental studies must be made to the current commercial species and the potential new (novel) ones, so as to provide specific insights as was made to cultivation protocols for *Pyropia* and *Saccharina* production based in their physiology.

Acknowledgments

Leila Hayashi thanks Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for the Productivity Fellowship (Process number 308631/2017-0).

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