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Microorganism-mediated algal biomass processing for clean products manufacturing: Current status, challenges and future outlook

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ABSTRACT

The global demand for clean products obtained from biobased resources has increased significantly with the rapid growth of the world's population. In this context, microbially-produced compounds are highly attractive for their safety, reliability, being environment friendly and sustainability. Nevertheless, the cost of the carbon sources required for such approaches accounts for greater than 60% of the total expenses, which further limits the scaling up of industries. In recent years, algae have been used in numerous industrial areas because of their rapid growth rate, easy cultivation, ubiquity and survival in harsh conditions. Over the past decade, notable advances have been observed in the extraction of high-value compounds from algae biomass (ABs). However, few studies have investigated ABs as green substrates for microbial conversion into value-added products. This review presents the potential of ABs as the substrates for microbial growth to produce industrially-important products, which sheds light on the importance of the symbiotic relationship between ABs and microbial species. Moreover, the successful algal-bacterial gene transformation paves the way for accommodating green technology advancements. With the escalated need for natural pigments, biosurfactants, natural plastics and biofuels, ABs have been new resources for microbial biosynthesis of these value-added products, resolving the problem of high carbon consumption. In this review, the fermentative routes, process conditions, and accessibility of sugars are discussed, together with the related metabolic pathways and involved genes. To conclude, the full potential of ABs needs to be explored to support microbial green factories, producing novel bioactive compounds to meet global needs.

1. Introduction

Owing to the exponential growth of the global population, the demand for energy, food, pure water, medicines and other essential materials has been increased dramatically [1]. Among these resources, bioproducts have had a boom in the global industry over the past two decades because of their excellent adaptability and durability. Bioproducts are biologically produced from a wide variety of substrates, including various wastes generated from the agriculture sector [2], food industry [3], chemicals industry [4], and pharmaceuticals industry [5]. The increasing awareness and demand for green products are forcing the members of industrial channels to modify marketing strategies for more economical options. Nevertheless, commercialization of the biobased products with reasonable affordability is still at an immature stage.

Being abundant in nature with attractive compositions, algae have received significant interest in various industrial sectors as promising starting materials for producing high-value materials [6]. Algae are attractive feedstocks since they do not require arable land, can remediate the nutrient-rich wastewater [7], maximize biomass usage, have low operating costs, use less energy and produce sustainable biochemicals [8–10]. Also, algae may generate more than 50 times the biomass of switchgrass, the fastest-growing terrestrial plant [8]. The ability to produce algal biomass in wastewater is another good technological capability in the production of algal biomass [11]. Furthermore,

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certain halophilic, halotolerant, and halo-adapted algal species that may be farmed in marine or saltwater have recently been described for sustainable biofuel generation [8]. In spite of these numerous merits, few studies have investigated ABs as affordable microbial feedstock to meet the growing need for bioproducts with lesser cost [9]. It is noteworthy that algae have a wide range of carbohydrate contents with low lignin levels, satisfying multiple microbial synthesis strategies [8]. Thus, the carbohydrate composition of ABs is crucial for their successful use as carbon sources in the development of novel bioproducts within microbial factories [9].

Microbial synthesis is highly advantageous in the industrial implementation of bio-based products. It eliminates the use of heavy metals, organic solvents, and strong acids and bases, allowing the synthetic process to adopt a more ecologically friendly path [12]. Also, microbial enzymes often have a very high substrate selectivity, which aids in the reduction of byproduct generation. Furthermore, microbial metabolic engineering provides an increased yield and productivity of a target compound, whereas combinatorial biosynthesis allows for the production of new compounds derivatives [13].

One of the most critical macromolecules in biotechnological, pharmaceutical and medical applications are multi-functional sulfated polysaccharides (SPSs) [14]. The enhancement of these compounds' productivity usually occurs through "algal-bacterial symbiosis". From another perspective, some Gram-negative bacterial strains such as *Nonlabens ulvanivorans* and *Alteromonas* sp. have shown a profound capability to use green algae in batch and fed-batch fermentation approaches, producing valuable microbial enzymes such as ulvan lyase [15]. Also, numerous microbial strains could ferment AB, producing butyric acid and kainic acid [16,17]. Red seaweed hydrolysates and other seaweeds have been suitable substrates for lactic acid bacteria yielding lactic acid to develop biodegradable polylactic acid materials [18]. In addition, the greenly-developed bioplastic materials, which are only produced by bacterial cells, are contemplated as more promising substitutes of non-biodegradable plastics. The industrialization of the energy or carbon sources needed for such fermentative approaches would address the concern of global plastic waste [9]. On another avenue, the high demands for clean labels, healthy lifestyles, strict legislation, and advanced technology urge replacing the synthetic coloring agent with natural sources. The global market for natural pigments in the food industry alone is expected to reach USD 1.7 billion by 2025 [19]. Microbial pigments have been proved to be safe due to their non-carcinogenic, non-toxic and biodegradable in nature properties. In this intellect, brown algae hydrolysates have served as beneficial fermentation media for cultivating different fungi and microbial species for the biosynthesis of natural colorants using solid-state fermentation (SSF) [20]. Finally, microalgal support produces one of the most important biofuels for future energy security and clean energy like bioethanol [21]. When it comes to using microbial cells as biofuel reservoirs, no extensive land use is needed, ensuring food security in the coming years [22].

This is the first review paper presenting ABs as microbial substrates for the production of various bioproducts rather than extracting such promising compounds from algal seaweeds directly. The main aim of this review is to provide an overview of the AB hydrolysates, juices, and powders as sustainable substrates for the generation of nine industrially valuable products, including sulfated polysaccharides (SPSs), ulvan lyase, butyric acid, kainic acid, lactic acid, polyhydroxyalkanoates (PHAs), biosurfactants, natural colorants, and bioethanol. Microbial utilization of AB simulation media, metabolic pathways, fermentation conditions, and involved genes are discussed. Furthermore, microbial producers of each compound, isolation sites, carbohydrate sources, and productivities are summarized and compared. Finally, the major technoeconomic challenges, potential prospects and future research needs are highlighted.

2. Bio-polymers produced by algal biomass utilization

2.1. Sulfated polysaccharides (SPSs)

SPSs are a broad collection of anionic polymers found in various organisms ranging from algae to mammals but not in soil plants. SPSs are considered as a physiological adaptation of marine organisms such as algae, marine invertebrates, and seagrasses to the high ionic force in the marine environment [23]. SPSs are economically valuable natural compounds generated by marine algae [24]. They play important functions in biology, either as tissue structural components or as signaling molecules in physiological processes [25]. They have been shown to exhibit a variety of potential properties, including anti-cancer, anti-oxidative, anti-radiation, anti-viral, and immunoregulatory properties [26]. As a result, SPSs are widely utilized in the cosmetic, chemical, biopharmaceutical, and nutraceutical industries. SPSs are the key components of the cell walls of seaweeds, including brown (Phaeophyceae), green (Chlorophyta), and red (Rhodophyta) marine macroalgae [27]. Algal SPSs are frequently complex and biosynthesized as heterogeneous combinations, with phylogenetic and environmental influences modulating composition and structure [28].

Several algae-derived SPSs, such as carrageenan (red algae), fucoidan (brown algae), and ulvan (green algae), originate from macroalgae. Complex SPSs consist of different monomers of sugars such as fucose, galactose, rhamnose, and xylose [29,30]. While the commercialization of macroalgal SPSs has been successfully done, little consideration has been paid to SPSs originating from microalgae (Table 1), representing crucial alternatives to the former [31]. This importance is correlated to the high mass productivity of microalgae, their ability to thrive at a wide range of temperatures, easy cultivation procedures, and their contribution to producing numerous valuable products [31]. Generally, SPSs are resulted from a symbiotic relationship between algal species and other organisms [32]. *Porphyridium cruentum* is a red unicellular microalga that can produce huge quantities of SPSs. It secretes SPSs and creates capsules around the cells, protecting them from salinity, UV irradiation, temperature, and pH [33]. Both the *Pseudoalteromonas* MEBiC 03,607 and MEBiC 03,485 bacterial strains were used to produce and examine SPS activity. The strain *Pseudoalteromonas* MEBiC03485 also enhanced *P. cruentum* SPS output and quality. The strains treatment group MEBiC 03,485 exhibited greater SPS production and sulfur content than the control group by 5.92% and 20.0%, respectively. On the other hand, the strain MEBiC 03,607 treatment group, SPS generation, and sulfur content were 0.0841% and 2.87%, respectively, lower than the control group [34]. These findings are intriguing since the biological activity of SPS is directly connected to its sulfur concentration. Many studies have found a link between sulfate concentration, polysaccharide-protein interaction and antioxidant activity [25,35]. This indicates that sulphate levels, antioxidant activity and polysaccharide-protein interactions are directly correlated. As a result, the most critical element determining the positive SPS characteristic is the sulfate (Sulphur) content [35]. However, the microbial symbiotic relationship can improve algal productivity and growth. Han et al. [34] indicated a novel symbiotic relationship between *Pseudoalteromonas* sp. MEBiC 03,485 (psychrophilic, aerobic, Gram-negative marine bacterium) and *P. cruentum*. The bacterial strain MEBiC 03,485 promoted the algal growth, pigment content, SPSs production, and SPSs sulfur content. These improvements were found to be due to several bioactive compounds excreted by MEBiC 03,485 strain, which were proven to improve the SPSs composition, enhancing their biological activity. In addition, these secretions were found to increase the phycocyanin and phycoerythrin (photosynthetic pigments extracted from several algae) content to 161% and 89.4%, respectively [34].

2.2. Polyhydroxyalkanoates (PHAs)

Plastic materials have attracted tremendous interest owing to their

Table 1
Summary on sulfated polysaccharides (SPSs) production by several algal species.

SPSs	Algal Biomass source	Extraction conditions	Product yield	Reference
Xylogalactoarabinans	*Cladophora falklandica* (Green seaweed)	Sequential extraction with alcohol at room temperature (RT) and 90 °C.	Max. 29.2%	[36]
Carrageenan	*Eucheuma cottonii*(Red seaweed)	With KOH at a concentration of 0.4 N	42%	[37]
	Kappaphycus alvarezii(Red seaweed)	With pre-heated potassium hydroxide (6 % KOH) solution for 30 min	69.9 ± 4.8%	[38]
	Eucheuma denticulatum (Red seaweed)	With water at 99 °C for 1.5 h.	35.5 ± 2.12	[39]
	Chondrus crispus(Red seaweed)	With at 85 °C for 30 min, grinding with a homogenizer, kept at 85 °C for 4 h, precipitation of polysaccharides with cold ethanol.	37.4 ± 1.68%	[40]
	Sarcothalia crispate(Red seaweed)	Mechanical stirring with water for 16 h at RT,	20.5 g	[41]
	Gigartina skottsbergii (Red seaweed)	dialyzing and concentrating the supernatant.	15.0 g	
Fucoidan	*Sargassum binderi* Sonder (Brown seaweed)	Extraction with 0.1 N HCl, stirred at RT for 6 h, addition of $CaCl_2$ (2%), centrifugation for 15 min, treatment of filtrate with ethanol (1:2), and dialyzed in 0.5 M NaCl.	18.74%	[42]
	Fucus vesiculosus (Brown seaweed)	Percolation with a 5% ethanol, pH 4, ultrasonic treatment.	10 ± 2%	[43]

diverse properties, such as thermal and high mechanical features, affordable cost and ease of biosynthesis. Researchers have chosen to explore bioplastics as potential alternatives to non-biodegradable plastics in light of environmental issues connected to the widespread usage of plastics [44]. This is due to their biocompatibility, biodegradability, and friendly environmental production methods [45,46]. It was estimated that 4.8–12.7 million tons of plastic wastes enter into the oceans each year from land, with an expected dramatic increase by 2025 if waste management does not improve (Fig. 1) [47]. PHAs have been discovered as potential replacements for non-biodegradable plastics [48]. These biobased plastics are intracellular and biodegradable polyesters produced by bacteria as a means of storing energy when cells are grown in an environment lacking nutrients such as nitrogen and phosphorus (Fig. 2).

However, feed costs for PHAs production as estimated up to 45% of the total production cost have a negative impact on the economy of this bioprocess technology. As a result, researchers are looking for biowastes and affordable stocks to use as feeds for PHAs biosynthesis [49]. The most appropriate method for PHA storage is aerobic dynamic feeding [45]. However, the cost of highly purified substrates has curtailed the industrial production of PHAs using this process [50]. In this context, accumulated pieces of evidence have revealed the significance of using sustainable raw materials as substrates for microbial fermentation to reduce the cost of PHA production as summarized in Table 2, which include waste cooking oil [51], whey [46], wheat bran [52] and defatted *Chlorella* biomass [53]. In the search for promising feedstocks for PHAs production, ABs obtained from marine green, brown and red macroalgae have recently been reported to have potentials for commercial PHA synthesis because of their high carbohydrate content and absence of lignin. These properties of ABs help in recovering fermentable sugars without the requirement of any costly pretreatments. Dilute acid treatment was found promising in converting algal carbohydrates into fermentable sugars among various methods at high temperatures, ranging from 120 to 220 °C [54,55].

Our research team [9] has recently investigated three seaweeds as the prospective alternative feedstocks for PHA production by *Halomonas* sp. through multiple production models to increase the polyester synthesis output. *Corallina mediterranea* hydrolysates were used as C (carbon) and N (nitrogen) sources to determine the highest concentrations of poly (3-hydroxybutyrate) (PHB). After 72 h of incubation, *H. pacifica* ASL10 and *H. salifodiane* ASL11 developed high concentrations of polymer ranges of 2.8 and 3.0 g/L, respectively. While in the case of *Spirulina* sp. and *Pterocladia capillacea* hydrolysates media, the PHB accumulation ranged from 1 to 1.5 g/L [9]. However, strains ASL10 and ASL11 showed a PHA concentration of 3.5 and 3.7 g/L, respectively, after incubation at 37 °C for 72 h in media containing 2% (w/v) sucrose and 0.05% (w/v) $(NH_4)_2SO_4$. The sucrose content and the accumulation of PHA have a positive correlation. Nicotinamide adenine dinucleotide hydride (NADH), Coenzyme A (CoA), and Nicotinamide adenine dinucleotide phosphate (NADPH) effect in cell proliferation and PHA production was considered as the main reason for this correlation. Because of their inhibitory impact on citrate synthase, high quantities of CoA inhibit PHA production, while excessive quantities of NADH decrease cell development. Furthermore, the presence of NADPH generally increases the production of polyester (PHA) [74].

Laminaria japonica (brown algae) biomass was used in the culture of three distinct bacterial strains, including *C. necator* NCIMB 11599, *Paracoccus* sp. LL1, and *B. megaterium* ALA2, as an uncovered carbon source of PHA buildup. The ABs were prepared by acid hydrolysis using various concentrations of HCl or H_2SO_4. Under 2% reducing sugar supplementation, *B. megaterium*, *C. necator* and *Paracoccus* sp. were capable of producing PHA at a rate of 19–32% of their cell dry weight (CDW). PHA accumulation reached the highest level in *C. necator* (1.58 g/L, or 32% of CDW) at 60 h owing to the high consumption of fermentable sugars in *L. japonica* acid hydrolysate. However, PHA content decreased after 60 h to 1.25 g/L [75] due to lack of nutrients forcing bacteria to consume PHA storage for cell growth [76]. Ghosh et al. [55] have utilized C source derived from macroalgae for regulating the synthesis of PHAs from *H. mediterranei*. PHA synthesis was analyzed using hydrolysates from seven different macroalgal biomasses. There was a maximum biomass concentration with the highest PHA content in the medium prepared from *Ulva* sp. (green macroalgae). When *H. mediterranei* was grown in a media model of 25% (w/w) *Ulva* sp. hydrolysate with an initial pH of 7.2 and at 42 °C, the maximum CDW, and PHA concentrations were found to be 3.8 g/L and 2.2 g/L, respectively [55]. Glucose was the most abundant monosaccharide in *Ulva* sp. hydrolysate, followed by rhamnose and galactose [77]. The increased PHA content in the *Ulva* sp. synthetic medium might be attributed to the higher glucose concentration compared to other hydrolysates. The pH value at the end of *Ulva* sp. culture was 5.12, which is relatively low as compared to the beginning value of 6.8. As a result, it was considered that a decline in pH value resulted in adverse growth circumstances, which finally resulted in growth and nutrient uptake inhibition [55].

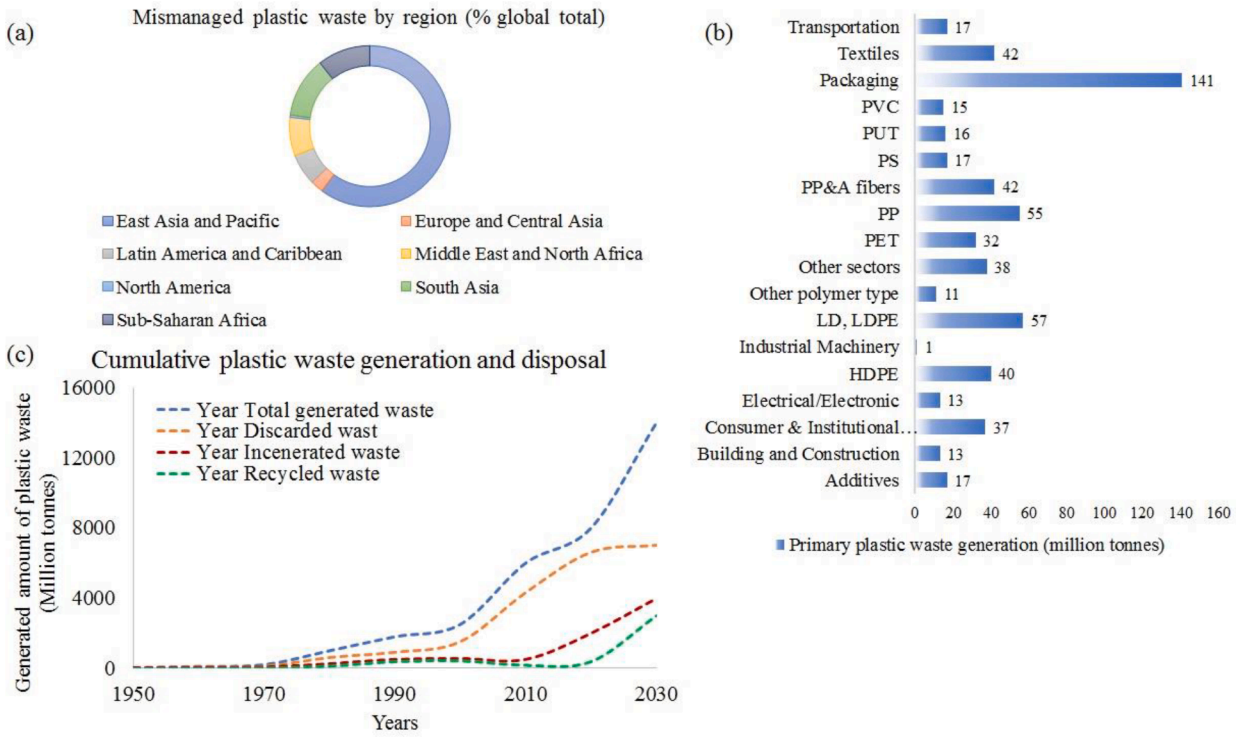

Fig. 1. The dramatic increase of waste accumulation problem illustrates (a) mismanaged plastic waste by region, (b) the amount of produced plastic waste according to the waste source, and (c) the general amount of plastic waste and estimation from 1950 to 2030.

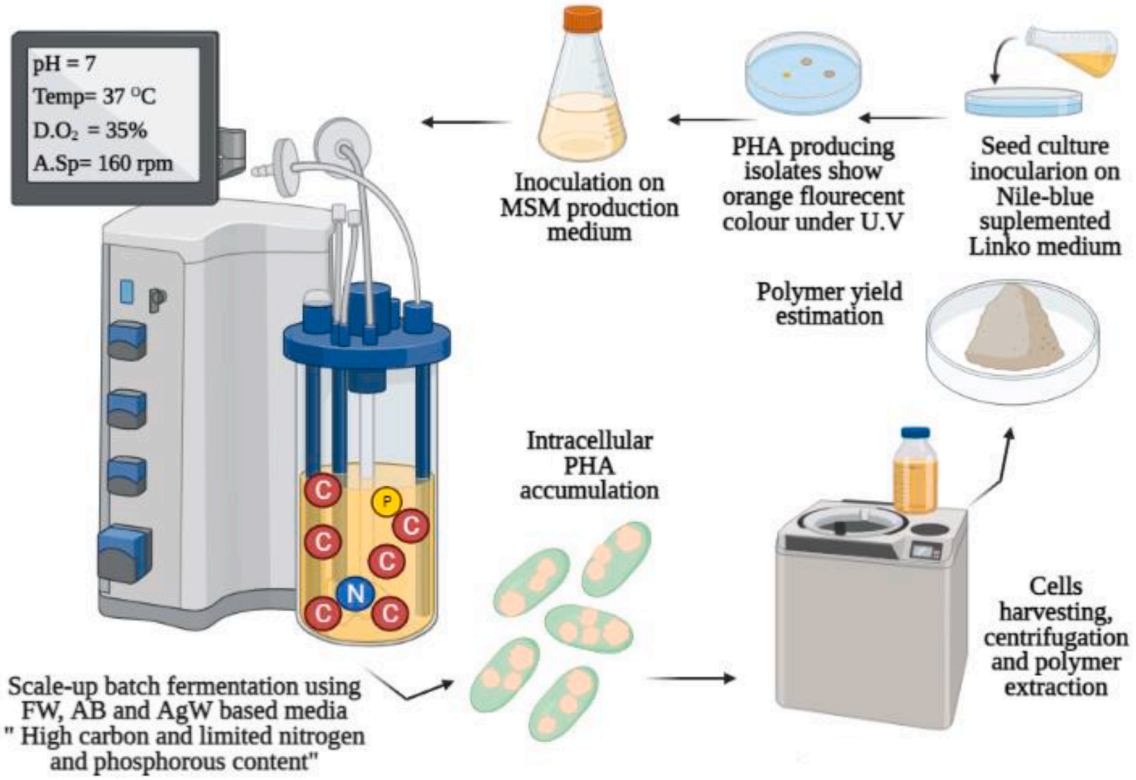

Fig. 2. Schematic illustration of scaling-up batch fermentation and polyester recovery.

Table 2
Microbial production of PHAs from various wastes.

Production organism	Isolation site	Main carbon source	PHA titer(g/L)	Reference
R. eutropha H16 (DSM-428)	Sludge	Plant oils	1.65	[56]
Pseudomonas putida LS46	Sewage sludge	Glucose	28.8	[57]
Haloferax mediterranei DSM1411	Solar salt pond	Whey	1.18	[58]
R. eutropha H16	Sludge	Digestate chicken manure + waste sunflower oil	4.6	[59]
Bacillus cereus NT-3	Municipal solid waste leachate	Volatile fatty acidsfrom food waste	0.42	[60]
Clostridium beijerinckii ASU10	Cultivated soil	Glycerol	0.42	[61]
		Sugarcane molasses	0.33	
*Bacillus megaterium*Ti3	Soil	Xylose	1.08	[62]
		Glucose	0.78	
		Arabinose	0.67	
		Corn husk hydrolysate	1.0	
Pseudomonasputida NX-1	Leaf mold	Lignin	0.11	[63]
*Schlegelella thermodepolymerans*DSM 15,344	Activated sludge	Glucose	1.24	[64]
		Mannose	0.3	
		Galactose	0.54	
		Fructose	1.0	
		Lactose	1.32	
		Sucrose	0.49	
		Xylose	2.85	
		Arabinose	0.40	
		Glycerol	1.67	
		Waste frying oil	0.01	
*Acinetobacter junii*BP 25	Rice mill effluent	Rice mill effluent	3.04	[47]
*Cupriavidus necator*DSM 545	Soil	Beer brewery waste water containing maltose	1.98	[65]
*Burkholderia glumae*MA13	Soil	Crude glycerol	1.81	[66]
Pseudomonas chlororaphis sub sp. *aurantiaca* DSM 19,603	Soil	Apple pulp, a glucose- and fructose-rich waste	4.15	[67]
E. coli	Sludge soil	Sago molasses	27.1	[68]
*Cupriavidus necator*H16(ATCC 17699)	Sludge from the Weende-Quelle	Peanut oil	3.9	[69]
*Paracoccus denitrificans*DSMZ 413	Soil	Glycerol	0.17	[70]
*Rhodovulum sulfidophilum*DSM-1374	Mud from intertidal flats	Lactate	0.41	[71]
Cupriavidus eutrophus B-10646	Soil	Glycerol	85.8(Pilot scale fermentation)	[72]
Pseudomonas putida KT2440 (ATCC 47054)	Sludge	Acetate	0.35	[73]

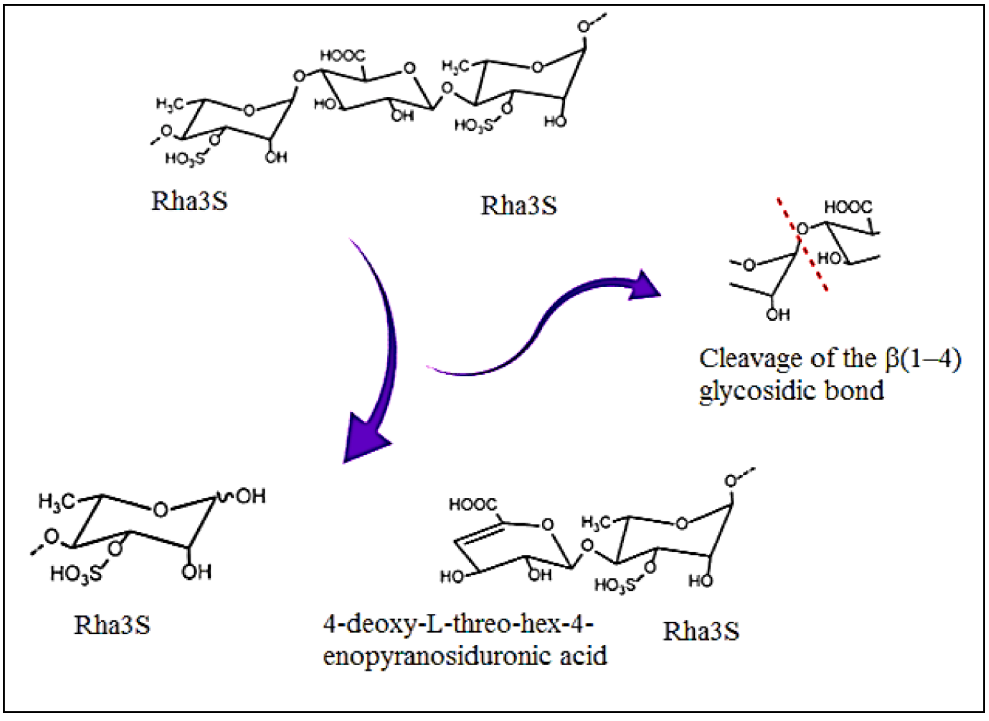

Fig. 3. The cleavage of β(1–4) glycosidic bond found between uronic acid and 3-O-sulfate-rhamnose (Rha3S) by Ulvan lyase *via* β- elimination mechanism.

3. Peptides produced from AB

3.1. Ulvan lyase

Ulvan lyase is a particular enzyme that depolymerizes ulvan into unsaturated sulfated oligosaccharides with various organic activities. Ulvan lyase is widely known to cleave β(1–4) glycosidic bond found between uronic acid and 3-O-sulfate-rhamnose (Rha3S) (Fig. 3) using the β-elimination mechanism [78,79]. In the Carbohydrate-Active Enzyme (CAZy) database, Ulvan lyases are now divided into three polysaccharide lyase (PL) families: PL24, PL25 and PL28 [80]. NLR42 (NCBI accession number AEN28574; 46 kDa with two domains) was the first ulvan lyase discovered and the first member of the PL28 family [81]. It was isolated from *Nonlabens ulvanivorans*, a Gram-negative bacterium, peach-colored, rod-shaped, and strictly aerobic.

Without isomerization, this mild enzymatic approach can yield all the oligosaccharides ingredients [82]. Producing these beneficial oligosaccharides could be reached by developing a fermentative strategy for ulvan lyase industrial production. Unfortunately, the lack of knowledge about ulvan lyase has limited this capacity. Several investigations on this enzyme have been primarily targeted at screening for microorganisms displaying enzyme activity and catalysis characteristics [78,83]. The fermentation scale was limited to the flask shaking, and the hot water technique confined the substrate used as the primary carbon source to pure soluble polysaccharides [82]. The generation of ulvan oligosaccharides has been conducted on a small scale owing to inadequate quality, insufficient fermentative substrates, and high production costs of the enzyme. Thus, innovative methods of producing ulvan lyase are still required.

Several studies have been carried out on large-scale ulvan lyase fermentation by reducing the cost of the raw materials and increasing the cost-effectiveness of high output production [78,82]. A recent research by Qiao et al. [15] aimed at ulvan lyase production using the *Ulva prolifera* (marine green algae) pure polysaccharide (PU). The purified PU is frequently used as the main carbon source for ulvan lyase production process. Qiao et al. replaced the PU with algal biomass powder to reduce the production cost. *Catenovulum* sp., a Gram-negative rod shape bacterium belongs to the Alteromonadaceae family, could successfully produce ulvan lyase by direct consumption of *U. prolifera* powder in the culture medium. The production was performed in a 5 L shake flask fermenter containing 5% (w/v) *U. prolifera* powder, 0.4% NH_4Cl, 0.5% NaCl, 0.05% $MgSO_4$ and 0.2% K_2HPO_4. The highest enzyme activity of 0.748 ± 0.031 (U/mL) was obtained by two-stage temperature conditions (28–32 °C), agitation (200–400 rpm), and initial pH 7.0. This fermentation model indicated that the short time of cultivation improved the activity of ulvan lyase. The authors recorded an ulvan lyase activity of 1.09 U/mL when the time of fermentation was shortened to 24 h in a 5-Liter fermenter. When the fermentation took place in a 30-Liter fermenter, a higher enzyme activity of 1.20 U/mL was yielded after 20 h [15].

4. Bio-acid production from AB

4.1. Butyric acid

Butyric acid is a 4-Carbon saturated short-chain fatty acid that is often utilized in the animal feed, medicinal products, and food industry with the global production of over 80,000 tons/year [84,85]. Biocatalytic and chemo-catalytic methods can convert butyric acid to biofuels and fine chemicals, such as ethyl butyrate, butyl-butyrate and 1-butanol [86,87]. Moreover, butyric acid is well known for its anticancer properties, as it causes morphological and biochemical differentiation in a number of malignant cells, resulting in the suppression of neoplastic properties. This opens up the possibility of using butyric acid prodrugs to treat tumors and hemoglobinopathies, including sickle cell anemia (SCA) and leukemia, as well as shielding hair follicles from radio and chemotherapy-induced alopecia [88,89]. Recently, lignocellulose-derived butyric acid synthesis has been investigated owing to the abundance of lignocellulosic biomass (LCB) (Fig. 4). However, because of the inhibitory effects of lignin-derived chemicals generated during pretreatment, detoxification of lignocellulosic hydrolysate is needed [90]. For instance, *Clostridium tyrobutyricum* ATCC25755; a well-known butyric acid-producing, has been significantly toxified by hydrolysates prepared from different kinds of plant biomass. In this context, ABs would be a promising feedstock for butyric acid production as they contain no or very less amount of lignin.

Both micro- and macro algae can be used as the feedstocks for butyric acid, where brown, green and red algae have been studied substantially for chemicals and biofuels production [9,91]. Among macroalgae, *Saccharina japonica*, is a favorable source of biomass feedstock. Alginate, cellulose, fucoidan, laminaran and mannitol are the main carbohydrates in *S. japonica* [92]. All carbohydrates except mannitol can be removed by enzyme hydrolysis for microbial fermentation [85]. Mannitol resembles 15% (w/w) of brown algae dry mass and may be recovered in water upon dilution with acid [93]. Butyric acid from brown algae was discussed in numerous investigations using mixed-bacterial cultures [17,94,95]. For example, a high concentration of butyric acid (11 g/L) was produced by *C. tyrobutyricum* ATCC25755 from *S. japonica* hydrolysate [17].

4.2. Kainic acid

Kainic acid is a frequently used neuropharmacological drug, helping to disassemble the major function of receptors for ionotropic glutamates, including the central nervous system kainite receptor. The kainoid family of natural neurochemicals is also regarded to be a flagship member. For decades, the tropical algae *Digenea simplex* was utilized to treat parasite worm diseases as an anthelmintic agent in Asia [96]. The active compound, kainic acid, was discovered in the 1950 s [97,98], allowing it to be used as Ascaris combination therapy until the 1990 s [99,100]. Furthermore, neuropathology studies have revealed that kainic acid-sensitive receptors (KARs) play a role in acute and chronic neurodegenerative diseases such as epilepsy, pain, and psychiatric disorders [101].

Several experiments have been designed for kainic acid synthesis. However, production of kainic acid is limited due to the low yields and long production pathway steps [102,103]. Likewise, there has been little progress in understanding how seaweeds produce kainic acid. The biosynthetic rationale for developing domoic acid in microalgal *Pseudonitzschia multiseries* diatoms was recently developed by identifying a four-gene cassette (dabA-D) and confirming its in vitro enzymatic activities [104]. Domoic acid and kainic acid have molecular similarities that have led researchers to suggest a conserved production pathway. An intermedia route of prekainic acids would be generated by a dabA homologation that may interact cyclically directly with a DabC homolog to make kainic acid DMAPP (dimethylallyl pyrophosphate) [104].

Several organisms, including unicellular algae, fungi, bacteria, and plants, are reported to contain cluster genes from the same metabolic pathway, such as the kainic acid biosynthesis (kab) cluster [104]. A recent research work done by Chekan et al. [16] discovered and characterized the precise two-enzyme kainic acid biosynthetic pathway in red macroalgae from L-glutamic acid and dimethylallylpyrophosphate. The research demonstrated that the biosynthesis genes are classified together in the *Palmaria palmata* and *D. simplex* genomes. Additionally, recent research has applied a crucial biosynthetic alpha-ketoglutarate-dependent dioxygenase enzyme to effectively create kainic acid on a gram scale in a biotransformation methodology. It separated the genes *dskabA* and *dskabC* from *P. palmata and D. Simplex* and expressed them successfully in *E. coli* [16]. The discovery of the biosynthetic genes of kainic acid allowed the development of kainic acid through biotransformation with *E. coli* cells which express the *dskabC* gene in the vector apET28 (Fig. 5).

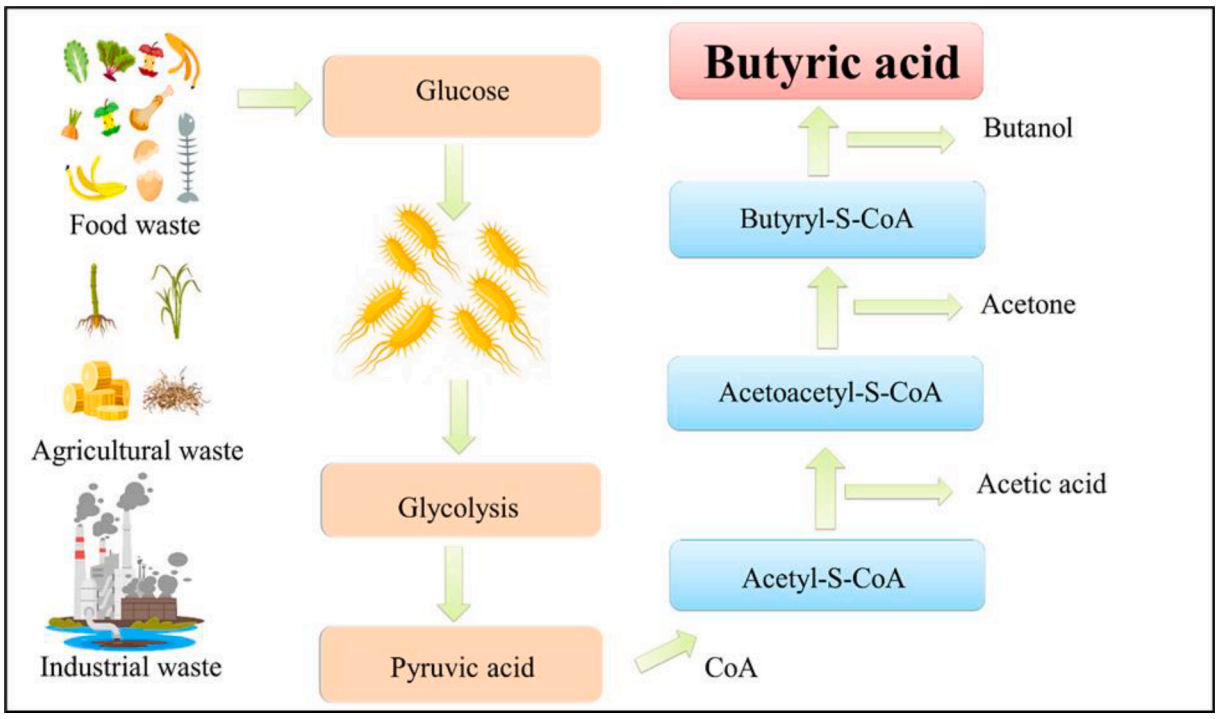

Fig. 4. Schematic diagram of butyric acid production from different carbon sources, including food, agricultural and industrial wastes.

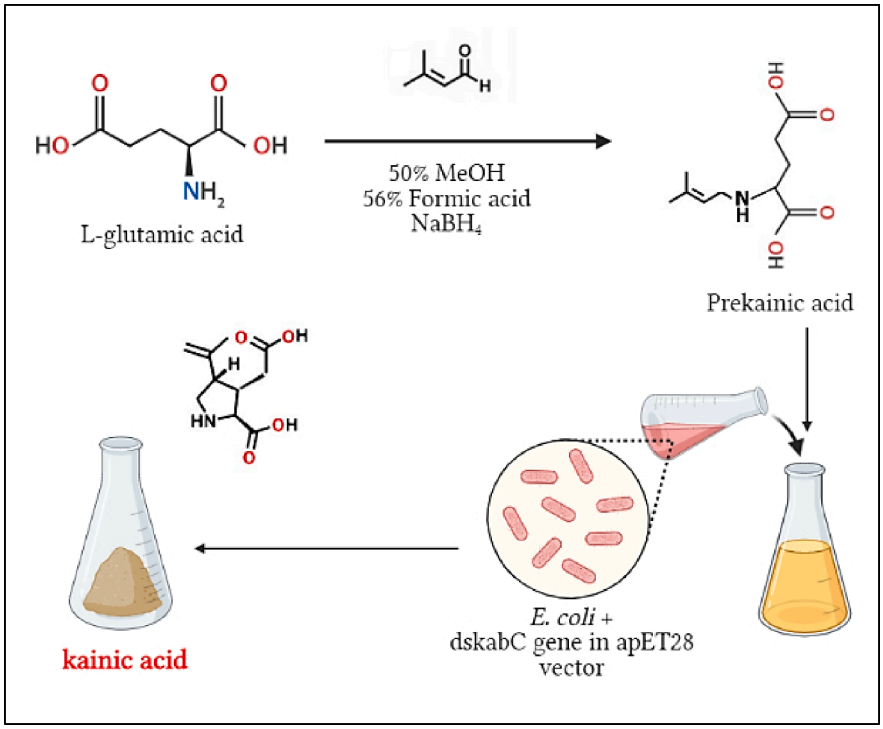

Fig. 5. Kainic acid biosynthesis through biotransformation with *E. coli* cells expressing the *dskabC* gene.

KabC was tested in an in *vitro* setup using prekainic acid, aKG, Fe2+, and DsKabC isolated from 1 L of the culture of *E. coli* cell to see if it could produce kainic acid. Over two phases, 10 mg of produced prekainic acid was entirely converted to 4.6 mg kainic acid after 16 h of incubation, yielding 46% isolated yield and 26% total isolated yield. Despite the efficacy of this chemoenzymatic technique, the necessity to purify DsKabC makes this technology unsuitable for large-scale kainic acid synthesis. As a result, a biotransformation technique was attempted to eliminate the request for enzymes purification and, rather, to convert produced prekainic acid directly to kainic acid, expressing DsKabC, into *E. coli* cells [16]. This simplified method was used to generate prekainic acid by *E. coli* cell culture. On the scale of 1L *E. coli* cell culture, virtually 8 mmol of prekainic acid were completely used in the kainic acid synthesis process. This technique produced 1.1 g of refined kainic acid, with a total yield of 32%, and more than 95% purity as determined by Nuclear magnetic resonance (NMR) spectroscopy. Following a reverse-

phase preliminary HPLC, a two-step purification method employing activated charcoal was developed [16].

4.3. Lactic acid

Lactic acid is an odorless and colorless monocarboxylic acid with numerous applications in food and non-food industries [105]. The production of polylactic acid, a biodegradable polymer that resembles a promising replacement to synthetic petroleum plastic, has increased the need for lactic acid in numerous industries [106]. Lactic acid has been implemented in various applications, including cosmetics, drug delivery systems, food, pharmaceuticals, and industrial biotechnology. Depending on the used bacterial strains, over 90% of commercial lactic acid is generated from corn starch, glucose, or sucrose as a carbon source to produce D- or L-lactic acid [107]. Lactic acid can be produced either by chemical synthesis or microbial fermentation. During its chemical synthesis, two optical isomers of lactic acid, L(+)- and D(-)-lactic acid, are produced, where the primary agent implicated in human acidosis is thought to be D(-)-lactic acid [108].

For lactic acid synthesis by microbial fermentation, a number of microbial strains, such as lactic acid bacteria (e.g., *Lactobacillus brevis* and *Lactobacillus plantarum*) [109], yeast (e.g., *Pichia stipites*) [110], and mold (e.g., *Rhizopus oryzae*) [111], have been utilized. The microbes producing lactic acid are generally isolated from animal feces, milk products, fruits, and soil that can convert a wide variety of feedstocks into lactic acid (Table 3). Lactic acid bacteria are classified into homo- and hetero-fermentative strains [112]. The aldolase enzyme gene is found in homo-fermentative lactic acid bacteria, which is the main product. They transform one glucose molecule into two lactic acid molecules that produce two ATP molecules. On the other hand, hetero-fermentative lactic acid bacteria use the phosphoketolase pathway (Fig. 6) to transform one xylose molecule into one lactic acid molecule and one ethanol or acetic acid molecule [113].

Despite the intensive research on enhancing lactic acid production, the high cost of lactic acid production remains a major impediment to their adoption. This means the expense of lactic acid synthesis from carbon sources must be alleviated for industrial application [126]. In this regard, lactic acid generation has been explored through fermentation of some agricultural products including, maize starch [127], potato starch [128], rice starch [129], and juice of sweet sorghum [130]. Nevertheless, scientists have been looking for more affordable lactic acid feedstocks for microbial fermentation. Apple pomace [131], corn stover [132], waste sugarcane [126], wheat straw [133], and wood waste [134] are examples of the low-carbon cost lactic acid-feedstock and renewable lignocellulosic biomass resources. However, lignocellulose based lactic acid production has several demerits, such as inefficient lignin extraction and being an inhibitory agent during fermentation.

In this intellect, marine algae have attracted tremendous attention in terms of providing affordable carbon sources for fermentative approaches. This is owing to their rapid growth, excessive abundance, and photocarbonity (act as a photoautotrophic organism). In a recent investigation by Lin et al. [18], brown, green, and red seaweeds were evaluated for lactic acid fermentation. The work reported that *Gracilaria* sp. (red seaweed) has the largest concentration of carbon in seaweed composition. At optimal conditions, the ultimate lactic acid concentration of *Gracilaria* sp. hydrolysate culture fermented by lactic acid bacteria was 19.32 g/L [18]. In the lactic acid fermentation from *Gracilaria* sp. hydrolysate, two-thirds of reducing sugars were consumed after 72 h. However, the polysaccharide chains of *Gracilaria* sp. are made up of repeated alternating units of the non-fermentable sugar, namely 3,6-anhydrogalactose that remained unconverted after fermentation, because lactic acid bacteria are not capable of using 3,6-anhydrogalactose [135]. In another study, *Lactobacillus paracasei* LA104 was cultured by Nguyen et al. [136] to co-ferment the enzymatic hydrolysates of *Hydrodictyon recticulum* (fresh-water green microalgae, includes various polysaccharides, mostly glucose and mannose) to produce lactic acid [136].

Table 3
Biosynthesis of lactic acid by various isolates from various substrates.

Producing organism	Isolation source	Production carbon source	Production efficiency	Reference
Lactobacillus delbrueckii (DSM 20074)	Sour grain mash	Municipal biopulp	82.0 ± 1.5%	[114]
Lactobacillus plantarum CRA52	Salt-fermented cucumber	Whey permeates based medium	85.9 ± 0.99%	[115]
Enterococcus hirae ds10	Soil	Beet molasses	71.9 ± 0.20	[116]
Lactobacillus sp. TERI-D3	Dairy water samples collected from local dairy farms	Glucose Lactose Galactose Sucrose	95% 90% 83% 86%	[117]
Lactobacillus plantarum SKL-22	Dairy plant	Rice straw	92.9%	[118]
Lactobacillus delbrueckii CECT 286	Sour grain mash	Orange waste enzymatic hydrolysates	93.7%	[119]
Lactobacillus rhamnosus ATCC 53,103	Human gastrointestinal mucosa of healthy individuals	Carob pod waste	76.9%	[120]
Lactobacillus delbrueckii subsp. *bulgaricus* ATCC 11,842	Dairy products; Bulgarian yogurt	Organosolv pretreated lignocellulosic biomass	82.7%	[121]
Bacillus coagulans LA-15–2	Dairy products; evaporated milk	Cassava bagasse	88.0%	[122]
Lactobacillus planatrum 23	Taiwanese pickle	Microalgal feedstock	72%	[123]
Bacillus coagulans DSM ID 14–300	Hemp leaves	Hydrolysate from sugarcane bagasse	87%	[124]
Lactobacillus pentosus CECT 4023 T (ATCC-8041)	Corn silage	Gardening residues	95%	[125]

5. Biofuel

5.1. Bioethanol

The most widely utilized liquid biofuel is bioethanol, and it is considered one of the latest solutions for tackling climate change and slowing the depletion of oil reserves [137]. Sugars fermentation by microorganisms for ethanol generation is the process used to make bioethanol. Because certain essential sugars are not readily available, treatments like pH, temperature, and prior to fermentation enzymes are required to hydrolyze the sugars (Fig. 7). Bioethanol is almost entirely produced commercially by fermenting sustainable agricultural waste, including sugarcane or maize. There are considerable advances in biomass conversion technologies to ethanol from various feedstocks [138]. While sucrose may be quickly converted to ethanol by fermentation in molasses made from sugar cane stalks, maize starch must be saccharified via liquefaction and hydrolysis utilizing amylolytic enzymes following significant pretreats. However, environmental concerns about the significant land-use change and food safety have raised questions about how safely these feedstocks may be used in the future [139,140]. Bioethanol may be mixed with petroleum and used in

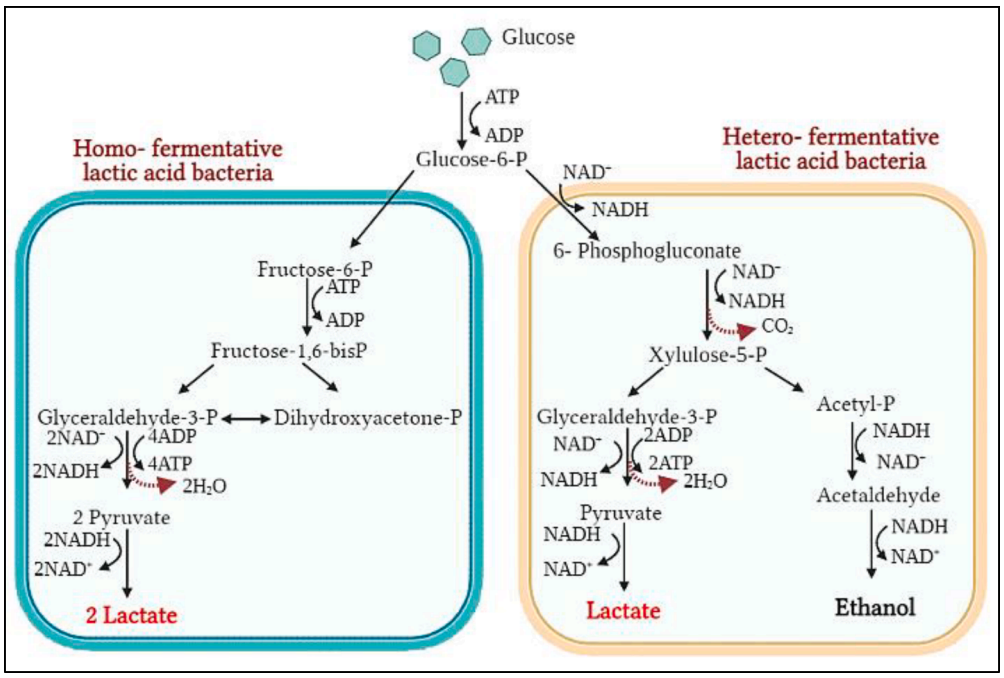

Fig. 6. Homo-fermentative and hetero-fermentative pathways of lactic acid bacteria.

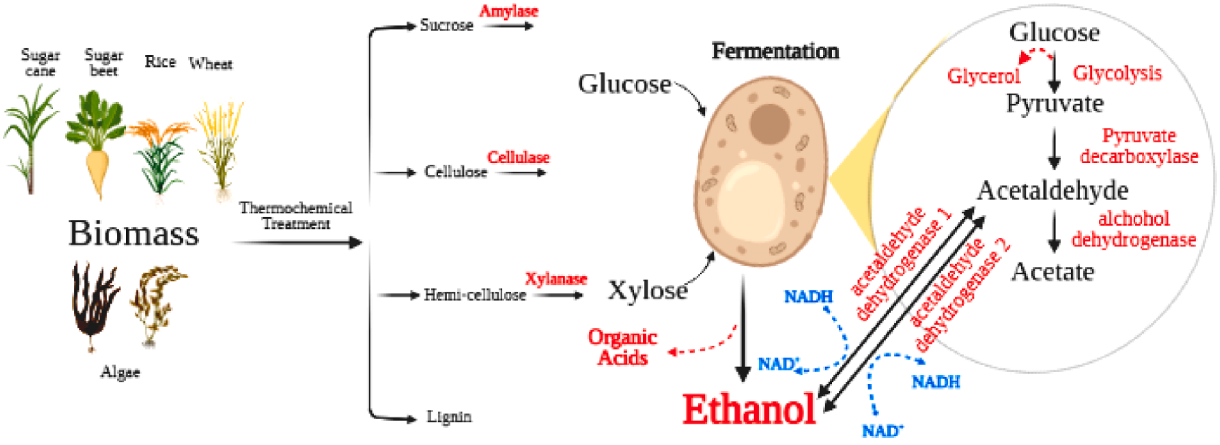

Fig. 7. Schematic illustration of the fermentation pathways for bioethanol production from different biomasses.

vehicles without modifications if many different vehicle manufacturers currently develop it in combination with 5% (v/v) or up to 85% (v/v) in flex-fuel vehicles.

Since marine algal biomass is thought to account for about half of all global biomass, it has much potential as a feedstock for future bio-ethanol production (Table 4). From another avenue, the problems related to increased land for biomass crops and the food and fuel dispute do not apply to macroalgae [141,142]. Macroalgae, especially *Porphyra* sp., *Undaria pinnatifida,* and *L. japonica*; widely cultivated in Asia, are the most prolific producers in China, Japan, and South Korea. An estimated 5.5–6 billion dollars are spent annually in the marine industry, and up to 7.5 million tons are collected, cultivated, and produced naturally around the globe. The most common application as human-use food stuffs is around 5 billion dollars per year [143].

Since seaweeds are not human food sources, reasonable exploitation of algal feedstocks for bioethanol production would not affect global food security [141]. Seaweeds are also advantageous in terms of having a high concentration of polysaccharides, non-lignin, complex sugars and a fast rate of biomass growth [141,152]. Alginates, agars, and carrageenans are three polysaccharides formed by seaweeds [153]. Brown seaweed extracts contain alginates, while red seaweed extracts contain agar and carrageenan [154]. The high carrageenan and agar content of red seaweeds is the reason behind being appealing as bio-ethanol sources [155,156]. Because of its high sugar content, *Gelidium amansii* has also been considered a bioethanol production candidate [157,158]. The three critical phases in the development of bioethanol from seaweed are (a) polysaccharide hydrolysis into monosaccharides, (b) bioethanol biosynthesis through the monosaccharides fermentation (c) accumulation and recovery of bioethanol [152]. Acid hydrolysis is preferred over enzymes and chemicals owing to its high reaction rate and low expense. It is, however, more likely to produce undesirable by-products that may interfere with fermentation and cell growth [149,152].

Bader et al. [22] examined whether a recently identified fungus strain *Trichoderma harzianum* could thrive only on undamaged cells of *Chlamydomonas reinhardtii* algal species as nutrients. Proteolytic, pectinolytic, amylolytic, and cellulolytic activities were found in the fungal medium, which successfully saccharified either milled or dry biomass or

Table 4
Recently conducted studies using AB-based media for bioethanol production by several microbial producers, their isolation sites and productivity.

Fermentation organism	Algal biomass	Bioethanol productivity (μL g − 1 DS)	Reference
Ambrosiozyma angophorae (Strain 5830, CBS-KNAW)	*Laminaria digitate* (Dark brown seaweed)	42.51	[143]
Saccharomyces cerevisiae	*Chlamydomona sreinhardtii* CC125 (Unicellular green algae)	10.8	[22]
Monascus sp. NP1	*Cladophora glomerata* (Filamentous green macro algae)	13.84	[144]
Escherichia coli KO11 (ATCC55124)	*Saccharina japonica* (Brown algae)	15.56	[145]
Saccharomyces cerevisiae	*Kappaphycus alvarezii* (Red algae)	33.20	[146]
Saccharomyces cerevisiae	*Gracilaria Verrucosa* (Red algae)	55.20	[147]
ATCC 200,062	*Gelidium latifolium* (Red algae)	108.30	
Saccharomyces cerevisiae TISTR no. 5339	*Gracilaria tenuistipitata* (Red algae)	190.0	[148]
	Gracilaria fisheri (Red algae)	160.0	
Saccharomyces cerevisiae	*Palmaria palmate* (Red algae)	129.02	[149]
Candida glabrata ABRC-S2	*Gracilaria fisheri* (Red algae)	2.50	[150]
Kodamaea ohmeri ABRC-S3		2.16	
Candida parapsilosis ABRC-S1		1.70	
Saccharomyces cerevisiae	*Laminaria digitata*	63.05	[151]
	Laminaria hyperborean	61.07	
	Saccharina latissima	65.05	
Pichia angophorae	*Laminaria digitata*	38.19	
	Laminaria hyperborean	29.17	
	Saccharina latissima	13.07	

DS: dry solids.

intact microalga cells. With the help of *T. Harzianum* enzymes, *C. reinhardtii* cell-wall biomass was saccharified effectively as the original strain biomass, demonstrating that these enzymes have complete potential to overcome cell wall resistance to hydrolysis [22]. Saccharification of AB provided up to 22.4 g/L reducing sugars that might be converted into ethanol efficiently using *S. cerevisiae* bio-fermentation. The efficiency of AB conversion to ethanol in this work is among the highest ever recorded, encouraging further research into the scaling up of *T. harzianum* enzyme production. About 10.8 g/L ethanol was produced from 22.4 g/L reducing sugars in 18 h using *S. cerevisiae* cultures. In comparison with Yeast Extract–Peptone–Dextrose medium as a positive control, the yeast was found to be able to develop and deplete the sugars in the medium [22]. Recently, these high ethanol levels from the microalgal biomass fermentation were obtained using *Desmodesmus* sp. biomass with carbohydrate concentration of 55% (w/w) and saccharified at 20% (w/v) biomass at 120 °C for 30 min. and in presence of 2% (v/v) H_2SO_4. Sugar content in such preparations was 98.3 g/L, which could be converted effectively to 49.1 g/L ethanol through fermentation [159]. Notably, the production of bioethanol from cyanobacterial biomass is considered as the most successful case. This is contributed to the substantially different composition and cell-walls structure as well as unlike most Chlorophytes, most cyanobacteria do not accumulate lipids as a carbon competing sink [160].

Similarly, yeast strains of *Candida glabrata*, *Candida parapsilosis*, and *Kodamaea ohmeri* were isolated and identified from the surface of *Gracilaria fisheri* seaweed. These three yeast species generated varied quantities of ethanol. *C. glabrata* produced the most ethanol concentration of 2.5 x10^{-2}g ethanol g^{-1} sugars, while *C. parapsilosis* produced the least amount of ethanol 1.7x 10^{-2}g ethanol g^{-1} sugars [150]. This result can be explained on the basis of the high carbohydrate content of *G. fisheri* agar, which yeast cells may have utilized as a carbon source. *K. ohmeri*, *C. parapsilosis*, and *C. glabrata* can ferment both glucose and galactose, where *C. glabrata* selectively ferments glucose and *C. parapsilosis* ferments galactose. This might explain why, even at low glucose concentrations, the fermentation processes were able to generate ethanol from galactose [150]. In the presence of low quantities of glucose in the feed medium, ethanol is formed as a secondary metabolite. During the first 10 h, *C. glabrata* used glucose and metabolized a limited quantity of galactose. This is due to *C. glabrata*'s capacity to generate ethanol even under aerobic circumstances in the presence of a high concentration of glucose in the medium [161].

6. Production of other valuable products from ABs

6.1. Natural pigments

Natural pigments are viable substitutes for the toxic colorants used widely in textile, food and biomedical sectors. Various operants have paved the way for microbe-derived pigments, including the scarcity of readily available natural food colorants, the significant environmental and safety issues caused by synthetic pigments, and the market preference for natural products over synthetics. Microorganisms-based pigments are of industrial interest since they can be produced rapidly under regulated conditions. This results in excellent product outputs with availability all year round [162,163]. Many fungi produced a wide range of high-yield, stable and low-light sensitivity pigments [162], but only a few were examined as possible food dyes. For example, *Penicillium* is a widely known fungus with possible application in the food industry and has been reported to produce monascus-like pigments with polyketide color and structure similarity to monascus pigment. Unlike *Monascus* spp., this culture does not produce the deadly citrin chemical [164]. The high expense of the industrial processing technologies currently in use prohibits naturally-produced pigments as a substitute for toxic chemical pigments. Therefore, natural pigments or coloring substances that are long-lasting, simple, and even dispersion in the substratum matrix are in great demand [165]. SSF has risen to attention as a feasible alternative to liquid culture-based fermentation technology, with higher pigment efficiency than the submerged culture [166]. SSF natural pigment processing has many advantages over the submerged culture, including better product, higher yield, simpler methods, catabolic repression, lower capital expenditure, reduced inhibition, and waste performance levels of the final products [167]. One of the main components impacting the SSF process is the solid substrate. SSF with a low-cost and easily accessible substrate might be an excellent way to make the fungus produce large amounts of pigment. This is owing to the fact that they are not a food source and possess a high level of carbohydrates, such as cellulose, alginate, mannitol, fucoidan, and laminarin [168,169]. In this context, seaweeds could be the attractive choice for microbial conversion processes due to having many merits, including being easy to grow, having 15–20% carbohydrates in total wet weight, and producing more dry biomass than fast-growing terrestrial crops [170]. Seaweeds also contain about 27% of minerals needed in pigment generation process (sodium, calcium, copper, iron, magnesium, potassium, zinc and so on) and amino acids (alanine, glutamate, aspartate, proline, and others) [168].

S. japonica is one of the essential algal species in the biotechnological industry for fungi producing pigments. Apart from the high content of carbohydrates, amino acids, and minerals, *S. japonica* also has a high

moisture content, ranging from 70 to 90%, making it ideal for fermentation. Adding to this, the FDA has approved *S. japonica* for human consumption, and it is regarded as an excellent source for other bioactive compounds [168]. General et al. [20] studied the effectiveness of using *S. japonica* as a feedstock for the fungus *Talaromyces amestolkiae* GT11 to produce pigments without requiring any salt or nitrogen addition. The pigment's overall absorption range was at 510 nm (red) and 410 nm (yellow) under optimal conditions, and pigment yields of 506.2 (red) and 1,153.5AU/gdfs (yellow). The results show that pigment synthesis by *T. amestolkiae* GT11 (newly isolated fungal strain) culture utilizing *S. japonica* as a substrate is strongly dependent on culture conditions. To illustrate, the culture has a great capacity to break down and use *S. Japonica* polysaccharides. The biomass of fungal mycelia was shown to be greater during the growth phase, however, by the end of fermentation, the pigment production was lower. This might be explained by the fact that when the sugar level of the medium increased, the fungal culture's pigment output dropped [20]. *T. amestolkiae* GT11 developed rapidly for 288 h without any further nutrient supplementation. This means that fermentation of *S. japonica* with *T. amestolkiae* GT11 is a low-cost technology. *T. purpurogenus* species has been shown to generate polysaccharide-degrading enzymes such cellulases, fucoidanases, β -glucosidases, and xylanases. *T. amestolkiae* GT11 produces hydrolyzing enzymes during the growth. As a result, the concentration of reducing sugar in the fermentation medium rises. [20]. Suraiya et al. [171] used *S. japonica* as an SSF substrate to maximize the natural pigment production from *Monascus* sp. under optimal physical and nutritional conditions. *Monascus purpureus* yielded 79.87, 80.07 and 83.01AU/gdfs, while *Monascus kaoliang* yielded 75.09, 77.22, and 83.23AU/gdfs red, orange, and yellow pigments, respectively at 30 °C for 20 days. *M. kaoliang* exhibited the maximum pigment content of 50% with a 3 mL inoculum size, whereas *M. purpureus* produced 60% pigment content [171].

6.2. Biosurfactant

Biosurfactants are biologically derived natural compounds produced by some bacterial strains. They are promising alternatives in various applications in terms of their biocompatibility, biodegradability and low toxicity. Several surfactin, iturin, and fengycin lipopeptide biosurfactants were previously produced by *Bacillus* genus bacteria [172]. Microbes either generate biosurfactants on the cell surface or secrete them extracellularly [173]. Biosurfactants outperform traditional surfactants owing to having a lower production cost. Surfactants are now employed in the solubilization and removal of heavy metal pollution from soil [174], the degradation of certain pollutants in residential wastewater [175], and the bioremediation of waste engine oil [176]. Market demand and new environmental legislation have led to the discovery of many natural surfactants as alternatives to traditional surfactants despite the omnipresence of commercial surfactants from petroleum derivatives [177]. However, the industrial development of biosurfactants is still in its early stages. The high expenditure of biosurfactant microbial culture processing (purification, cultivation, production and recovery) is the reason behind its production problems [178,179]. Biosurfactants can be produced by microorganisms and chemical processes/synthesis [178].

In a recent study by Yun et al. [180], he have proven the production of *Bacillus subtilis* C9′s high-value biosurfactant, utilizing defatted AB hydrolysate as the sole fermentation substratum. Despite the potential for by-products produced during hydrolysis to inhibit the production, the results indicated that the diluted defeated *Chlorella* biomass (DCB) hydrolysate was suitable for facilitating high bacterial growth compared to the control culture. After extracting the crude biosurfactant by acid precipitation, the culture grown on DCB hydrolysate medium produced 1.21 g/L of C9-biosurfactant, while only 0.89 g/L were generated by cultivation in glucose supplemented LB. The productivity for raw biosurfactants from LB supplemented with glucose and DCB was 0.30 g/L/day and 0.40 g/L/day, respectively. However, for cultures grown on LB supplemented with glucose and DCB hydrolysate medium, the C9-biosurfactant yield was 0.06 g/g and 0.08 g/g, respectively, based on monosaccharide substrate [180]. These findings strongly suggested that DCB hydrolysate might be used as the only substrate for the generation of bacterial biosurfactants. However, it should be emphasized that by adjusting fermentation parameters and optimizing the growing medium, the production of *B. subtilis* biosurfactant might be further enhanced.

According to the authors, the supplementation of metal co-factors in the culture DCB hydrolysate medium has led to a higher biosurfactant yield than the traditional LB [180]. Despite the low biosurfactant yield (20%) and the additional costs of purifying crude biosurfactant [181,182], the synthesis of C9-biosurfactant might be significantly assisted by adding metal-containing cation residues. The higher yield of C9-biosurfactant in DCB hydrolysate than in LB was most likely due to better availability of metal cofactors, which have been linked to the synthesis of biosurfactant from *Bacillus subtilis* [183]. Further studies will be needed to investigate the effect on the hydrolysate media nutritional values obtained in various treatment protocols of algae biochemical composition and species identification to examine the potential for integration into microbial fermentation of critical metal cofactors from upstream AB processing [184]. Furthermore, investigating the fermentation of hydrolysate of AB *via* a number of bacterial species, including different strains of *Bacillus*, could lead to the discovery of new marketable bioproducts, bolstering the economic viability of industrial algal biorefining.

7. Current challenges and future perspectives

7.1. Techno-economic and policy constraints

AB is presently regarded as a sustainable and renewable feedstock for the manufacture of a variety of valuable products. The abundance of ABs in both freshwater and saltwater conditions is one benefit of the intensive algae production systems. Despite the considerable potentials, large-scale exploitation of AB-based production technologies is yet limited because of the complexity of the biomass generation systems (separation, drainage, and conversion into various products), which results in environmental and economic issues [6].

Most algae species are not capable of surviving in open ponds for long periods owing to the high susceptibility to contamination by fast-growing microbes [185]. In addition to this, researchers struggle to discover algae species with high biomass and high carbon content at the same time which impedes the scaling up of the production system. Low production yield and process optimization are also growing obstacles against ABs downstream processing. The chemical profile of ABs (proteins, lipids, enzymes and other compounds) differs among the species, which needs hundreds of trials to select the optimum algal strain for the microbial producer [185]. To overcome these limitations and develop an integrated biomass system, some natural and safe antimicrobials could be introduced to the production system to avoid contaminations. The low production yield issue could be mitigated by using algal consortia to achieve full nutrient supplementation for the microbial producer.

Large-scale algae-based production necessitates a number of economic considerations in terms of capital cost, labor, land usage, electricity, and water [186]. Because the manufacturing costs are considerable, these sorts of production on an industrial scale are limited, impeding the route to industrialization and commercialization. To illustrate, the production cost of algal biofuels is roughly 1.50–2.50 US $/L, while the cost of petroleum is 1.10 US$/L, where the latter is obviously cheaper [187]. Furthermore, the harvesting of ABs accounts for 30% of the total cost and has become a burden to the producers [188]. According to Brentner et al. [189], there is an increase in the power requested to harvest microalgae by ultrasonication (110%), centrifugation (90%), filtration (79%) and supercritical CO_2 (66%). As a result, an energy-efficient extraction method is required to ensure that

production is economically sustainable. Further research on the cost-effective production of these compounds is required not only to discuss the utilization of ABs, but also to keep improving the valorization of residue streams or co-products to enhance the productivity plans of commercial algae-based production.

It seems that microbial cultivation and generation of desirable products is not free of demerits. First of all, some genetically engineered strains could be very susceptible to mutations producing undesirable byproducts. These byproducts might interrupt the metabolic pathway hindering the generation of useful products. Secondly, since ABs are highly nutritive, the production reactors could be easily contaminated with undesirable microbes which results in severe economic issues. Last but not least, some microbial enzymes that catalyze bioconversion processes are usually produced in low yield, which requires extremely humongous bioreactors to achieve the required output [190].

7.2. Practical implications of this study

Tremendous efforts are still required to overcome the existing obstacles with the microbial conversion of ABs for scaling up these technologies and sustainable production of bioactive products from ABs. Since bacterial cells have shown significant enhancement in maximizing the yield of SPSs, more investigations are needed on potential microbial/algal symbiotic relationships as innovative sources of SPSs. Owing to the favorable aspects of the microbial enzyme, more experimentations are required to search for PU for higher yields and enzyme activities. In addition, compared to lignocellulosic biomass fermentation that faces problems with phenolic compounds produced during pretreatment of these biomass, ABs are more practical for producing value-added products, such as butyric acid production [91]. Genes transformation between algal and bacterial species could open the possibility of locating more biosynthetic genes in algal sp. producing vital products for potential microbial expression of other acids. Furthermore, some studies have illustrated the importance of AB as an outstanding carbon source for the development of PHAs [9]. Algal juices rather than algal hydrolysates should be utilized in large scale PHA production as they are more practical and cost effective for supporting the microbial culture since the former does not require extraction costs. Based on the study of Yun et al. [180], which discussed the potential of diluted defeated *Chlorella* biomass (DCB) hydrolysate as a carbon source for *Bacillus subtilis* C9, more research is needed for maximizing biosurfactants production to be approved as safe anti-cancer and anti-oxidant drugs in global healthcare. Despite the pressing demand for natural colorants in the textile industry, there has been a limited investigation about using AB fermentation media [171]. Resolving the problem of fuels vs food advocates the high need for the industrial implementation of AB microbial fermentation. Overall, owing to the emergence of life-threaten issues, such as bacterial resistance, HIV/AIDS, resistant tumors and COVID-19, microbial-algal biotechnology could be a new resort for generating innovative bioproducts as potential treatments [191].

8. Conclusion

This review was conceptualized to investigate the potential of ABs as promising feedstocks for microbial conversion with the purpose of generating innovative compounds including SPSs, ulvan lyase, butyric acid, kainic acid, lactic acid, PHAs, biosurfactants, natural colorants, and bioethanol. These compounds could be incorporated into different industries including food, personal care, biomedical, pharmaceutical, tissue engineering and transportation. Recent studies have focused on obtaining novel compounds from ABs rather than exploiting them as energy sources for microbial synthesis. Some natural compounds with distinctive properties can be extracted only from microbial cells such as PHAs, bio-acids and microbial enzymes, replacing the synthetic materials with lower cost. Each microbial species has certain metabolic pathways, process conditions and sugar availability for utilizing ABs for optimal production of the bioactive compounds. The potential for downstream processing of ABs for microbial cultures will help to produce more desirable high-value products, paving the way for significant advancement in the future of microbial-algal-based biotechnology.

CRediT authorship contribution statement

Fady Abd El-Malek: Conceptualization, Writing – original draft. **Marian Rofeal:** Writing – original draft. **Hossain M. Zabed:** Writing – review & editing. **Abdul-Sattar Nizami:** Writing – review & editing. **Mohammad Rehan:** Writing – review & editing. **Xianghui Qi:** Writing – review & editing, Supervision.

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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