Seaweed fermentation within the fields of food and natural products

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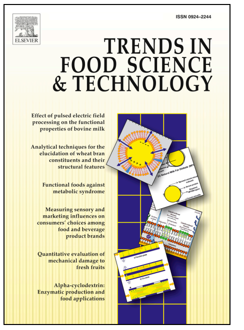

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Seaweed Fermentation within the fields of Food and Natural Products

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Highlights

- Seaweed fermentation remains an underdeveloped branch of marine biotechnology.
- Fermentation can facilitate the extraction of bioactive compounds from seaweeds.
- Products of seaweed fermentation show enhanced bioactive and sensory profiles.
- Full scope of applicability, bioactivities and mechanisms relies on further research.

Keywords

Bioactive compounds, Extraction enhancement, Functional foods, Marine Biotechnology, Nutraceuticals

Abstract

Background:

Seaweeds are promising substrates for biotransformation via fermentation, something that has been primarily utilized by the field of biofuels but focused less attention from other fields of research.. Considering that the fermentation of abundant land resources has become an important means by which new added-value compounds can be obtained, exploring the same process for seaweeds can contribute to an effective and sustainable exploitation of marine resources.

Scope and approach

In this review, recent advances demonstrating the potential behind the fermentation of seaweeds are evaluated. A breakdown of the most relevant seaweed compounds and their effect on potential bioprocesses is presented, along with pre-processing techniques that have become popular in biofuel fermentations. The applications of seaweed fermentation products in the fields of natural product research, functional foods and nutraceuticals, as well as the limitations and opportunities of seaweed fermentation are also highlighted.

Key findings and conclusions

Research revealing that seaweed fermentation can be used to create novel food and nutraceutical products that demonstrate high bioactivity and sensory quality was presented. The studies included demonstrate the use of this process in algal tissues and extracts as an enhancer of antioxidant, antimicrobial, anti-inflammatory and antidiabetic activities, among others.. Many of the difficulties related to fermenting seaweed have been addressed by research within the field of biofuels, providing insight on the conditions and pre-treatments necessary to improve seaweed fermentability. Food applications for seaweed fermentation products are still underdeveloped, but the nutritional, sensory and bioactive profiles collected so far highly encourage further developments.

Introduction

Fermentation has accompanied humanity throughout the evolution of its living practices and social developments, becoming the source of its most popular drug, the very first means of preserving food and an important enhancer of bioavailability. (McGovern et al., 2017). The term was initially used to define the yeast-driven transformations that occurred on fruit and cereal mashes, but has now come to represent many different microbiological processes across various industries and fields of study (Stanbury et al., 2017). In the strict biochemical definition, fermentation refers to energy-generation bioprocesses in which organic compounds, as opposed to oxygen, act as electron acceptors (Marquez et al., 2015). This contrasts with the broad industry definition, which defines fermentation as any process aiming to obtain a product from microorganisms cultivation (Maneein et al., 2018). These can include single cell protein from pure cultures, metabolites as products of substrate catabolism, enzymes, modified substrate compounds, or the production of recombinant metabolites (Stanbury et al., 2017). The earliest archaeological and archaeobotanical evidence for purposeful fermentation of natural products for human consumption is wine production from grape in the Near East, dating back to the early Neolithic (ca. 6,000–5,800 BC). Fermented foods became central to civilization as we know it in the West, and these products are presented as some of the earliest illustrations of human ingenuity and technological development (McGovern et al., 2004). Since then, a variety of fermentation products and technologies have been developed independently across the entire globe. Indeed, no sedentary civilization reached a level of development beyond tribal structures without use of fermentation for the preservation and enhancement of their food stockpiles (McGovern et al., 2017). In modern times, the role fermentation has expanded across many different fields, including medicine and pharmaceuticals (Hussain et al., 2016). Within these fields, fermentation became a key tool in the synthesis of new compounds, and in the enhancement of already existing sources of treatment. A characteristic example lies in the production of vitamin B12 via the aerobic metabolism of *Pseudomonas denitrificans*, enabling cheap and effective treatment of pernicious anemia (Uchida & Miyoshi, 2013).

In the beginning of the 21st century, the fields of food, pharmaceuticals and cosmetics were dominated by chemical industry products, following significant developments in chemical processes in the previous century, (Ferreira et al., 2021; Francavilla et al., 2021; Singla & Sit, 2021). These products aimed at solving specific needs of each sector (e.g. chemical leavening agents), are commercialized as bioactive molecules, capable of exerting a desired biological activity in a target matrix, and can be either extracted from natural sources, or entirely synthesized from precursor compounds. In the traditional approach, organic solvents and hazardous substances are commonly employed in the production or extraction of these substances (Sanches-Silva et al., 2014). Increased environmental awareness and the urge for sustainable processes has highlighted significant disadvantages in the use of chemical industry products and in turn benefited novel sources of natural bioactive products, capable of matching or surpassing the effectiveness of traditional synthetic molecules. In this context, fermentation has the opportunity to take precedent as a leading tool in the discovery, extraction, and processing of novel compounds with industrial applications (Philippsen et al., 2014). It presents itself as a process capable of transforming perishable and low-value natural resources into stable and valuable commodities that are nearly impossible to replicate with alternative means. It is also highly energy-efficient when compared to other biomass processing technologies, gaining increased attention now that sustainability is a major investment priority. Due to these factors and an ever-increasing understanding of the underlying biological processes, fermentation is expected to have a growing relevance in the modern food, feed and pharmaceutical industries (Uchida & Miyoshi, 2013).

Many processes that fall under the designation of fermentation involve complex substrate matrixes subjected to unfettered microbial metabolism. Under these circumstances, a wide variety of biochemical processes can occur, ultimately leading to an abundance of secondary metabolites in the fermentation products. (Houngbédji et al., 2019; Stanbury et al., 2017). A standout example of this lies in traditional food fermentations, such as those involved in the production of cured cheese or sourdough. These processes, safe for highly optimized industrial adaptations, still occur in loosely monitored conditions where pH, water content/activity, temperature culture composition and other stress factors can shift greatly (Houngbédji et al., 2019). These shifting parameters frequently expose cultures to undesirable growth conditions and can, in combination, favour the production of bioactive secondary metabolites. Microbial synthesis of antimicrobial peptides, vitamins, folates and organic acids has been associated with stress-inducing culture systems (Adewumi & Science, 2018; Cuvas-Limon et al., 2020).

In agreement with the main motivators of biotechnology research, taming this unstable synthesis can be the key to unlock an unprecedented new source of valuable bioactive compounds.

While it is still limited in scope and in number of publications, the increased demand for new sources of natural bioactive compounds has led to research on how fermentation can enhance the bioactive potential of complex edible substrates (Abdel-Aty et al., 2019; Chye et al., 2018; Hur et al., 2014; Hussain et al., 2016). Specific organisms with recognized biotechnological uses have provided much insight that allowed researchers to predict how fermentations can modify and enhance a specific substrate, as well as some of the most relevant metabolites that a given culture can produce. Unravelling the metabolomics of most spontaneous fermentations associated with traditional food products is still however, a work in progress. The complexity of this task and the limited short-term industrial applicability, discourage funding and hold back this type of research (Reese et al., 2020). The principle behind the enhancement of biological activities in fermentation products, when compared to their unfermented counterparts, is widely attributed to microbial-driven hydrolysis and the release of intracellular compounds. It is for this reason that phenolic compounds and bioactive peptides, compounds that are naturally present in plant cells in the case of the former, and products of protein hydrolysis in the latter, are pointed out as the most frequent culprits of bioactivity enhancement via fermentation (Hur et al., 2014).

The recovery of bioactive compounds from fermented plant material has now evolved to the point that the most recent publications often target the optimized production of a single compound (Li et al., 2019; Moccia et al., 2019). Despite this, certain authors insist on exploring new cultures, conditions and substrates within plant fermentation, offering interesting new insights on how this process can still be expanded Enhanced recovery of antimicrobial and antioxidant phenolic compounds has been achieved using filamentous fungi (Abdel-Aty et al., 2019; Olukomaiya et al., 2020), and lactic acid bacteria (Budiari et al., 2019). Outside the realm of plant products, extensive research is being conducted on the proteolytic potential of yeast and lactic acid bacteria on milk, with the latest publications focusing on recovery and purification efforts (Daliri et al., 2019; Fan et al., 2019; García-Tejedor et al., 2013).

Distanced from the examples provided so far, macroalgae (also known as seaweeds) are an alternative source of fermentable biomass that has received a great deal of attention from the biofuel industry, where they are used in the production of ethanol and methane. (Buschmann et al., 2017; FAO et al., 2018; Lafarga et al., 2020). The fermentation of seaweeds for food or pharmaceutical applications has been explored to a much lesser extent (Uchida & Miyoshi, 2013). The topics that follow present an overview of the research surrounding the use of seaweeds as a fermentable biomass to produce food and natural bioactive products. Seaweed compounds that can play pivotal roles in the process of fermentation are also described in detail, and the potential uses of the end-products of fermentation are discussed.

Seaweed consumption has followed a steady increase in the last decades, owing greatly to Asian market demand, which has led into steep increases in aquaculture yields. In 2016, 29 million tonnes of seaweed were harvested worldwide. Their usage was mainly distributed between human consumption, animal feed, and hydrocolloid production for food and pharmaceutical applications (FAO et al., 2018). This number corresponds to a 39% increase since 2014, and a clear sign of increased recognition as a critical raw material. As with all novel sources of biomass, the energy industry was quick to pick up on the possibility of using this abundant resource as a source of biofuel. Seaweeds are particularly desirable to this end as early studies showed promising yields, and their growth systems do not compete with agricultural crops nor require fresh water supply (Kerrison et al., 2015; Milledge & Harvey, 2016; Milledge & Heaven, 2014). Thus, a rising interest in the possibilities of seaweed fermentation had begun and is growing steadily, which is reflected in the number of publications on this subject (Figure 1).

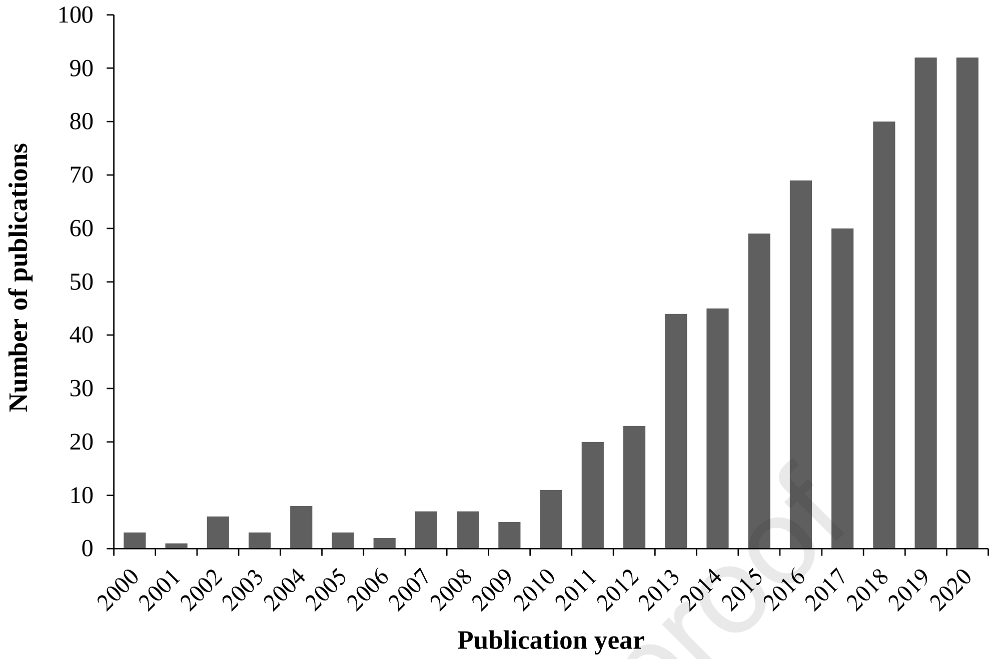

Figure 1. Web of Science Core Collection matches for the number of publications matching the topic keyword search "seaweed+fermentation" between Jan 2000 and Dec 2020.

Researchers in the field of energy fuels have split the microbially-driven digestion of organic biomass between the terms "fermentation" and "anaerobic digestion" depending on whether the target is the production of ethanol or biogas, respectively (Buschmann et al., 2017; Chye et al., 2018).. Even the most recent publications on biofuels research highlights important factors that make seaweeds a desirable fermentation substrate (Nguyen et al., 2020). Some of these include high (>80%) water content, which makes them readily suitable for wet biomass processes, and high energy-to-area yields as an aquaculture cultivation, with ratios comparable to maize (Allen et al., 2015; Milledge et al., 2014). These promising statistics have led to greater funding of research into the biochemical processes underlying the anaerobic microbially-induced digestion of seaweeds for the purposes of biogas production.

Figure 2 provides a diagram of the most biotechnologically relevant products of seaweed fermentation. In all commercially useful fermentations, hydrolysis of the main structural polysaccharides occurs, resulting in a sugar-rich mash. The most abundant polymer depends on the type of seaweed: laminarin, alginate, and fucoidan are present in brown seaweeds, agar and carrageenans in red seaweeds, and starch and ulvan in green seaweeds. Brown seaweeds have additional fermentable sugars, in the form of mannitol and glucuronic acid, that can further enrich the fermentable mash - assuming mannitol-fermenting cultures are used (Chades et al., 2018; Tajima et al., 2018). These sugars, along with the hydrolysed polysaccharides, are converted to pyruvate through glycolysis and then ethanol and CO_2 via alcoholic fermentation, or lactic acid via lactic acid fermentation (Marquez et al., 2015). Ethanol fermentation of seaweeds has a significant hurdle in the fact that most microbial cultures are incapable of utilizing certain seaweed sugars, including mannuronic and uronic acids, fucose, rhamnose, and xylose (Bobin-Dubigeon et al., 1997). Genetically engineered cultures have been developed for this purpose, as some of these sugars are present in plant biomass, and have demonstrated efficient conversion of seaweed sugars as well (Katahira et al., 2004; Parachin et al., 2011; Poblete-Castro et al., 2020; Surendhiran & Sirajunnisa, 2019; Tajima et al., 2018).Increased sugar conversion compatibility is the most common target of these modifications, given their goal of maximizing biofuel production., but future enhancements of seaweed-processing cultures could also attempt to maximize their competitive advantages against undesirable cultures, increasing the viability of fermenting unsterilized substrates (Poblete-Castro et al., 2020). Further still, highly proteolytic microbial strains could lead to the development of new food and nutraceutical products from protein-rich macroalgae such as *Palmaria palmata* and *Porphyra* spp. (Øverland et al., 2019).

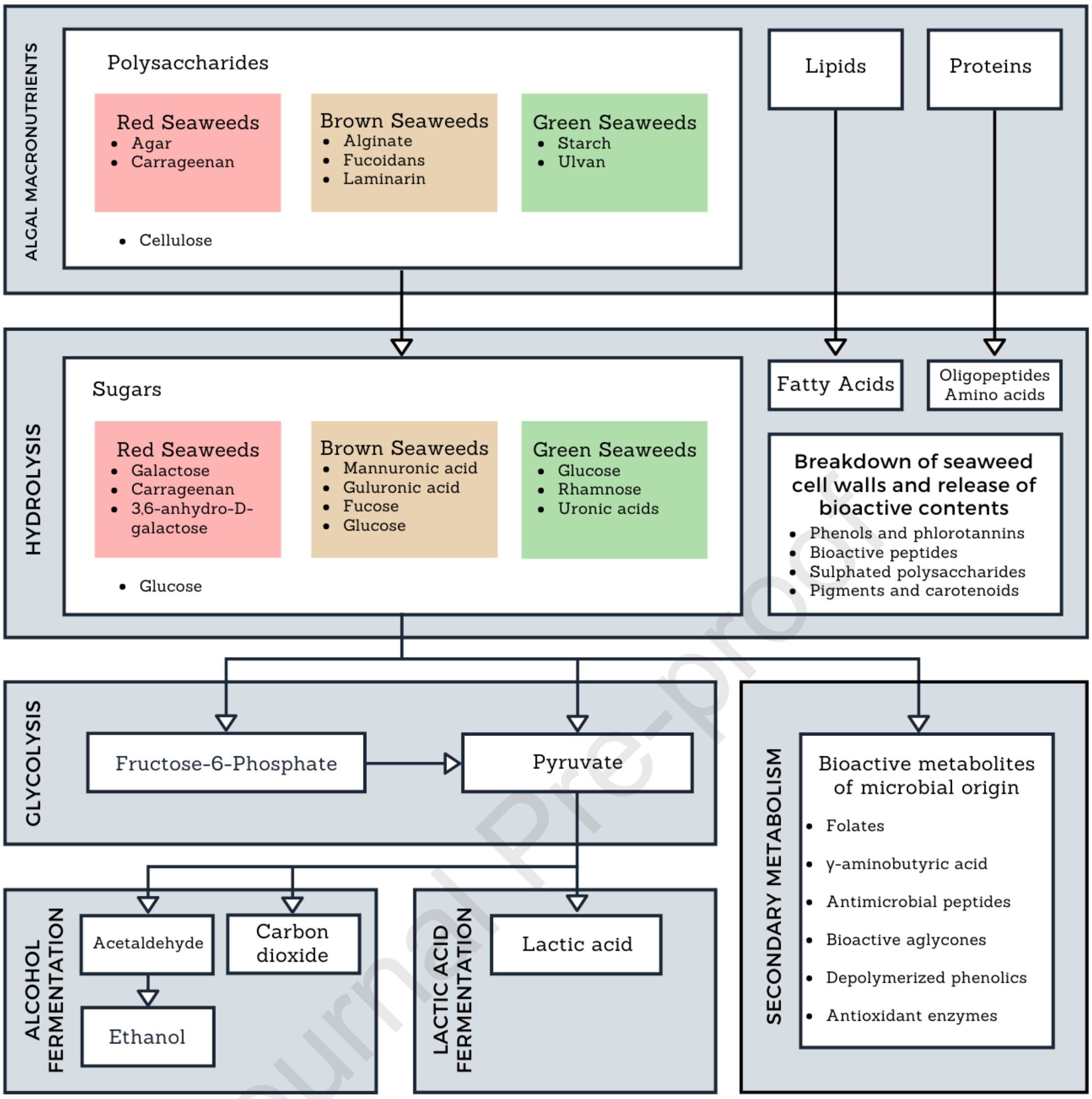

Figure 2. Overview of the production of added-value compounds from seaweed fermentation.

Successful seaweed fermentation has proven to be highly dependent on effective pre-treatment of the algal biomass and in the last decade, there have been continuing efforts to optimize pre-treatments to achieve better yields at lower costs (Maneein et al., 2018). While most of this research was directed towards energy yields, it has seen successful adaptation in other instances of seaweed fermentation (Park & Han, 2013; Suraiya, Lee, et al., 2018; Uchida et al., 2017). Milledge & Harvey (2016), have discussed the challenges of handling seaweed during harvest and post-harvest processing (cleaning, size reduction and storage). The authors highlighted the importance of effective storage of seaweed post-harvest, achieved using ensilage. Jung, Lim, Kim, & Park (2013) have also briefly reviewed characteristics of different seaweeds, highlighting microorganisms capable of hydrolysing seaweed carbohydrates, and different hydrolysis treatments developed to produce bioethanol from seaweed. The extensive research, development and optimization of pre-processing methods developed for the production of biofuels is a highly valuable source of information for any seaweed-fermenting endeavour, regardless of goal or target product. The following section will focus on highlighting certain compounds of seaweed origin from the perspective of their fermentability, and how they can affect either positively or negatively most microbially-driven processes.

Seaweed as fermentation substrate

The variability of environmental conditions, seasonal and acute, has a substantial influence on seaweed composition. Changes in sea currents, temperature, heavy metal concentrations and light intensity have proven to incur significant differences in amino acid, polysaccharide and ash content in brown seaweeds (Jung et al., 2013). The thickening of cell walls is an adaptation mechanism intended to limit the absorption of toxic compounds, and involves the modification of polysaccharide chain length, branching, and degree of sulphation (Habig & Ryther, 1983; Zeroual et al., 2020). The amount of phenolic compounds, an important class of seaweed bioactive compounds that can have a significant inhibitory effect on fermentation, can also be subject to change depending on environmental and seasonal changes (Michalak, 2018). Seaweed sodium, ash and polyphenols content, along with a unique composition of structural polysaccharides can minimize solid-liquid extraction yields but remain compatible with biotransformation via fermentation, given that tailored cultures and conditions are defined (Milledge & Harvey, 2016). There is no shortage of published work detailing the healthcare and technological uses of seaweed compounds. The value associated to some of these compounds is often retained in fermented seaweed products and therefore, can supplement the benefits of fermentation. Seaweed compounds with either novel or known value are briefly detailed below, as well as their general known role in seaweeds microbial processing.

Polysaccharides

One of the most distinguishing features of seaweeds as a source of natural products and as a fermentation substrate comes from their unique polysaccharide composition. Much of the modern use of seaweeds in the food and pharmaceutical industries relates to the use of these molecules as thickening agents and hydrocolloids. Phycocolloids have a broad range of applications and are very difficult to replace with cost-effective alternatives (Holdt & Kraan, 2011). Bioactive polysaccharides are also abundant in many species, with some highlighted bioactivities including anticoagulant, anti-inflammatory, and antitumoral (Magalhaes et al., 2011; Michalak & Chojnacka, 2015). Part of these activities have been associated with the high amounts of sulphated polysaccharides, present in brown seaweeds as sulphated fucans, in red seaweeds as sulphated galactans, and in green seaweeds as a variety of sulphated heteropolysaccharides, including xyloarabinogalactans (Berteau & Mulloy, 2003; Percival, 1979; Rodríguez-Jasso et al., 2013). The presence of these sulphated polysaccharides, as well as their structure and degree of sulfation is also highly variable across geographical distribution and season (Rodriguez-Jasso et al., 2014).

Table 1. Sugars and polysaccharides in red, green, and brown seaweed, and published research detailing their fermentation. Studies that resorted to or have developed genetically modified strains are marked as “Eng.” (engineered). * Study focuses on the fermentation of plant-based xylan. Presently, and to the best knowledge of the authors, no research on the degradation of seaweed xylan was performed. Search performed in April of 2021.

Seaweed type	Polysaccharide	Sugar	Fermenting cultures	Target compound/modification	Reference
Rhodophyta	**Agar**	D-galactose	Spontaneous fermentation	Hydrogen	Jung, Kim, & Shin Hang-Sik, 2011
	Carrageenan	D-galactose	Spontaneous fermentation	Hydrogen	Jung et al., 2011
			Saccharomyces cerevisiae	Ethanol	Meinita et al., 2012
	Xylan	Xylose	Eng. *S. cerevisiae*	Xylan breakdown; ethanol	Katahira et al., 2004*
	--	D-galactose	Lactic acid bacteria	Lactic acid, acetic acid	Hwang, Lee, Kim, & Lee, 2011
		D-glucuronic acid	Eng. *Corynebacterium glutamicum*	L-lysine, L-ornithine and lycopene	Hadiati et al., 2014
Phaeophyceae	**Alginate**		Spontaneous fermentation	Hydrogen	Jung et al., 2011
			Eng. *Sphingomonas sp*. A1	Ethanol	Takeda, Yoneyama, Kawai, Hashimoto, & Murata, 2011
			Endophyte fungal isolates	MW reduction	Hifney, Fawzy, Abdel-Gawad, & Gomaa, 2018
		Glucose, D-mannitol, mannuronic acid, guluronic acid	*Clostridium beijerinckii*	Butanol, acetone, ethanol, butyrate	Hou, From, Angelidaki, Huijgen, & Bjerre, 2017
	Fucoidan		*Aspergillus*, *Penicillium*, and *Mucor* fungal strains	Fucan-degrading enzymes	Rodríguez-Jasso, Mussatto, Pastrana, Aguilar, & Teixeira, 2010
			Endophyte fungal isolates	MW reduction	Hifney et al., 2018
	Laminarin		Spontaneous fermentation,	Hydrogen	Jung et al., 2011
		D-mannitol	*Pichia angophorae*	Ethanol	Horn, Aasen, & Emptyvstgaard, 2000
	--	L-fucose	*Escherichia coli*	Induction of propanediol oxidoreductase expression	Boronat & Aguilar, 1981
		D-mannitol, D-glucuronic acid, L-fucose	Lactic acid bacteria	Lactic acid, acetic acid	Hwang et al., 2011
		D-mannitol	*Thermoanaerobacter pseudoethanolicus*	Ethanol	Chades et al., 2018
Chlorophyta	**Celulose**	Glucose	*S. cerevisiae*	Ethanol	Yanagisawa, Nakamura, Ariga, & Nakasaki, 2011
	Starch		*S. cerevisiae*	Ethanol	Yanagisawa et al., 2011
	Ulvan	Xylose	Eng. *S. cerevisiae*	Ethanol	Parachin et al., 2011
	--	L-rhamnose	*E. coli*	Induction of propanediol oxidoreductase expression	Boronat & Aguilar, 1981
			Lactic acid bacteria	Lactic acid, acetic acid	Hwang et al., 2011

	C. beijerinckii	Acetic acid, butyric acid, isopropanol, butanol, ethanol, 1,2-propanediol	Diallo et al., 2018

The cell wall structure of seaweeds also varies greatly between classification and is highly relevant when considering using this source of biomass in an industrial bioprocess. Cellulose is the main cell wall component in brown seaweeds, structured as ribbon-shaped microfibrils of variable orientation depending on species. In turn, these microfibrils are meshed within a matrix of proteins, phenols and sulphated or carboxylic polysaccharides, which are theorized to act as binders of the cellulose fibrils, and can have a determinant effect on the fermentability of seaweed species with specific cultures (Deniaud-Bouët et al., 2014). Red and green seaweeds have xylans and mannans, as well as cellulose as major constituents of their cell walls. Green seaweeds in particular, while rich in cellulose compared to the brown and red variants, can also have high amounts of ulvans (Lakshmi et al., 2017). These polysaccharides are rich in sugars with low fermentability, including galactose, rhamnose, uronic acid, and xylose, making them not only difficult to process via microorganisms, but also reducing the access to other, more fermentable compounds. Red seaweeds with high carrageenan content, and alginate-rich brown seaweeds are similarly associated with lower yields of fermentation products (Bobin-Dubigeon et al., 1997; Lakshmi et al., 2017). These factors have discouraged the exploration of certain seaweed species for biofuel exploits outside of a few enzymatic pre-treatment trials (Maneein et al., 2018). This in turn signifies that ulvan, carrageenan and alginate-rich seaweeds remain largely unexplored when it comes to the products of their fermentation. Table 1 exemplifies studies that have addressed the fermentation of seaweed polysaccharides from different types of seaweed.

Pre-treatments used in the production of ethanol and biogas successfully increase the fermentability of seaweed polysaccharides but have reported disadvantages. Thermal pre-treatments of algal biomass have reportedly led to the production of toxic/carcinogenic or otherwise undesirable compounds, such as furfural and 5- hydroxymethylfurfural (HMF) (Wei et al., 2013). While pre-treatments and fermentation are often used in tandem, certain processes have successfully achieved useful fermentations without pre-treatments, and when wielding environmental and sustainability concerns, these should be regarded as highly valuable (Monlau et al., 2014).

Peptides

Protein is the macronutrient present in seaweeds that is subject to the highest seasonal variability. Contents can change from 10 to 40 % (w/w, dry weight) across different species and seasons, with higher percentages during winter months (Pangestuti & Kim, 2015). Seaweed protein amino acid profile has long been the focus of interest within the food industry, as most seaweed protein contains all the essential amino acids. Brown seaweeds are already becoming a popular source of protein in human diet, as they are also rich sources of alanine, glycine, leucine, lysine, threonine, and valine, with cysteine, methionine, histidine, tryptophan, and tyrosine are also present lower amounts (Holdt & Kraan, 2011). Additionally, aspartic and glutamic acids are present in high concentrations in brown seaweeds, making up to 44% of total amino acids content (Mæhre et al., 2014; Munda, 1977). Certain species of red seaweed also contain nearly all the essential amino acids, such as *Hypnea charoides* and *Hypnea japonica,* both boasting a complete amino acid profile with the exception of tryptophan (Wong & Cheung, 2000). A significant amount of these amino acids are found in free form in red and brown seaweeds and are considered major contributors to the sensation of umami (Mouritsen et al., 2019). This sensation is increased when in presence of ribonucleotides such as guanosine-5′-monophosphate and inosine-5′-monophosphate (Milinovic et al., 2020). The concentration of these compounds is often below the detectable threshold in seaweeds, with the majority of exceptions being red seaweeds such as *Chondrus crispus, Gracilaria gracilis* and *Osmundea pinnatifida* (Milinovic et al., 2020; Mouritsen et al., 2012).

Since their discovery, umami compounds have been widely accepted as the source of the perceived fifth taste. Seaweeds have been historically linked to the discovery of these compounds, as the Japanese chemist Kikunae Ikeda first identified monosodium glutamate in *dashi*, a broth made with the brown seaweed *Saccharina japonica* (Mouritsen et al., 2012). Verified umami receptors in the human tongue, such as the mGluR4 and T1R1+T1R3 taste receptors, along with proven taste enhancing capabilities of monosodium glutamate, succinic acid, theanine and gallic acid, among other additives, have placed umami compounds in constant high demand in the food industry (Yin Zhang et al., 2017).

However, the synthetic origin of many of these additives is becoming undesirable and incompatible with modern dietary trends, motivating a search for new natural sources of umami compounds.

The organoleptic properties of protein-rich foods can be greatly enhanced by proteolytic processes and in fact, protein hydrolysates via microbial or enzymatic degradation have become a major source of flavour enhancers (Nasri, 2017). This phenomenon is partially responsible for the unique sensory profiles of many fermented food products, including cheese, fermented meat products and soy sauces (Schlichtherle-Cerny & Amadò, 2002). While all five basic tastes have been perceived in both synthesized and natural peptides, the most common flavour contributions they provide are bitter and umami, making them desirable sources of these flavours (Temussi, 2012). It is thus no surprise that hydrolysates of abundant sources of protein have already been developed and commercialized, leaving most of recent published work focused on the extraction and purification of target peptides for highly specific use within the fields of food and pharmaceuticals (Ang & Ismail-Fitry, 2019; Yamasaki & Maekawa, 1978; Yin Zhang et al., 2017). Surprisingly, the more recent research delving into the secrets of the flavour of peptides has revealed underwhelming flavour abilities in single isolated specimens, and a struggle to specify the mechanisms behind the sensory appeal of complex hydrolysate mixtures. As described by Temussi (2012) many authors have been unable to find significant umami flavour in short peptides after thorough purification. The author further attributes the possibility of Asp and Glu residues, obtained by partial hydrolysis, as the culprits for their reported umami taste.

It is evident, however, that peptides do not play a role in food taste exclusively via their own contribution. Oligopeptides and polypeptides play a significant role in the early stages of the Maillard reaction, defining another mechanism by which peptides can determine food taste, texture, and aroma. This set of reactions is responsible for important colour changes during the fermentation of rice and soybeans in many east-Asia dishes, including *miso* and *douchi* (Yuhao Zhang et al., 2015). New information regarding the reactivity and rate of Amadori rearrangements of specific peptides has uncovered useful information regarding their potential as ingredients and additives for novel food products (Van Lancker et al., 2011). Scalone, Cucu, De Kimpe, & De Meulenaer (2015) have highlighted the importance of peptides in the production of substituted and unsubstituted pyrazines via Maillard reaction, reporting higher rates of formation when compared to free amino acids. These volatile compounds are responsible for the roasted, meaty or nutty aroma of many cooked food products. Combining this understanding with assessments of the organoleptic and nutritional potential of protein hydrolysates could lead to tailored processes of protein cleavage (including fermentation), that maximize positive flavour, texture and aroma traits. A simplified overview of the process of protein hydrolysis via fermentation and its most valuable products is presented in figure 3.

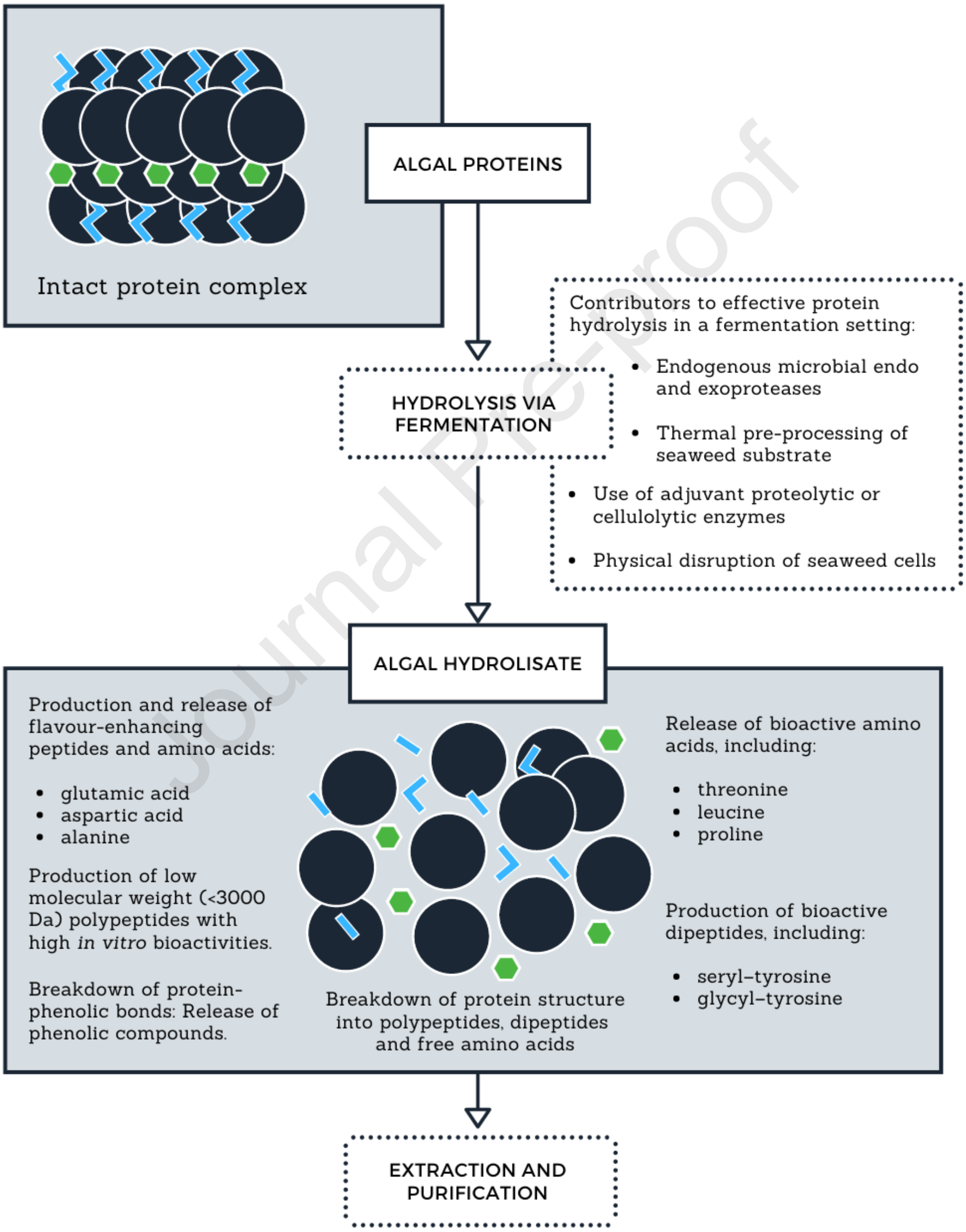

Figure 3. Flowchart depicting steps, contributors and products of a microbially-driven seaweed protein hydrolysis. Dotted line boxes address processes, while continuous lines address products and substrates. The examples provided of flavour-active or bioactive peptides and amino acids are standouts reported by Cian, et al. (2012), Lafarga et al. (2020), and Uchida et al. (2018), and do not represent a complete list of products of seaweed protein hydrolysis.

The production of protein hydrolysates and the search for new functional biomolecules has also led to great strides in uncovering the bioactive potential of bioactive peptides. Some of the most potent angiotensin-converting enzyme inhibitors include microbially-obtained milk protein hydrolysates, with the tripeptides Val-Pro-Pro and Ile-Pro-Pro being two famous examples (Nasri, 2017). It is now well-established that bioactive peptides are responsible for part of the antioxidant activity of algal extracts (Harnedy & Fitzgerald, 2011). Heo, Park, Lee, & Jeon (2005) generated a large amount of antioxidant hydrolysates of proteins isolated from *Ecklonia cava*, *Ishige okamurae*, *Sargassum fullvelum*, *Sargassum horneri*, *Sargassum coreanum*, *Sargassum thunbergii*, and *Scytosipon lomentaria* using the commercial enzymes Alcalase, Flavourzyme, Neutrase, Protamex, and Kojizyme. Japan has begun commercializing novel food products with seaweed-derived peptides, with the recent approval of the Ministry of Health and Welfare regarding the stated health claims. Wakame peptide jelly (Riken Vitamin Co., Ltd., Tokyo, Japan) and Nori peptide S (Shirako Co., Ltd., Tokyo, Japan) are two examples of these products readily available for the mass market (Nakai et al., 2011). Cian, Martínez-Augustin, & Drago (2012) obtained different enzymatic hydrolysates from co-products of *Porphyra columbina* using alcalase, trypsin, and combinations of both. In addition, Harnedy, O'Keeffe, & FitzGerald (2017) generated an enzymatic hydrolysate of *P. palmata* using the food-grade enzyme Corolase PP. Bioavailability of peptides with antioxidant properties has been also evaluated, and the antioxidant activity of peptides derived from *P. columbina* increased after a simulated gastrointestinal digestion (Cian et al., 2015).

Given that bioactive peptides have been obtained through microbial-driven breakdown of plant protein, and considering the rich source of unique proteins that certain species of seaweeds are, then the abundant production of bioactive and flavour-enhancing peptides as a result of seaweed fermentation is a possibility worthy of investigation, that has so far only been superficially explored (Hou et al., 2015; Wijesinghe & Jeon, 2012).

Phenols

Phenols are a class of organic compounds predominantly found in plants and algae (Naczk & Shahidi, 2006; Philippus et al., 2018). These highly diverse phytochemicals are secondary metabolism products that can occur both as a consequence of natural development or as a response to environmental stress (Naczk & Shahidi, 2006). Their prevalence in plants and herbs, long associated with traditional medicine, has cemented their role as bioactive compounds with major importance to human development (Rai et al., 2019). Modern biomedical research has associated a multitude of bioactivities to phenolic compounds, including but not limited to antimicrobial, antioxidant, anti-inflammatory, antidiabetic, and anti-carcinogenic (Bulzomi et al., 2012; Plouguerné et al., 2006).

A number of authors have linked the antimicrobial effects of phenolic compounds to inhibition of desired fermentations in plant and algal biomass (Maneein et al., 2018). Monlau et al. (2014) have reported a significant antimicrobial effect by low molecular weight phlorotannins. This effect was attributed to disruption of cell membrane permeability and enzyme inactivation. The bactericidal effects of phloroglucinol extracted from brown seaweed *Laminaria digitata* were evidenced in anaerobic bacteria, where the same membrane disruption phenomena was observed (Hierholtzer et al., 2013). Inhibition of certain plant and algae-processing enzymes such as α-amylase and α-glucosidase was observed upon treatment with phenolic-rich *Ascophyllum nodosum* extracts, and attributed to the well-known protein-binding effects of phlorotannins (Pantidos et al., 2014). Recent work performed by Milledge, Nielsen, & Harvey (2019), thoroughly evaluated the inhibitory effect of specific phenolic compounds present in a desired fermentation substrate (*Sargassum muticum)* in a model anaerobic digestion of glycerol, cellulose, alginic acid and sodium alginate. Their work revealed that the fermentation of readily digestible glycerol was not affected by the presence of phenolic compounds, but high concentrations of pholorglucinol and epicatechin significantly inhibited the microbial processing of alginic acid and sodium alginate.

These potent antimicrobial activities have proven to be a significant difficulty when attempting to ferment seaweed biomass, but can be circumvented with the use of adequate cultures and pre-treatments (Chye et al., 2018; Maneein et al., 2018). Among the wide variety of phenolic compounds residing in seaweed cells lie caffeic, p-coumaric and ferulic acids, which are fermentable by some lactic acid bacteria, such as *Lactobacillus plantarum* and *Lactobacillus brevis*, into their vinyl and ethyl derivatives (Curiel et al., 2010). Bioprocess inhibition due to phenolic compounds affects in a similar manner the processing of plant matter (Jönsson et al., 2013). Similar solutions to the ones presented in this topic were proposed by Jönsson, Alriksson, & Nilvebrant (2013) and for the purpose of lignocellulose degradation, included the use of genetically engineered strains of *S. cerevisae* and alkaline pre-treatments. Figure 4 provides an overview of these strategies in the context of a potential industrial-scale seaweed fermentation process. Further examples of seaweed fermentations that resulted in modified or enhanced phenolic content are given in the sections below.

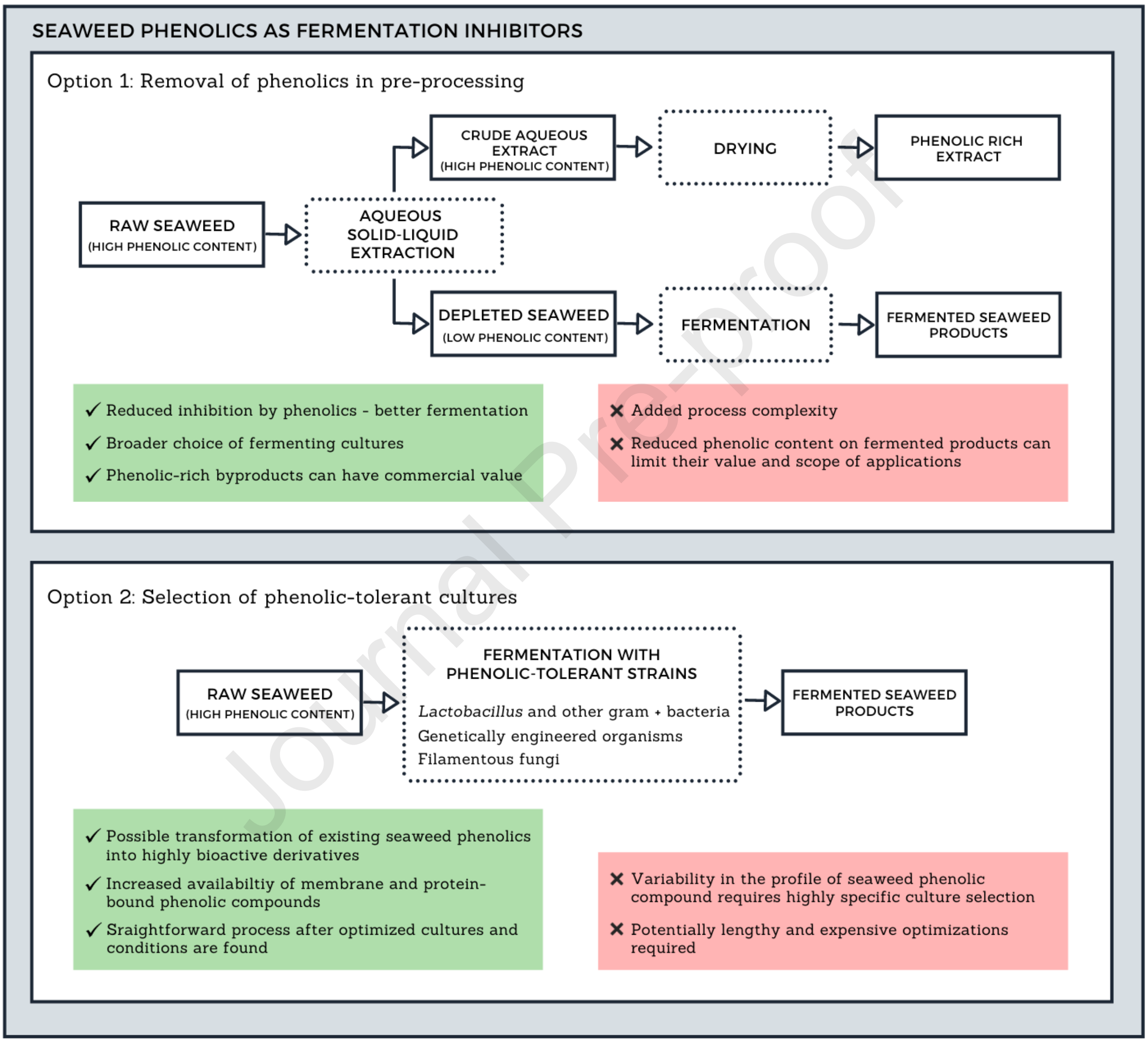

Figure 4. Strategies addressing the potential difficulties in industrial-scale fermentation of seaweeds rich in phenolic compounds. The flowcharts depict processes in dotted lines and raw-materials or products in continuous lines.

As mentioned previously, seaweeds have become a popular source of novel natural bioactive compounds, and phenolic compounds make up a large slice of the research associated with this effort (Boisvert et al., 2015; Lordan et al., 2013; Tierney et al., 2013). Previous discussions on how to best add value to fermentable seaweed have mentioned the possibility of a sophisticated biorefinery circuit that can combine the extraction of compounds with uses for other industries (including microbialinhibiting phenolics), from raw algae, and follow it with a fermentation of the spent biomass (Maneein et al., 2018), promoting a circular economy framework. This idea has been suggested by several authors detailing the implementation and improvement of seaweed biorefineries and is a promising solution to the still expensive cultivation and harvest of both macro and microalgae, and the large amounts of waste that the extraction of phycocolloids generates (Álvarez-Viñas et al., 2019; Ubando et al., 2020). While this approach can certainly seem more promising within the scope of biofuel fermentation, its potential can be far wider if these post-extraction fermentations are optimized for the synthesis of other bioactive compounds. The lack of scientific publications exploring the use of spent seaweed biomass for any purpose other than biofuels is simultaneously a demonstration of how underexplored seaweed fermentation is, and a remarkable opportunity to provide valorisation to the growing industry of seaweed production.

Biotechnological applications of seaweed fermentation

Seaweed fermentation resulting in enhanced bioactivity

The role of microorganisms in the biosynthesis of bioactive molecules has a long history, and has been developed in tandem with modern medicine, as well as with the chemical, food and cosmetic industries (Wee et al., 2006). Through time, the biochemical processes involved and their relevant metabolic pathways have revealed valuable information on how these organisms catabolise different substrates, and how to best manipulate the conditions and organisms involved in order to maximize the usefulness of the overall process. The entire process of discovering, optimizing and manipulating the microbial biotransformation of natural resources must be adapted to new cultures, substrates and target metabolites, and as such, is still a continuous labour of investigation for biotechnology researchers. The fermentation of seaweeds to produce novel bioactive compounds is one such new frontier, that has barely over two decades of dedicated research, and is still in the first stages of exploitation. Detailed below are some of the most significant studies performed so far by authors aiming to evaluate the bioactivity potential of fermented seaweeds products. These reported bioactivities are attributed to transformed components of the original substrate via fermentation, in contrast with the previous section, where the goal was to use microbial degradation to extract bioactives already present in the seaweed matrix.

While there were many earlier attempts to obtain valuable fermentation products from marine biomass, these were mostly focused on producing ethanol and methane. (Chye et al., 2018; Maneein et al., 2018). This research was heavily influenced by the growing biofuels industry, and it is only natural that the first publications deviating from the standard use of fermented algal products shared much in common with the earlier approaches. One such study was conducted by Sawabe et al. (2003). Initially targeting the synthesis of acetic acid from alginate using *Vibrio halioticoli*, an abalone gut bacterium, the fermentation produced high quantities of formic acid, a potent antimicrobial agent. Around this time, other researchers were also starting to comment on the functional and biotechnological potential of fermented seaweed products upon preliminary studies (Uchida & Murata, 2002, 2004b).

Publication numbers detailing bioactive compound production from seaweed fermentation started increasing from 2010 onwards, with the search terms "seaweed+fermentation+bioactive" reaching 24 records between 2010 and 2020 in a Web of Science search conducted in July of 2020. Extracts from *Laminaria japonica* processed using *Aspergillus oryzae* resulted in increased antioxidant activities, total phenolic content, and a sharp increase in γ-aminobutyric acid (GABA), from 14.19 to as high as 44.02 μmol/100g. Most free amino acid content was also increased, peaking at around 4 days of fermentation (Bae & Kim, 2010). Similar results were published the same year using a *L. brevis* strain isolated from traditional fermented foods. The study revealed that increased GABA concentrations were likely due to the conversion of glutamic acid, an amino acid present in high concentrations on many seaweed species (Lee et al., 2010). Several studies detailing the hepatoprotective effect of fermented seaweed GABA were performed shortly after, and confirmed a high bioactive potential, and promising nutraceutical and pharmaceutical applications (Cha et al., 2011; Kang et al., 2011). More recently, these GABA-enriched fermented *L. japonica* products exhibited promising cognitive improving properties (Reid et al., 2018a).

The fermentation of brown seaweed *Eisenia bicyclis* with *Cyberlindnera jadinii*, originated a significant increase in antioxidant activity, with a maximum of 72% DPPH radical reduction inhibition reported for a fermented sample (control exhibited approximately 65% reduction inhibition). There was also an increase in phenolic content for the samples that underwent fermentation, from an initial 36.1 mg to a final 47.5 mg of phloroglucinol equivalents per gram of dry weight (Eom et al., 2011). This enhanced activity was later correlated with higher concentrations of phlorotannins, including eckol, dieckol, dioxinodehydroeckol, and phlorofucofuroeckol-A suggesting that the effect was likely caused by facilitated release of algal compounds, instead of novel microbial metabolites (Eom et al., 2013).

Enriched seaweed broths were fermented with several LAB, *Weissella sp.* SH-1, *Lactobacillus sp.* SH-1, *Leuconostoc sp.* SH-1, and *Streptococcus sp.* SH-1 in a study published by Lee et al. (2015). Antioxidant activity, phenolic content, and angiotensin converting enzyme inhibition were increased in all fermented samples, but maximum activities in each assay varied greatly depending on culture (*Lactobacillus sp.* produced the highest antioxidant response and angiotensin converting enzyme inhibition, while *Weissella sp.* and *Leuconostoc sp.* had a greater increase in phenolic content). While the mechanisms responsible for the measured activities were not assessed, the results raise interesting questions about the role of fermentation in this assay. Either a selective tissue degradation occurred, releasing different seaweed compounds depending on the dominant culture, or entirely different secondary metabolites were produced in each case. *S. thunbergii* fermented with *Lactobacillus* obtained from *kimchi* was used to produce extracts with high anti-inflammatory activity (Mun et al., 2017). While the authors discuss the possibility of higher phenolic release due to fermentation, the modification of seaweed compounds via microbial metabolism was not excluded.

Some of the most recent studies on bioactive fermented seaweed extracts were performed by Suraiya et al. (2018) using filamentous fungi *Monascus* spp. and *Monascus purpureus.* Targeting the optimized production of lovastatin, these studies revealed that the unique blend of polysaccharides in seaweeds made them a highly suitable substrate for the production of this compound, either for isolation and purification, or for the production of functional foods. Additional phenolic content, antioxidant and antidiabetic activities were reported in *S. japonica* and *Undaria pinnatifida* fermented with *M. purpureus* and *Monascus kaoliang* (Suraiya, Lee, et al., 2018). Further studies conducted by these authors revealed immunomodulatory effects and anti-adipogenic activities in *Monascus* spp. fermented *S. japonica* (Suraiya, Choi, et al., 2019b; Suraiya, Jang, et al., 2019).It becomes clear that the potential of seaweeds as a substrate for the synthesis of powerful bioactive compounds is still underdeveloped. While the study of plant-derived fermentation compounds can certainly help determine what to expect from some scenarios, it still paints an incomplete picture of the most promising results when working with algal substrates, particularly when the degradation of sulphated polysaccharides can be involved (Huynh et al., 2014). Table 3 shows a collection of recently published content that linked enhanced bioactivity of samples to the process of fermentation.

482 **Table 2.** Recent publications reporting enhanced bioactivity upon fermentation of seaweed substrate. Search performed in April of 2021.

Substrate	**Culture/enzyme**	Measured bioactivity	Featured fermentation products	Reference
Seven species of brown seaweed	Several commercial mixtures of hydrolytic enzymes	Antioxidant (DPPH, superoxide anion, hydroxyl radical, hydrogen peroxide scavenging and oxidative DNA damage inhibition)	N/A	Heo et al., 2005
Lomentaria catenata	Spontaneous fermentation	Anticoagulant (activated partial thromboplastin time, prothrombin time, thrombin time)	Anticoagulant sulphated proteoglycan	Pushpamali et al., 2008
L. japonica	*A. oryzae*	Antioxidant (DPPH, phenolic content), likely unrelated to the identified compounds	γ-aminobutyric acid	Bae & Kim, 2010
Commercial "sea tangle" (*L. japonica*)	*L. brevis*	Antioxidant (DPPH, superoxide scavenging, xanthine oxidase inhibition).	γ-aminobutyric acid	Lee et al., 2010
Hizikia fusiforme aqueous extracts	*L. brevis*	Antioxidant (DPPH, hydroxyl radical, superoxide scavenging, alkyl radical)	N/A	Song, Eom, Kang, Choi, & Kim, 2011
E. bicyclis aqueous extracts	*Candida utilis (C. jadinii)*	Antioxidant (DPPH, phenolic content)	N/A	Eom et al., 2011
L. japonica	*L. brevis*	Hepatoprotective (glutathione content level and gamma-glutamyl transpeptidase activity on ethanol-induced toxicity in HepG2 cells)	N/A	Kang et al., 2011
L. japonica	*L. brevis*	*In-vivo* hepatoprotective (protection against ethanol-induced hepatotoxicity in Sprague-Dawley rats)	γ-aminobutyric acid	Cha et al., 2011
P. columbina	Proteolytic enzymes (trypsin and alcalase)	Antioxidant (DPPH, TEAC, ORAC, copper-chelatng activity); Immunomodulatory (cytokine determination and lactate dehydrogenase assay); Antihypertensive (angiotensin-converting enzyme inhibitory activity)	Low molecular weight bioactive peptides	Cian et al., 2012
E. bicyclis	*C. utilis (C. jadinii)*	Antimicrobial (MIC in methicillin-resistant *Staphylococcus aureus*);	eckol, dieckol, dioxinodehydroeckol, and phlorofucofuroeckol-A	Eom et al., 2013
Sargassum siliquanstrum	*Weissella sp.;* *Lactobacillus sp.;* *Leuconostoc sp.;*	Antioxidant (DPPH, phenolic content) Antihypertensive (angiotensin-converting enzyme inhibitory activity)	N/A	Lee et al., 2015

Substrate	**Culture/enzyme**	Measured bioactivity	Featured fermentation products	Reference
	Streptococcus sp.			
L. japonica	*L. brevis*	Anti-obesity (brain derived neurotrophic factor-related muscle growth and lipolysis in middle aged women)	γ-aminobutyric acid	Choi et al., 2016
S. thunbergii	*Lactobacillus sp.*	Anti-inflammatory (assorted inflammatory responses in LPS-induced RAW 264.7 macrophage cells)	N/A	Mun et al., 2017
E. bicyclis; Sargassum fusiforme; Pyropia sp.; Gloiopeltis furcate; *Chondrus ocellatus; Chondrus elatus; Gelidiaser sp.; Monostroma nitidum; Ulva sp.*	*L. plantarum*	Antioxidant (Phenolic content, DPPH, Fe-reducing power, Superoxide anion radical scavenging)	N/A	Takei et al., 2017
L. japonica	*L. brevis*	Anti-ageing (assortment of neuropsychological tests and antioxidant enzyme activities)	N/A	Reid, Ryu, Kim, & Jeon, 2018
L. japonica	*L. brevis*	Anti-dementia (cognitive impairment tests in model mice with ethanol-induced dementia)	γ-aminobutyric acid	Reid et al., 2018a
S. japónica; U. pinnatifida	*M. purpureus; M. kaoliang*	Antioxidant (phenolic content, ABTS radical scavenging activity, oxidative DNA damage inhibition); Antidiabetic (intestinal α-glucosidase inhibition, pancreatic lipase inhibition, pancreatic α-amylase inhibition)	Increased reducing sugar, protein and essential fatty acid content; Increased phenolic compound concentration	Suraiya, Lee, et al., 2018
Cystoseira trinodis	Six endophyte fungal isolates	Antioxidant (TAC, DPPH, FRAP, hydroxyl radical scavenging activity)	Low molecular weight fucoidan and alginate residues	Hifney, Fawzy, Abdel-Gawad, & Gomaa, 2018
Ulva sp. hydrolisate	*C. jadinii*	Antioxidant (phenolic content, DPPH)	N/A	Dhandayuthapani & Sultana, 2019
S. japonica	*Monascus spp.*	Anti-adipogenesis (inhibition of adipogenic gene expression and inhibition of lipid accumulation)	Authors claim high lovastatin content in fermented extracts from previous studies	Suraiya, Choi, et al., 2019
S. japonica	*M. purpureus; M. kaoliang*	Immunomodulatory (enhanced cytokine gene expression of THP-1 cells);	Fermented extracts rich in bioactive esters, alcohols, ketones, alkanes, fatty acids, and phenolic compounds,	Suraiya, Jang, et al., 2019

Substrate	**Culture/enzyme**	Measured bioactivity	Featured fermentation products	Reference
		Antioxidant (phenolic content)	but no specific association between bioactivities and identified compounds was made	
Macrocystis pyrifera; Industrial waste composed of unspecified brown seaweed	*Paradendryphiella salina*	Antioxidant (phenolic content, DPPH)	Analysis of amino acid profiles reveals increased concentrations of antioxidant peptides, including histidine and tyrosine, but otherwise there are no other bioactive compounds identified	Salgado et al., 2021
Kappaphycus spp.	*A. oryzae*	Antioxidant (total phenolic content and complete phenolic compound profile)	Complete characterization of phenolic content, with significant increases to caffeic acid, gallic acid, quinic acid and ferulic acid; Complete characterization of amino acid content, with increases to histidine, glutamic acid, tyrosine likely contributing to increased antioxidant potential	Norakma et al., 2021

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Seaweed fermentation as an enhancer of extraction yields

The popularity of seaweeds as novel sources of bioactive compounds has garnered great interest and funding from the food, feed, pharmaceutical, and cosmetic industries. This has led to extensive profiling of their bioactivities and constant innovation on the techniques applied to the extraction of desired compounds. Environmental concerns overlap this interest and shape innovation in the methodologies used, attempting to mitigate the use of toxic organic solvents, in favour of green and sustainable processes that can still effectively disrupt the cellular structures of seaweeds and allow easy access to the content inside (Martins et al., 2011). Innovations such as the microwave extraction have greatly enhanced the yields of certain extractions and/or even assisted in reducing costs. Yet, any novel compound detected, or seaweed species tested, is often accompanied with difficulties in the extraction process. Even if these are overcome in laboratory trials, it is likely that completely different solutions are required when attempting to increase the scale of the process (Michalak & Chojnacka, 2015).

Fermentation presents itself as an alternative to other novel natural product extraction methods. The microbial-induced digestion of cellular compounds can be less expensive, generate less toxic waste, and be highly specific to certain cellular structures such as the cellulosic cell wall, or the vacuole membrane, and achieve simultaneous cellular disruption and compound transformation (Huynh et al., 2014; Khosravi & Razavi, 2020; Maneein et al., 2018). It should be noted that enzymatic treatments are still better suited for highly specific digestive actions, with fermentations holding more potential as a broader, less controllable digestion/transformation hybrid method (Wijesinghe & Jeon, 2012). However, most published work on the fermentation of natural resources for production of bioactive compounds fails to acknowledge the role that this process can have as a tool for tissue breakdown, adopting enzymatic pre-processing of the substrate and focusing its relevance on secondary metabolites.

Some of the first research involving microbial degradation as a process for seaweed tissue breakdown was carried out by Uchida, Nakata, & Maeda (1997). The unconventional *Pseudoalteromonas espejiana* was used to degrade wet mashes of seaweed into Single Cell Detritus (SCD), fragments with 5.8 to 11.5 µm in diameter, as defined by the authors, prepared by decomposing seaweed to a cellular level. Further improvements to this approach involved the use of lactic acid bacteria and the addition of cellulase on top of a thorough optimization of fermentation conditions and enhanced cell wall degradation (Uchida & Murata, 2002; Uchida, Murata, & Ishikawa, 2007). These experiments set the authors in a pioneering path to reveal the multifaceted potential of fermented seaweeds, as will be detailed in later topics. A less controlled approach to tissue degradation via fermentation was executed by Pushpamali et al. (2008) on the isolation and purification of anticoagulant proteoglycans from *L. catenata.* In this study, spontaneous fermentation of the algal biomass was selected specifically for its simplicity and cost-effectiveness. It also fulfilled the necessary hydrolysis of carrageenans needed for them to exhibit anticoagulant activity and did so with comparable yields to an enzyme-treated control after 4 weeks of fermentation.

C. jadinii, formerly known as *C. utilis*, was used by Wijesinghe et al. (2013) to enhance the bioactive potential of phlorotannin-rich extracts obtained from *E. cava*. The authors attributed the higher anti-inflammatory activity of the fermented seaweed extracts to an increased phlorotannin availability, consequence of the yeast-driven breakdown of algal tissues (Wijesinghe et al., 2012). The same authors had previously reviewed enzymatic approaches to assist the extraction of seaweed compounds, and mentioned the underappreciated advantages that fermentations have in replacing this process in the studies that followed (Wijesinghe et al., 2013; Wijesinghe & Jeon, 2012).

In a recent literature review, Khosravi & Razavi (2020) pointed out that fermentation is one of the most promising extraction techniques for the recovery of polyphenols from agricultural waste. This was attributed not only to the cost and environmental advantages already stated, but also due to the production of complex mixtures of cell wall degrading enzymes that include α- amylase, β-glycosidase, xylanase, among others (Huynh et al., 2014; Wang et al., 2014). Considering that seaweeds are a proven source of phenolic compounds, and that fermentation optimizations are carried out so that the thorough degradation of seaweed tissue is achieved, extraction yields of bioactive phenolics can be highly increased.

Table 3. Reported use of seaweed fermentation as an extraction yield enhancer and algal tissue breakdown.

Substrate	Fermenting culture(s)	Target compound/effect	Reference
Ulva sp.	*P. espejiana*	Seaweed size reduction	Motohara Uchida et al., 1997

Substrate	Fermenting culture(s)	Target compound/effect	Reference
		Increased protein content of fermented blend	
U. pinnatifida	*L. brevis* *Debaryomyces hansenii* *Candida sp.*	Seaweed size reduction Optimized cellulase and NaCl concentrations	Uchida & Murata, 2002
P. palmata	*Rhizopus microscopus var. chinensis* *A. oryzae* *Trichoderma pseudokoningii*	Improved digestibility via degradation of insoluble fibers	Marrion, Schwertz, Fleurence, Guéant, & Villaume, 2003
L. catenata	Spontaneous fermentation	Anticoagulant sulphated proteoglycan	Pushpamali et al., 2008
E. bicyclis	*C. utilis (C. jadinii)*	eckol, dieckol, dioxinodehydroeckol, and phlorofucofuroeckol-A	Eom et al., 2013
E. cava	*C. utilis (C. jadinii)*	triphlorethol-A, eckol, dieckol, and eckstolonol	Wijesinghe et al., 2013; Wijesinghe & Jeon, 2012
S. japonica	*M. purpureus*	Lovastatin	Suraiya, Kim, et al., 2018

Given the early stage of research that the literature cited so far addresses, there is little mention of downstream processes, or of different approaches for the recovery of select compounds within seaweed fermentation products. There are considerable advantages in the early recognition and consideration of downstream hurdles when developing new bioprocesses (Castro-Muñoz, Boczkaj, et al., 2020). An early optimization of fermentation conditions that takes into account specific separation techniques and limits desired outputs within a certain molecular weight (among other exclusion parameters) can be met with success in later stages of scale-up and implementation, as it avoids unexpected investment and adaptations for the efficient recovery of compounds, otherwise incompatible with the available means of recovery (Díaz-Montes & Castro-Muñoz, 2019). While this concern can appear limiting, modern compound separation technologies are highly flexible, with membrane separations receiving particular attention in recent years for this very characteristic (Castro-Muñoz, Boczkaj, et al., 2020; Castro-Muñoz, Díaz-Montes, et al., 2020).

As demonstrated in table 2 of the last section, most bioactive compounds recovered from seaweed fermentations so far are either phenolic compounds or other smaller sized biomolecules, including peptides, amino acids and γ-aminobutyric acid. Membrane technologies, such as Ultrafiltration and Nanofiltration present themselves as the ideal separation and purification methods for the range of compounds identified, while maintaining the newly developed process compatible with sustainability goals (Cassano et al., 2018; Castro-Muñoz, Boczkaj, et al., 2020). One of the major challenges these technologies face is the medium to long-term accumulation of biological matter along the membranes, a phenomenon known as biofouling. This phenomena is greatly accentuated when paired with bioprocesses involving large amounts of residual microorganisms, as is the case with fermentations (Stavros Kalafatakis et al., 2020; Pichardo-Romero et al., 2020). Fortunately, the rising popularity of membrane separation technologies has led to an accelerated resolution of many of its drawbacks. Biofouling has been tackled via clever manipulation of the physico-chemical properties of membranes, aiming mainly at an increase in their hydrophilic properties. The embedding of nanomaterials into the polymer matrix is one such approach, but modern systems often combine advanced materials with optimized flow-rates and adjustments of the feed solution pH and cell concentration (S. Kalafatakis et al., 2018; Pichardo-Romero et al., 2020).

Seaweed fermentation for biosynthesis of other valuable compounds

The production of any type of compound as a result of seaweed fermentation is valuable insight when attempting to create added-value products using this combination of raw-material and process. Much of the microbial breakdown of seaweeds has been detailed through the study of methanogenesis and alcoholic fermentation for the biofuels industry, and even the synthesis of organic acids can provide further knowledge on optimal process conditions for a given culture and substrate (Maneein et al., 2018; Sawabe et al., 2003; Uchida & Miyoshi, 2013).

The production of lactic acid has seen a shift in methodologies over the last two decades. A highly desired compound in the pharmaceutical, cosmetic, food and chemical industries, its source has shifted away from chemical synthesis due to environmental concerns (Wee et al., 2006). Hwang, Lee, Kim, & Lee (2011) performed an early benchmark on lactic acid production via seaweed fermentation by comparing the microbial consumption of seaweed sugars (D-galactose, D-mannitol, L-rhamnose, D-glucuronic acid, and L-fucose) against that of plant sugars (D-glucose, D-xylose, D-mannose, and L-arabinose). Several *Lactobacillus* species were tested, and the results were used to predict lactic acid yields across various species of seaweeds and terrestrial plants. The authors reported a promising similarity in terms of both real and estimated yields, and noted that further knowledge of seaweed tissue breakdown, as well as adequate pre-treatments of algal biomass, could improve these yields further. A contemporary and similarly pioneering study by Gupta, Abu-Ghannam, & Scannell (2011) also reported high compatibility of *L. plantarum* with an algal substrate, along with high lactic acid yields at optimized conditions. A comprehensive list of seaweeds and LAB, along with their lactic acid yields with a cellulase pre-treatment was then compiled by Uchida & Miyoshi (2013), but new insights on lactic acid fermentation of seaweeds are now continually published, and slowly expand the range of tested cultures and conditions (Lin et al., 2020).

Even within the field of biofuels, the unique composition of seaweeds has motivated integrated approaches to bioenergy production, with simultaneous use of protein-rich hydrolysates having been studied by Hou, Hansen, & Bjerre (2015).

Seaweed polysaccharide-cleaving enzymes have also been produced in controlled seaweed fermentations (Rodríguez-Jasso et al., 2013). While to the best of our knowledge no further use of this enzyme was published, the authors have contributed with valuable insight on the fermentation of seaweeds with *Aspergillus niger* and *Mucor sp.* in rotating drum bioreactors.

Inspired by a similar use of fermentation performed on *Paratapes undulatus* hydrolisates, Du et al., (2021) employed this process to reduce the concentrations of undesired volatile compounds present in *Bangia fuscopurpurea*. Fermentations with *S. cerevisae*, having achieved the highest reduction in undesired aromas, were further profiled via SPME-GC-MS. This analysis revealed significant increases in alcohols, acids, and alkanes of microbial origin, including nonanol, non-(2E)-enoic acid, (E,E)-2,4-decadienol, 2,4-decadienoic acid, and nonadiene. Norakma et al., (2021) also achieved a reduction of the undesired volatile pentadecanoic acid methyl ester when fermenting *Kappaphycus* spp. using *A. oryzae*, accompanied by an increase in hexadecane pentadecane and heptadecane. These two recent studies provide a rare exploration on how fermentation can modify the sensory profile of seaweeds and greatly encourages the employment of its methods in a wider scope, with the study of a greater number of substrate and culture combinations.

Table 4. Fermentation of seaweeds and seaweed compounds for the production of organic acids, biomass or for other miscellaneous goals.

Substrate	Fermenting culture(s)	Target compound/effect	Reference
U. pinnatifida	14 strands of LAB	Lactic acid Culture predominance	Uchida et al., 2007
Alginate	*V. halioticoli*	Acetic acid	Sawabe et al., 2003
Ulva spp.	Spontaenous fermentation	Identification of predominant microorganisms; Lactic acid; Ethanol;	Uchida & Murata, 2004a
Himanthalia elongata; *L. digitata;* *L. saccharina*	*L. plantarum*	Acetic acid; Lactic acid; Optimum growth conditions	Gupta et al., 2011
Mixture of seaweed sugars	7 *Lactobacillus* species	Lactic acid	Hwang et al., 2011
Gracilaria sp.; *Sargassum siliquosum;* *Ulva lactuca*	*Lactobacillus acidophilus;* *L. plantarum*	Lactic acid Content of reducing sugars	Lin et al., 2020
Kappaphycus spp.	*A. oryzae*	Complete characterization of phenolic, amino acid and volatile content in fermentation products	Norakma et al., 2021
B. fuscopurpurea	*S. cerevisiae; Acetobacter pasteurianus; L. plantarum*	Reduced concentration of undesired volatile compounds	Du et al., 2021

Novel food, feed, and nutraceutical products

Given the current-day concerns of climate change, loss of farmable land, overpopulation and crop sustainability, it is expected that any research field concerned with adding value to edible biomass dedicates substantial focus on food and feed applications (Darcy-Vrillon, 1993; FAO et al., 2018). Though still limited in volume, the study of fermenting seaweeds for non-energy applications has dedicated much of its published content to innovation in human nutrition.

Early studies of seaweed fermentation have expressed the potential that lies in the use of the fermented products for food applications, ranging from its functional properties granted by enriched bioactivities, to promising organoleptic profiles (Uchida et al., 2017; Uchida & Miyoshi, 2013; Uchida & Murata, 2002, 2004b). These studies have culminated in a recent set of publications detailing a fermented seaweed sauce with flavour profile similar to standard soy sauce, but lower sodium content (Uchida et al., 2018, 2017). The sauces were prepared from *Pyropia yezoensis* fermented with commercially available *Tetragenococcus halophilus*, over the course of two years. The high umami flavour profile was attributed to high concentrations of glutamic and aspartic acid, as well as an unusually high concentration of taurine. A fermented seaweed beverage was also developed using *Gracilaria fisheri* and a previously isolated culture of *L. plantarum,* achieving moderate acceptance from a 30-member sensory evaluation panel and a stability of at least 3 months (Prachyakij et al., 2008). So far, these studies remain the only published academic work detailing novel functional food products entirely based on fermented seaweeds, setting ground for the potential use of fermented seaweed as novel functional products and ingredients.

Other authors have stated the potential usefulness of their findings, or even the fermentation products they developed, for the food industry. Bae & Kim (2010) stated in their early tests with GABA-enriched fermented *L. japonica* that their product had direct application as a functional food product, and that similar fermentations could unlock a whole set of processed foods compatible with current consumer trends. A similar assessment was made by Takei et al. (2017) upon fermenting a variety of edible seaweeds that included *S. fusiforme, Gloiopeltis furcata*, *Chondrus ocellotus*, *C. elatus, E. bicyclis, Pyropia sp.*, among others. They noted significant increases in the antioxidant potential of the tested red seaweeds using *L. plantarum* and suggested their use as novel functional foods. The recently published work of Salgado et al. (2021), intended to create a unique food product made from the mycelium of *P. salina* upon fermenting *M. pyrifera*. An alternative formulation using pre-treated industrial by-products containing an unspecified brown seaweed as substrate was also tested and analysed. The authors reported a highly protein-enriched product in both formulations, as well as an abundance of functional amino acids and increased antioxidant activity and phenolic content (Salgado et al., 2021). Norakma et al. (2021) performed a similar set of analysis on aqueous extracts obtained from *A. oryzae*-fermented *Kappaphycus* spp. A detailed profiling of amino acids as well as phenolic and volatile compounds revealed a nutritionally, functionally and sensory-enriched product. Concentrations of histidine, glutamic acid and tyrosine reached values of 0.44, 4.27 and 0,64 g/100g respectively on fermented *Kappahycus striatum* var., and an improvement in volatile composition was verified in all fermented seaweed samples (Norakma et al., 2021).

There is little published content detailing a true in-depth exploration of fermented seaweed products as potential nutraceuticals. Shifts to preventive medicine practices and new consumer trends have placed nutraceuticals and functional food products on the sights of many researchers and entrepreneurs and yet, when attempting to collect information regarding nutraceutical applications of fermented algae, enzymatically-processed seaweed derivatives remain the best approach (Charoensiddhi et al., 2017). Considering reported bioactivities compiled in this study, product development aimed at novel food products is the most unfulfilled premise of fermented seaweeds, and one that can be readily exploited by new research and new business ventures. This is strengthened by the fact that the main difficulties associated with the process have long been resolved by the efforts of the biofuel industry, which have optimized the primary metabolic process as extensively as needed. Only the optimization of functional properties and secondary metabolite production remains and can be done in a case-by-case approach. This unique opportunity was identified by Uchida & Miyoshi (2013) and remains unfulfilled today.

Table 5. Edible fermented seaweed products developed with a focus on nutraceutical and functional food properties.

Substrate	Fermenting culture(s)	Product description	Functional features	Reference
G. fisher	*L. plantarum*	Fermented seaweed beverage	Possible antimicrobial activity due to prolonged shelf-life	Prachyakij et al., 2008v
L. japonica	*A. oryzae*	Fermented aqueous extract	High γ-aminobutyric acid content; Antioxidant activity	Bae & Kim, 2010
P. yezoensis	*T. halophilus*	Fermented seaweed sauce	Organoleptic quality; Inhibitory activity of angiotensin-converting enzyme	Uchida et al., 2017
E. bicyclis; *S. fusiforme;* *Pyropia sp.;* ***G. furcata;*** *C. ocellatus;* *C. elatus;* *Gelidiaser sp.;* *M. nitidum;* *Ulva sp.*	*L. plantarum*	Fermented aqueous solutions	High antioxidant activity	Takei et al., 2017
S. thunbergii	*Lactobacillus sp.*	Fermented aqueous supernatant	High anti-inflammatory activity	Mun et al., 2017
P. yezoensis	Spontaneous fermentation	Fermented seaweed sauce	Low allergen-risk	Uchida et al., 2018
Nori *(P. yezoensis)*	Commercially available koji (*A.*	Nori koji and nori sauces made with nori koji	Enhanced protein content Low allergen-risk	Uchida et al., 2019

Substrate	Fermenting culture(s)	Product description	Functional features	Reference
	oryzae and *Aspergillus flavus*)			
Nori (*P. yezoensis*) Kombu (*S. japonica*)	Commercially available koji	Nori and kombu aged koji	Enhanced protein content Enhanced amino acid profile	Murayama et al., 2020
M. pyrifera; Industrial waste composed of unspecified brown seaweed	*P. salina*	*P. salina* mycelium and algal biomass under the designation of "mycoprotein"	Enhanced protein content; Enriched amino acid profile; High antioxidant activity and total phenolic content	Landeta-Salgado et al., 2021 Salgado et al., 2021
Kappaphycus spp.	*A. oryzae*	Aqueous extract from solid fermented seaweed	High phenolic content; High histidine, glutamic acid and tyrosine concentrations within amino acid profile	Norakma et al., 2021
Saccharina latissimi; ***Alaria esculenta***	*L. plantarum; Leuconostoc mesenteroides*	Sauerkraut-like product from lactic acid fermentation	Antioxidant activity (unclear if related to fermentation)	Skonberg et al., 2021
Porphyra dentata	*Kombucha consortium*	Fermented beverage from seaweed infusions	High α-ketoglutaric and acetic acid content; Enhanced antioxidant activity	Aung & Eun, 2021

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Conclusions and Perspectives

Though nowadays recognized as an important source of novel bioactive compounds, seaweeds are still considerable underexploited when compared to terrestrial plant biomass. As their role in the modern food, feed, pharmaceutical, cosmetic and energy industries increase, novel processes to extract value from this abundant and sustainable biomass become increasingly valuable. Most currently employed techniques for the extraction of seaweed compounds either have reduced yields due to the difficulties in processing algal cell walls, have low cost-effectiveness, or resort to undesirably toxic organic solvents.

There is strong evidence that the fermentation of seaweeds for the production and extraction of bioactive compounds is a viable process for the valorisation of this resource. Biofuel research has provided a robust set of knowledge on the microbial processing of macroalgae and revealed that fermentation conveniently addresses the difficulties involved with the extraction of algal compounds. Seaweeds can be a highly fermentable substrate upon careful selection of cultures and processing conditions, resulting in a microbial-driven cell wall degradation that is cost-effective and environmentally friendly. Additionally, the research conducted so far has demonstrated the potential to generate novel compounds from both marine and microbial origin, including bioactive peptides and polysaccharides, processed phenolic compounds, enzymes and organic acids. The fermentation products are also an underexplored food resource, and the limited studies conducted so far demonstrate that these could constitute a new and important entry in the functional food and nutraceutical markets. Thus, the research gathered here points to seaweeds as a promising substrate for the development of new bioprocesses that fulfil the modern demands of sustainability and fit within a circular economy-driven system of added-value compound recovery.

Further research in this field would need to start by addressing the limited knowledge of fermenting seaweeds for natural products. This could be achieved via large scale screening of different seaweed species and microorganism combinations. Monitoring the products of these fermentations for bioactivities in *in vitro* assays, sensory properties and growth conditions would provide a clear picture of which of these processes are deserving of further attention. These conditions could then be adequately optimized to maximize the output of positive bioactive responses or sensory properties. Additionally, this type of preliminary research would reveal challenges that are still unknown in seaweed fermentation, including the necessary pre-treatments of the mash and how to best manipulate, store and extract the products of fermentation. Intricate chemical analysis of these products should run parallel to the screening process. Identification of the most relevant chemical agents responsible for the bioactivities and sensory features of seaweeds, fermented or otherwise, remains one of the greatest vacuums in this field. Such elucidation could then allow precisely targeted optimizations of fermentation processes and entice the pharmaceutical and food industries with a novel source of valuable compounds. This should then be followed by careful consideration of the most suitable downstream process, paying close consideration to their environmental impact and sustainability. Membrane-based separation technologies can easily be implemented on newly developed processes that seeks to isolate smaller biomolecules, such as those that may result from microbial degradation of algal biomass. Once a larger set of information is gathered about the processes, substrates and cultures yielding the best results, making seaweed fermentation compatible with modern industry demands will likely involve using advanced biotechnological tools. Genetic engineering of fermenting cultures requires a detailed understanding of their metabolic profiles when processing this unique substrate, something that has, so far, only been done in limited amounts for the biofuel industry. Only after these research milestones have been met can the feasibility of seaweed fermentation be evaluated in earnest, and its potential as a novel source of useful products come to fruition.

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Highlights

- Seaweed fermentation remains an underdeveloped branch of marine biotechnology.
- Fermentation can facilitate the extraction of bioactive compounds from seaweeds.
- Products of seaweed fermentation show enhanced bioactive and sensory profiles.
- Full scope of applicability, bioactivities and mechanisms relies on further research.