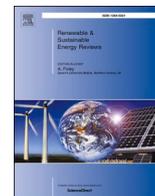


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## Macroalgal biorefinery concepts for the circular bioeconomy: A review on biotechnological developments and future perspectives

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### ABSTRACT

The imminent need for transition to a circular bioeconomy, based on the valorisation of renewable biomass feedstocks, will ameliorate global challenges induced by climate change, environmental pollution and population growth. A reduced reliance on depleting fossil fuel resources and ensured production of eco-friendly and cost-effective bioproducts and biofuels, requires the development of sustainable biorefinery processes, with many utilising macroalgae as feedstock, showing promising and viable prospects. Nonetheless, macroalgal biorefinery research is still in its infancy compared to lignocellulosic biorefineries that utilise terrestrial plants. This article presents a review on the latest scientific literature associated with the development and status of macroalgal biorefineries, and how bioproducts generated from these bioprocesses have contributed towards the bioeconomy. The fundamental need to understand how the unique biochemical composition of macroalgae fit within a biorefinery concept are explained, alongside discussion of the novel biotechnologies that have been applied. In order to comprehend the increasing significance of this exciting field, the review will also provide insight, for the first time, on the current global funding and intellectual property landscape related to macroalgae and their implementation across the entire biorefinery concept. Imperative areas for further research and development, to bridge the gap between fundamental bioscience in the laboratory and the successful application of compatible biotechnologies at a commercial scale, to boost the macroalgae industry are also covered.

### 1. Introduction

There are many challenges that our planet is currently facing which include climate change, an increase in global population (expected to reach 9.7 billion by 2050 [1]), as well as issues surrounding the growing demand for food, natural resources and raw materials [2]. In order to maintain global economic growth whilst simultaneously minimising negative impacts on the environment and preserving natural resources, the utilisation of renewable feedstocks as an alternative to fossil fuels require immediate and more widespread adoption. This would also involve the application of alternative clean energies and renewable inputs into production processes, to ultimately enable societies to transition towards a biobased bioeconomy [3]. As such, interest in promoting the bioeconomy is reflected by the number of countries and organisations worldwide that are currently pursuing explicit policies and

strategies, to expand their bioeconomies, in order to achieve as many of the 17 Sustainable Development Goal's (SDG) set by the United Nations (UN) as possible [4,5]. For example, the European Union (EU) revised their bioeconomy strategy in 2018 to put greater emphasis on the three pillars of sustainability: 'economy, society and environment' to align better with the UN's SDGs [6,7]. The UK government also released its own strategy that aims to double its bioeconomy spending from £220 billion to £440 billion by 2030 [8].

The biorefining of biomass feedstocks for the production of marketable products such as food, animal feed, chemicals, materials and energy (in the forms of biofuels, power and/or heat) via eco-innovative and sustainable bioprocess systems align with a number of the SDGs [5]. Due to the fact that biomass is of biogenic origin, any CO<sub>2</sub> released from the biomass via different biochemical processes does not contribute towards an increase in atmospheric CO<sub>2</sub> [9]. Macroalgae (seaweeds), an underutilised yet attractive resource, are known to not only play a key

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### Abbreviations

UN	United Nations
EU	European Union
EC	European Commission
U-S DoE	United States Department of Energy
SDG	Sustainable Development Goals
LCA	Life Cycle Analysis
TEA	Technoeconomic Analysis
dw	Dry Weight
IMTA	Integrated Multi Trophic Aquaculture
m	Million
bn	Billion

spp	Species
HTL	Hydrothermal liquefaction
<i>D. tenuissima</i>	<i>Derbesia tenuissima</i>
<i>U. ohnoi</i>	<i>Ulva ohnoi</i>
<i>U. lactuca</i>	<i>Ulva lactuca</i>
<i>U. fasciata</i>	<i>Ulva fasciata</i>
<i>C. linum</i>	<i>Chaetomorpha linum</i>
<i>S. muticum</i>	<i>Sargassum muticum</i>
<i>L. digitata</i>	<i>Laminaria digitata</i>
<i>L. hyperborea</i>	<i>Laminaria hyperborea</i>
<i>F. spiralis</i>	<i>Fucus spiralis</i>
<i>S. latissima</i>	<i>Saccharina latissima</i>
<i>S. cerevisiae</i>	<i>Saccharomyces cerevisiae</i>

ecological role in coastal ecosystems, but through sustainable cultivation approaches, they may also have the potential to address global challenges. These include issues related to food consumption, agriculture, human health and coastal management; all of which, if efficiently implemented, would contribute towards a sustainable circular bioeconomy with enhanced growth [10]. Compared to lignocellulosic feedstocks, which have represented a cornerstone of the bioeconomy to date [11], macroalgae are potentially more suited for biorefinery processes due to their large biomass yields, fast growth rates and absence of terrestrial land requirements for cultivation [12]. Their lack of a recalcitrant lignocellulosic structure [13] implies that less energy intensive bioprocesses can be applied to recover high value bioproducts of commercial interest; this would favour life cycle and techno-economic analyses (LCA and TEA) of any putative biorefinery process that employs macroalgae as a feedstock. Furthermore, the presence of speciality polysaccharides that are inherent to macroalgal species belonging to the three different taxonomical groups offer unique properties for either direct use and/or as platform biocompounds for the bioeconomy.

Despite the clear advantages macroalgal species offer, and their potential to be implemented within a biorefinery, both the research and commercialisation aspects of macroalgal biorefineries are still in their infancy and few have progressed beyond laboratory scale. Fig. 1 shows the number of scientific publications related to biorefinery processes utilising lignocellulosic biomass compared to macroalgae that appeared between 1993–July 2021.

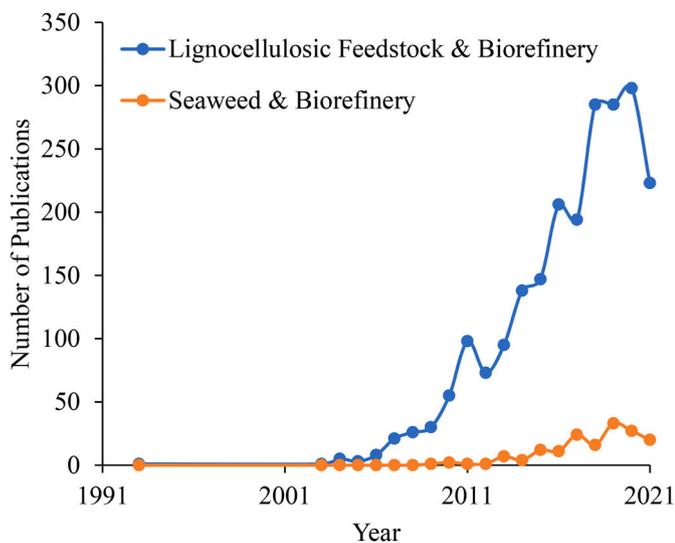


Fig. 1. Evolution of the number of scientific publications related to macroalgae or lignocellulosic biorefineries during 1993–2021 (July 2021) (keywords: ‘macroalgae’ or ‘lignocellulosic’ AND ‘biorefinery’) (Source: Scopus®).

It is evident that the myriad of publications related to lignocellulosic feedstocks continue to surpass macroalgae biorefinery research year-on-year. This stems from the first and second-generation biofuel revolution, which drove global bioethanol research from the early 1970s using terrestrial plants and waste residues [14]. The use of macroalgae are considered to be third or even 4th/advanced generation feedstocks [15], and research interests utilising macroalgae began to increase once hindrances associated with lignocellulosic biomass began to surface, mainly the high costs and harsh thermochemical pretreatments that are required. Unfortunately, the biotechnologies originally designed for lignocellulosic feedstocks have proved to be incompatible with the unique biochemical composition of macroalgal biomass and could therefore not be applied [16]. Consequently, new lines of research had to commence for the development of novel macroalgal specific bioprocesses. Nevertheless, the scientific interest and industrial applications of macroalgae continue to increase which has ultimately aided the production of 31 million tonnes of macroalgae (fresh weight) per annum, worth an estimated market value of USD400 per tonne (dry weight) [17].

Macroalgal biorefinery systems, once fully optimised, have the potential to economically strengthen a number of industrial sectors whilst helping the circular bioeconomy and mitigate climate change. This awareness has led to the establishment of a promising 2020 manifesto ‘Seaweed Revolution: A manifesto for a sustainable future’ led by the Lloyd’s Register Foundation together with the UN’s Global Compact’s Action Platform for Sustainable Ocean Business. This essentially outlines the potential of macroalgae to deliver on the UN’s sustainable development goals, including a contribution to food safety and security, climate change mitigation, poverty alleviation and support to marine ecosystems. Further, with collaborative input from organisations across businesses, academia and government, the vision of an up-scaled, responsible and restorative macroalgal industry is articulated, highlighting the continued need for global collaborative research on macroalgal biomass utilisation. A recent study also emphasised the potential of the European macroalgae industry’s contribution towards the EU’s Bioeconomy Strategy aims, as macroalgae production is currently being developed in 13 European countries with France, Ireland and Spain representing the top three countries with the highest macroalgae production units [18]. In order to witness the sustainable growth of this sector in Europe nevertheless, successful up-scaling of production volumes alongside technological and market developments still require addressing.

A number of recent reviews have addressed some of the aspects described in the current work (Table 1).

For example, Rajak et al. [19] and Torres et al. [20] reviewed the processes involved in bioethanol, value added products and chemicals production from seaweed feedstocks, while Filote et al. [21] focussed on non-bioenergy products and advances in metabolite and bioactive molecule separation. Jung et al. [22] highlighted the importance of

**Table 1**  
Recently published review articles on seaweed biorefineries relevant to the current review article.

Review article title	Key features of review article	Reference
A holistic zero waste biorefinery approach for macroalgal utilisation: A review	<ul style="list-style-type: none"> <li>- Global seaweed production, cultivation and harvesting</li> <li>- Seaweed hydrolysis for fermentable sugars production</li> <li>- Fermentation and seaweed bioethanol production</li> <li>- Value added products from fermented residual biomass</li> <li>- Challenges for seaweed biofuel production</li> </ul>	[19]
Seaweed biorefinery	<ul style="list-style-type: none"> <li>- Seaweed composition, properties and uses</li> <li>- Seaweed biorefineries and bioproduct/biofuel production</li> <li>- Challenges and constraints associated with seaweed biorefineries</li> </ul>	[20]
Biorefinery of marine macroalgae into high-tech bioproducts: a review	<ul style="list-style-type: none"> <li>- Wild and cultivated seaweed resources for biorefinery applications</li> <li>- Chemical composition of seaweed</li> <li>- Advances in metabolite and bioactive molecule separation, including novel extraction methods and biorefinery approaches</li> </ul>	[21]
Potential of macroalgae as feedstocks for biorefinery	<ul style="list-style-type: none"> <li>- Mass cultivation of seaweed</li> <li>- Biomaterials, bioproducts and bioenergy production from seaweed species</li> <li>- Advanced technologies for biofuel production from seaweeds, mainly seaweed-specific enzyme production for polysaccharide hydrolysis</li> </ul>	[22]
Green technology in green macroalgal biorefineries	<ul style="list-style-type: none"> <li>- Cultivation of seaweed</li> <li>- Green seaweed derived bioproducts, biomaterials, biostimulants and biofuels</li> <li>- Green cascading biorefinery processes</li> <li>- Bio and thermochemical conversion processes, green solvents and emerging 'smart' technologies</li> </ul>	[23]
Successful approaches for a red seaweed biorefinery	<ul style="list-style-type: none"> <li>- Red seaweed biorefineries</li> <li>- Bioproducts and biofuels obtained from red seaweed biorefinery processes</li> </ul>	[24]
Current review article	<ul style="list-style-type: none"> <li>- Seaweed composition and cultivation</li> <li>- Brown, red and green seaweed biorefinery concepts, including novel biotechnology development</li> <li>- Commercialised seaweed-based bioproducts and markets</li> <li>- Seaweed biorefinery funded projects and intellectual property (patents)</li> <li>- Challenges and issues associated with future macroalgal biorefineries</li> </ul>	-

identifying new ways to effectively and efficiently utilise seaweeds. In addition, Zollman et al. [23] considered advancements in technologies tailored specifically towards green species of seaweed, and Álvarez-Viñas et al. [24] focussed on cascading approaches developed for red species of seaweed. The current review provides updates on some of these areas but focusses on the novel biotechnologies that have recently been applied and the use of macroalgal bioproducts across the bioeconomy. The integration of biofuels and biochemical processing has undoubtedly led society a step closer towards the commercialisation of

macroalgal biorefineries, and as such, particular attention will be devoted to explaining the important need for continued collaborative research funding in this area, and the range of exciting on-going macroalgal projects currently funded around the world. In addition, for the first time, the macroalgal biorefinery patent landscape will be explored in order to gain an understanding of the evolving growth within this important field. Lastly, the technological challenges that currently exist within macroalgal biorefineries and the future areas of research that ought to be addressed for future industrial expansion of such bio-processes are discussed.

## 2. Methodology

An electronic literature-based search was conducted using Google Scholar (<https://scholar.google.com/>) to identify articles published from 1993 up until 2021 related to macroalgal based biorefinery approaches for biofuels and bioproduct generation. Keywords “macroalgae” or “seaweed” or “brown seaweed” or “red seaweed” or “green seaweed” AND “biorefinery” or “bioprocess” or “biofuels” or “bioproducts” or “biochemicals” were included. All searches were limited to studies published in the English language, since these contributed to the majority of the articles found. To compare the number of macroalgae and lignocellulosic biorefinery articles that have been published each year until 2021, a document search was conducted using Scopus® (<https://www.scopus.com/search/form.uri?display=basic>) using keywords “macroalgae” or “lignocellulosic” AND “biorefinery”.

An advanced search using the European Patent Office’s patent search database to gather information on the number of macroalgal patent documents across different biotechnological industrial market sub-groups, which have been published up until 2021, was conducted. The search criteria consisted of using a set of keywords [‘macroalgae’ OR ‘seaweed’] AND ‘X’, where ‘X’ was the class of industrial application (‘food’, ‘processing’, ‘health’, ‘chemical’, ‘cosmetic’, ‘aquaculture’, ‘agriculture’, ‘genes’, ‘biofuels’ and ‘bioremediation’). For comprehensive coverage, the searches were performed with these keywords in the patent document’s title, abstract or claims. It is important to note however, that, the search results do not necessarily solely reflect granted patents; the search results also return applications that may have either been withdrawn, rejected or are pending. Further, due to varying lead times between filing a patent application and publication, it is inevitable that there may in fact be more unpublished applications that were not returned. For example, in the UK there is lead time of approximately 18 months between the filing of and publication of the patent application [25]. Nonetheless, the results provide an indication into the industrial and developmental growth of the field. To identify whether any patent documents have been registered specifically for biorefinery processes utilising macroalgae, another advanced search was conducted using keywords [‘macroalgae’ OR ‘seaweed’] AND ‘X’, where X was either ‘biorefinery’, ‘bio-refinery’, ‘bioprocess’, ‘bio-process’, ‘bioproducts’ or ‘bio-products’. To achieve a thorough search, the returned documents (n = 772) were screened by eye and shortlisted to ensure that the document did indeed solely focus on a biorefinery process that yielded more than at least two bioproducts from macroalgae.

## 3. Macroalgae composition

Macroalgae are macroscopic, multicellular organisms consisting of thousands of species that are frequently grouped depending on the colour of their photosynthetic pigment and cell wall chemistry [22]. Red (*Rhodophyta*), green (*Chlorophyta*) and brown (*Phaeophyta*) macroalgae require different intensities of light to photosynthesise, and thus are typically found in different marine habitats and environments [26]. Table 2 summarises the main biochemical constituents of these three taxonomical groups.

The carbohydrate fraction represents the largest component of their

**Table 2**

Biochemical composition and main carbohydrate compositions (based on dry weight) of the three macroalgal taxonomical groups [11,117,213].

	Phaeophyta (Brown)	Rhodophyta (Red)	Chlorophyta (Green)
Proximate composition % dry weight basis			
Ash	8.7–41.2	2.5–25.7	18.0–30.0
Protein	1.1–26.8	10.2–22.7	10.7–25.9
Lipid	0.6–3.4	0.7–7.4	1.0–3.5
Carbohydrate	33.9–76.0	53.2–75.8	53.0–69.9
Polysaccharides	Laminarin 0.8–24	Carrageenan 7–12	Starch 17
	Mannitol 5–20	Agar 6–36	Hemicellulose 20
	Alginate 10–30	Cellulose 7–10	Cellulose 9
	Fucoxanthin 1–10		Ulvan 25
	Cellulose 2–7		
Photosynthetic pigment	Chlorophyll A and C Carotenoids (fucoxanthin)	Phycobilin Chlorophyll A	Chlorophyll A and B Carotenoids

biochemical composition (34–76 % dry weight (dw)), comprised of different polysaccharides that are divided into three functionally different groups: 1) structural cell wall polysaccharides, 2) intracellular mucilage polysaccharides and 3) storage polysaccharides [27]. Further, macroalgae contain a relatively high protein content with typical values varying between 10 and 30 % (dw) [28], thus representing a complementary source of food proteins for human and animal nutrition [29,30]. The high ash content (5–30 % (dw)) results from the capacity of the macroalgal species to accumulate high levels of metal ions, mostly potassium, sodium, magnesium and calcium from their aquatic environment [31–33]. Lipids on the other hand, represent less than 5 % of the total dry weight [34]. Despite this low value, macroalgae are an excellent source of long chain  $\omega$ -3 and  $\omega$ -6 polyunsaturated fatty acids (PUFA) compared to land based plants [35].

The harsh marine environment macroalgae inhabit exposes them to a combination of different light and oxygen concentrations, which essentially leads to the formation of free radicals and other strong oxidizing agents [36]. Consequently, a number of polyphenolic compounds (tannins, phenolic acids) and pigments (carotenoids such as fucoxanthin) have naturally accumulated which have proved to avert free radical formation [37], which have proved to possess different biological activities, including anti-oxidant [38], anti-inflammatory [39], anti-microbial [40], anti-viral [41], anti-diabetic [42], anti-cancer [43], neuroprotective [44], hepatoprotective [45] and hypertension [46] properties.

Significant variations in composition exist between the groups of macroalgae and studies have confirmed that seasonal and environmental factors, including light intensity, water temperature and nutrient content influence their overall composition, particularly the assimilation of distinctive polysaccharides [12,33,47,48]. Thus, it is vital that biorefinery processes utilising macroalgae, not only account for total biomass yield and weight (dw) availability, but also biochemical composition seasonality. This would ensure that the feedstock's target constituents of interest are at their greatest compositional yield at the time of harvest in order to propose a biorefinery approach with an integral valorisation of the raw species.

### 3.1. Red macroalgae (Rhodophyta)

Red macroalgae are composed of around 4000 different species, making them the most abundant macroalgal group, and can be extensively found in both deep cold waters or warm shallow waters [49]. Species belonging to red macroalgae typically contain high carbohydrate contents (53–76 % (dw)) i.e. polysaccharides such as carrageenans, agar and cellulose [50]. Carrageenans, the main component in the cell wall of *Rhodophytes*, are sulphated linear polysaccharides of

D-galactose and 3,6-anhydro-D-galactose [51]. Three main commercial classes of carrageenan exist ( $\kappa$ -carrageenan,  $\iota$ -carrageenan and  $\lambda$ -carrageenan), which vary compositionally relating to the amount and position of sulphate groups; with the propensity for different carrageenan types depending on species, growth conditions and process of extraction [52,53]. Each form has its own unique properties and application in industry. For example,  $\kappa$ -carrageenan (typically sourced from *Kappaphycus alvarezzi*) makes an extremely strong gelling agent, whereas  $\iota$ -carrageenan (typically sourced from *Eucheuma denticulatum*) can be used to create gels with greater elasticity [53]. Agar, the main polysaccharide found in agarophytes such as those belonging to the *Gracilaria* and *Gelidium* genera, is a linear polymer with alternating 3-linked  $\beta$ -D-galactopyranosyl and 4-linked 3,6-anhydro- $\alpha$ -galactopyranosyl units [54]. Typically, it is used as a gelling agent within the food, pharmaceutical and biotechnology industries due to its gel forming abilities in aqueous environments [55].

### 3.2. Green macroalgae (Chlorophyta)

Approximately 1500 different species of green macroalgae can be found in coastal waters with shallow tides, such as in bays, estuaries or tide pool zones [49]. Species belonging to the *Ulva*, *Codium* and *Halimeda* genera are representative of the main green macroalgal groups [56] and contain carotenoids and chlorophylls A and B, as their main photosynthetic pigments [22]. Green macroalgae also contain relatively high levels of carbohydrates (53–70 % dw) that include cellulose and hemicellulose, but are mainly represented by the complex sulphated hetero-polysaccharide ulvan that is typically found in the cell walls of *Chlorophyta* [57]. Ulvan is built on repeating disaccharide unit sequences composed of sulphated rhamnose and glucuronic acid, iduronic acid or xylose [58]. Although the polysaccharide displays numerous physico-chemical and biological features of interest for applications across the pharmaceutical [59,60] and agricultural industries [61], there is a lack of commercial utilisation at present due to its poor gelling properties; ulvan solutions exhibit low viscosities and demonstrate a viscosity decrease with increasing shear rate (pseudoplastic behaviour) [62].

### 3.3. Brown macroalgae (Phaeophyta)

Brown macroalgae, which include species belonging to the *Fucus*, *Laminaria*, *Himantalia*, *Undaria*, *Alaria* and *Ascophyllum* genera, make up a total of around 1500 different species [49], and preferably grow in colder and/or shallow waters [56]. The biochemical composition of brown species of macroalgae is highly complex, and possess a unique yet heterogeneous carbohydrate composition present in high concentrations (34–76 % dw) [63]. One of the main structural polysaccharides found in *Phaeophyta* spp, is alginate (also known as algin or alginic acid) [64], an unbranched polymer consisting of 1,4-linked  $\beta$ -D-mannuronic acid (M) and  $\alpha$ -L-guluronic acid (G) [65]. A regular repeating pattern is absent in this polysaccharide as the alginate polymer is composed of homopolymorphic M or G regions, interspersed with heteropolymorphic M and G regions [64]. Fucoxanthin, another cell wall polysaccharide suggested to have a protective role against drying [66], is composed of sulphated esters of L-fucose [67] that may also contain other monosaccharides such as xylose, galactose and mannose depending on the species, along with some proteins [68]. Interest in fucoxanthin has significantly increased due to the range of biological activities the polysaccharide has been shown to exhibit, including antioxidant [69], antiviral [70], anti-inflammatory [71] and antitumor [72] effects, that are directly related to its structure, composition, sulphate content, position of sulphate ester group and molecular weight [73]. Laminarin, a storage glucan typically used as a food reserve in *Phaeophyta*, is found in cell vacuoles and consists of a linear polysaccharide of  $\beta$ -(1–3)-D-glucose with terminating chains of D-mannitol and occasional  $\beta$ -(1–6)-glycosidic linkages [74]. The structural features of laminarin vary according to

species with respect to the M:G and degrees of polymerisation, which are believed to influence its biological activities [75] including anti-tumour and wound-healing activities [76].

### 3.4. The importance of understanding macroalgal cell wall structure

The majority of lignocellulosic plant cell walls consist of large, complex and rigid biopolymers such as cellulose, hemicellulose, lignin and pectin [77]. The interconnected structure of plant cell walls has been extensively studied and is well understood. In contrast, macroalgal cell walls are chemically and structurally more complex and heterogeneous compared to terrestrial land plants, and existing methodologies developed for lignocellulosic cell wall characterisation are not compatible.

Deciphering the structural composition and architecture of macroalgal cell walls is a challenging task and, due to the fact that macroalgae are a polyphyletic group [78], attempts to accurately depict the variations in structure is hindered by the dynamic chemical diversity that exists between *Rhodophyta*, *Chlorophyta* and *Phaeophyta*. To date, structural models of macroalgal cell walls are generalisations of how polysaccharides and proteins are organised and interlinked [79] as depicted in Fig. 2.

Macroalgal cell walls typically consist of a fibrillar skeleton material, usually cellulose, yet can be replaced by xylan and mannan according to taxonomical group, and an amorphous embedded matrix also containing polysaccharides unique to each taxa [80]. Red macroalgal cell walls

(Fig. 2 A) generally consist of cellulose microfibrils and a family of hydrocolloids made up of sulphated glucans, such as carrageenans and agars, more complex xylogalactans and glucomannans [81]. Green macroalgae (Fig. 2 B) also contain a cellulose fibrillar material, which may have fibrillary components including  $\beta$ -D-xyloglucans and mannans that replace cellulose [82]. However, these skeletal polysaccharides form double fibrillar layers (inner and outer layers), with an amorphous matrix in between mainly comprising of sulphated polysaccharides such as ulvan and glucuronan layers [83]. Brown macroalgal cell walls (Fig. 2C) additionally consist of a fibrillar framework of cellulose microfibrils that are present in layers which are parallel to the cell surface, but with no clear orientation [82]. Alginate polysaccharides are enmeshed within the cellulose layers, but also reside within the interfibrillar matrix alongside fucose containing sulphated polysaccharides, proteins and phenols [84]. Clearly, the majority of macroalgal bio-products, including polysaccharides, are either stored within the cell wall, or are bound to cell membranes, which ultimately need to be disrupted prior to extraction.

An additional barrier also exists with macroalgae, the macrostructure, which also requires disruption to gain access to the internal cell wall and cell membrane [85]. A greater structural understanding of cells walls belonging to the most promising macroalgal species (across all taxonomical groups) that will be used as feedstock for future biorefineries require attention at this present time. This underlying knowledge will assist in optimising biorefinery development and efficient deconstruction of this unique feedstock.

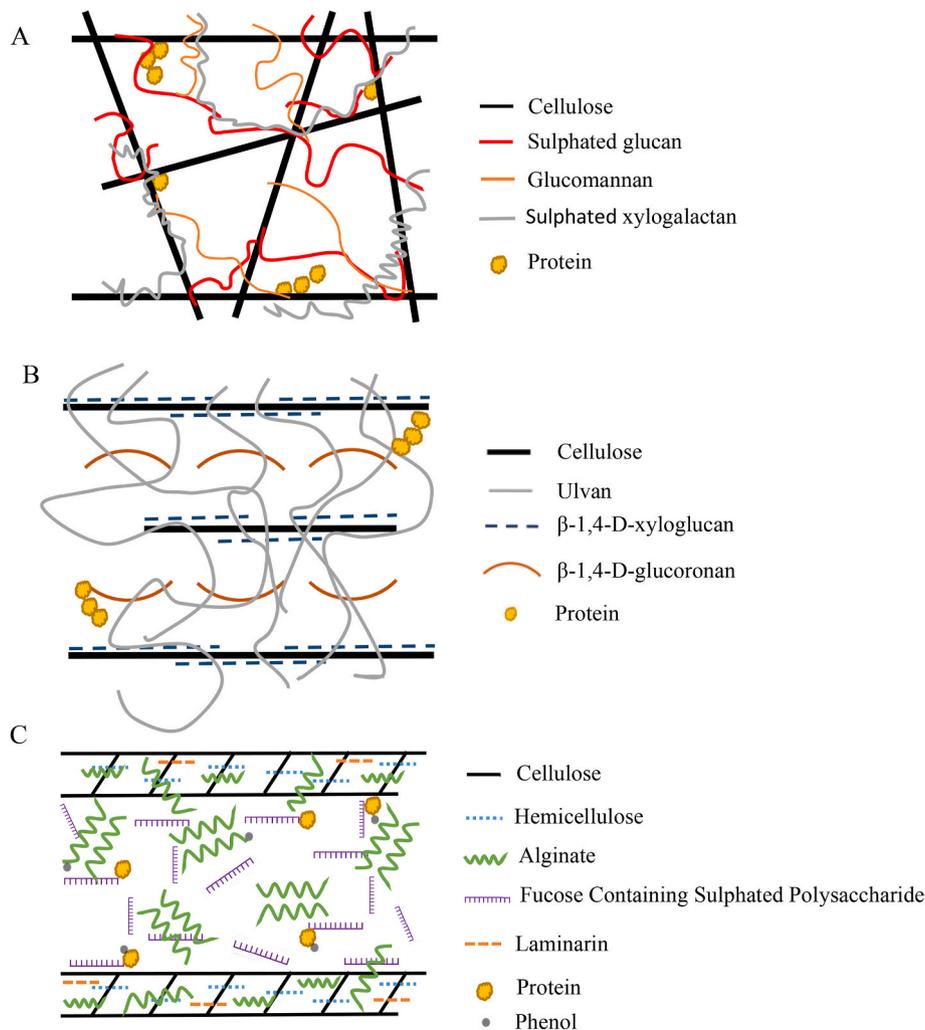


Fig. 2. Schematic generalisations of cell wall models belonging to A) red, B) green and C) brown macroalgae (Adapted from: [79,83,221–224]).

#### 4. Current status of macroalgal production and cultivation

The macroalgae aquaculture sector continues to grow in both size and value on an annual basis, with Food and Agriculture Organisation of the United Nations (FAO) data stating that global macroalgal aquaculture production in 2016 equated to ca. 30 m tonnes at a value worth USD11.6 bn [86]. The largest global producer of macroalgae is Asia, with China leading production volumes of 14 m tonnes valued at USD8.6 bn, followed by Africa with a production volume of around 140,000 tonnes and the Americas with 15,634 tonnes [86]. In Asia, mass cultivation technologies have already been established for a number of different macroalgal species, including *Laminaria japonica*, *Eucheuma* spp., *Kappaphycus alvarezii*, *Pyropia yezoensis*, *Undaria pinnatifida* and *Gracilariaria verrucosa* [22]. Europe, on the contrary, still has a relatively small aquaculture industry, and cultivation technologies are lagging in comparison. Nevertheless, the drive to stimulate the European macroalgal market and aquaculture sector is at a much earlier stage, and both academic and business-related interests have propelled strategies to cultivate macroalgae on a larger scale. This is evident by the increasing number of European research projects focussing on the development of macroalgal cultivation techniques, biorefinery processes and the production of marketable macroalgal-based products (discussed further in Section 6). Furthermore, EU and national policy initiatives have led to the establishment of macroalgal farms in Dutch, Norwegian, Portuguese and Irish waters, with the aim of producing commercial species of macroalgae (such as *Saccharina* spp., *Alaria* spp. and *Ulva* spp.) and macroalgal based products [87].

Cultivation is an extremely important aspect, which needs to be supported and integrated, for the development of large-scale sustainable macroalgal biorefineries. For such biorefineries to flourish sustainably and economically, the process cannot be reliant upon the wild-stock harvesting of species, or on the cultivation of on-shore or near shore farms [88,89]. Wild-harvesting will inevitably lead to over-exploitation, whilst on-shore and near-shore cultivation could compete with coastal uses (such as fishing) and food-crops. The implementation of large-scale off-shore cultivation systems have been proposed to be the most promising alternative able to withstand the challenges associated with the aforementioned systems, particularly if coupled with integrated multi-trophic aquaculture systems (IMTA) and wind energy production [90,91].

The constant supply and high-volume production of a suitable species of macroalgae as feedstock underpins biorefinery development. However, one of the main hindrances associated with biorefinery development remains the macroalgal cultivation part itself. Life cycle analyses (LCA) and techno-economic assessments (TEA) of such processes have often highlighted that the cultivation phase of the system is the most costly and energy intensive, and advancements in research and development are needed here in order to make macroalgal biorefineries economically viable [92]. Improvements in the understanding and knowledge of macroalgal life cycles, as well as the design of new optimal and compatible cultivations systems (mainly for offshore cultivation) for each species of macroalgae are vital for successful development. Furthermore, the energy balance or energy return of the process are also required for each species. This includes decreasing operational and capital costs (such as labour costs, technology and energy inputs) whilst simultaneously improving and increasing biomass yields and the value of prospective bioproducts [93]. Although the prospects of offshore cultivation will propel the bioeconomy of any country through job and wealth creation for coastal communities, including the societal acknowledgement of macroalgae as a biorenewable feedstock, the economic feasibility of macroalgal cultivation will undoubtedly differ between global regions. For example, labour and materials costs are more expensive in Europe compared to Asia and South America, and therefore will require more technological advances to compensate. A number of excellent reviews regarding the topic of macroalgal cultivation and large-scale farming have been published, of which the authors

recommend the following articles for a more in-depth evaluation on this topic: [94–98].

#### 5. The macroalgal biorefinery concept

Implementation of a biorefinery that follows a holistic zero waste approach is a fundamental requirement to comply with the key principals of the EC bioeconomy framework [99]. There is an imminent need to reduce waste and maximise the economics of a bioprocess, by generating multiple products from the same biomass via the implementation of sustainable biotechnologies. General bioprocess design principles would suggest that bioproducts of higher value should be recovered first followed by lower value products. This essentially translates to the extraction of bioactive and functional based compounds, sugars and minerals. Subsequently all the remaining residue needs to be used as a feedstock for biofuel or platform chemicals production to avoid waste generation [100].

Even though macroalgae contain a plethora of untapped biochemical constituents, numerous challenges still need to be overcome to facilitate the fruition of macroalgal biorefineries. These include the identification of the range of high value bioproducts (i.e. quantities and values) that can be acquired from different macroalgal feedstocks and, importantly, the technological and economic feasibility of the bioprocess and cascading approach which has been employed [101]. In recent years nonetheless, researchers have understood the imminent need to move away from feedstock programmes that focus on single-based product objectives and have started to explore multiple cascading approaches to biorefine different species of macroalgae for multiple bioproduct generation. An example of a macroalgal biorefinery flowchart is illustrated in Fig. 3. This depicts both upstream and downstream processing sections in addition to the numerous biotechnological processing routes that may be employed for feedstock valorisation.

The most suitable bioprocessing route for a particular product(s) will ultimately depend on the species of macroalgae used as feedstock and its susceptibility to the bioprocess technology used. It is also vital to recognise that, for macroalgal biomass in particular, upstream bioprocessing may significantly determine the range of downstream end-products; the biochemical composition of macroalgae can be significantly influenced by a range of cultivation parameters [102]. Furthermore, depending upon the targeted bioproduct of interest, selection of the most ideal approach or combination of approaches are paramount. A typical example of this is for bioethanol production [103]. This involves either physical, chemical and biological (or a combination of both) pretreatments which serve to expose the feedstock's cell wall constituents, followed by the subsequent enzymatic hydrolysis of polysaccharides into their respective monomeric constituents [104,105]. The vital pretreatment/s stage is used to enhance the liberated sugar yields that are achieved through enzymatic hydrolysis, for fermentation of liberated sugars into bioethanol. Nonetheless, the biochemical composition and structure of cell walls in seaweeds significantly differ from the complex lignocellulosic structures of plant-based materials, that have traditionally been utilised for the production of bioethanol [106]. As such, less labour intensive and costly pretreatments can, in theory, be applied to seaweeds. However, identification of the most ideal pretreatment/s and bioprocessing route, tailored towards seaweeds, need investigation particularly in biorefinery processes where bioethanol/biofuel production take centre stage.

The formulation of detailed and preferably optimised, species-specific macroalgal biorefinery roadmaps, which link both upstream and downstream bioprocessing should become focus of the academic research community, with the specific aim of cataloguing the range of potential biobased products and their yields. To support this effort, the latest literature on cascading macroalgal biorefineries developed specifically for each taxonomical group are discussed in this section. The co-valorisation of multiple bio-products generated from the original starting macroalgal feedstock are also examined.

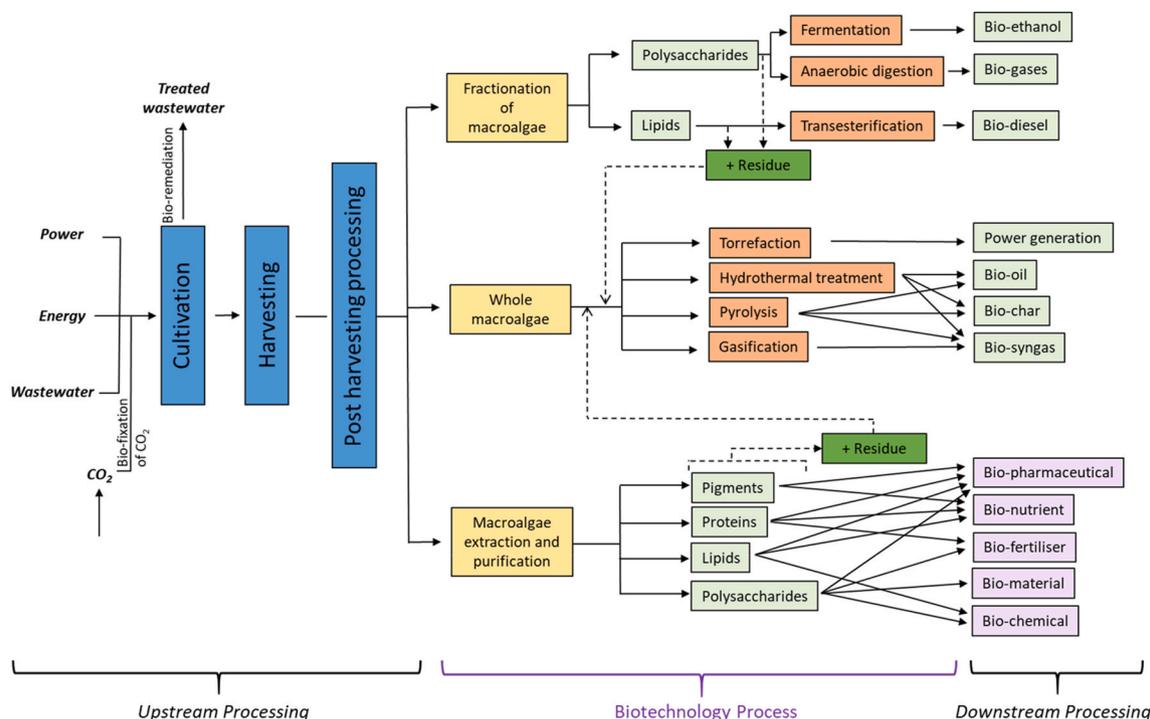


Fig. 3. Macroalgal biorefinery pathway flowchart (Adapted from Ref. [102]). Residues generated from either of the fractionation/extraction pathways ought to be compatible with subsequent physical treatment methods for energy or chemical feedstock generation.

### 5.1. Red macroalgal biorefineries

*Rhodophyta*, from both historical and current perspectives, are an economically relevant resource. Representing approximately 60% of the total global seaweed production [107], they are mainly processed for the extraction of agar or carrageenan, depending on species. The hydrocolloids carrageenan and agar, have frequently been the primary target for recovery during the initial stages of a bioprocesses, using mild extraction procedures in to avoid structural damage. Masarin et al. [108] and Kumar et al. [109] explored the extraction of carrageenan and agar, respectively, and assessed the suitability of the remaining residues as feedstock for bioethanol production. Masarin et al. [108] identified that 60–63.5 % carrageenan can be extracted from *Kappaphycus alvarezii*, and the glucan in the remaining residues could be targeted for glucose liberation (11.5–13.7 g L<sup>-1</sup> of glucose was successfully liberated post enzyme hydrolysis). Similarly, Kumar et al. [109] suggested that a biorefinery approach utilising *Gracilaria verrucosa* for the production of agar and bioethanol could be commercially viable, and yielded 0.43 g of bioethanol g<sup>-1</sup> of liberated sugar from an agar-free residue. Glucose and additional monosaccharides that remain in post extraction process residues are key precursors to produce carbon-based end-point products, such as bioethanol. Additionally, alternative industrially suitable chemicals can also be recovered from macroalgal waste residues. This includes levulinic acid, a decomposition product of cellulose, which has been identified as one of twelve top value added chemicals from biomass that can serve as a platform chemical for the manufacture of polymers, pharmaceuticals, plasticisers and fuel additives [110]. A levulinic acid yield of 16 wt % was produced from the microwave pretreatment of *Gracilaria lemaneiformis* food waste, under the experimental conditions of 0.2 M H<sub>2</sub>SO<sub>4</sub> for 20 min at 180 °C, with a biomass loading rate of 5 % (w/v) [111]. This process additionally generated a residual biochar that may be used a direct fuel source, particularly since higher heating values of 19–25 MJ kg<sup>-1</sup> were reported.

Cascading biorefinery approaches can also be applied. Francavilla et al. [112] recovered phycobilirubens R-phycoerythrin (7 mg g<sup>-1</sup> dw), allophycocyanin (3.5 mg g<sup>-1</sup> dw) and phycocyanin (2 mg g<sup>-1</sup> dw) from

*Gracilaria gracilis*, before subjecting the residue to fast pyrolysis to generate bio-oil and biochar. However, due to the high content of nitrogenous-based compounds that were present in the bio-oil the authors suggested it was unsuitable for direct use as a biofuel. The biochars generated from this study contained inorganic nutrients such as P, K, Ca, Fe and Mg and were in accordance with previous studies that suggest macroalgal biochar has properties that provide soil nutrient benefits, a recurring theoretical concept which does not stand up to practical assessments [113] (see also section 5.3 below).

Trivedi et al. [114] demonstrated the feasibility of developing a sequential extraction process that recovers valuable commodity bioproducts, such as pigments, lipids, agar, minerals and cellulose, from the red species *Gelidium acerosa* and *Gracilaria dura*. The authors calculated that from 1 tonne of fresh macroalgal biomass, 0.3–0.7 kg of R-phycoerythrin, 0.1–0.3 kg of R-phycoerythrin, 1.2–4.8 kg of lipids, 28.4–94.4 kg of agar and 4.4–41.9 kg of cellulose (from which 1.8–17.4 kg bioethanol is achievable) could be obtained. In another study, a similar approach was employed where integrated aqueous extraction steps were followed in order to recover a stream of similar biobased products from another red macroalgal species, *Gracilaria corticata* [115]. From the sequential bioprocess, R-phycoerythrin and R-phycoerythrin were recovered from fresh seaweed feedstock, whilst crude lipids, agar, soil conditioner and bioethanol were generated from dried feedstock. A mineral rich liquid with potential fertilizer applications also remained. Such seaweed biorefinery approaches are attractive since the initial recovery of pigments was accomplished on wet feedstock, thus eliminating the early requirement to thermally dry the feedstock material which is often a relatively energy intensive step. Additionally, complete utilisation of the entire feedstock was achieved without the generation of any waste material, and any solvents used were recycled.

The successful reduction of waste within a biorefinery process is a desirable target that ought to be obtained, as this factor is one the key criteria embedded within the circular biorefinery concept. Offei et al. [116] accomplished this during their study which demonstrated the feasibility of generating bioelectricity from residues of macroalgae that remained post bioethanol production. The study explored this integrated

biorefinery approach of bioethanol and bioelectricity production from three diverse species of macroalgae from the Ghanaian coast: *Ulva fasciata* (green), *Sargassum vulgare* (brown) and *Hydropuntia dentata* (red). Bioethanol yields of 5.1, 3.7 and 2.4 g per 100 g (of dried matter) were obtained from the respective samples, after which the residues were used as substrates in microbial fuel cells (MFC) to generate bioelectricity. The respective power densities obtained were 0.50, 0.46 and 0.48 W m<sup>-1</sup>. These values showed initial promise in what appears to be the first study at the time of writing this review, to explore macroalgal bioethanol residues as substrates in MFCs, particularly since the most efficient MFC substrate sodium acetate (control), had a power density of 0.95 W m<sup>-1</sup>.

## 5.2. Green macroalgal biorefineries

It is becoming increasingly evident that the utilisation of seaweeds belonging to the *Chlorophyta* are one of the most promising alternative biorefinery feedstocks. One of the earliest studies to assess the potential of generating multiple biobased products was in 2013, where van der Wal et al. [117] produced 0.35 g bioacetone, biobutanol and bioethanol g<sup>-1</sup> sugar from an *Ulva lactuca* hydrolysate liquid fraction (generated from hot-water treatment followed by enzymatic hydrolysis) fermented with *Clostridium acetobutylicum* and *Clostridium beijerinckii*. Although these findings opened the prospects of multiple carbon-end point product generation from a single macroalgal feedstock, the recovery of additional biobased compounds of greater value than biofuels and platform biocommodity products are now generally considered to be incorporated within the bioprocess [24]. This would serve to ensure the bioeconomic stability of a biorefinery process. Nonetheless, such approaches ultimately require an in-depth understanding of the availability of such bioproducts and their potential industrial applications; and how their yields differ annually within the macroalgal feedstock itself. As such, a study by Magnusson et al. [118] calculated the productivity of bioproducts in *Ulva ohnoi* and *Derbesia tenuissima* with potential nutraceutical and cosmetic applications. Average annual biomass productivities of 56 tonnes dw Ha<sup>-1</sup> yr<sup>-1</sup> for *D. tenuissima* and 138 tonnes dw Ha<sup>-1</sup> yr<sup>-1</sup> for *U. ohnoi* were achievable (under controlled land-based cultivation), and lipids (13% dw) and fatty acids (5% dw) for *D. tenuissima* and soluble fibres (ulvan, 12% dw) for *U. ohnoi* were calculated. Annual amino acid productivities of *U. ohnoi* and

*D. tenuissima* were recorded to be 18 Ha<sup>-1</sup> yr<sup>-1</sup> and 14 Ha<sup>-1</sup> yr<sup>-1</sup>, respectively. Such studies are vital to gain an insight into yields and financial prospects of any potential biorefinery process, regardless of the starting macroalgal feedstock.

The application of macroalgal fractions as functional ingredients for dietary consumption has attracted significant attention in recent years, and studies have explored novel approaches in the biorefinery of green macroalgae with the inclusion of additional proprietary steps targeted at the mineral (salt) content of green macroalgae. Macroalgal salts have been considered to be associated with a healthy balance of vital minerals required for human nutrition, particularly since they contain high proportions of potassium and magnesium, with favourable sodium to potassium ratio features that can prevent hypertension and cardiovascular disease [119,120]. The works of one particular group have highlighted the prospects of incorporating an initial fresh water washing treatment as a first step in a cascading biorefinery for natural salt fractionation, and how subsequent residues can be valorised for additional bioproduct generation that include the polysaccharide ulvan and proteins [121–123]. This has ultimately led to culmination of multiple bioprocessing options on *U. ohnoi*, outlined in Fig. 4, which depicts the pre-defined processes and the protein enrichment processing options that were trialled on the salt and ulvan-free residue, including enzyme hydrolysis, microwave assisted extraction, a combination of both microwave assisted extraction and enzyme hydrolysis, and protein isolation. The quality of certain protein fractions, PEB-I and PI (Fig. 4) were similar to soybean meal containing 41.6 and 43.4 mol % of essential amino acids, respectively, representing a potential avenue for product development. Nevertheless, it is noteworthy to mention that simpler biorefinery processes (possibly made up by two-stages) may be more suitable over a complex, multi-stage bioprocess, as the overall LCA and TEA would be more favourable. This is certainly a factor that requires consideration when developing bioprocesses for multiple bioproduct generation; more bioprocessing steps must be implemented.

One way to enhance the LCA and TEA of a bioprocess is the adoption of ‘green extraction technologies’, which are particularly attractive to incorporate within cascading biorefineries due to their environmentally friendly and less hazardous status plus their ability to reduce energy consumption and promote the recovery of bioproducts of greater purity and quality [124]. Subcritical water hydrolysis treatment (180 °C, 10.5 bar for 40 min at a solids loading rate of 8 % (w/w)) using seawater, was

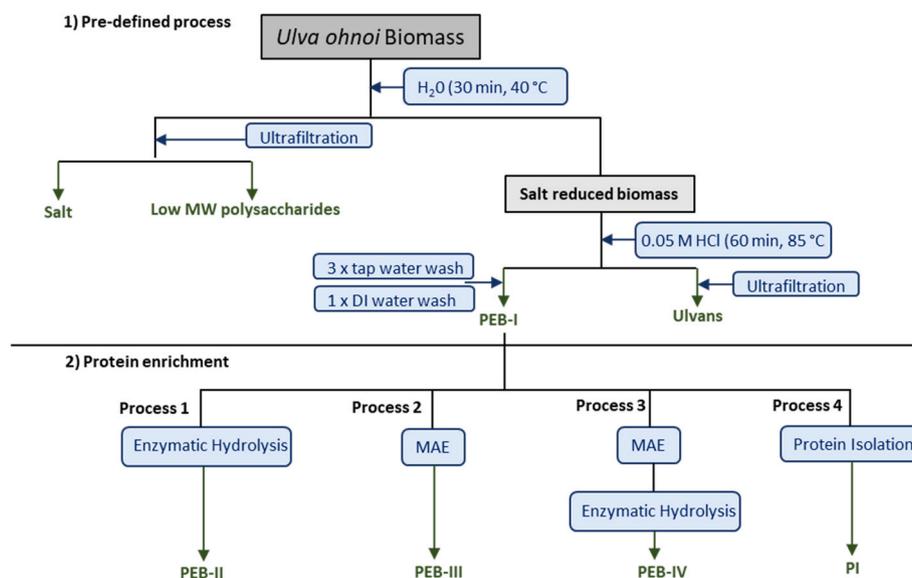


Fig. 4. Schematic outline of the biorefinery process options (processes 1 to 4) investigated by Magnusson et al. [123] to generate protein-enriched biomass (PEB) fractions I-IV from the green macroalgal species *Ulva ohnoi*. The pre-defined process was previously established in the works of Glasson et al. [122]. MAE, Microwave Assisted Extraction; MW, Molecular weight; DI, deionized water (milli-Q); PI, protein isolate. Figure taken from Magnusson et al. [123].

applied to a mixed composition of *Ulva rigida* and *Ulva fasciata* in an integrated biorefinery study by Polikovskiy et al. [125]. The treatment yielded multiple bioproducts that included a biochar residue and a liquid hydrolysate fraction containing a plethora of biocompounds such as 5.2 mg HMF, 24.1 mg total monosaccharides, free amino acids, protein corresponding to 84.9 % of the total protein, and 4.6 mg of bioethanol ( $\text{g}^{-1}$  of dried *Ulva* spp). Bottlenecks associated with the separation feasibility of certain key products on a commercial scale were raised, however, the use of seawater reducing the freshwater footprint opens a new pathway for the generation of multiple niche bioproducts for the bioeconomy.

In the work outlined by Prabhu et al. [101], six different bioproducts were sequentially extracted from *U. ohnoi* using a green extraction approach; a mineral salt-rich fraction (45.4 % dw), a starch-rich fraction (3.7 % dw), a lipid-rich fraction (3.8 % dw), an ulvan-rich fraction (13.9 % dw), a protein-rich fraction (14.8 % dw) and finally a cellulose-rich fraction (8.7 % dw). The study recovered total extractable yields of all biobased products equating to 90.3 % dw of the macroalgae that was used, significantly reducing the waste potential of the biorefinery process. The generation of zero-waste is a vital factor in the development of any biorefinery process utilising any feedstock material, yet this may ultimately be influenced by the methodology and biotechnology that has been applied to recover bioproducts from the macroalgae. Postma et al. [85] identified that by using a high shear homogenisation technique on *U. lactuca*, in particular a two-phased experiment with a rotor speed of 21–11  $\text{m s}^{-1}$  and a fixed biomass concentration of 10.7  $\text{g kg}^{-1}$ , protein and carbohydrate extraction yields of 39 and 51 % were obtained, respectively. Scanning electron microscopy validated that this technique ‘broke’ and ‘emptied’ individual cells from the thallus of the macroalgae, confirming cell wall disintegration. Nonetheless, the authors revealed the process was relatively energy intensive ( $\geq 11 \text{ kWh kg dw}^{-1}$ ) compared to the energy density of the macroalgae (4.8  $\text{kWh kg dw}^{-1}$ ), and the technique requires further validation on a larger scale.

In addition to recovering multiple components, typically of higher added-value across a range of bio-industries, particular biochemical fractions have also been reserved for conversion into biofuel. Residues that are a prime waste-product from bioprocesses offer additional value which can support the bioeconomy. The production of biofuels such as bioethanol has been explored from *U. fasciata* residues which had already undergone a sequential bioprocess that recovered 26 % mineral rich liquid extract, 3 % lipid and 25 % ulvan [126]. Bioethanol was produced at 0.45  $\text{g g}^{-1}$  reducing sugar, highlighting the significance of utilising the remaining cellulose fraction in green macroalgal residues. Residues have also been evaluated for biomethane potential (BMP) with the aim of enhancing the repertoire of biofuels that can be generated from different species. Biomethane production was analysed on *U. lactuca* residues that had undergone both individual and sequential extraction of sap, ulvan and protein, in a study conducted by Mahtre et al. [127]. The highest biomethane yield of 408 mL biomethane  $\text{g}^{-1}$  of volatile solid was produced from residues that had undergone a sequential extraction of sap and ulvan fractions. Furthermore, research by Yahmed et al. [128] developed a bioprocess using the species *Chaetomorpha linum* that co-produced both bioethanol (0.093 g bioethanol  $\text{g}^{-1}$  of pre-treated macroalgae using *S. cerevisiae*) and biomethane (0.26 L  $\text{g}^{-1}$  of volatile substrate). The study additionally employed the filamentous fungus *Aspergillus awamori* to secrete hydrolytic and proteolytic enzymes (endoglucanases,  $\beta$ -glucosidases, xylanases,  $\beta$ -xylosidases and  $\alpha$ -L-arabinofuranosidases) onto a 3 % NaOH pre-treated *C. linum* prior to biofuel production. Such an approach would undoubtedly aid to improve the overall LCA and TEA of the proposed bioprocess, as the use of expensive commercial enzymes was avoided.

### 5.3. Brown macroalgal biorefineries

Species of macroalgae belonging to the *Phaeophyta* have also attracted much attention, particularly since the group consist of

commercially exploitable relatively large, high-alginate, rapid growth genera such as *Ascophyllum*, *Laminaria*, *Macrocystis* and *Sargassum*.

Alginate has often been the initial extract compound at the start of a *Phaeophyta* biorefinery process, employing milder treatment conditions in order to avoid thermal degradation that may lead to a loss of bio-functionality. Alginate-free residues from the species *Sargassum muticum* have subsequently undergone non-isothermal auto-hydrolysis to yield liquid fractions assessed for anti-oxidant activity in a study by González-López et al. [129]. The study also found that the antioxidant activity of the solubilised fraction decreased after auto-hydrolysis treatments greater than 190 °C were applied to the alginate-free residues. In order to enhance the number of added-value compounds that can be generated from *S. muticum*, Balboa et al. [130] proposed an alternative valorisation approach by applying green extraction and fractionation processes. Subcritical water, ethanol, ethylacetate and supercritical CO<sub>2</sub> were applied, as well as employing green biotechnologies such as auto-hydrolysis and supercritical fluid extraction with CO<sub>2</sub> to recover fucoxanthin, alginate, phlorotannin and fucoidan rich fractions with antioxidant activity. The study also found that microwave drying (two cycles at processing conditions of 400 W for 10 s followed by 200 W for 5 s) of the initial *S. muticum* biomass was found to be the most optimal drying methodology to use, compared to oven, freeze-drying and press drying methods, with moisture reductions up to 83 % being reported. The drying of biomass is a necessary pre-requisite prior to processing, yet is one of the most energy-intensive unit operations [104] and finding an ideal drying technology that is both cost-effective and compatible with any feedstock is vital. This is due to the fact that the different forms of drying may have either a beneficial or negative influence on the feedstock material, which consequently could impact on downstream processing or the availability of the target compounds of interest. For example, oven drying may be detrimental to the phenolic content and the antioxidant properties of extracts [131] whereas microwave drying, which is normally significantly faster due to the inherent volumetric heating effects, has been found to promote changes in feedstock microstructure, thus enhancing mass transfer and favouring molecular interactions between solvent and solutes during extraction [132].

Biorefinery processes utilising *Phaeophyta* species have also focussed on the recovery of additional polysaccharides, such as fucoidan and laminarin, alongside alginates, in order to enhance the overall LCA and TEA of the bioprocess. This was explored in the sequential yet selective extraction process developed by Abraham et al. [133] to extract polysaccharides alginate, laminarin and fucoidan from the Australian giant bull kelp *Durvillaea potatorum*. By employing an initial acidic extraction (optimal conditions identified as 0.05 M HCl at 60 °C for 3 h), followed by a conventional alkaline extraction step (28 % Na<sub>2</sub>CO<sub>3</sub> at 60 °C with stirring for 2 h), 43.6 % (w/w) of total polysaccharide products were recovered; fucoidan/laminarin, acidic extractable alginate and alkaline extractable alginate. The authors identified that the two alginate extracts, acidic and alkaline extracted alginate, possessed different properties including the mannuronic to guluronic acid ratio, viscosity and pH solubility range, which are factors that may ultimately influence the extracted alginates’ industrial applications. This will influence which extraction process is employed during the biorefinery process, yet simultaneously opens the prospect of targeting multiple industries that require different biochemically structured types of alginate.

Exploration of different bioprocessing approaches on macroalgal species and their generated residues is imminent to identify compatible methodologies for implementation within a bioprocess. Furthermore, alternative compound prospecting from process liquid waste streams and residues, post initial polysaccharide recovery, has the potential to identify novel bioproducts with industrial value. Fig. 5 illustrates the development of two independent bioprocessing routes, both utilising the UK native species *L. digitata*, that can be interlinked as a result of the suitability and compatibility of the biochemical processing technologies employed.

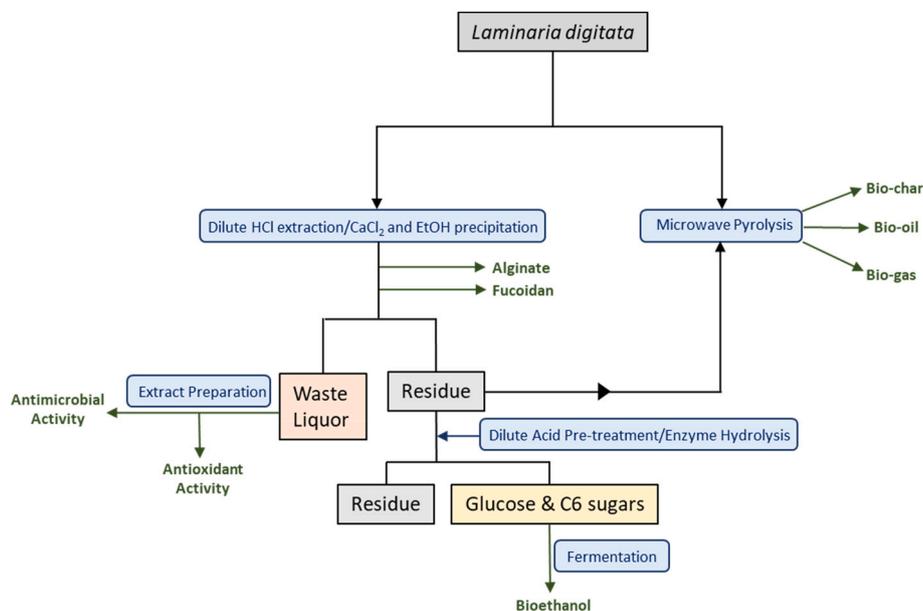


Fig. 5. Schematic diagram of the biorefining processes for *Laminaria digitata* for the extraction of value added compounds, bioethanol, waste streams with bioactivity, and the production of microwave pyrolysis bioproducts i.e. biochar, biogas and bio-oil [134,135].

The overall bioprocess, developed in the works of Kostas et al. [134, 135], recovered polysaccharides alginate and fucoidan, then identified the post extraction liquor waste-stream possessed antioxidant activity ( $EC_{50}$   $15.3 \text{ mg mL}^{-1}$ ) and anti-microbial activity against the human bacterial pathogen *Burkholderia cenocepacia*. The remaining solid residue was converted to bioethanol (via enzyme hydrolysis and fermentation with *S. cerevisiae* NCYC2592) and to bio-oil and biochar (via microwave pyrolysis). Although both studies were not fully optimised, potential routes that are compatible with *L. digitata* and its residue were highlighted in addition to the promising incorporation of microwave pyrolysis within the biorefinery paradigm to cover the range of alternative products and value-added compounds that can be obtained. Such research is imperative, in order for future biorefinery processes using different species of macroalgae and processing technologies to come to fruition.

Another thermochemical technology that has proved to be promising for inclusion within a macroalgal biorefinery is hydrothermal liquefaction (HTL). The process utilises water at sub to near critical conditions ( $200\text{--}380 \text{ }^\circ\text{C}$ ) which thus acts as both a solvent and a reactant, converting the treated biomass into biocrude oil, solid biochar and biogas as well as generating a nutrient-rich aqueous phase [136]. HTL has been suggested to be ideal for wet biomass feedstocks, avoiding the necessary prerequisite and energy intensive step of feedstock drying, making freshly harvested macroalgae a suitable candidate for this particular processing technology. Work carried out by Raikova et al. [137] screened a number of common macroalgal species, across the three taxonomical groups with the majority in the *Phaeophyta*, from the UK South-West coastline for their potential to produce both biocrude and nutrients that can partition into aqueous phases from a HTL process. Previously optimised HTL processing conditions ( $345 \text{ }^\circ\text{C}$ ; at a heating rate of  $30 \text{ }^\circ\text{C min}^{-1}$ ) for biocrude and nutrient recovery on *Ascophyllum nodosum* were applied. Under HTL processing conditions of  $345 \text{ }^\circ\text{C}$ ; at a heating rate of  $30 \text{ }^\circ\text{C min}^{-1}$ , the brown species of macroalgae generated greater biocrude yields ( $12\text{--}16 \text{ } \%$  dw biocrude) than the red macroalgal species which were investigated ( $6\text{--}8 \text{ } \%$  dw biocrude). However, biocrude yields generated from green macroalgae, namely *Ulva* spp., outperformed the brown species and produced between  $29$  and  $30 \text{ } \%$  dw. A high concentration of ammonia,  $224 \text{ mg kg}^{-1}$ , was identified in the aqueous phase produced from the HTL of *L. digitata*, and the highest phosphate concentrations ( $>100 \text{ mg kg}^{-1}$ ) were identified for *Fucus*

*ceranoides* and *Pelvetia canaliculata*. These results are relatively promising, as such concentrations are comparable to the levels found in microalgal growth media; and the aqueous phases generated from the HTL of these brown species of macroalgae could possibly be used as growth supplements for either micro or macroalgal cultivation, or even terrestrial crops.

Fig. 6 highlights prospective applications of brown macroalgal biorefinery process waste streams that have been explored, which include applications such as aquaculture diet replacements or supplements, heavy metal biosorbents and soil amendment agents.

Due to the economic and technical constraints associated with generating a suitable feed for aquaculture, these feed supplements traditionally consist of microalgae or concentrated preparations of preserved non-viable microalgae, yeast or bacteria and insect larvae or juveniles [138]. Schiener et al. [139] on the contrary, developed a suitable microalgae substitute meal from residues which remained following the enzymatic hydrolysis and bioethanol production of *Saccharina latissima* and *Alaria esculenta*; an inexpensive material that can be produced at large scale. Waste residues generated from a *Fucus spiralis* biorefinery process proved to successfully act as heavy metal bio-sorbents, as a study by Filote et al. [140] proved that *F. spiralis* waste, generated from a bioprocess that sequentially recovered polyphenols, fucoidan and alginate, removed  $100 \text{ } \%$  Pb (II) from an aqueous solution at a dosage of  $0.5 \text{ g L}^{-1}$ . The authors additionally proposed a

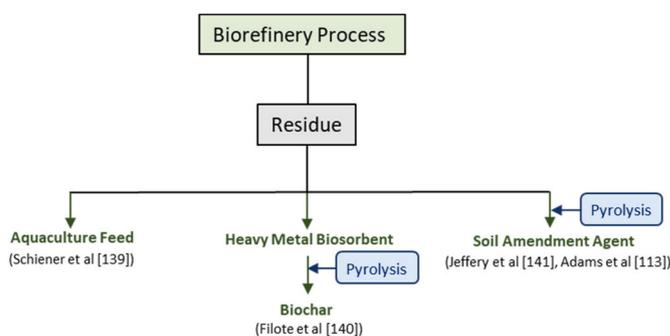


Fig. 6. Applications of waste residues generated from brown macroalgal biorefinery processes, including aquaculture feed [139], heavy metal biosorbents [140] and soil amendment agents (Jeffery et al. [141] Adams et al. [113]).

potential final step that converts the remaining post-desorption macroalgal waste into biochar. Although macroalgal-derived biochars have often been proposed as agricultural soil amendment agents that can improve crop yields, enhance the soil carbon pool and increase rhizosphere microbial diversity [141], a study reported by Adams et al. [113] proved that pyrolysed *Phaeophyta* macroalgal biochars do not necessarily validate this assumption. The authors identified, in one of the first pyrolysed macroalgae char plant trials, that pyrolysed biochars (from initially ensiled *L. digitata*, *L. hyperborea* and *S. latissima*), applied at 2 % (w/w) to soil, prolonged germination in germinating lettuce seeds and inhibited growth in transplanted ryegrass seedlings. It is vital that similar concepts, which are often proposed hypothetical solutions for bioprocess generated residues, are accurately trialled and validated in similar studies. This would ensure that biorefineries which truly fulfil zero-waste circular bioeconomy concepts for all brown macroalgal species, are achievable.

## 6. Commercialisation of macroalgal biobased products and markets

The emergence of the putative macroalgal biorefineries detailed above have clearly highlighted the prospects of generating novel compounds from macroalgae, with various macroalgal biochemical constituents already having known industrial value. Notwithstanding the fact that these bioprocesses are still under development, the generation of such biobased products offer significant opportunity for commercialisation and market distribution. This section details the industrial applications and uses of attainable biorefinery products and their potential role within the blue bioeconomy.

Macroalgal polysaccharides have been used across multiple industries including food and textile due to their hydrocolloidal and stabilising properties [142], as well as the pharmaceutical, medical, therapeutic, nano-medical and biological industries due to their broad range of biological activities [143,144]. These include anti-oxidant [145], anti-inflammatory [146], anti-coagulant [147], anti-proliferative effects on cancer [148] and anti-viral, anti-bacterial and anti-protozoan properties [149]. An increase in research has proved the successful application of macroalgal polysaccharides, particularly agarose, alginate,  $\kappa$ -carrageenan and ulvan, in the field of regenerative medicine, which includes tissue engineering [150–160]. Research is required to understand the structural and biological function of the natural extracellular milieu which is responsible for directing cell fate, and therefore, by gaining knowledge on the mechanisms behind cell function, responses to matrix development and tissue growth is imminent for advances in regenerating damaged biological components [161]. Macroalgal polysaccharides have the ability to form hydrogels that can mimic the native extracellular matrix, which is itself hydrogel-like in structure [162], and have been proposed as ideal biomaterials for regeneration strategies with varying properties and compositions. In particular, macroalgal polysaccharides have shown promise in cartilage tissue engineering applications [163] and cartilage repair [164], due to their structural and chemical similarity with native tissue components, non-harsh processing, and variable degrees of hydrophilicity and bio-compatibility [165]. An in-depth review by Bilal and Iqbal [166] discusses further biomedical applications of macroalgal polysaccharides and is highly recommended. Furthermore, the nutraceutical potential of macroalgal polysaccharides has been reviewed by Tanna and Mishra [167].

An additional application of polysaccharides that have hydrogel forming properties, such as alginates, ulvans and carrageenans, is the production of edible films and coatings for food packaging [168]. In the presence of divalent cations, the carbohydrate groups of G blocks in the alginate polysaccharide backbone are able to crosslink, thus constituting an egg-box model [169] which enables the formation and subsequent commercialisation of bio-degradable and edible bio-plastics. For example, the sustainable packaging start-up company NotPla Ltd, who

use alginate from brown macroalgae to create a range of bio-degradable products, including their revolutionary Ooho! flexible packaging biomaterial that can hold beverages and sauces [170]. Such biomaterials have the potential to replace single-use plastics, which can be detrimental to the environment following incorrect disposal or loss; the company are also in the process of patenting their in-house methodology for the encapsulation of liquid products into a cross-linked matrix for packaging applications [171]. Ulvan, extracted from *Ulva* spp., has also been trialled as a 'smart' biofilm for eco-friendly food packaging applications [172–174], however, further research is required to understand which factors (including concentration and plasticiser type) affect the properties of smart packaging films. The global market for biobased plastics was estimated to be 2.11 m tons in 2018 and is expected to increase to 2.62 m tons by 2023 [175]. Bioplastics such as polylactic acid (PLA), polyhydroxyalkanoates (PHAs) starch plastics, cellulose plastics and protein plastics, which are already commercialised and in circulation, have been the major driving force for this increase [176] and have already overcome the sustainability and waste disposal issues associated with traditional petro-chemically derived polymer plastics. Nonetheless, it is evident that hydrocolloidal polysaccharides are emerging as promising precursor candidates to aid the development of next generation bioplastics. Macroalgal polysaccharide based bioplastics have the potential to replace current bioplastics [177] particularly since not all bioplastics, such as PLA, form a closed loop cycle from 'cradle to cradle' and can decompose in all environments [178]; PLA is only compostable and not marine biodegradable unlike PHAs and hence could possibly leak into the environment [179].

Macroalgal biofuels are an additional bioproduct that have been attained from biorefinery processes, regardless of the fact that macroalgae were initially regarded as a viable feedstock solely for biofuels production. With the realisation that macroalgal biofuels production alone is not entirely economically viable and their full commercialisation is yet to be realised [95,180], their production as a secondary or tertiary product from within a biorefinery process has become more recognised. Bioethanol, biobutanol, biomethane and biodiesel are the main types of biofuels that are generally produced from macroalgae, with additional biofuels such as bio-oil, biogas and other forms of hydrocarbon derivatives being less common though continuing in research [49,181]. Liquid biofuels, which include bioethanol, biobutanol and biodiesel, are globally the fastest growing bioenergy sector, as an increase in government incentives attempt to incorporate such biofuels into the transportation sector in order to replace petrol and diesel [182]. In particular, bioethanol has been considered one of the most important biofuels [183]. Although a tremendous amount of research has been devoted to macroalgal bioethanol production, one of the main hindrances affecting its commercialisation is the difficulty of converting macroalgal polysaccharides and monosaccharides into bioethanol with traditional fermenting yeast and/or bacterial strains [184]. Significant research efforts have been made to generate robust strains via metabolic and bioengineering strategies that utilise the inherent macroalgal monosaccharides and yield bioethanol [185–188]. Nonetheless, a handful of putative biorefinery processes generate a cellulosic-rich residue (post the initial recovery of alternative bioproducts) which can then be hydrolysed to glucose and subsequently fermented with greater feasibility into bioethanol using conventional yeast strains [126,128,134]. As the likelihood of generating higher yields of bioethanol from cellulose-rich waste-streams appear more promising, researchers may attempt to optimise this processing stream further particularly as the production of liquid biofuels is expected to increase to 6–8% per year by 2050 [189] and alternative sources for achieving this target are necessary. Alternative biofuels, such as biomethane [127,128] and bio-oil [135] have additionally been explored as potential bio-fuel options from macroalgal biorefinery process waste streams, opening novel research avenues for further exploration and potential commercialisation into the energy sector.

Biochemical products such as succinic acid, lactic acid, citric acid,

pyruvate, polyhydroxyalkanoates (PHA), chemical building blocks such as bio-butanol and isobutanol, replacement fossil-fuel derived chemicals including 2,3-Butanediol and 1,2-Propanediol, and even natural products such as pigments [190,191], have been at the forefront of research with their targeted production from feedstock materials. This is associated with the fact that they comply with the U.S DoE's building block chemicals list with the specific aim to potentially overcome petro-chemically derived products. Research has shown that macroalgal biomass have successfully been utilised as feedstock to produce such desired biochemicals and biomaterials. These include the production of citric acid from *Gelidiella acerosa* [192], succinic acid from *L. digitata* [193], *S. latissima* [194] and *Palmaria palmata* [195], lactic acid from *Laminaria japonica* [196] and *Gelidium amansii* [197], 2,3-Butanediol from *L. japonica* [198], 1,2-Propanediol from *U. lactuca* [199] and poly-3-hydroxybutyrate from *Laminaria* sp [200]. A handful of the aforementioned biocompounds and bioproducts already have established industrial markets, with biobased levulinic acid and PHA maintaining the highest prices both valued at USD6500 per ton [201], and it is expected that other biobased products are due to also increase in the near future as long as the bioconversion technologies prove successful. Nevertheless, biobased products and biocompounds will still need to compete with the price of petro-chemically derived compounds, despite the fact that biobased products are highly likely to replace fossil-fuel derive products in the near future [202].

## 7. Macroalgal funded research and intellectual property

It is clear that recent research is enhancing the potential applications of macroalgae and the commercial viability of macroalgal biorefineries. Nonetheless, further research and developmental funding is required to ensure fruition of putative biorefinery processes into industrial reality. Although interest in macroalgae for bioenergy started to develop in the 1970s, primarily as a potential source of biofuel [95], a surge in funded research projects related to macroalgal biofuels was seen from 2010 onwards, including a number of pilot projects that focussed on the technical aspects of biofuel production from macroalgae, and also food additives and chemicals [182]. These included projects such as The SeaGas Project, MacroFuels, MacroBioCrude, and GlobalSeaweed, which have now concluded. Nonetheless, there is still a significant amount of interest, on a global scale, to continue macroalgae research and Table 3 lists the diversity of current research projects reported in the English language that are funded with a worth of  $\geq$  £/USD 100,000.

As detailed in Table 3, the majority of projects are supported by government funds, such as the U.S. Department of Energy, UK Research and Innovation, the Australian Government (Department of Industry, Science, Energy and Resources), the New Zealand ministry, and the EC who have a key role in implementing EU policies. A significant number of projects funded by the U.S. Department of Energy focus on the development of cultivation systems and off-shore farms, whereas the majority of UK, European, Australian and New Zealand government funded projects focus on end product generation driven with the potential for downstream by-product commercialisation. The fact that all aspects of the macroalgal biorefinery production process, which includes cultivation, harvesting, post-harvesting processing, product recovery/generation and application, and trials of macroalgal bioproducts, are being funded will enhance research knowledge and help elucidate the realisation of macroalgal biorefineries. This is encouraging, not only because it will enable any biological and engineering challenges to be addressed, but also because issues associated with bioprocessing technologies will be highlighted as well as the sustainability and environmental issues, and bottlenecks that may impact policy and legislation.

A useful indicator to further understand the success and developmental growth of the macroalgal biotechnology sector, is the number of patents that have either been applied for, and/or granted, in the field. Patent documents, particularly granted applications, provide useful

evidence of innovation, novelty, global technological development and economic benefit, regardless of the fact of whether the invention is necessarily an effective use of the resource material [203]. Fig. 7 shows the number of patent documents obtained across all the different biotechnological industrial applications related to macroalgae and seaweed.

Patents related to the food industry dominated the search, with almost 7500 patents registered, and documents associated with processing and health followed with just under 5000 documents each. This is not surprising, particularly since the links between macroalgae serving as a nutritious food ingredient and the health benefits of macroalgal extracts have been previously established through the publication of numerous research articles [204,205]. Marine aquaculture and agriculture is additionally an expanding area of research, with a significant amount of research focussing on the scalability of macroalgal cultivation and the important need for integrated multi-trophic aquaculture. Further, with the ever-increasing demand and realisation of macroalgal products and biotechnology, an increase in knowledge is required in order overcome key hindrances and challenges that are associated with macroalgal aquaculture. Even so, less than 1000 patent documents were returned for this particular search, suggesting a lower number of applications being filed compared to other industrial markets which highlights the difficulties associated with novel and innovative developments in this sector. Interestingly, the macroalgal biofuel market search only returned 40 patent documents. While biofuel production from macroalgae has been an area of research focus for a number of years, the handful of patent documents that were returned in the search uncover the fact that commercialisation of this market is relatively slow. This is mainly due to the fact that the biotechnologies and infrastructure being applied to macroalgae are most likely still not optimal for upscaling, and biofuel production as a sole process lacks viability.

A total of seven patent documents that describe bioprocesses which have yielded a number of different industrially relevant bioproducts are listed in Table 4. These include renewable and platform chemicals such as fermentation sugars, sugar acids, sugar alcohols (US9688595B2), HMF, levulinic acid and formic acid (US9452993B2), biofuels including bio-methane, bio-butanol, bio-oil (US9688595B2) and bioethanol (CN101024847, US2013005009A1), and agricultural feed and bio-fertiliser (US2013005009A1, CN101024847, US1000579B2). One patent in particular describes a process for the recovery of a range of diverse, industrially attractive bioproducts, which include the hydro-colloid agar, lipids, pigments and agricultural feed from the red seaweed *Gracilaria corticata* (US1000579B2).

The fact that only seven documents were returned could be due to a number of different factors and may not necessarily be related to a lack of research advancements in the field. It is evident from Section 5 that numerous research articles detailing the development of novel biorefinery type processes, utilising macroalgae as feedstock and yielding a plethora of desirable bioproducts and biochemicals have been published. This may be due to academics preferring to publish their findings in academic journals to disseminate and enhance the knowledge in the scientific community. Patenting is also a time consuming and costly process and there is the possibility of the patent application not being successful and the even more complicated prospect of not being able to patent the entire bioprocess, but only part of it, depending on its novelty and inventiveness. This is evident in patent US8167959B2, where the document describes the invention of a bioprocess using the kelp *Macrosystis pyrifera*, which has the potential to generate bioproducts with applications that include energy-saving lubricants and lubricant additives, biofuels, biochemicals, oil remediation dispersants and sorbents, non-toxic health applications, nutraceuticals, cosmeceuticals and pharmaceutical products/ingredients, and horticultural and aquacultural feed or supplements. The broadest legal definition of the invention in the patent, however, is only directed to the algal synthetic lubricant and its associated environmentally friendly methodology of production, and does not include the other bioprocess streams and products detailed

**Table 3**Diversity of funded English-language macroalgal research projects that are currently on-going, worth  $\geq$  £/D100,000.

Name of Project	Recipient/s	Funders	Country	Amount	Project Term	Description
Autonomous tow vessels	C. A. Goudey and Associates	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD909,901	April 06, 2018–April 05, 2021	Development of an autonomous marine tow vessel to enable the deployment of large-scale seaweed farming systems.
Ocean energy from macroalgae	Fearless Fund	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD496,483	July 02, 2018–September 30, 2020	Novel system design and development to enable large scale macroalgae 'ranching' using remote sensing, imaging and modelling technologies.
Performance and impact of macroalgae farming	Macai Ocean Engineering	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD995,978	May 21, 2018–November 20, 2020	Development of tools to stimulate the biological performance of offshore macroalgal systems.
Biofuels from kelp	Marine Bioenergy	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD2,623,787	June 06, 2016–December 31, 2020	Development of an open ocean cultivation system for kelp biomass (with the University of Southern California and Wrigley Institute for Environmental Studies). Biomass will then be converted to bio-crude (in collaboration with researchers at Pacific Northwest National Laboratory).
Techniques for tropical cultivation	The Marine Biological Laboratory	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD7,515,793	May 01, 2018–April 30, 2023	Cultivation system design and development for <i>Eucheuma isiforme</i> , for biofuels production.
Single point mooring array for macroalgae	Ocean Era (formally known as Kampachi Farms)	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD4,249,547	May 10, 2018–April 16, 2023	Design and development deep seawater nutrients delivery to a macroalgae production farm concept, suitable for deployment in tropical and subtropical deep ocean environments.
Continuous, high-yield kelp production	Trophic/Otherlab/The University of New Hampshire	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD5,202,016	March 16, 2018–December 04, 2022	A rugged and resilient offshore sea farm with high yield and low capital cost will be developed.
Scalable coastal and offshore macroalgal farming	The University of Alaska Fairbanks	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD3,132,133	April 11, 2018–March 01, 2023	Replicable model farms capable of cost-effective production of sugar kelp along the Alaskan coastline will be developed.
Macroalgae cultivation modelling system	The University of California, Irvine	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD1,815,529	May 11, 2018–May 10, 2021	Computational modelling project that integrates an open-source regional ocean model with a fine-scale hydrodynamic model that is capable of simulating forces and nutrient flows in various seaweed farming systems.
Scalable aquaculture monitoring system	The University of California, Santa Barbara	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD2,003,893	May 01, 2018–April 30, 2021	Development of a system-level solution to continuously monitor all stages of seaweed biomass production, providing farm managers with farm data products to monitor farm status from outplant to harvest.
Modelling tool for ocean-deployed farms	The University of New England	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD1,323,867	February 06, 2018–February 05, 2022	A high-resolution, 3D computational modelling tool for simulating hydrodynamic forces on macroalgae cultivation and harvest system will be developed, to help inform decisions about farm structure and the requirement of significant capital investment.
Genome-wide seaweed studies			USA	USD5,151,250		

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Table 3 (continued)

Name of Project	Recipient/s	Funders	Country	Amount	Project Term	Description
	The University of Wisconsin-Milwaukee	Advanced Research Projects Agency-Energy U.S. Department of Energy			March 15, 2018–March 31, 2022	Development a breeding program and to enable the development of macroalgae varieties that consistently produce high yields under farmed conditions.
Seaweed hatchery and selective breeding technologies	The Woods Hole Oceanographic Institution	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD3,704,276	June 15, 2018–June 14, 2021	A selective breeding program for sugar kelp, <i>Saccharina latissima</i> , will be developed with the aim to improve productivity and cost effectiveness of seaweed farming
Monitoring macroalgae using acoustics and UUV	The Woods Hole Oceanographic Institution	Advanced Research Projects Agency-Energy U.S. Department of Energy	USA	USD2,056,621	February 08, 2018–August 07, 2021	An autonomous unmanned underwater vehicle (UUV) system for monitoring large-scale seaweed farms for extended periods will be developed, as a cost-efficient alternative to costly human labour and boat operations.
Teleconnected SARGassum risks across the Atlantic: building capacity for TRansformational Adaption in the Caribbean and West Africa (SARTRAC)	University of Southampton (lead research organisation)	<sup>a</sup> UKRI <sup>b</sup> ESRC	UK	£876,346 (USD1,210,263)	Nov 2019–Oct 2022	Project seeks to gain an understanding for the reasons behind the inundation of <i>Sargassum</i> seaweed on the beaches of the Caribbean, Central America and West Africa.
GCRF GlobalSeaweed <sup>d</sup> - Safeguarding the future of seaweed aquaculture in developing countries	Scottish Association for Marine Science (lead research organisation)	UKRI <sup>c</sup> BBSRC ESRC <sup>d</sup> NERC	UK	£5,419,058 (USD7,483,903)	Oct 2012–Dec 2021	Vision of this programme is to grow the research and innovation capability of developing countries that are engaged in seaweed farming.
SeaGas: Production of bio-methane from seaweed by Anaerobic Digestion (AD)	Queen's University of Belfast (lead research organisation)	UKRI BBSRC <sup>e</sup> EPSRC	UK	£534,373 (USD737,987)	July 2015–Oct 2020	Project investigating the replacement of grass silage in anaerobic digestion with seaweed.
Oceanium: Seaweed-based compostable, marine safe bio-packaging	Oceanium Ltd	UKRI Innovate UK	UK	£99,756 (USD137,766)	Aug 2019–Oct 2020	Project focuses on developing innovative, circular life-cycle bio-packaging derived from sustainable sources seaweed to replace single use fossil-fuel based plastics to meet the growing consumer, government and corporate demand for sustainable packaging.
Development of the automated Ooho! Machine – reducing single use plastic packaging for <100 mL liquids, condiments and cosmetics through seaweed alginate membrane	Skipping Rocks Lab Limited (lead participant) Lucozade Ribena Suntory Limited, Vita Mojo International Ltd (participants)	UKRI Innovate UK	UK	£343,734 (USD474,708)	Feb 2019–Mar 2020	The inventors have developed a unique, patented, natural membrane packaging derived and manufactured from seaweed alginate (Ooho!). This project will enable the developers to create an automated machine to produce Oohos at scale (3000 per day, compared to the 100 per day that are currently manufactured using a semi-manual machine).
SeaBest (SME-Instrument)	Seaweed Energy Solutions AS	European Commission (Horizon 2020)	Norway	€1,660,881 (USD1,963,892) (EC contribution)	Mar 2019–Feb 2021	The project will launch the first large-scale organic seaweed-to-food cultivation and processing in the EU, allowing 1000–14,000 tonnes of seaweed to be produced in Europe at up to 56% less cost compared to current practices.
GENetic diversity exploitation for Innovative macro-ALGal biorefinery (GENIALG)	Centre National de la Recherche Scientifique CNRS	European Commission (Horizon 2020)	France	€10,885,817 (USD12,871,825) (EC contribution) €12,224,237 (USD14,454,426) (total budget)	Jan 2017–Dec 2020	Project consists of a consortium of 19 partners from 6 different countries (including Seaweed Energy Solutions AS). The project aims to boost the Blue Biotechnology Economy by increasing the production and sustainable exploitation of two

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Table 3 (continued)

Name of Project	Recipient/s	Funders	Country	Amount	Project Term	Description
Algae based climate feed additive for methane reduction in dairy cows - Climate Feed	Danish Technological Institute (Project manager)	Innovation Fund Denmark	Denmark	17 M DKK (USD1,908,018)	2019–2023	high yielding EU species of seaweed: <i>Saccharina latissima</i> and <i>Ulva</i> spp. Develop suitable methods for cultivating, harvesting and processing/drying seaweed into finished goods, which farms can easily supplement in their feed to cattle. The project collaborators include Aarhus University, University of Waikato (New Zealand), and companies Vilofoss, DLG, Ocean Rainforest, Dansk Tang, DryingMate, Naturmælk, and SEGES.
University of Exeter GCRF Global Research Translation Award: Sustainable solutions to food security challenges.	The University of Exeter	UKRI <sup>f</sup> GCRF Newton Fund Innovate UK	UK	£621,951 (USD858,159)	Oct 2019–Mar 2021	Strategic priority project: Removal and industrial conversion of Mexico's problematic seaweed bloom biomass into high quality, low cost sustainable agricultural fertiliser products, through the development of a novel hydrothermal processing technique.
Marine Bioproducts and Biotechnology Corporative Research Centre (Bid in progress)	Flinders University	Australian Government, Department of Industry, Science, Energy and Resources Cooperative Research Centres program	Australia	n.a	n.a	Flinders University leading bid to establish a Marine Bioproducts and Biotechnology Corporative Research Centre with focus on identification and bioproduct development from marine resources such as seaweeds and microalgae.
Expanding Marine Biotech Production & Refinery Facility to meet demand	Venus Shell Systems Pty Ltd	Australian Government, Business Regional Jobs and Investment Package	Australia	AUSD600,000 (USD449,586) (total grant amount) AUSD1,326,569 (USD994,011) (total project value)	2019–2022	Expansion of Marine Biotech production and a refinery facility to meet the increasing demand for a range of seaweed products.
Seaweed solutions for sustainable aquaculture	Tassal Group Limited Deakin University University of Tasmania Spring Bay Seafoods Pty Ltd	Australian Government, Department of Industry, Science, Energy and Resources Cooperative Research Centres program	Australia	AUSD2,385,067 (USD1,787,154) (total grant amount) AUSD5,468,110 (USD4,097,309) (total project value)	Jan 2019–Jan 2022	Collaborative project to develop a sustainable Integrated Multi-Trophic Aquaculture (IMTA) model that supports commercial seaweed production.
Seaweed production as a nutrient offset for Moreton Bay	University of the Sunshine Coast (USC)	Fisheries Research and Development Corporation	Australia	AUSD370,000 (USD277,244)	2019	This project, in collaboration with Queensland Urban Utilities, will evaluate the nutrient offset and sequestration potential of target seaweeds in Moreton Bay, a 1500 km <sup>2</sup> urbanised estuary, to determine the seaweed farming capacity for Moreton Bay.
Turning a pest seaweed into a high-value agricultural product	Waikaitu Ltd	New Zealand Ministry of Primary Industry's (MPI) Sustainable Food and Fibre Futures programme	New Zealand	NZD75,000 (USD52,584)	June 2019–Dec 2020	Transformation of the costly mussel-industry pest seaweed species <i>Undaria pinnatifida</i> into a sustainable, high-value agricultural product for the global market.
A cattle feed supplement to reduce greenhouse gas emissions	Cawthron Institute	New Zealand Ministry of Primary Industry's (MPI) Sustainable Food and Fibre Futures programme	New Zealand	NZD100,000 (USD70,112)	Oct 2019–Oct 2020	<i>Asparagopsis armata</i> will be investigated in trials to evaluate the potential of lowering greenhouse gas emissions from cattle and livestock, and trial the production systems that are required to grow the seaweed as a feed supplement at pilot-scale.
Mussel with fucoidan as supplemented superfood –	Auckland University of Technology	New Zealand Ministry of Business, Innovation and	New Zealand	NZD803,000 (USD563,003)	2020–2022	Project aims to develop a new Greenshell™ mussel <i>Perna canaliculus</i> as a New Zealand

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Table 3 (continued)

Name of Project	Recipient/s	Funders	Country	Amount	Project Term	Description
product development and clinical benefits		Employment High-Value Nutrition National Science Challenge				superfood that is supplemented with fucoidan extracted from <i>Undaria pinnatifida</i> .
Realising the value of algae as a source of alternative protein	Cawthron Institute	New Zealand Ministry of Business, Innovation and Employment Catalyst: Strategic – New Zealand – Singapore Future Foods Research Programme	New Zealand	NZD3,000,000 (USD2,103,375)	Oct 2020–Dec 2023	In collaboration with Riddet Institute, University of Auckland, Plant and Food Research, Singapore's Agency for Science, Technology and Research, Singapore Institute of Food and Biotechnology Innovation and Bioprocessing Technology Institute, and industry partners Wakatu Incorporation and Te Runanga o Ngai Tahu, the project seeks to investigate how the red seaweed Karengo and the microalga <i>Chlorella</i> could become everyday alternative sources of protein.

<sup>a</sup> UK Research and Innovation.

<sup>b</sup> Economic and Social Research Council.

<sup>c</sup> Biotechnology and Biological Sciences Research Council.

<sup>d</sup> Natural Environment Research Council.

<sup>e</sup> Engineering and Physical Sciences Research Council.

<sup>f</sup> Global Challenges Research Fund.

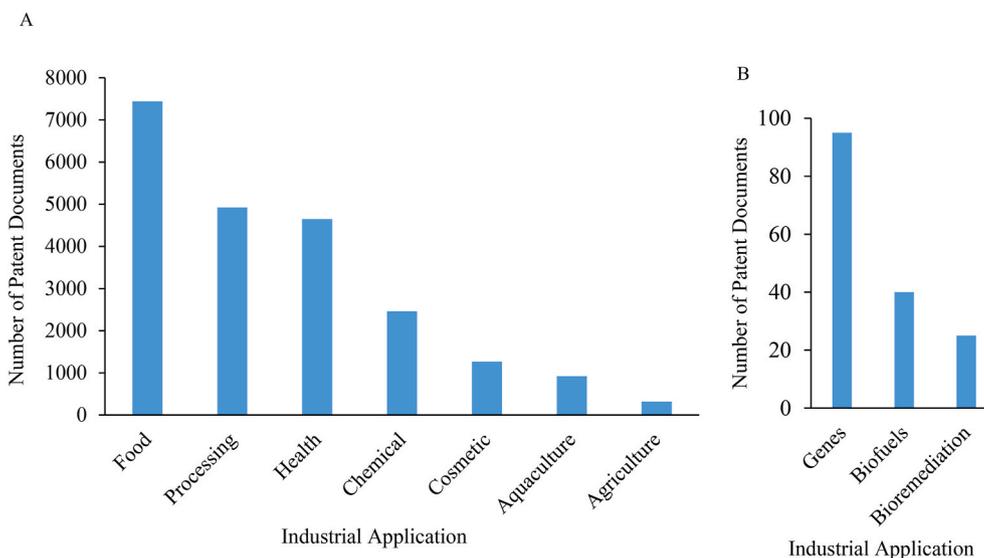


Fig. 7. Number of patent documents recorded per biotechnological industrial application identified until July 2021 using [www.epo.org/searching-for-patents/technical/espacenet.html](http://www.epo.org/searching-for-patents/technical/espacenet.html) (Accessed 07/07/2021).

in the patent document's title and description.

Further, published research is automatically non-patentable due to public disclosure and as such, manuscripts can only be submitted for peer review after the patent application has been filed (which requires time and money). This appeared to be the case for the biorefinery process developed by Trivedi et al. [115]; a patent application was filed in 2013 (US10000579B2) and the work was subsequently published in 2016 [115]. In the current climate where one of the main assessment criteria for academic success is the output of publications, it may be possible that academics are facing with the difficult choice of either publishing research, or patenting various or entire aspects of their work.

## 8. Challenges and future perspectives

Macroalgae have been recognised as one of the most sustainable and attractive feedstocks for a transition into a blue bioeconomy, with prospects for biobased products and biofuels expanding into multiple industrial markets and sectors. Issues associated with the use of lignocellulosic feedstocks can be overcome, such as the use of large areas of agricultural land for cultivation and the requirements of lignin degradation or removal. This has enabled researchers to explore the potential of macroalgae and their incorporation into biorefinery type processes, highlighted by numerous publications and patents (seen in Sections 6 and 7). Despite this wealth of research, the growth of industrial biorefinery processes utilising macroalgae as feedstock is, and may continue to be, somewhat limited by an apparent lack of fundamental

**Table 4**

Patent documents registered specifically for biorefinery processes utilising macroalgae. Identified using [www.epo.org/searching-for-patents/technical/espacenet.html](http://www.epo.org/searching-for-patents/technical/espacenet.html) (Accessed 07/07/2021).

Patent Number <sup>a</sup>	Title	Year of first application	Status <sup>b</sup>	Description	Applicants	Country
US8167959B2	Environmentally-friendly kelp-based energy saving lubricants, biofuels, and other industrial products	2009	Granted in the US and still in force.	Invention relates to a natural algal synthetic lubricant derived from an environmentally-friendly method for harvesting kelp ( <i>Macrocystis pyrifera</i> ) and its subsequent processing.	Copp Emmanuel Anthony [US], Glantz Dale [US], Knocean Sciences, Inc.	US
US9452993B2	Process for improved seaweed biomass conversion for fuel intermediates, agricultural nutrients and fresh water	2012	Granted in the US and Australia, still in application stage in Japan and India.	An integrated step-wise process for the production of 5-hydroxymethylfurfural (HMF), levulinic acid and formic acid from $\kappa$ -carrageenan extracted from <i>Kappaphycus alvarezii</i> .	Council of Scientific & Industrial Research	India
NL2019949B1	Improved biorefinery of brown macroalgae	2017	Granted in the Netherlands, still in application stage in Australia, Canada and the US.	An improved cost-efficient and durable process for biorefinery of brown macroalgae ( <i>Laminaria</i> , <i>Saccharina</i> , <i>Sargassum</i> , <i>Macrocystis</i> , <i>Nereocystis</i> , <i>Lessonia</i> , <i>Alaria</i> , <i>Ascophyllum</i> and/or <i>Fucus</i> ) which comprises of an initial solvent-induced dehydration step.	TNO; Netherlands Organisation for Applied Scientific Research	Netherlands
US9688595B2	Process of production of renewable chemicals and biofuels from seaweeds.	2011	Granted in China and the US, still in application stage in Europe.	A process for production of one or more renewable chemicals (fermentable sugars, sugar acids, sugar alcohols) or biofuels (methane, butanol, bio-oils and green crude) from seaweed ( <i>Kappaphycus</i> , <i>Ulva</i> , <i>Enteromorpha</i> , <i>Sargassum</i> , <i>Macrocystis</i> ).	SEA6 Energy Private Ltd. Balendiran Sowmyalashmi, Kumar Sawan, Kumar, Sayash, Nori Sri Sailaja, Suryanarayan Shrikumar, Vadassery Nelson	India
US1000579B2	An integrated process to recover a spectrum of bioproducts from fresh seaweeds.	2013	Granted in Australia, Spain and the US.	An integrated process for the complete utilisation of fresh seaweed biomass ( <i>Gracilaria</i> , <i>Gelidiella</i> , <i>Gellidium</i> , <i>Kappaphycus</i> , <i>Sarconema</i> ) to recover agar, cellulose, lipids, pigments and a liquid rich in minerals of agricultural importance.	Council of Scientific & Industrial Research	India
CN101024847	Method for producing alcohol and feed by utilising seaweed chemical waste material	2007	Granted in China.	A method for producing bioethanol and feed from seaweed chemical waste (kelp, <i>Sargassum</i> , macroalgae, <i>Ascophyllum nodosum</i> , wakame, Hijiki and ropeweed).	Shandong University	China
US2013005009A1	Process for integrated production of ethanol and seaweed sap from <i>Kappaphycus alvarezii</i>	2009	Granted in China, Europe, Japan and the US.	A process for production of bioethanol and seaweed biofertilizer from fresh seaweed <i>Kappaphycus alvarezii</i> .	Brahmbhatt Harshad Ramanbhai, Council of Scientific & Industrial Research, Eswaran K, Ghosh Pushpito, Kumar, Gnanasekaran G, Jha Bhavanath, Mody Kalpana Hareesh, Sana Barindra, Shah Bharatiben Gunavantray, Shukla Atindra Dinkerray, Thampy Sreekumaran	India

<sup>a</sup> Patent number presented may be just one document or multiple documents that are filed in various countries covering similar or the same technical content.

<sup>b</sup> Status as of July 2021.

understanding that needs addressing to enable the successful commercialisation of their design and development. This section identifies and discusses what the authors believe to be key issues and challenges associated with macroalgal biorefineries (summarised in Table 5) that ought to be addressed, and the future directions required to fully exploit the potential of macroalgal biorefineries.

**Macroalgae cultivation and supply.** Problems related to macroalgal cultivation and harvesting, the availability of an annual feedstock supply chain, species selectivity and suitability, and the effective hydrolysis and conversion/utilisation of the unique polysaccharides inherent to macroalgae by conventional microorganisms [19,32] are hindrances which have been recognised by researchers and have previously been reported as factors restricting the commercialisation of macroalgal bio-refineries. Nonetheless, there is continued research to address these challenges.

**Bioprocess scalability and integration.** One major obstacle that could impede the development of macroalgal biorefineries, and requires

further research, is the scalability of the biotechnologies that have been employed. At present, the vast majority of research has been conducted on laboratory-scale equipment and it is not clear how scalable some of these technologies will be. Furthermore, biorefineries that aim to generate more than two bioproducts will require the full integration of each particular unit operation [206] on a significantly larger scale, which to date, has not been trialled. Bioprocess efficiencies and bioproduct yields will also need to be re-evaluated to monitor losses which may arise due to the increase in scale.

**Water utilisation and energy demand.** Another significant issue that may prohibit the advancement of macroalgal biorefineries, are the necessary but extremely costly removal of water; washing; and drying steps that take place post-harvesting. A significant amount of research has been conducted on thoroughly washed biomass, typically using fresh or deionized water to remove salts, epiphytes and sand [207]. The removal of salt from the feedstock is also a vital requirement to prevent any corrosive damage inside bioreactors and the bioprocess

**Table 5**  
Challenges and issues associated with future macroalgal biorefineries.

Stage in biorefinery process	Potential challenges, issues and solutions
Upstream process Cultivation	<ul style="list-style-type: none"> <li>- Regulations and licensing of aquaculture are still relatively complex and vary according to country and international waters.</li> <li>- Seasonality issues may affect biochemical composition and thus bioproduct potential.</li> <li>- Biomass quantities could be variable per season, which would therefore affect TEA of the overall process.</li> <li>- Scalability of cultivation and mass macroalgal farming requires further R&amp;D and ought to be embedded within an IMTA approach.</li> <li>- Public engagement/acceptance of seaweed farms (and biorefineries) in local coastal communities are needed to avoid public opposition. Early communication and transparency on responsible innovation aspects are essential to increase public acceptance.</li> <li>- Shortage of skilled individuals with knowledge and practical experience may slow cultivation development. Further collaborations between research organisations (who have predominant knowledge of cultivation technologies) and commercial or governmental research entities needed, and the establishment of training programs would strengthen macroalgal cultivation techniques to drive the industry.</li> </ul>
Harvesting	<ul style="list-style-type: none"> <li>- Manual labour costs for harvesting of macroalgae vary according to country and could be relatively costly. Novel approaches to automated harvesting may alleviate manual labour and overheads.</li> </ul>
Post-harvesting processing	<ul style="list-style-type: none"> <li>- Storage of harvested macroalgae associated difficulties and transportation issues/costs exist at present. Location of future biorefinery plants may have to be within close proximity to cultivation and harvesting/farming site.</li> <li>- Dewatering of macroalgal biomass and the removal of salt are necessary pre-processing steps to aid subsequent bioprocessing, transportation and for mass-balance calculation purposes but are energy-intensive and costly. Macroalgal processing may have to be performed on wet biomass, or biorefinery plant may have to be on-site or close to macroalgal farm.</li> </ul>
Biotechnology conversion process	<ul style="list-style-type: none"> <li>- Estimation of individual product value difficult and hence choice of product mix within integrated whole biorefinery subject to uncertainty and risk.</li> <li>- Biocompatibility of bioprocesses and technologies need to be understood and tailored towards each species of macroalgae, and ensure utilisation of all biochemical fractions. Insights into how variable processing parameters influence the overall bioprocess and bioproduct formation are also required.</li> <li>- Bioprocessing technologies currently function as unit operations. Further research is required to fully integrate each unit of operation for multiple applications within a biorefinery such as biofuels and bioproducts.</li> <li>- Several successful biotechnology processes developed for macroalgae have been demonstrated at laboratory scale, yet their potential for scalability is often overlooked. The reliability and efficiency of the processes for commercialisation need investigating.</li> <li>- Sustainability features of macroalgal biorefineries need further investigation with multiple and advanced environmental assessment tools such as emergy/LCA/ and exergy-based methods.</li> </ul>
Downstream process	<ul style="list-style-type: none"> <li>- Separation technologies suitable for each bio-product require development, selectivity, and efficiency.</li> <li>- Product purity and impurity profiles need to consistently meet regulatory requirements of end use applications.</li> <li>- Bio-product types and yields may vary according to macroalgal species initially used as feedstock and biochemical composition. The seasonal growth and availability of different macroalgal species ought to be</li> </ul>

**Table 5 (continued)**

Stage in biorefinery process	Potential challenges, issues and solutions
	considered for biorefinery processes, and the range of bio-products and biofuels that can be obtained per annum.

infrastructure itself, as well as potential effects on downstream chemical and biological processes such as pretreatments and microbial fermentations [137]. Furthermore, subsequent stages within a bioprocess all require fresh water thus ultimately increasing the water footprint of any given biorefinery, which is particularly concerning since global freshwater sources are limited [208]. For example, in the specific case of bioethanol production alone, the water footprint ranges from around 1.5 to 10 L of water for each litre of bioethanol produced [209]. In light of this, researchers have started to investigate ways of incorporating seawater, or salt water, into bioprocesses, and have shown the feasibility of utilising seawater in both the hydrolysis and fractionation of macroalgae [210,211], and fermentation into bioethanol [210,212,213]. It should be noted, however, that although these studies have highlighted the technical ability of employing seawater in a specifically distinct process, the application of the sole use of seawater within an entire macroalgal biorefinery process, which consists of combined unit operations, is still yet to be achieved. Further research is required to evaluate whether each unit operation in a biorefinery can be interlinked with seawater, and what impacts this may have on the overall bioprocess, range of bioproducts, bioproduct yield and purity, and their applications. Nonetheless, the potential for an entirely salt-based macroalgal biorefinery is starting to become promising.

**Overall biorefinery process design and environmental sustainability.** An understanding of the optimal, holistic and integrated bioprocessing pathways for each species of macroalgae, that can be cultivated sustainably at scale off-shore, is required along with the range of potential bioproducts and biofuels that can be generated. Such information will be vital for the future of the bioeconomy in terms of sustainability and economic benefit. Each bioprocessing pathway ought to be logged in a central database that is available globally along with the plethora of potential bioproducts, as this will enable the macroalgal industry to continue to prosper. Although this may appear to be overly optimistic, it is entirely feasible with strong collaborative links between academia and industries, and multidisciplinary groups consisting of bioscientists, marine biologists, cultivation specialists, engineers and social scientists. Such collaborations are key to the pursuit of this field. With optimal bioprocessing routes identified and logged, it is additionally important that the sustainability features of each seaweed specific bioprocess are accurately assessed using different advanced environmental assessment tools. These include LCA, exergy and emergy-based models that will help to advance the seaweed industry, and recommend the excellent article published by Rosen [214] where these assessment tools are explained in greater detail for the reader.

**Adaptability to specific geographic and regulatory constraints.** Challenges will include, for example, the need to overcome significant differences in each countries' regulations and licensing of macroalgal farms for species that have potential for off-shore cultivation, the temperament of native species of macroalgae belonging to the waters of each country, and the differences and affordability of bioprocessing technologies tailored for each species. Additionally, it is recognised that the range of bioproducts may differ according to country, as biorefineries will utilise species that are native to each country's coastal waters. This could potentially have an impact on the bioeconomy of each country, or coastal region, as the biochemical constituents of macroalgae, which essentially dictate the range of potential bioproducts that can be produced, differ according to taxonomical group. Furthermore, there may also be the challenge of obtaining planning permission to build a biorefinery at a coastal area, with laws differing between

countries.

**Resilience to environmental change.** There is a possibility that the bioeconomy infrastructure of an individual country may also dramatically change in future decades, due to the influences of global warming. Studies have demonstrated potential changes in the geographical distribution and abundance of macroalgae in different coastal environments as a result of rising temperatures due to climate change [215–219]. Macroalgal distribution shifts will inevitably affect established macroalgal biorefineries, their sites, jobs, and the overall prosperity of the bioeconomy. It is vital, therefore, that species distribution studies continue to model and project how macroalgal species of commercial interest continue to change in response to climate change. Sustained research and development of novel macroalgal biorefineries will be a necessary requirement in the decades to come, as farming sites may eventually face depleted feedstock sources, or new species invasions due to distribution shifts.

**Public/local community acceptance and economic impact.** Although the development of large-scale biorefineries at coastal sites (and off-shore macroalgae cultivation systems which ideally ought to be in close geographical proximity), will undoubtedly provide societal benefits, including job creation, energy security and economic development through employment [220], there may be opposition from the public and local community. To ensure the social acceptance of biorefineries, responsible innovation approaches need to be considered and implemented in order to gain public acceptance. This could be achieved by educating coastal communities of the biotechnologies and benefits before the biorefinery is introduced. Delivery through open and inclusive focus group meetings and/or workshops could serve as a platform to engage academics, funders, stakeholders and the public.

## 9. Conclusions

Macroalgae have shown, and will continue to display, a remarkable potential for their incorporation within the landscape of future biorefineries. Research studies have highlighted promising biochemical processing routes, utilising a range of different species of macroalgae belonging to the three taxonomical groups, for the generation of biofuels, bioproducts and high value biochemicals. The increasing interest and applications of macroalgal intellectual property, along with the number of funded research projects across the entire macroalgal biorefinery pathway, underpins global awareness of their exciting prospective to contribute towards the bioeconomy and serve as a sustainable renewable feedstock. However, it is clear that macroalgal biorefineries are still in their infancy and the associated biotechnologies, which show promise, are yet to proceed beyond the laboratory to industrial scale. Nevertheless, macroalgal bioproducts and biofuels have the aptitude to influence the progression of government policy and regulations development, which would enable countries to continue to establish bioeconomic strategies and drive the urgent necessity of avoiding the use of finite non-renewable sources. This would ultimately require successful scale up of efficient macroalgal biorefinery processes, yet with effective transfer of knowledge and transparency between academia, industry, stakeholders, government and the public, the commercialisation of such biorefineries will eventually become a reality.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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