Emerging technologies for conversion of sustainable macroalgal carrageenan biomass into L-lactic acid: A state-of-the-art review

Kevin Tian Xiang Tong [1], *Inn Shi* Tan [1,*], *Henry Chee Yew* Foo [1], *Stephanie Yen San* Chan [1], *Tony* Hadibarata [1], *Man Kee* Lam [2, 3]

[1] Department of Chemical and Energy Engineering, Faculty of Engineering and Science, Curtin University Malaysia, CDT 250, 98009 Miri, Sarawak, Malaysia

[2] Chemical Engineering Department, Universiti Teknologi PETRONAS, 32610 Seri Iskandar, Perak, Malaysia

[3] HICoE-Centre for Biofuel and Biochemical Research, Institute of Self-Sustainable Building, Universiti Teknologi PETRONAS, 32610 Seri Iskandar, Perak, Malaysia

* Corresponding author: tan.s@curtin.edu.my

Abstract. The environmental awareness and concerns (plastic pollution) worldwide have driven the development of sustainable and environmentally friendly biopolymer derived from renewable materials. Biopolymers, especially L-lactic acid (L-LA) have played a crucial role in manufacturing polylactic acid, a biodegradable thermoplastic. Recently, L-LA production from non-edible macroalgal biomass has gained immense attraction due to it offers the simplest saccharification process for the biorefinery route. However, the commercialization of macroalgal-based L-LA is still limited due to high production costs. This paper has comprehensively reviewed the potential and development of third-generation feedstock for L-LA production, including significant technological barriers to be overcome for potential commercialization purposes. Then, an insight into the state-of-the-art hydrolysis and fermentation technologies using macroalgae as feedstock are also deliberated in detail. Furthermore, this review provides a conceivable picture of macroalgae-based L-LA biorefinery and future research directions that can be served as an important guideline for scientists, policymakers, and industrial players.

1. Background

In the last decades, the interest in synthetic petrochemical-based plastics has increased in various industrial applications including packaging and biomedical applications [1]. The annual production of plastics in 2018 had increased dramatically to approximately 300% compared to the year 1950s (1.5 million tons) and reached 360 million tons per annum [2]. The generality of plastic products consisted of single-use packaging, which has a short service lifespan before ending as pollutants entering the oceans and natural environment [3]. Approaching 7 million tons per annum of plastic waste entering the oceans, the total volume of plastic waste in the oceans is approximately 270 million tons, which has resulted in devastating damage and deaths of aquatic animals [4]. Besides, the global contradiction between the COVID-19 pandemic and increased content of plastic waste as a human propensity towards wearing personal protective equipment and slowly shifted their lives online by getting their meals, groceries, and goods delivered, which drive the interest toward the development of biodegradable polymer materials through the biorefinery concept for substituting synthetic plastics.

Poly-L-lactic acid (PLLA) shows great potential as an alternative to synthetic plastics and is considered one of the most commercially popular bioplastics due to its good mechanical properties, biodegradability, and processability [3]. Recently, PLLA application has seen tremendous growth in various fields, including packaging, biomedical applications (implants, bone fixation, and sutures), printing filament, and regulated drug delivery [5]. Further, the annual production volume of PLLA worldwide had increased by approximately 35% in 2020, corresponding to 395 kilotons as compared to 293 kilotons in 2019 [6]. PLLA is a type of biodegradable and aliphatic polymer of L(+)-lactic acid (L-LA), which is produced via ring-opening polymerization of L-LA; while L-LA can be derived from carbohydrate-rich renewable resources such as starchy materials, cellulosic materials, and agricultural wastes through a biotechnological approach using lactic acid bacteria (LAB) for microbial fermentation [7]. Thus, an effective and economically feasible production route must be discovered to intensify the production rate of L-LA from renewable resources to cope with the high demands of PLLA as polymer for bioplastics.

2. L-lactic acid Production Route

L-LA can be derived either using chemical synthesis or a biotechnological approach. The L-LA produced under the chemical synthesis approach mainly include base-catalyzed degradation of sugars, oxidation of propylene, and hydrolysis utilizes non-renewable resources including acetaldehyde and lactonitrile with the aid of hydrogen cyanide and concentrated acid as catalysts and reagents, respectively [8].Although chemocatalytic approach may produce L-LA in a variety of routes, none of these routes are technically and economically practical as these processes yield a racemic lactic acid which is inapt for bio-based industries [9]. In contrast, the biotechnological route utilizes carbohydrate-rich renewable resources to produce L-LA through microbial fermentation [10]. In recent decade, the biotechnological approach was chosen over the chemical synthesis approach as L-LA production route due to it offers the strength to target the enantiomer of lactic acid produced by implementing a specific type of LAB [11]. Several strains have been reported to produce L-LA naturally, such as *Bacillus coagulans*, *Lactobacillus helveticus*, and *Lactobacillus lactis* [12, 13]. Whilst, *Lactobacillus plantarum* is the strain that is commonly applied in D(-)-lactic acid (D-LA) production as it can produce only the D-enantiomer [14]. However, the lactic acid produced through the chemical synthesis route was only in racemic enantiomer which consists of D-LA and L-LA that could increase the separation cost [15].

Based on the feedstocks implemented for L-LA production via microbial fermentation, the biopolymers produced can be distinguished into three different generations. First-generation (1G) L-LA is generally derived from edible food, which consists of starch-based (barley, corn, and soybean) and sugar-based (sugarcane molasses, sweet sorghum, and sugar beet) materials [16–18]. The utilization of edible food as raw material raises a strongly polarized debate and substantial ethical dilemma, generally referred to as the "food vs. biopolymer". Thus, the global food security caused by 1G L-LA makes it unfeasible for large-scale production [10]. To address the detrimental impacts associated with 1G L-LA, second-generation (2G) L-LA incorporated lignocellulosic biomass (LCB) and agricultural residues as the feedstocks [11, 12]. However, the commercialization of 2G L-LA is constrained due to the associated environmentally unfavorable pretreatment (delignification) and the use of arable land for cultivation [13]. The delignification process is one of the crucial and costly stages for 2G L-LA production as this process is carried out to optimize the sugar recovery from LCBs incorporated with chemicals [19]. Hence, the switch of L-LA using LCBs had arisen the problem of land-use competition and high production cost, which is unfeasible as compared to 1G L-LA production. Thus, a sustainable renewable resource must resolve the economic and technical challenges faced by 1G and 2G feedstocks.

3. Utilization of Macroalgae as Feedstock for Third-generation L-lactic acid Production

The detrimental properties of 1G and 2G L-LA have fuelled the search for an alternative low-cost and renewable substrate which will warrant the year-round availability of L-LA. While bioconversion of red macroalgae to third generation (3G) L-LA has become a research topic of interest in recent years

attribute to its mild operating conditions, characteristics, and abundance in supply as its world production has reached approximately 17.3 million tons in 2018 [15, 20]. The absence of lignin complex, an obdurate lignocellulosic structure in macroalgal biomass implicates that less energy-extensive bioprocesses could be implemented to extricate high value-added bioproducts of commercialized interest, which favour techno-economic and life cycle analyses (TEA and LCA) of any presumptive macroalgal biorefinery process. Moreover, the speciality polysaccharides present in the macroalgal biomass are instinctive to macroalgal species that are categorized by the three different taxonomical groups which render unique properties for either platform biocompounds or direct use for the biorefinery. However, in Malaysia, red macroalgae *Eucheuma denticulatum* (ED) or known as *spinosum* have been widely cultivated at the east coast of Sabah (district of Semporna, Kunak, and Tawau) for the last 30 years [21]. Despite the vast ED production in Malaysia, macroalgal-based industry development has been limited, owing to the agricultural-livestock tradition such as oil palms, considering one of the nation's principal economic activities [22]. Recently, the macroalgal-based business activity is confined to carrageenan and agar extraction. While ED species is cultivated mainly for the extraction of *iota*-carrageenan phycocolloid, a thickening and emulsifying agent in food industries and a source of human food [23]. Besides being utilized for human consumption, there is a growing opportunity to produce biopolymers from *i*-carrageenan attributed to their high carbohydrate content, approximately 85.62 ± 0.38 wt% dry weight basis [6, 24]. *i*-carrageenan is a heterogenous sulfated galactan that typically consists of repeating ester sulfate 3,6-anhydrogalactose and D-galactose which showed suitability as feedstock for carbohydrates-based biorefinery [6]. The hydrolysis process converts *i*-carrageenan into galactose, and it is further valorized or fermented using lactic acid bacteria to produce 3G L-LA. Hence, this paves the way in converting the food-grade *i*-carrageenan into L-LA which has higher commercial value and is considered as an alluring investment option from environmental, social, and economic points of view for Malaysia. Moreover, the sustainability of red macroalgae biorefineries had been assessed in various LCA [25–27].

4. Saccharification of Macroalgal Carrageenan

Saccharification is an essential step prior to L-LA production, where the complex polysaccharides inside the biomass are hydrolyzed or disrupted into its monomer form, namely fermentable sugars (glucose, galactose, and rhamnose). An overview of the macroalgal biorefinery process can be shown in Fig. 1. Recently, chemical hydrolysis, namely acidolysis is a widely implemented approach for hydrolyzing the polysaccharides from the biomass into fermentable sugars [28, 29]. Acidolysis of green macroalgae *Ulva rigida* using hydrochloric acid (HCl) and sulfuric acid (H_2SO_4) as solvent with a 10:1 of liquid-to-solid (L/S) ratio at condition of 121 ºC for 1 h was conducted successfully by El Harchi et al. [30]. The authors reviewed that the total fermentable sugars (glucose and rhamnose) yield in the hydrolysate was significantly improved by 34% when replacing the acid type from HCl to H_2SO_4 under similar concentration [30]. Acids such as H_2SO_4 are superior to HCl and typically applied as the protic catalyst for chemical hydrolysis as it acquires an extra hydrogen (H^+) ion that creates a more acidic medium which can facilitate the disruption of acid-sensitive glycosidic bonds of carrageenan, leading to a high hydrolytic efficiency on the fermentable sugar extrication process [31]. Noteworthy, the concentration of H_2SO_4 is one of the influential process parameters that needs to be optimized to augment the fermentable sugars yield. However, acid hydrolysis is constrained by the degradation of sugars into 5-hydroxymethylfurfural and furfural, which are known as undesired products or toxic compounds that will inhibit microbial fermentation performance [32]. The undesired products can obviate the activities of the fermentative microorganisms by impeding the protein and RNA synthesis and damaging the DNA, which prevent the fermentation process of fermentable sugars [33]. These undesired products are generated from degradation or carbonization of fermentable sugars motived by the high acid concentration, long reaction duration, and high reaction temperature [34]. Ra et al. [35] revealed that the total fermentable sugars yield attained after acidolysis of red macroalgae *K. alvarezii* significantly decreased from 34.85 g/L to 7.20 g/L when the reaction temperature was increased from 140 ºC to 200 ºC under the similar conditions (360 mM H_2SO_4, 10 min). Moreover, a longer reaction duration will also

enhance the interaction between the released fermentable sugars and acid solvent, leading to a low total fermentable sugars yield and hydrolytic efficiency [35–37]. The carbonization of fermentable sugars is considered a side reaction of acidolysis which cannot be eliminated completely. Thereby, lower reaction severity is preferable, and a neutralization process is considered to be performed after acidolysis to minimize the negative impacts of the undesired products on the activities of the fermentative microorganisms [38].

Besides chemical hydrolysis, the biological hydrolysis assay is an attractive alternative assay to hydrolyze or disrupt the macroalgal biomass. This assay comprises the usage of biological microorganisms (bacteria or fungi) or enzymes to promote the disruption of the hydrogen bonding between the complex macroalgal polysaccharides into monomeric fermentable sugars, and typically acknowledged as enzymatic hydrolysis [39]. Recently, enzymatic hydrolysis is preferred over acidolysis for macroalgal cell wall disruption which attributes to the hydrolysis process can be performed under low reaction temperatures (35 – 50ºC) and generate minimum amount of undesired products [40]. Differently from 1G and 2G raw materials, macroalgal polysaccharides are contrary in terms of macroalgal taxonomic, in which red macroalgae mainly consists of glucose and galactose; brown macroalgae consists of glucose, mannose, and fructose; while green macroalgae consist of glucose, xylose, and rhamnose [6, 41, 42]. Thus, a multiple-enzymes system, namely an enzyme cocktail is required to augment the extrication of the fermentable sugars [43]. Sharma et al. [18] demonstrated that 48.65% of total fermentable sugars yield corresponds to 74 g/L of sugars (mannose and glucose) that can be released during enzymatic hydrolysis of brown macroalgae *Saccharina latissimi* using an enzyme cocktail consisting of cellulase (CellicCtec 2) and alginate lyase. The hydrolysis process was performed under different reaction conditions, in which reaction duration of 17 h at 50 ºC for alginate lyase and 3 h at 37 ºC for CellicCtec2 to hydrolyze alginate and cellulose, respectively. From this study, the authors concluded that the distinctiveness of the enzyme was contingent on its strain and will only perform optimally under their optimum conditions [18]. Albeit high fermentable sugars and low undesired product yield can be attained, the employment of this process is still limited which is attributed to require a longer reaction duration that ranged between 1 – 4 days [18, 44]. Therefore, the employment of enzymatic hydrolysis normally entails with pretreatment process or other hydrolysis assays (chemical or thermal) to increase the fermentable sugar productivity and reduce the hydrolysis duration [39].

Thermal hydrolysis assay, namely hydrothermal hydrolysis or autohydrolysis, is substantially manipulated based on the nucleophilic substitution of water molecules to generate hydronium (H_3O^+) ions to acidify the reaction medium for hydrolyzing the biomass polysaccharides at elevated levels of pressure and temperature in a closed system by modifying their physiochemical and thermal properties [45]. Autohydrolysis assay is regarded as a cost-effective and environmentally friendly hydrolysis assay for macroalgal biorefinery purposes which benefits from (I) the process can be operated using only water as reagent without requiring additional of catalysts or chemicals; (II) minimized corrosion issues on equipment as the process is chemical-free; (III) simple and economical operation [46]. del Río et al. [47] conducted autohydrolysis of brown macroalgae *S. muticum* under the condition of 180 ºC for a reaction duration of 25 min with a 7:1 L/S ratio in a pressurized batch reactor and attained the fermentable sugars yield of 34.89%. The authors concluded that the reaction temperature was the crucial parameter for optimum fermentable sugar yield, followed by reaction duration [47]. Comparable results were also discovered in the study of Gomes-Dias et al. [48] that the optimal fermentable sugar yield of 38.34% was attained from red macroalgae *Gelidium sesquipedale* through autohydrolysis at an optimum condition of 170 ºC for 40 min compared to that at 127.60 ºC and 212.40 ºC for identical reaction duration. Further, the authors revealed that increasing the reaction temperature beyond the optimum reaction temperature (170 ºC) would promote the generation of 5-hydroxymethylfurfural from 1.05% to 3.24% after the hydrolysis [48]. Thus, an effective hydrolysis approach is required to minimize the formation of 5- hydroxymethylfurfural and maximize the rare sugars yield from the macroalgal biomass.

For effective hydrolysis of macroalgal biomass, mild acid is incorporated with microwave irradiation. The sugar recovery of macroalgal biomass can be improved using microwave-assisted dilute acid hydrolysis as microwave heating and irradiation offers a rapid internal heating process that enhance the stereoselectivity and energy absorption by the polysaccharide particles, which can accelerate the hydrolysis process [49]. Dilute H_2SO_4 hydrolysis was conducted by Tong et al. [6] in a microwave reactor with power of 230 W to study the effect of acid concentration and reaction temperature on the fermentable sugar extrication and undesired products generation from *i*-carrageenan of ED. The authors concluded that the *i*-carrageenan was hydrolyzed effectively to attain the fermentable sugar yield of 50.70% corresponding to 27.90 ± 1.64 g/L of galactose along with a low undesired products 5-hydroxymethylfurfural of 0.74 ± 0.18 g/L with the collaboration of microwave heating and 0.1 M H_2SO_4 for 25 min [6]. From the view of microwave heating, the superficial heat transfer circumstances created by the microwave irradiation to the feedstock can enhance the fermentable sugar extrication while surpassing the formation of undesired products [50]. In contrast to microwave irradiation, conventional heating manipulates convection and conduction heat transfer, where the heat energy generated during conventional heating are transferred from the superficial appearance to the centre of the biomass by convection and conduction [51]. Hence, the heating duration for conventional heating is longer than microwave irradiation for the biomass and solvent to obtain the targeted temperatures [52]. With these limitations, this process will result in an increment of the 5-hydroxymethylfurfural which attributed to the carbonization of fermentable sugars and decrement of the fermentable sugars during the heating process [53]. Moreover, seawater as a natural resource that is rich in Cl^- ions can lead to significant improvements in reducing sugar production [54]. The involvement of Cl^- ions in the carrageenan saccharification will interact extremely with the end hydroxyl group of the D-galactose unit of carrageenan in a 1:1 ratio, that enhancing the cleavage of both intra- and intermolecular hydrogen bonding of carrageenan polysaccharide [55]. In addition, the seawater-based reducing sugar production from red macroalgae in the process of microwave-assisted dilute-sulfuric acid could improve the sugar recovery as compared with the traditional fresh distilled water-based process [56]. Hence, seawater is considered one of the highly efficient catalysts for macroalgae hydrolysis and reducing sugar production. From the technical perspective, the hydrolysis process assisted with microwave irradiation is found to be the most promising emerging bioconversion process due to can lead to higher sugar recovery yield in a short period of reaction time.

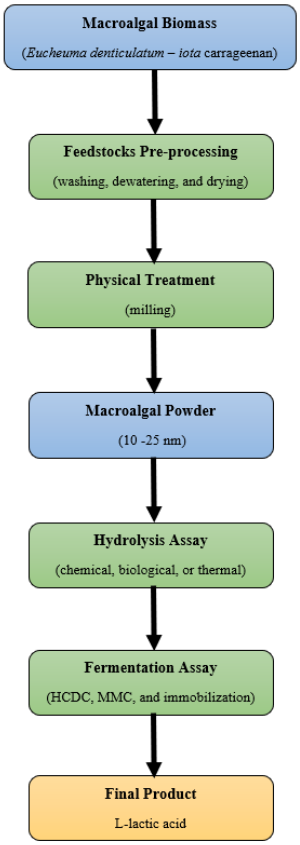

Fig. 1. Overview for macroalgal L-lactic acid production process.

5. Bacteria Selection and Immobilization for Microbial Fermentation

L-LA is widely produced through the biotechnological route by microbial fermentation of sugars extracted from carbohydrate-rich renewable resources [57]. The primary issue of this production assay is the enantiomer of lactic acid generated by fermentation depends on the lactate dehydrogenase (LDH) specificity of the microbial taxonomic implemented [58]. Among thousands of identified LAB strains, heterogeneous LAB such as *Bacillus coagulans* and *Lactobacillus acidophilus* species are the excellent producer of L-LA, which contains enzymes of L-LDH [59, 60]. With respect to the literature, high optical purity PLA can be developed either from optically pure D-lactic acid (D-LA) isomer or L-LA isomer through opening-ring polymerization [8, 61]. Nevertheless, isomer L-LA was preferred against D-LA as the monomeric block for PLA attributed to PLLA have higher tensile strength (14.5 – 140 MPa) and melting point (165 – 195 ^{o}C) than that of developed by using D-LA [62]. Further, PLLA is widely applied for biomedical applications as D-LA possess harmful element that may harm human health in terms of neurotoxicity of the human body [14]. The titer of L-LA produced also relies on the fermentation technique employed, in which the most efficient route to increase the volumetric productivity is employing the high cell density culture (HCDC) technique. HCDC offers higher fermentation efficiency to the microbial fermentation process by offering a higher metabolization rate compared low cell density culture in the same system [63]. Furthermore, employment of HCDC will significantly reduce the cell propagation cost due to all the cells can be remain, recycle, and reused in

the same system. Since the yeast or LAB cells are recycled throughout the fermentation process, the unproductive lag period of these cells during the cell development stages may be removed [64]. With respect to this, the anaerobic bioconversion of fermentable sugars to value-added bioproducts can be performed in a smaller fermenter volume [65]. Tong et al. [6] demonstrated the fermentation of microwave-assisted dilute acid hydrolyzed *i*-carrageenan at pH 5.2 and 37°C for 14 h and improved the L-LA productivity rate in the fermentation broth up to 89.4% when elevating the inoculum cell concentration of *B. coagulans* ATCC 7050 from 2% to 4 % (v/v).

Moreover, mixed microbial culture (MMC) also offers a better conversion efficiency of sugars to L-LA. In fact, unlike monocultures, MMC shows a complementary metabolism and can utilize different carbon sources [66]. For this reason, the high density of MMC is considered a promising alternative approach, where it shows better performance than pure strain [11]. For effective microbial fermentation, a high density of MMC is incorporated with cell immobilization. Where immobilization of LAB offers several advantages over freely suspended cells in fermentation systems, including repeated usage of cells, high productivity of bio-products, and sustainable biological activity retained over a long fermentation duration [67]. Thus, a high density of immobilized MMC is a useful strategy for the continuous production of L-LA. Furthermore, the fermentation performance of the microbial strain is also constrained by the trace metals accumulated in the macroalgal biomass [52]. Some metal ions are essential in compact quantities for microbial life to burgeon, but this is dependent on the microbial taxonomic and fermentation route that is implemented, in which the metal ions can act as inhibit crucial biological processes in their exclusion or even a catalyst [68]. This can be supported by Bikker et al. [69], in which the presence of nickel chloride and sodium selenite with the concentration of 100 mg/L in the *Ulva lactuca* collected from the Irish coast for biobutanol production using the bacterial strain of *Clostridium acetobutylicum* was successfully increased the biobutanol yield with a nearly 2-fold increase compared to the absence of the trace metals [69]. Different bacterial strains show contradictory performances of response to metal ions exposure concentrations in macroalgae feedstock, while different metal ions possess varying ecotoxic potency to given bacterial strain [68]. Thus, for the purpose of improving microbial fermentation process for biochemical synthesis, a deeper comprehension of metal toxicity is required.

6. Challenges and future perspectives

The rapid growth rate and yield of macroalgae have led to the description of L-LA processing research as one of the sustainable and clean procedures. Nevertheless, the commercialization of 3G L-LA is still limited by several challenges which include existing technologies and biorefinery approaches for macroalgae bioconversion [70]. Further, all the recent research related to macroalgal L-LA production is restricted to only laboratory scale; therefore, the viability of a process in a continuous system is unreliable for large-scale commercialized performance in an industrial context [71]. Thus, the fermentation and hydrolysis procedures must be improved and refined in order to successfully scale up to higher amounts. Moreover, the implementation of enzyme cocktail or engineered enzymes, where modifying the genetic of the enzymes in the hydrolysis procedures, will be an interesting way for increasing the yield of extricated fermentable sugars as this can fully hydrolyzed the biomass [72]. Additionally, macroalgae competitiveness may be further boosted by optimizing the extraction of all accessible high value compounds by cascade biorefinery (lipids, ash, pigments, and proteins) [23]. In addition, because fourth generation (4G) bioproducts are mostly produced by genetically engineered yeast and macroalgae, thereby, macroalgae can be regarded as a potential feedstock for 4G L-LA [73].

Conclusion

Literature related to macroalga-derived L-LA had a rising inclination with the inflating research outputs [18, 19]. However, the usage of macroalgae carrageenan as biomass for L-LA generation is still limited and in the early stages. Thereby, more advanced research is required to reveal the full potential of macroalgae carrageenan as 3G feedstock. In order to enhance the sugar recovery from carrageenan and

the productivity of L-LA, a process- and time-efficient innovative hydrolysis and fermentation approach is needed.

Acknowledgement
The authors would like to admit Curtin University Malaysia for supporting this research through the Curtin Malaysia Postgraduate Research Scholarship (CMPRS).

References

1. Laaziz, S.A., Raji, M., Hilali, E., Essabir, H., Rodrigue, D., Bouhfid, R., Qaiss, A. el kacem: Bio-composites based on polylactic acid and argan nut shell: Production and properties. Int J Biol Macromol. 104, 30–42 (2017). https://doi.org/10.1016/J.IJBIOMAC.2017.05.184
2. European Bioplastics: Global production capacities of bioplastics 2019-2025. (2020)
3. Jem, K.J., Tan, B.: The development and challenges of poly (lactic acid) and poly (glycolic acid). Advanced Industrial and Engineering Polymer Research. 3, 60–70 (2020). https://doi.org/10.1016/J.AIEPR.2020.01.002
4. Prata, J.C., Patrício Silva, A.L., da Costa, J.P., Mouneyrac, C., Walker, T.R., Duarte, A.C., Rocha-Santos, T.: Solutions and Integrated Strategies for the Control and Mitigation of Plastic and Microplastic Pollution. Int J Environ Res Public Health. 16, (2019). https://doi.org/10.3390/IJERPH16132411
5. Singhvi, M.S., Zinjarde, S.S., Gokhale, D. v.: Polylactic acid: synthesis and biomedical applications. J Appl Microbiol. 127, 1612–1626 (2019). https://doi.org/10.1111/JAM.14290
6. Tong, K.T.X., Tan, I.S., Foo, H.C.Y., Tiong, A.C.Y., Lam, M.K., Lee, K.T.: Third-generation L-Lactic acid production by the microwave-assisted hydrolysis of red macroalgae Eucheuma denticulatum extract. Bioresour Technol. 342, 125880 (2021). https://doi.org/10.1016/J.BIORTECH.2021.125880
7. Goulas, K.A., Toste, F.D.: Combining microbial production with chemical upgrading. Curr Opin Biotechnol. 38, 47–53 (2016). https://doi.org/10.1016/J.COPBIO.2015.12.019
8. Rahmayetty, Whulanza, Y., Sukirno, Rahman, S.F., Suyono, E.A., Yohda, M., Gozan, M.: Use of Candida rugosa lipase as a biocatalyst for L-lactide ring-opening polymerization and polylactic acid production. Biocatal Agric Biotechnol. 16, 683–691 (2018). https://doi.org/10.1016/J.BCAB.2018.09.015
9. Shuklov, I.A., Dubrovina, N. V., Kühlein, K., Börner, A.: Chemo-Catalyzed Pathways to Lactic Acid and Lactates. Adv Synth Catal. 358, 3910–3931 (2016). https://doi.org/10.1002/ADSC.201600768
10. Mazumder, A., Holdt, S.L., de Francisci, D., Alvarado-Morales, M., Mishra, H.N., Angelidaki, I.: Extraction of alginate from Sargassum muticum: process optimization and study of its functional activities. J Appl Phycol. 28, 3625–3634 (2016). https://doi.org/10.1007/S10811-016-0872-X
11. Liang, S., Gliniewicz, K., Gerritsen, A.T., McDonald, A.G.: Analysis of microbial community variation during the mixed culture fermentation of agricultural peel wastes to produce lactic acid. Bioresour Technol. 208, 7–12 (2016). https://doi.org/10.1016/J.BIORTECH.2016.02.054
12. Cubas-Cano, E., Venus, J., González-Fernández, C., Tomás-Pejó, E.: Assessment of different Bacillus coagulans strains for l-lactic acid production from defined media and gardening hydrolysates: Effect of lignocellulosic inhibitors. J Biotechnol. 323, 9–16 (2020). https://doi.org/10.1016/J.JBIOTEC.2020.07.017
13. Komesu, A., Maciel, M.R.W., Filho, R.M.: Separation and purification technologies for lactic acid - A brief review. Bioresources. 12, 6885–6901 (2017). https://doi.org/10.15376/BIORES.12.3.6885-6901
14. Pohanka, M.: D-Lactic Acid as a Metabolite: Toxicology, Diagnosis, and Detection. Biomed Res Int. 2020, (2020). https://doi.org/10.1155/2020/3419034

15. FAO, F. and A.: Fisheries and Aquaculture Department - Yearbook of Fishery and Aquaculture Statistics - Aquaculture production, http://www.fao.org/fishery/static/Yearbook/YB2017_USBcard/navigation/index_content_aquaculture_e.htm
16. Radosavljević, M., Lević, S., Belović, M., Pejin, J., Djukić-Vuković, A., Mojović, L., Nedović, V.: Encapsulation of Lactobacillus rhamnosus in Polyvinyl Alcohol for the production of L-(+)-Lactic Acid. Process Biochemistry. 100, 149–160 (2021). https://doi.org/10.1016/J.PROCBIO.2020.10.006
17. Ayodele, B.V., Alsaffar, M.A., Mustapa, S.I.: An overview of integration opportunities for sustainable bioethanol production from first- and second-generation sugar-based feedstocks. J Clean Prod. 245, 118857 (2020). https://doi.org/10.1016/J.JCLEPRO.2019.118857
18. Sharma, S., Horn, S.J.: Enzymatic saccharification of brown seaweed for production of fermentable sugars. Bioresour Technol. 213, 155–161 (2016). https://doi.org/10.1016/J.BIORTECH.2016.02.090
19. Mithra, M.G., Jeeva, M.L., Sajeev, M.S., Padmaja, G.: Comparison of ethanol yield from pretreated lignocellulo-starch biomass under fed-batch SHF or SSF modes. Heliyon. 4, e00885 (2018). https://doi.org/10.1016/J.HELIYON.2018.E00885
20. Chai, C.Y., Tan, I.S., Foo, H.C.Y., Lam, M.K., Tong, K.T.X., Lee, K.T.: Sustainable and green pretreatment strategy of Eucheuma denticulatum residues for third-generation L-lactic acid production. Bioresour Technol. 330, (2021). https://doi.org/10.1016/j.biortech.2021.124930
21. Phang, S.-M., Yeong, H.-Y., Lim, P.-E.: The seaweed resources of Malaysia. Botanica Marina. 62, 265–273 (2019). https://doi.org/10.1515/BOT-2018-0067
22. Parveez, G.K.A., Tarmizi, A.H.A., Sundram, S., Loh, S.K., Ong-Abdullah, M., Palam, K.D.P., Salleh, K.M., Ishak, S.M., Idris, Z.: Oil palm economic performance in Malaysia and R&D progress in 2020. J Oil Palm Res. 33, 181–214 (2021). https://doi.org/10.21894/JOPR.2021.0026
23. Cesário, M.T., da Fonseca, M.M.R., Marques, M.M., de Almeida, M.C.M.D.: Marine algal carbohydrates as carbon sources for the production of biochemicals and biomaterials. Biotechnol Adv. 36, 798–817 (2018). https://doi.org/10.1016/J.BIOTECHADV.2018.02.006
24. Chai, C.Y., Tan, I.S., Foo, H.C.Y., Lam, M.K., Tong, K.T.X., Lee, K.T.: Sustainable and green pretreatment strategy of Eucheuma denticulatum residues for third-generation l-lactic acid production. Bioresour Technol. 330, 124930 (2021). https://doi.org/10.1016/J.BIORTECH.2021.124930
25. Seghetta, M., Hou, X., Bastianoni, S., Bjerre, A.B., Thomsen, M.: Life cycle assessment of macroalgal biorefinery for the production of ethanol, proteins and fertilizers – A step towards a regenerative bioeconomy. J Clean Prod. 137, 1158–1169 (2016). https://doi.org/10.1016/J.JCLEPRO.2016.07.195
26. Zhang, X., Border, A., Goosen, N., Thomsen, M.: Environmental life cycle assessment of cascade valorisation strategies of South African macroalga Ecklonia maxima using green extraction technologies. Algal Res. 58, 102348 (2021). https://doi.org/10.1016/J.ALGAL.2021.102348
27. Sadhukhan, J., Gadkari, S., Martinez-Hernandez, E., Ng, K.S., Shemfe, M., Torres-Garcia, E., Lynch, J.: Novel macroalgae (seaweed) biorefinery systems for integrated chemical, protein, salt, nutrient and mineral extractions and environmental protection by green synthesis and life cycle sustainability assessments. Green Chemistry. 21, 2635–2655 (2019). https://doi.org/10.1039/C9GC00607A
28. Yun, E.J., Kim, H.T., Cho, K.M., Yu, S., Kim, S., Choi, I.G., Kim, K.H.: Pretreatment and saccharification of red macroalgae to produce fermentable sugars. Bioresour Technol. 199, 311–318 (2016). https://doi.org/10.1016/J.BIORTECH.2015.08.001
29. Tong, K.T.X., Tan, I.S., Foo, H.C.Y., Lam, M.K., Lim, S., Lee, K.T.: Advancement of biorefinery-derived platform chemicals from macroalgae: a perspective for bioethanol and

lactic acid. Biomass Conversion and Biorefinery 2022. 1, 1–37 (2022). https://doi.org/10.1007/S13399-022-02561-7
30. el Harchi, M., Fakihi Kachkach, F.Z., el Mtili, N.: Optimization of thermal acid hydrolysis for bioethanol production from Ulva rigida with yeast Pachysolen tannophilus. South African Journal of Botany. 115, 161–169 (2018). https://doi.org/10.1016/J.SAJB.2018.01.021
31. Teh, Y.Y., Lee, K.T., Chen, W.H., Lin, S.C., Sheen, H.K., Tan, I.S.: Dilute sulfuric acid hydrolysis of red macroalgae Eucheuma denticulatum with microwave-assisted heating for biochar production and sugar recovery. Bioresour Technol. 246, 20–27 (2017). https://doi.org/10.1016/J.BIORTECH.2017.07.101
32. Derman, E., Abdulla, R., Marbawi, H., Sabullah, M.K.: Oil palm empty fruit bunches as a promising feedstock for bioethanol production in Malaysia. Renew Energy. 129, 285–298 (2018). https://doi.org/10.1016/J.RENENE.2018.06.003
33. Feldman, D., Kowbel, D.J., Glass, N.L., Yarden, O., Hadar, Y.: Detoxification of 5-hydroxymethylfurfural by the Pleurotus ostreatus lignolytic enzymes aryl alcohol oxidase and dehydrogenase. Biotechnology for Biofuels 2015 8:1. 8, 1–11 (2015). https://doi.org/10.1186/S13068-015-0244-9
34. Shobana, S., Kumar, G., Bakonyi, P., Saratale, G.D., Al-Muhtaseb, A.H., Nemestóthy, N., Bélafi-Bakó, K., Xia, A., Chang, J.S.: A review on the biomass pretreatment and inhibitor removal methods as key-steps towards efficient macroalgae-based biohydrogen production. Bioresour Technol. 244, 1341–1348 (2017). https://doi.org/10.1016/J.BIORTECH.2017.05.172
35. Ra, C.H., Nguyen, T.H., Jeong, G.T., Kim, S.K.: Evaluation of hyper thermal acid hydrolysis of Kappaphycus alvarezii for enhanced bioethanol production. Bioresour Technol. 209, 66–72 (2016). https://doi.org/10.1016/J.BIORTECH.2016.02.106
36. Hamouda, R.A., Sherif, S.A., Dawoud, G.T.M., Ghareeb, M.M.: Enhancement of bioethanol production from Ulva fasciata by biological and chemical saccharification. Rendiconti Lincei. 27, 665–672 (2016). https://doi.org/10.1007/S12210-016-0546-2
37. Hessami, M.J., Cheng, S.F., Ambati, R.R., Yin, Y.H., Phang, S.M.: Bioethanol production from agarophyte red seaweed, Gelidium elegans, using a novel sample preparation method for analysing bioethanol content by gas chromatography. 3 Biotech. 9, 1–8 (2019). https://doi.org/10.1007/S13205-018-1549-8
38. Ran, H., Zhang, J., Gao, Q., Lin, Z., Bao, J.: Analysis of biodegradation performance of furfural and 5-hydroxymethylfurfural by Amorphotheca resinae ZN1. Biotechnology for Biofuels 2014 7:1. 7, 1–12 (2014). https://doi.org/10.1186/1754-6834-7-51
39. Thompson, T.M., Young, B.R., Baroutian, S.: Advances in the pretreatment of brown macroalgae for biogas production. Fuel Processing Technology. 195, 106151 (2019). https://doi.org/10.1016/J.FUPROC.2019.106151
40. Tan, I.S., Lam, M.K., Foo, H.C.Y., Lim, S., Lee, K.T.: Advances of macroalgae biomass for the third generation of bioethanol production. Chin J Chem Eng. 28, 502–517 (2020). https://doi.org/10.1016/J.CJCHE.2019.05.012
41. Poespowati, T., Riyanto, A., Hazlan, Mahmudi, A., Kartika-Dewi, R.: Enzymatic hydrolysis of liquid hot water pre-treated macro-alga (Ulva lactuca) for fermentable sugar production. MATEC Web of Conferences. 156, (2018). https://doi.org/10.1051/MATECCONF/201815601015
42. Kostas, E.T., White, D.A., Cook, D.J.: Development of a bio-refinery process for the production of speciality chemical, biofuel and bioactive compounds from Laminaria digitata. Algal Res. 28, 211–219 (2017). https://doi.org/10.1016/J.ALGAL.2017.10.022
43. Pathiraja, D., Lee, S., Choi, I.-G.: Model-Based Complete Enzymatic Production of 3,6-Anhydro-l-galactose from Red Algal Biomass. J Agric Food Chem. 66, 6814–6821 (2018). https://doi.org/10.1021/ACS.JAFC.8B01792

44. Jmel, M.A., Ben Messaoud, G., Marzouki, M.N., Mathlouthi, M., Smaali, I.: Physico-chemical characterization and enzymatic functionalization of Enteromorpha sp. cellulose. Carbohydr Polym. 135, 274–279 (2016). https://doi.org/10.1016/J.CARBPOL.2015.08.048
45. Cervantes-Cisneros, D.E., Arguello-Esparza, D., Cabello-Galindo, A., Picazo, B., Aguilar, C.N., Ruiz, H.A., Rodríguez-Jasso, R.M.: Hydrothermal Processes for Extraction of Macroalgae High Value-Added Compounds. Hydrothermal Processing in Biorefineries: Production of Bioethanol and High Added-Value Compounds of Second and Third Generation Biomass. 461–481 (2017). https://doi.org/10.1007/978-3-319-56457-9_20
46. Michalak, I., Chojnacka, K.: Algae as production systems of bioactive compounds. Eng Life Sci. 15, 160–176 (2015). https://doi.org/10.1002/ELSC.201400191
47. del Río, P.G., Domínguez, E., Domínguez, V.D., Romaní, A., Domingues, L., Garrote, G.: Third generation bioethanol from invasive macroalgae Sargassum muticum using autohydrolysis pretreatment as first step of a biorefinery. Renew Energy. 141, 728–735 (2019). https://doi.org/10.1016/J.RENENE.2019.03.083
48. Gomes-Dias, J.S., Romaní, A., Teixeira, J.A., Rocha, C.M.R.: Valorization of Seaweed Carbohydrates: Autohydrolysis as a Selective and Sustainable Pretreatment. ACS Sustain Chem Eng. 8, 17143–17153 (2020). https://doi.org/10.1021/ACSSUSCHEMENG.0C05396
49. Yuan, Y., Macquarrie, D.: Microwave assisted extraction of sulfated polysaccharides (fucoidan) from Ascophyllum nodosum and its antioxidant activity. Carbohydr Polym. 129, 101–107 (2015). https://doi.org/10.1016/J.CARBPOL.2015.04.057
50. Boulho, R., Marty, C., Freile-Pelegrín, Y., Robledo, D., Bourgougnon, N., Bedoux, G.: Antiherpetic (HSV-1) activity of carrageenans from the red seaweed Solieria chordalis (Rhodophyta, Gigartinales) extracted by microwave-assisted extraction (MAE). J Appl Phycol. 29, 2219–2228 (2017). https://doi.org/10.1007/S10811-017-1192-5
51. Kundu, C., Lee, J.W.: Optimization conditions for oxalic acid pretreatment of deacetylated yellow poplar for ethanol production. Journal of Industrial and Engineering Chemistry. 32, 298–304 (2015). https://doi.org/10.1016/J.JIEC.2015.09.001
52. Amini, A., Ohno, K. ichiro, Maeda, T., Kunitomo, K.: A kinetic comparison between microwave heating and conventional heating of FeS-CaO mixture during hydrogen-reduction. Chemical Engineering Journal. 374, 648–657 (2019). https://doi.org/10.1016/J.CEJ.2019.05.226
53. Dussán, K.J., Silva, D.D. V, Moraes, E.J.C., Arruda, P. V, Felipe, M.G.A.: Dilute-acid Hydrolysis of Cellulose to Glucose from Sugarcane Bagasse. Chem Eng Trans. 38, 433–438 (2014). https://doi.org/10.3303/CET1438073
54. Mao, L., Zhang, L., Gao, N., Li, A.: Seawater-based furfural production via corncob hydrolysis catalyzed by FeCl3 in acetic acid steam. Green Chemistry. 15, 727–737 (2013). https://doi.org/10.1039/C2GC36346A
55. Jiang, Z., Yi, J., Li, J., He, T., Hu, C.: Promoting Effect of Sodium Chloride on the Solubilization and Depolymerization of Cellulose from Raw Biomass Materials in Water. ChemSusChem. 8, 1901–1907 (2015). https://doi.org/10.1002/CSSC.201500158
56. Greetham, D., Adams, J.M., Du, C.: The utilization of seawater for the hydrolysis of macroalgae and subsequent bioethanol fermentation. Scientific Reports 2020 10:1. 10, 1–15 (2020). https://doi.org/10.1038/s41598-020-66610-9
57. Ahmad, A., Banat, F., Taher, H.: A review on the lactic acid fermentation from low-cost renewable materials: Recent developments and challenges. Environ Technol Innov. 20, 101138 (2020). https://doi.org/10.1016/J.ETI.2020.101138
58. Wu, W., Zhang, B.: Lactic Acid Bacteria and B Vitamins. Lactic Acid Bacteria. 43–60 (2019). https://doi.org/10.1007/978-981-13-7283-4_3
59. Lin, H.-T.V., Huang, M.-Y., Kao, T.-Y., Lu, W.-J., Lin, H.-J., Pan, C.-L.: Production of Lactic Acid from Seaweed Hydrolysates via Lactic Acid Bacteria Fermentation. Fermentation 2020, Vol. 6, Page 37. 6, 37 (2020). https://doi.org/10.3390/FERMENTATION6010037

60. Murru, N., Blaiotta, G., Peruzy, M.F., Santonicola, S., Mercogliano, R., Aponte, M.: Screening of Oxalate Degrading Lactic Acid Bacteria of Food Origin. Ital J Food Saf. 6, 6345 (2017). https://doi.org/10.4081/IJFS.2017.6345
61. Laaziz, S.A., Raji, M., Hilali, E., Essabir, H., Rodrigue, D., Bouhfid, R., Qaiss, A. el kacem: Bio-composites based on polylactic acid and argan nut shell: Production and properties. Int J Biol Macromol. 104, 30–42 (2017). https://doi.org/10.1016/J.IJBIOMAC.2017.05.184
62. Yu, B., Cao, Y., Sun, H., Han, J.: The Structure and Properties of Biodegradable PLLA/PDLA for Melt-Blown Nonwovens. J Polym Environ. 25, 510–517 (2016). https://doi.org/10.1007/S10924-016-0827-Y
63. Genzel, Y., Vogel, T., Buck, J., Behrendt, I., Ramirez, D.V., Schiedner, G., Jordan, I., Reichl, U.: High cell density cultivations by alternating tangential flow (ATF) perfusion for influenza A virus production using suspension cells. Vaccine. 32, 2770–2781 (2014). https://doi.org/10.1016/J.VACCINE.2014.02.016
64. Bähr, L., Wüstenberg, A., Ehwald, R.: Two-tier vessel for photoautotrophic high-density cultures. J Appl Phycol. 28, 783–793 (2016). https://doi.org/10.1007/S10811-015-0614-5
65. Guljamow, A., Kreische, M., Ishida, K., Liaimer, A., Altermark, B., Bähr, L., Hertweck, C., Ehwald, R., Dittmann, E.: High-Density Cultivation of Terrestrial Nostoc Strains Leads to Reprogramming of Secondary Metabolome. Appl Environ Microbiol. 83, (2017). https://doi.org/10.1128/AEM.01510-17
66. Pinto, T., Flores-Alsina, X., Gernaey, K. v., Junicke, H.: Alone or together? A review on pure and mixed microbial cultures for butanol production. Renewable and Sustainable Energy Reviews. 147, 111244 (2021). https://doi.org/10.1016/J.RSER.2021.111244
67. Abudi, Z.N., Hu, Z., Sun, N., Xiao, B., Rajaa, N., Liu, C., Guo, D.: Batch anaerobic co-digestion of OFMSW (organic fraction of municipal solid waste), TWAS (thickened waste activated sludge) and RS (rice straw): Influence of TWAS and RS pretreatment and mixing ratio. Energy. 107, 131–140 (2016). https://doi.org/10.1016/J.ENERGY.2016.03.141
68. Qiang, H., Niu, Q., Chi, Y., Li, Y.: Trace metals requirements for continuous thermophilic methane fermentation of high-solid food waste. Chemical Engineering Journal. 222, 330–336 (2013). https://doi.org/10.1016/J.CEJ.2013.02.076
69. Bikker, P., van Krimpen, M.M., van Wikselaar, P., Houweling-Tan, B., Scaccia, N., van Hal, J.W., Huijgen, W.J.J., Cone, J.W., López-Contreras, A.M.: Biorefinery of the green seaweed Ulva lactuca to produce animal feed, chemicals and biofuels. J Appl Phycol. 28, 3511 (2016). https://doi.org/10.1007/S10811-016-0842-3
70. Zollmann, M., Robin, A., Prabhu, M., Polikovsky, M., Gillis, A., Greiserman, S., Golberg, A.: Green technology in green macroalgal biorefineries. Phycologia. 58, 516–534 (2019). https://doi.org/10.1080/00318884.2019.1640516
71. Ocreto, J.B., Chen, W.-H., Ubando, A.T., Park, Y.-K., Sharma, A.K., Ashokkumar, V., Ok, Y.S., Kwon, E.E., Rollon, A.P., De Luna, M.D.G.: A critical review on second- and third-generation bioethanol production using microwaved-assisted heating (MAH) pretreatment. Renewable and Sustainable Energy Reviews. 152, 111679 (2021). https://doi.org/10.1016/J.RSER.2021.111679
72. Rajak, R.C., Jacob, S., Kim, B.S.: A holistic zero waste biorefinery approach for macroalgal biomass utilization: A review. Science of The Total Environment. 716, 137067 (2020). https://doi.org/10.1016/J.SCITOTENV.2020.137067
73. Abdullah, B., Syed Muhammad, S.A.F. ad, Shokravi, Z., Ismail, S., Kassim, K.A., Mahmood, A.N., Aziz, M.M.A.: Fourth generation biofuel: A review on risks and mitigation strategies. Renewable and Sustainable Energy Reviews. 107, 37–50 (2019). https://doi.org/10.1016/J.RSER.2019.02.018