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Current Opinion in Biotechnology

Cascaded valorization of seaweed using microbial cell factories

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Sustainable production from seaweed has grown into an area of intense research and development. Meanwhile, more than 30 million tonnes of seaweed are produced, of which 70% are used as food and 30% have other applications such as feed, fertilizer, chemicals, and energy. Towards biorefining seaweed in an environmentally friendly and economically viable manner, we need efficient approaches that convert its biomass and residuals into added value products. Smart cell factories and fermentation strategies which can be integrated into future seaweed biorefineries are at the heart of the development and therefore receive increasing attention. Here, we review advances in the field including novel fermentation routes from seaweed to chemicals, materials, pharmaceuticals, fuels and energy, and discuss challenges and opportunities.

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Introduction

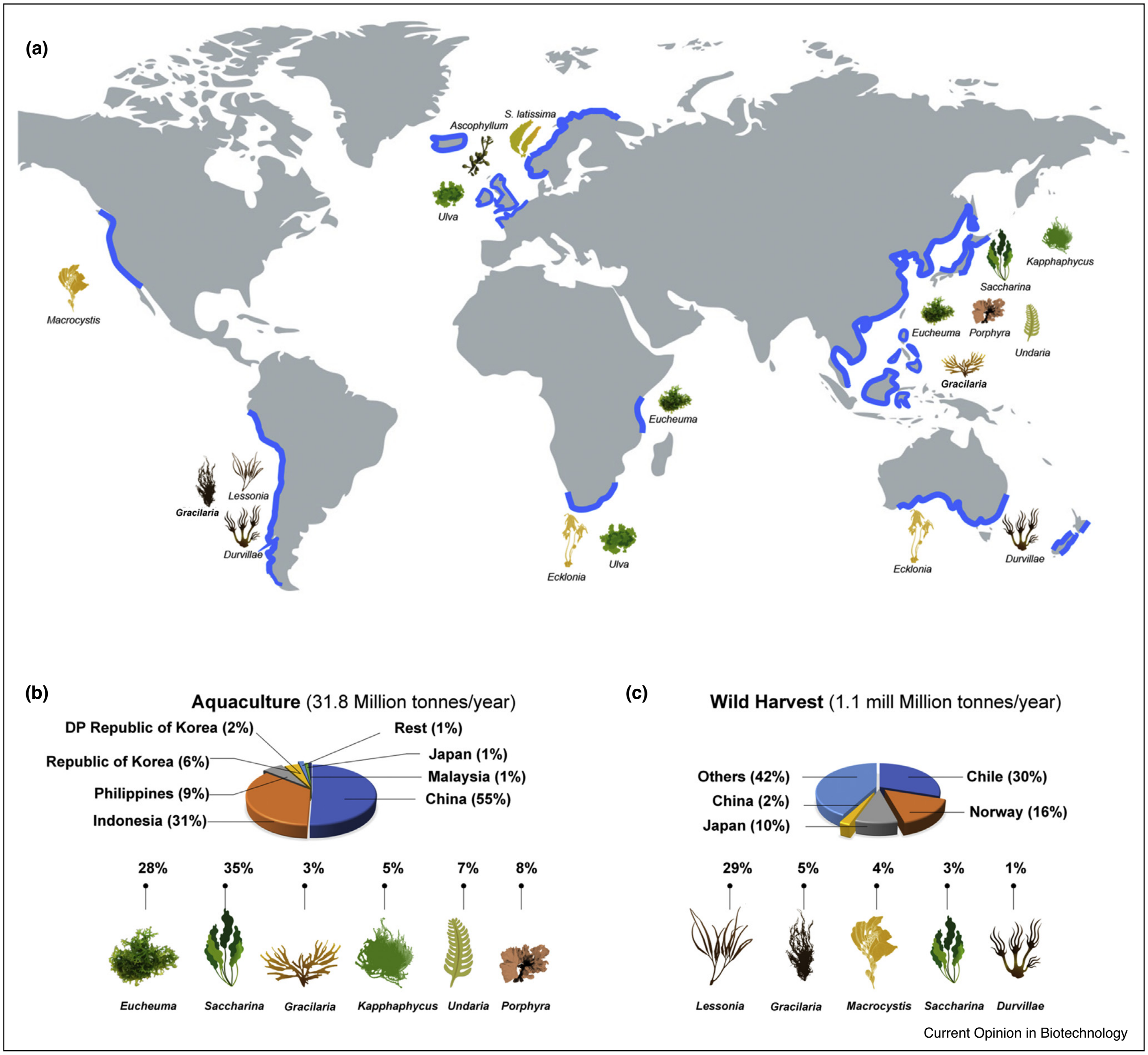
In search for sustainable chemicals, materials and fuels, the eyes of the industry are turning to the sea. Here we find huge amounts of seaweeds, more than 10 000 different plant-like macroalgae that fall into three groups: red (*Rhodophyta*), green (*Chlorophyta*), and brown seaweed (*Ochrophyta*). On a first glance seaweeds may not make a real impression when washed up at the beach, but more and more researchers say that they will become a substantial resource of future green production [1,2]. Humans have been using seaweeds since Neolithic times and countries such as China, Japan and Korea traditionally add them to their diet [3]. Meanwhile seaweed has become much more than a nutritious addition to soups, salads and sushi: 32 million tonnes are produced on an annual basis from aquacultures and cast seaweed. Ingredients such as hydrocolloids display well-established products for food, cosmetics and pharmaceuticals [4,5]. Further momentum is gained by efforts to use seaweed as resource for chemicals, materials, and energy [6] and provides attractive growth perspectives. Forecasts predict production volumes of 500 million tonnes by 2050 [7]. Towards optimal sustainability and economy, research aims at integrated seaweed biorefineries. Yet to be secured at full commercial scale, this development needs efforts from various disciplines, including viable fermentation routes that valorize seaweed biorefinery streams.

The global seaweed markets

As a resource, seaweeds offer striking properties, including fast and most efficient photosynthetic growth. Kelps (large brown seaweeds) are the fastest linearly growing organisms on Earth. They expand up to 60 cm per day, reach 50 m in length [8••] and form underwater forests and beds that cover 25% of the world's coast lines [9]. Furthermore, seaweeds have important advantages in terms of sustainability: production does not depend on arable land, fertilizers, pesticides, and freshwater and needs minimal intervention [2]. Moreover, most seaweeds produce multiple crops per year in the same space and can be farmed all year long, which offers twofold to eightfold higher yields per hectare as compared to corn and soybean [10]. Finally, seaweeds are amazing ecosystem builders: they shelter hundreds of species of marine life, reduce atmospheric greenhouse carbon and thus mitigate global warming, deoxygenation and ocean acidification [11].

Seaweed production has grown into an industry of substantial value. In 2017, aquaculture provided 32 million metric tons with a value of almost 12 billion US$ (Figure 1) [12]. Most seaweed is used as food (70%) and other applications account for 30% including hydrocolloids (carrageenan, alginate, agar), feed, fertilizers, and chemicals. Asian nations produce more than 99% of the world market with China (17.5 million tonnes) and Indonesia (9.7 million tonnes) as the largest producers [12]. Most of the world's countries and territories with coasts are yet to begin seaweed farming [13]. The most important commercial crops are *Saccharina*, *Eucheuma*, *Gracilaria* and *Porphyra* (Table 1). *Porphyra* (Nori) and *Saccharina* (kombu) are sold for food purposes at US$ 16,000 and US$ 8000 per dry tonne, respectively [14]. Cast seaweed annually provides 1 million tonnes of *Lessonia*

Figure 1



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Commercial seaweed markets worldwide.
The coastal areas for aquaculture farming and harvesting of wild seaweeds are highlighted in blue, whereby Asian countries produce 99% of all seaweed **(a)**. Aquaculture farming meanwhile accounts to 32 million tonnes of seaweed with a few dominant crops **(b)**. Harvesting of wild seaweeds provides 1 million tonnes per year and covers a wider spectrum of species depending on natural abundance **(c)**.

(29%), *Gracilaria* (5%) and other species and is led by Chile, China and Norway [3,15,16]. The seaweed markets have strongly grown over the past decades. Given that calculated annual growth rates (CAGR) of approximately 8–12% will hold, they might exceed US$ 40 billion in 2030.

In addition to being farmed, seaweed species such as *Ulva* and *Sargassum* naturally grow into gigantic floating mats on the open sea, which are washed as green and golden tides up the coasts [17]. At present, more than 20 million tonnes of *Sargassum* form an 8850-km-long belt between West Africa, the Caribbean Sea and the Gulf of Mexico [18]. This recently increasing phenomenon is likely caused by climate change and increasing eutrophication. Beached seaweeds cover hundreds of kilometers of coast, turn into rotting piles with severe effects on ecosystems, tourism and aquaculture economy [19], and display a significant waste, almost 200 000 tons per year along the coastline of Korea alone [20]. Its

Table 1

Commercial seaweed market in 2017 [12]

Species	Location	Production (Wet tonnes)	Industrial application	Harvesting
Laminaria japonica	China, Japan, Korea Rep, Korea DP Rep	11 200 000	Alginate, mannitol, iodine	8 months
Eucheuma spp.	Indonesia, Philippines, Zanzibar China, Tanzania, Kiribati, Cambodia, Timor-Leste	8 840 000	Carrageenan	10–12 weeks
Gracilaria spp.	China, Indonesia, Chile, Philippines, Vietnam, Namibia	4 310 000	Agar	30–45 days
Porphyra spp. *Porphyra tenera*	China, Korea Rep, Japan, Korea DP Rep	2 560 000	Food (Nori)	10 days to 5 months
Undaria pinnatifida	China, Korea Rep, Japan	2 340 000	Food (Wakame)	Yearly
Kappaphycus alvarezii	Philippines, Malaysia, Sri Lanka, Vietnam, India, Papa New Guinea, Zanzibar, Solomon Islands	1 550 000	Carrageenan	10–12 weeks

disposal causes huge costs (estimated to be US$ 10–150 per tonne), creating opportunities for seaweed bioconversion.

Second-generation extraction of valuable ingredients

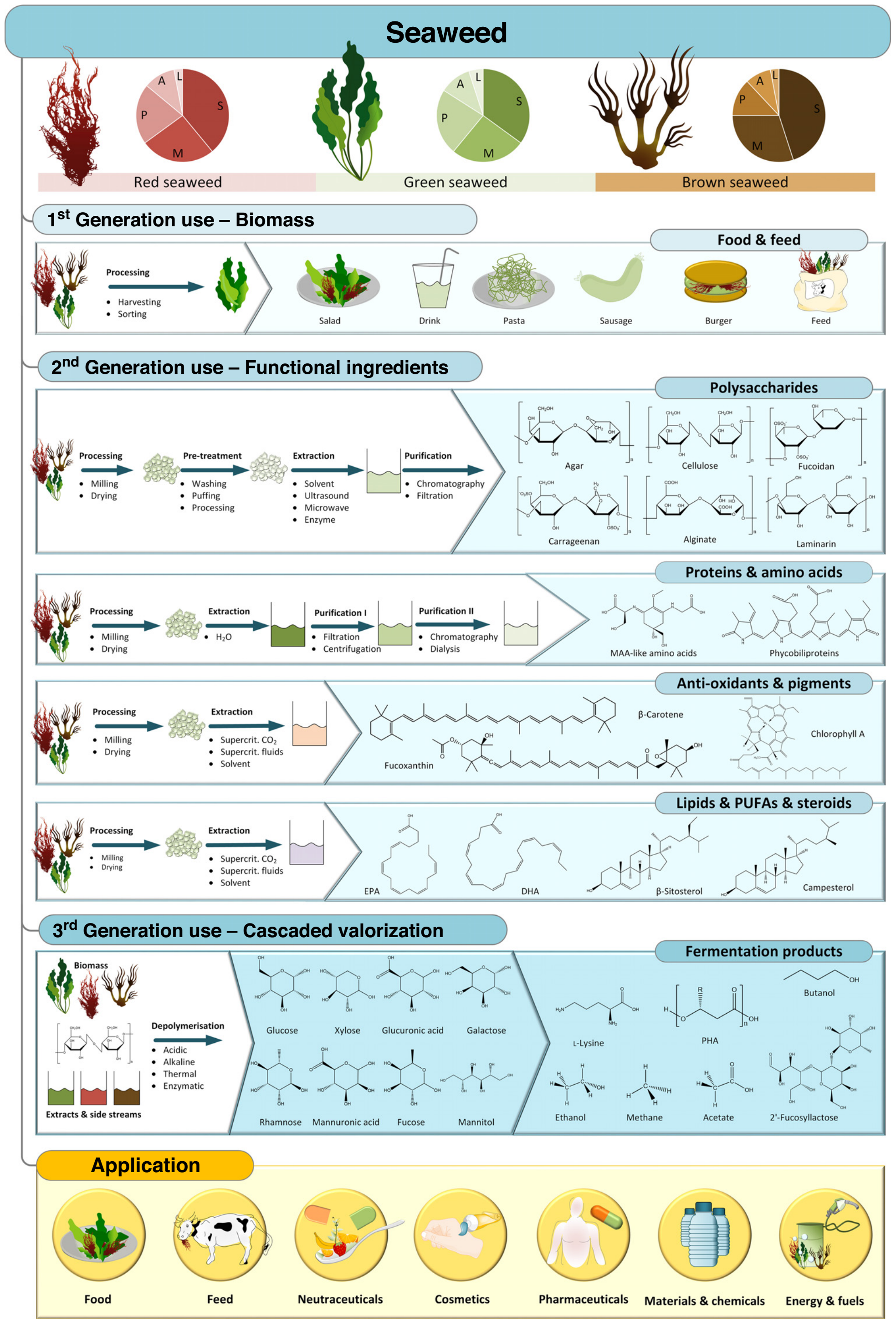
Seaweeds are multicellular species with varying pigmentation and morphology, but a common basic structure. They comprise a holdfast, a (partly branched) stipe, and one or more leaf-like blades (Figure 2). Some applications use only the blade, leaving the rest as a waste [21]. The major seaweed constituents are sugars, minerals, proteins, lipids, and small metabolites, whereby species and their parts vary in composition (Figures 2, 3) [2,22]. Seaweed biomass is gaining more and more attention in human nutrition, such as gluten-free pasta [23]. Feed related research has high hopes to reduce climate gas emission in livestock production, due to findings that already a 1% inclusion of red seaweed (*Asparagopsis*) in the diet of dairy cattle reduces their methane production up to 67% [24].

In addition, individual seaweed components have recognized industrial value. Polysaccharides, for example, carrageenan, alginate, agar, fucoidan and laminarin display premium products with regard to abundance (Figure 2) and commercial impact [25]. The sugar polymers are usually extracted from dried, ground biomass by solvent extraction [26], partly supported by ultrasound [27], microwave [28,29] and enzyme [30] treatment, and purified by chromatography or membrane filtration (Figure 2) [26]. Given their functional properties as dietary fibers, gelling agents, and active ingredients, they are used as food supplements, pharmaceuticals, and cosmetic ingredients. As example, carrageenan is a well-known thickener, stabilizer, emulsifier and fat supplement. Oligo-carrageenan and oligo-agarose have anti-inflammatory, antimicrobial and antiviral activity and promote plant growth [4]. Extraction of seaweed further provides phycobili-proteins, mycosporine-like amino acids [5,31] and carotenoids with coloring, antioxidant and UV-protecting activity [32] (Figure 2). Finally yet important, seaweed contains essential omega-3 polyunsaturated fatty acids [4], (Figure 2) which entail various health benefits [33]. For recovery, dried and crushed biomass is extracted with solvents, assisted by microwave treatment [34], supercritical fluid extraction [34] or supercritical CO_2 extraction [35]. Mannitol, a free sugar alcohol (contained up to 30% in seaweed) is easily extracted by hot water (Figure 2) [1] and used as a low calorie sweetener and pharmaceutical ingredient [36].

Seaweed as a feedstock for third generation biorefineries

Seaweed biomass largely consists of sugars, sugar alcohols and sugar acids, up to 70% and more [37]. Most of them are present as polysaccharides, whereas others occur as free monomers (Figure 3). Likewise, side streams obtained after seaweed extraction contain high sugar levels. At present, the fermentative use of (extracted) seaweed is underexploited. Challenges revolve around (i) the seasonal and species-to-species variation in carbohydrate content, (ii) the recalcitrance of several of the seaweed polysaccharides, and (iii) the crude mixtures of seaweed sugars, which differ substantially from that of terrestrial crops. The fermentable sugars are mainly bound in polymers and thus not available for most microbes, although pioneering studies have demonstrated the possibility to directly ferment seaweed polymers into fuels and poly(3-hydroxybutyrate) [38–40]. Beneficially, seaweed contains no or only little amounts of lignin [22] so that hydrolysis conditions are milder as compared to lignocellulosic biomass [41–43]. Acidic hydrolysis yields up to more than 90% of the carbohydrate fraction as monosugars [37]. Moreover, enzymes can be used for depolymerization. Research in this area continuously discovers novel enzymes, which specifically act on individual polysaccharides or catalyze the breakdown of a broader spectrum [44]. Some enzymes have been commercialized as mixes with complementing activity [45]. Recent findings identified glycoside hydrolase [46], laminarinase [47], cellulase [47] and β-glucanase [48] to catalyze the breakdown of laminarin into glucose and mannitol. For the depolymerization of alginate, more than 100 types of

Figure 2



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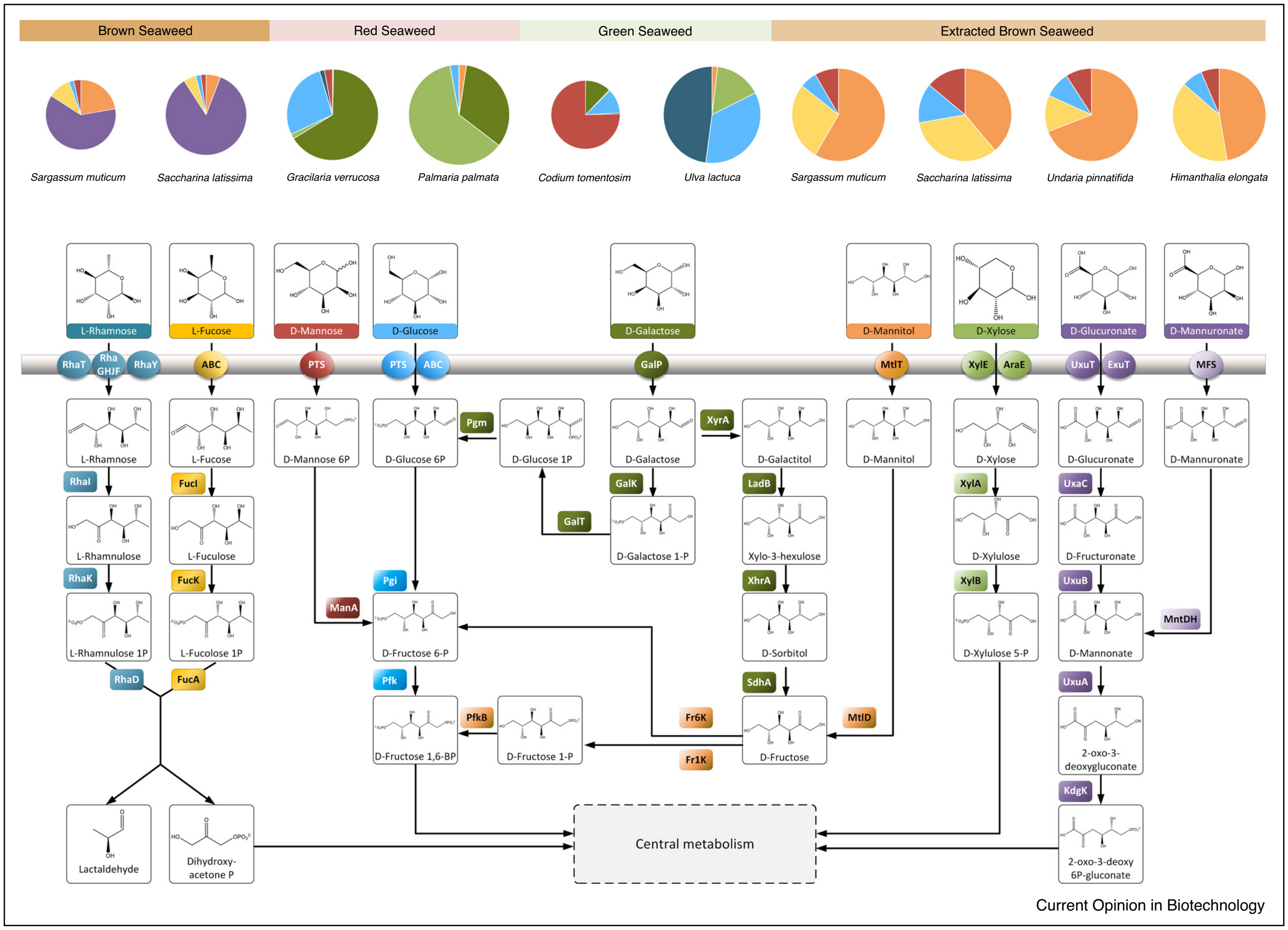
Cascaded valorization of seaweed.
The three major groups of seaweed (red, brown and green) are rich in nutritive value, functional constituents and fermentable carbon. In addition to the first-generation use of seaweed as food and feed, the second-generation use employs extraction strategies to derive naturally abundant active ingredients and functional materials. The third-generation use envisions advanced biorefinery concepts, which fractionate and valorize the biomass through multi-step cascades for maximum utilization and minimum waste production. Data on composition of seaweed was taken from Ref. [2].

Figure 3



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Microbial pathways for utilization of the complex and unique mixtures of seaweed sugar.
Natural seaweeds (red, brown and green) and (extracted) fractions and streams from seaweed refineries contain different sugars, sugar alcohols, sugar acids and further derivatives, whereby the composition can largely differ (data from Ref. [110]). Microbes have catabolic pathways for the breakdown of these monomers, which can be naturally and metabolically engineered towards seaweed-based call factories.

alginate lyases are reported [49], which include endo-type (producing oligosaccharides), and exo-type lyases (producing monomers). Similarly, carrageenolytic enzymes [50] have been reported.

Utilization of seaweed sugars by natural and engineered microbes

Seaweed hydrolysis produces a complex sugar mixture (Figures 2, 3). The mixture varies in content and composition depending on the hydrolysis method, the employed seaweed, and eventual upstream treatment (Figure 3). Ultra-high pure fucose (>99.9%), an industrially useful rare sugar, is obtained from hydrolyzed seaweed using simulated moving bed chromatography [51•], leaving the residual sugars as a waste. Preferably, the sugars have to be entirely used. The good news is that microbial pathways have been described for degradation of all relevant monosaccharides (Figure 3), including the more uncommon ones. Natural microbes degrade fucose [52], mannitol [53•], and hexuronates [54] and were recently employed to produce bio-ethanol from hydrolyzed seaweed, including strains of *Pichia* [55••] and thermophilic clostridia [47,48].

Substantial interest lies on using well-established microbial workhorses such as *Escherichia coli* [56–58], *Corynebacteirum glutamicum* [59–61] and *Saccharomyces cerevisiae* [57,62], given their global acceptance and performance in industrial biotechnology [63]. *E. coli* is a Swiss army knife in using seaweed sugars. In addition to glucose, the microbe naturally uses galactose, mannitol, xylose, fucose, rhamnose, and glucuronate [52,64–66], whereas the utilization of some of the substrates appears inefficient, leaving space for improvement [67]. *C. glutamicum* is naturally less flexible

[59,68], but catabolic pathways could be successfully reconstituted in the bacterium to use mannitol [8••], glucuronate [69], galactose [70] and xylose [71,72]. Likewise, *S. cerevisiae* naturally utilizes only a small selection of the seaweed sugars [66], but has meanwhile been engineered to degrade xylose [73], alginate and its hexuronic acid constituents [74–76], and its natural mannitol pathway was activated [75].

In addition, progress has been made to orchestrate the co-utilization of sugar mixtures towards shorter fermentation times. Interesting concepts have used co-cultures. Following pioneering studies in using yeast communities for butanol production from seaweed [74], co-cultures of *E. coli* and *S. cerevisiae* converted a complex sugar mixture into ethanol and achieved a final titer of 46 $g L^{-1}$ [77•]. Adaptive laboratory evolution (ALE) of a community of *S. cerevisiae* and *Pichia angophorae* enabled the complete conversion of glucose, mannitol and galactose from waste seaweed into 13 $g L^{-1}$ ethanol [78]. Moreover, novel isolates start to reveal useful properties. As example, the Antarctic isolate *Pseudomonas* MPC6 exhibits an unusual capability to catabolize xylose, arabinose and mannitol and is found tolerant to osmotic stress [79•], suggesting further exploration [80]. Regarding the high salt content of seaweed sugar hydrolysates, (*E. coli* and *S. cerevisiae* are known to be sensitive to NaCl concentrations above 1%) recent reports describe the use of ALE to obtain salt-tolerant biocatalysts [81,82].

Fermentative biofuels from seaweed

Given its high sustainability and easy processability, seaweed is regarded as major source for third generation biofuels [22,83,84]. Full commercialization of algal biofuels is yet to be realized [85], but gets more and more in reach with progressing developments [22,83,84]. Attention is given to achieve high-yield conversion processes. While glucose is a beneficial substrate for most yeasts, mannitol is not. Fortunately, strains of *Pichia stipidis* and *P. angophorae* naturally utilize mannitol [55••]. After adaptation to higher mannitol levels, *P. angophorae* converted all mannitol from a hydrolysate of *Ascophyllum nodosum* into 13.6 $g L^{-1}$ ethanol at a yield of 0.5 $g g^{-1}$ [55••]. Another study recently reports biofuel production from seaweed using thermophilic clostridia [53•]. Species from the genus *Thermoanaerobacter* performed equally well on pure mannitol and on mannitol extracts and reached up to 88% of the theoretical maximum ethanol yield. *Clostridium beijerinckii* DSM-6422 was found capable to convert a *Laminaria digitata* hydrolysate into a mixture of acetone, butanol and ethanol [86]. The microbe also consumed traces of alginate monomers in the hydrolysate. The yield for butanol (the energy richest of the products) was exceptionally high, that is, 0.42 $g g^{-1}$. An interesting study used beached waste seaweed as a raw material for butanol [20]. Following enzymatic digestion, a two-stage fermentation with *C. tyrobutyricum* and *C. acetobutylicum* yielded acetone, butanol and ethanol at a titer of 12.5 $g L^{-1}$ and a yield of 0.37 $g g^{-1}$. This approach could help to handle seaweed waste massively washed-up the world's coasts.

Fermentative bio-methane from seaweed

Marine crops hold a gigantic energy potential (100 $EJ yr^{-1}$) almost fivefold higher than that of the land-based biomass, which explains the interest in marine biogas [87]. Given costs fluctuating seasonal composition and technical hurdles, economic biogas production appears most feasible as end part of a seaweed biorefinery [88]. However, even pre-extracted seaweed residues compete with terrestrial crops in theoretical methane yield [6], which provides promising proof-of-value. Still, digestion of seaweed into biogas is challenging: some algae are rich in sulfur and nitrogen, which causes inhibiting levels of hydrogen sulfide and ammonia and poses corrosion problems to technical equipment [89]. However, as concluded by the authors the attractive energy yields per area and the beneficial sustainability measures make seaweed-based bio-methane an attractive area.

Fermentative L-lactate from seaweed

For L-lactate production, *E. coli* was equipped with an L-lactate dehydrogenase instead of its native D-lactate specific enzyme [90]. Towards high selectivity, competing pathways to other typical fermentation by-products [91] were disrupted. Beneficially, cells generated excess ATP from a seaweed hydrolysate, containing glucose and mannitol. It could be concluded that L-lactate production from the algae was comparable to that from lignocellulosic biomass [90].

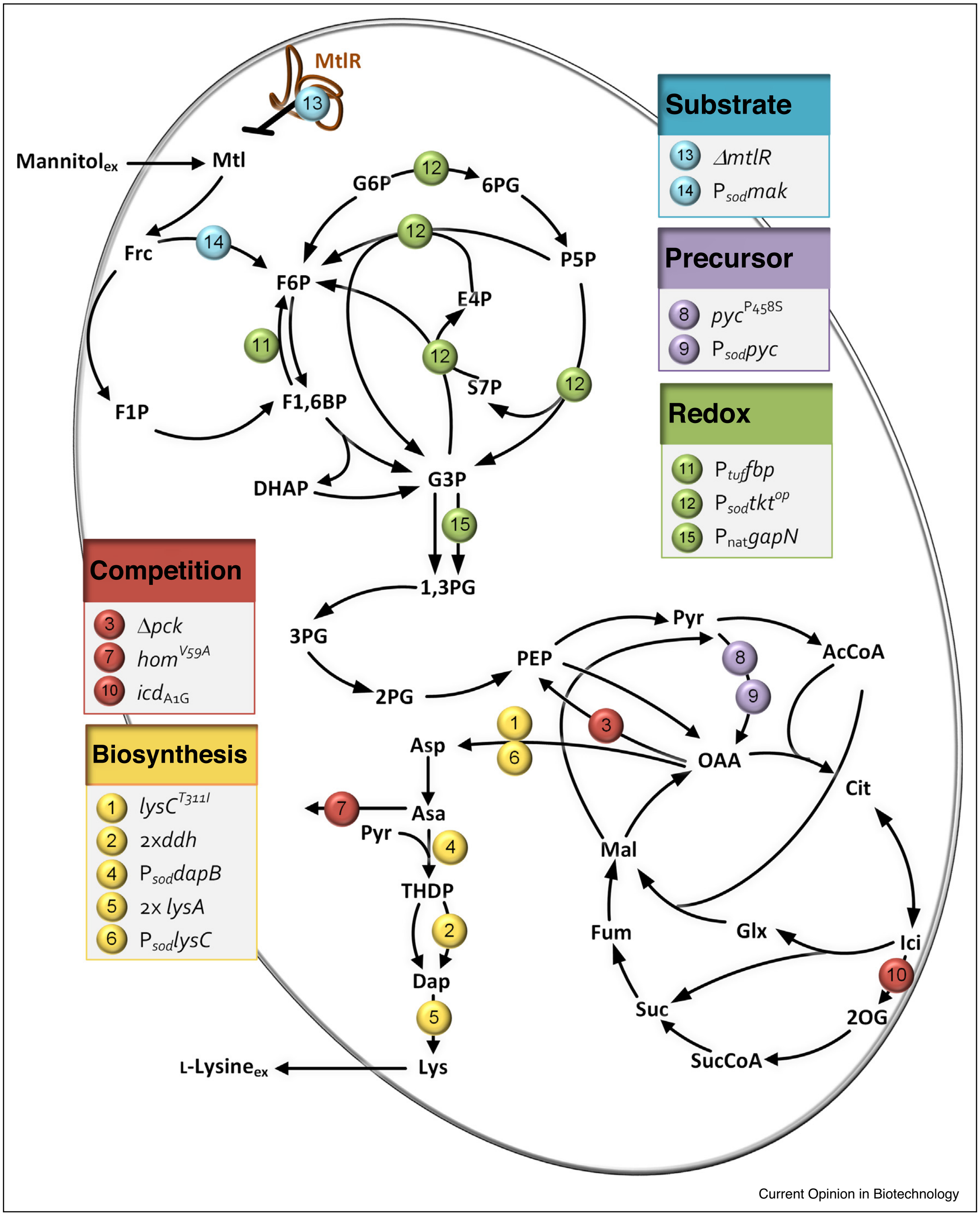
Fermentative L-lysine from mannitol

An interesting product to be made from seaweed is L-lysine, presently produced from first generation feedstocks and used as a feed additive in livestock production. Seaweed itself is deficient in L-lysine so that it cannot help as a direct feed supplement [92]. In a recent seminal study, the L-lysine-producer *C. glutamicum* LYS-12 [93] was upgraded to produce L-lysine from mannitol (Figure 4) [8••]. Following engineering of mannitol catabolism, metabolic flux analysis identified a limiting supply of redox power (NADPH) as major bottleneck in *C. glutamicum*. In subsequent rounds of systems metabolic engineering, the NADPH supply was stepwise increased and L-lysine production performance from mannitol could be optimized to the high level of glucose-based strains [93]. The study provides an important proof-of-concept to produce L-lysine from marine macroalgae in the future.

Fermentative 2′-fucosyllactose (2FL) from fucose

Fucose is present in different fucosylated human milk oligosaccharides, high value food supplements. 2FL is a prominent example. Fucose from seaweed [51•] in combination with the microbial salvage pathway (forming the 2FL precursor GDP-fucose from fucose) [94] appears promising

Figure 4



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Systems-wide metabolic engineering of *Corynebacterium glutamicum* SEA-3 for the production of L-lysine from mannitol [8••]. Stepwise improvement was achieved by engineering of the biosynthesis (yellow), carbon precursor supply (purple), NADPH supply (green), competing pathways (red) and substrate assimilation (turquois). *dapB*: dihydrodipicolinate reductase; *ddh*: diaminopimelate dehydrogenase; *fbp*: fructose 1,6-bisphosphatase; *gapN*: NADP-dependent glyceraldehyde 3-phosphate dehydrogenase from *S. mutans*; hom^{V59A}: homoserine dehydrogenase with amino acid exchange valine → alanine at position 59; icd^{A1G}: isocitrate dehydrogenase with start codon exchange ATG → GTG; *lysA*: diaminopimelate decarboxylase; $lysC^{T311I}$: aspartokinase with amino acid exchange threonine → isoleucine at position 311; *mak*: fructokinase from *E. coli*; *mtlR*: mannitol repressor; *pck*: phosphoenolpyruvate carboxykinase; P*sod*: promoter of the *sod* gene, encoding superoxide dismutase; P*tuf*: promoter of the *tuf* gene, encoding elongation factor tu; pyc^{P458S}: pyruvate carboxylase with amino acid exchange proline → serine at position 458; tkt^{op}: expression unit comprising the genes *tkt* (transketolase), *tal* (transaldolase), *zwf* (glucose 6-phosphate dehydrogenase), and *pgl* (phosphogluconolactonase).

Table 2

Comparison of key performance parameters using seaweed or lignocellulose-based feedstocks for microbial fermentation

	Substrate	Titer [g L^{-1}]	Yield [g g^{-1}]	STY[a] [g L^{-1} h^{-1}]	Ref.
L-lysine					
C. glutamicum	Mannitol	2.0	0.19	0.09	[8••]
C. glutamicum	Xylose	1.8	0.12[b]	0.04	[100]
C. glutamicum	Rice straw hydrolysate	6.9	0.14[b]	0.14	[100]
Lactate					
E. coli	Mannitol	13.6	0.70	0.19	[90]
E. coli	Seaweed hydrolysate	37.7	0.80	0.52	[90]
C. glutamicum	Glucose, Xylose	119	0.88[b]	1.49	[101]
E. coli	Xylose	62	0.89	1.63	[102]
Kluyveromyces marxianus	Corncob residues	103	0.56	1.44	[103]
Ethanol					
S. cerevisiae	Mannitol	20[b]	0.36[b]	0.44[b]	[104]
P. angophorae	Seaweed hydrolysate	16.3	0.50	0.38	[55••]
S. cerevisiae	Seaweed hydrolysate	2.1	0.17[b]	0.02	[74]
S. cerevisiae	Glucose, Xylose	15.5[b]	0.43	0.22[b]	[105]
S. cerevisiae	Lignocellulose hydrolysate	30.0	0.48	1.25	[106]
E. coli	Xylose	23.5	0.48	0.52	[107]
Butanol					
C. beijerinckii	Seaweed hydrolysate	7.2	0.42	0.12	[86]
C. tyrobutyricum *C. acetobutylicum*	Seaweed hydrolysate	7.0	0.21	0.05[b]	[20]
E. coli	Xylose	4.3	0.13[b]	0.03[b]	[108]
C. beijerinckii	Sugar cane bagasse hydrolysate	3.2	0.18	1.23[c]	[109]

[a] STY: space time yield.
[b] estimated from reference.
[c] given in g L^{-1} d^{-1}.

to drive its production. The expression of three heterologous genes recently reconstituted an active salvage pathway in *S. cerevisiae* and enabled 2FL production up to a level of 500 mg L^{-1} [95••].

Conclusion

The operation of seaweed farms that sequester climate carbon and supply sustainable resources is appealing. The seaweed market has evolved from a first generation use of its entire biomass for food and feed, a second generation use of its ingredients as functional materials, into a meanwhile third generation concept of cascaded valorization: biorefineries that make use of all components including residuals. Pioneering examples recently showcased that (extracted) seaweed fermentation can provide fuels and energy [20,84,86], bulk [8••,90] and fine chemicals [94,95••], and polymers [40,80]. Compared to established valorization concepts for lignocellulosic biomass (Table 2), the first steps into seaweed biorefineries are very encouraging. The success stories provide an excellent starting point to develop next-level generation cell factories, designed to efficiently convert the unique mix of seaweed sugars into a portfolio of added value products. Concepts from systems metabolic engineering [91,96–98] promise to drive this multi-purpose upgrade. We have, however, to be aware that we are yet still at the beginning. A global blue economy, where fourth generation integrated seaweed farms (including complementary species such as fish, mussels and electricity generating wind parks) feed the world, would need a massive transition of the seaweed market today. As example, the EU has recently capped first generation biofuels and concluded that “1.25% of future energy consumption in transportation should come from advanced biofuels sourced from seaweed and certain types of waste” [99]. Preliminary estimates revealed that (assuming conversion into biomethane) approximately 170 million tonnes of seaweed and 3 million hectare would be needed to fill this gap [89]. This amount is five to sixfold more than the present world production and would require an area of the size of Belgium, which illustrates the scale of production and challenges ahead. Nevertheless, seaweed biorefining has a great future and novel cell factories and fermentation routes on processing this marine biomass should be intensively studied in the coming years.

Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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