



Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Kappaphycus alvarezii macroalgae: An unexplored and valuable biomass for green biorefinery conversion

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ARTICLE INFO

Keywords:

Red seaweed
Bioactive molecules
Circular economy
Eco-friendly extraction methods
Algae carbohydrates

ABSTRACT

Background: *Kappaphycus alvarezii* is the 5th world's most cultivated macroalgae, since it is an essential source of carrageenan, widely used in food industry. However, *K. alvarezii* is an unexplored biomass for green biorefinery conversion, since its composition includes valuable proteins, lipids, phenolic compounds, among others. Although there are reviews on *K. Alvarezii* cultivation and pharmacological properties, no information is available regarding extraction techniques applied to this algae biomass. Therefore, this review covers the lack of information on biorefinery concept applied to *K. alvarezii* and suggest sequential extractions to recover carrageenan and high-added value molecules by using non-conventional methods.

Scope and approach: This critical review presents the most recent data on *K. alvarezii*, including its scientific trends, production and potential. It also deals with non-traditional methods for sequential extractions applied to *K. alvarezii*. The search for available data was extended to the group of red algae to consider the concept of biorefinery.

Key findings and conclusions: *K. alvarezii* biomass can be used to obtain chlorophyll, β -carotene, essential amino acids (aspartic acid, glutamic acid and phenylalanine) and phytohormones (indole acetic acid, zeatin, kinetin and gibberellic acid). Therefore, we provide several sustainable insights to sequentially recovery carrageenan and other bioactive compounds from *K. alvarezii*.

1. Introduction

The oceans are remarkable sources of unexplored and valuable materials, in particular seaweed, since they contain very unique molecules including phenols, pigments, polysaccharides, proteins and bioactive peptides, among others (Pangestuti, Getachew, Siahaan, & Chun, 2019; Pangestuti, Siahaan, & Kim, 2018). Furthermore, it is worth mention that the seaweed cultivation is well aligned with the principles of sustainable production, since seaweed can mitigate around 20 tons of CO₂/hectare/year, there is no need of fresh water, and no competition for land, in relation to food production (Hargreaves, Barcelos, da Costa, & Pereira, 2013).

Based on the photosynthetic pigments, seaweeds can be classified into three groups: green algae (Chlorophyta), brown algae (Phaeophyta) and red algae (Rhodophyta). Among them, red algae comprise more than 60% out of 30 thousand tons of algae cultivated around the world (FAO, 2018a). The main interest on red algae is related to their easy cultivation and high content of unique polysaccharides (40–50% of the dry weight), in particular carrageenan and agar (FAO, 2018b;

Khambhaty et al., 2012; Solorzano-Chavez et al., 2019; Torres, Flórez-Fernández, & Domínguez, 2019). In this sense, red seaweed species, *Kappaphycus alvarezii* (KA), *Euचेuma denticulatum*, *Chondrus crispus*, and *Sarcothalia crispate*, are the main sources of carrageenan, at industrial scale (Naseri, Holdt, & Jacobsen, 2019).

Besides, seaweed in general present several high-added value molecules such as minerals, polyphenols, lipids and proteins (peptides) which are mostly scientifically and industrially unexplored.

According to the green chemistry principles, the recovery of high added-value molecules by using environmental friendly extraction methods should be inherently associated to the concept of biorefinery, which aims to obtain, as extended as possible, a wide variety of products and energy (Cherubini, 2010; Herrero & Ibañez, 2018). In this context, green non-conventional extraction methods such as pressurized liquid extraction (PLE), subcritical water extraction (SWE), supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), and ultrasound-assisted extraction (UAE) have been only recently associated to biorefinery concept by the scientific community.

Although there are some scientific reports about red algae

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Received 7 May 2020; Received in revised form 10 July 2020; Accepted 17 July 2020

Available online 25 July 2020

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biorefinery (Torres et al., 2019; Álvarez-Viñas, Flórez-Fernández, Torres, & Domínguez, 2019); when it comes to KA, to the best of our knowledge, most works deal exclusively to KA cultivation (Bindu & Levine, 2011; Hayashi, Bulboa, Kradolfer, Soriano, & Robledo, 2014; Hayashi et al., 2011; Reis, Pereira, & de Góes, 2014) or its pharmacological properties (Hayashi & Reis, 2012). Therefore, in order to cover the lack of information about biorefinery concept applied to KA, this review highlights the key features of KA as potential biomass for green biorefinery conversion. It also includes the KA main high-valuable molecules, and its potential applications, with special focus on non-conventional extraction methods applied to red algae, particularly concerning KA.

2. Red seaweed

Rhodophyta or red algae can be cultivated in temperate and sub- or tropical zones. The most important, industrially, red algae species are *Euचेuma denticulatum*, *Kappaphycus alvarezii*, *Chondrus crispus* and *Sarcosthalia crispate*; since they are sources of carrageenan (Naseri et al., 2019).

2.1. Red algae world production

According to Food and Agriculture Organization of the United Nations (FAO), in 2016 the production of aquatic plants (macroalgae and microalgae) was over 30 million tons (FAO, 2018b). China, Indonesia, and the Philippines were the main producers (Fig. 1a), in which red algae representing near 60% of the total production. As already mentioned, the industrial interest on red seaweed is mainly associated with agar and carrageenan extraction, since they are widely used as

additives for different industrial segments, especially in food industries. Carrageenan, for instance, is used by food industry for the production of ice-cream, cheese, jam and bread, as well as for cosmetic industries as thickeners and stabilizers. Besides, the carrageenan applications depend on its types (ι , κ , and λ - section 3.1). In this sense, a quite novel approach is the application of hybrid carrageenan, which is a copolymer composed of different unit types (ι , κ , λ) in a single polymer chain. When compared to homo-polymeric chains, the hybrid carrageenan has wider range of applications, since the different properties from each carrageenan type can be complementary to one another (Azevedo, Torres, Sousa-Pinto, & Hilliou, 2015). Also, spreading the applications, antiviral activities were recently associated to alginates from brown macroalgae; and the microsphere and microcapsule properties of carrageenans from red macroalgae have been drawing increasing attention from pharmaceutical industry (Rhein-Knudsen, Ale, & Meyer, 2015).

According to FAO data, in 2016 the KA production was 1527 thousand tons, which corresponds to approximately 5.1% out of the total macroalgae production (Fig. 1b). It is noteworthy that the first five most produced macroalgae are *Euचेuma* spp., *Laminaria Japonica*, *Undaria pinnatifida*, *Gracilaria* spp., and KA, respectively (FAO, 2018b). KA is an endemic seaweed from Philippines. Until 2008, the Philippines was the largest supplier of *Kappaphycus* species. However, in 2008 they were overcome by Indonesia (Hayashi et al., 2017).

2.2. Red algae in Brazil

The extractive exploitation of macroalgae means that there are no cultivations handled by humans. In Brazil, the “agar project” started in 1964 at Federal University of Rio Grande do Norte (UFRN) and detected that some marine algae species could be economically explored. In the following years, 3 companies started to explore two native red seaweeds: *Gracilaria* spp. and *Hypnea musciformis*. Nevertheless, the over-exploitation and the lack of legislation led to resource depletion in less than 10 years (Câmara Neto, 1987). Later, the first attempts of macroalgae cultivation (*Gracilaria* spp.) were implanted in Northeast Brazil, with studies carried out by a consortium of Brazilian institutions, composed by UFRN, Superintendence for Development of the Northeast (SUDENE), International Foundation of Science (IFS) and the Superintendence for Fisheries Development (SUDEPE) (Câmara Neto, 1987). Since then, the cultivation of *Gracilaria birdiae* in the States of Ceará, Rio Grande do Norte and Paraíba (Northeastern Brazil) is an interesting alternative for local producers. Currently, *Gracilaria* species are still cultivated in the Northeast Region, and also in São Paulo (Southeastern Brazil) (Andrade et al., 2020; Hayashi et al., 2014).

Regarding KA, it was introduced in Brazil in 1995 in São Paulo, mainly to supply the Brazilian carrageenan market (Hayashi & Reis, 2012). Commercial cultivation began in 1998 in Ilha Grande Bay-RJ (Southeastern Brazil). Later, in 2003, a commercial farm was established in Sepetiba Bay-RJ. In 2008, after more than 10 years of research, the Brazilian Institute for the Environment and Renewable Natural Resources (IBAMA), a governmental agency, authorized the KA cultivation by the normative instruction n° 185, 2008, exclusively, in the area between Sepetiba Bay-RJ and Ilha Bela-SP. In 2008, the KA cultivation was implanted in Florianópolis-SC (Southern Brazil), a subtropical climate, by Federal University of Santa Catarina (UFSC) and the Company of Agricultural Research and Rural Extension of Santa Catarina (EPAGRI) (Hayashi et al., 2011; Simioni, Hayashi, & Oliveira, 2019). Currently, the commercial cultivation of KA between Itapoá (SC) and Jaguaruna (SC) was authorized by the normative instruction n° 1, 2020, IBAMA.

Brazil has remarkable potential as a seaweed biomass producer due to its enormous coastline (8500 km) (16th world's largest coastline) (Ministério do Meio Ambiente, 2020), and different climate, tropical to subtropical (cultivation possibilities), with average sea temperatures of 27.8 °C and 22.5 °C, respectively. However, the industrial macroalgae cultivation is underexplored. According to FAO between 2012 and 2016, Brazil was among the 20th higher carrageenan importers, with up to

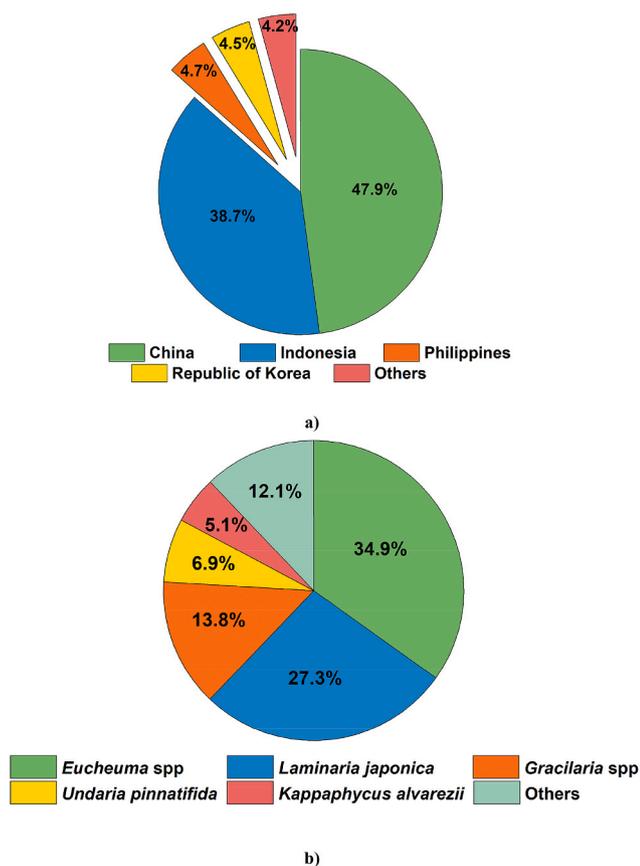


Fig. 1. Algae production in the world: (a) percentage of major farmed seaweed producers in 2016 (b) main algae produced in 2016. Source: FAO (2018b).

2731 tons of carrageenan per year. Furthermore, 1409.8 tons of seaweed per year were also imported.

3. *Kappaphycus alvarezii*

The alga KA (Fig. 2), also known by its commercial name *cotonii*, is a class of Rhodophyceae. This type of alga is found in reddish, yellowish, brown and green colors depending on the phycoerythrin pigment concentration. It is easily cultivated and grows fast, with an increase near 4.5% daily (Gereniu, Saravana, Getachew, & Chun, 2017).

KA is the major industrial source of κ -carrageenan (Das & Prasad, 2015; Gereniu, Saravana, Getachew, & Chun, 2017), since this polysaccharide represents up to 37 wt% of the algae, in dry base (Lechat et al., 1997). Due to the physicochemical properties of κ -carrageenan such as gelling, thickening, emulsifying and stabilizing, it has a wide range of applications such as thickening agent for milk based desserts (Zarzycki, Ciołkowska, Jabłońska-Ryś, & Gustaw, 2019) and sausages (Atashkar, Hojjatoleslami, & Sedaghat Boroujeni, 2018; Baracco, Furlán, & Campderrós, 2017), and also assisting the formation of drug delivery systems (Rasool et al., 2020; Vijayakumar et al., 2020), and skin lotions, tooth paste, shaving foams (Ahsan, 2019).

The chemical constituents and its concentrations present in KA are highly variable and depend of the cultivation conditions, such as water temperature, salinity, sunlight, climatic conditions, light intensity, depth, waves power and others. In general, the KA is composed on average by 50.8% carbohydrates, 3.3% proteins, 3.3% lipids, 15.6% ash, 12.4% sulphated groups and 3.0% insoluble aromatics (Masarin et al., 2016; Solorzano-Chavez et al., 2019). The lipidic fraction is mostly composed of saturated fatty acids (64.28%), in particular C16:0 (46.51%). In addition, KA presents essential amino acids, up to 43% of the total amino acid content, in particular phenylalanine, leucine and threonine (Naseri et al., 2019).

In general, KA is essentially cultivated for carrageenan extraction. However, KA contains high added-value molecules and other



Fig. 2. Green variant of *Kappaphycus alvarezii*. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Source: The authors

compounds that can be converted into a variety of products (Table 1) that can be commercially exploited - simultaneously to the production of carrageenan – as detailed below.

3.1. Carrageenan

Carrageenan is the major sulphated polysaccharide found in red seaweed, most particularly in high content at KA (Pangestuti et al., 2018). Carrageenan is located on the algal cell wall in amorphous form and hydro soluble (Lechat et al., 1997). The carrageenan is a linear molecule, formed by glycosidic linkages between β -galactopyranose and 3,6-anhydro- α - β -galactopyranose, and alternatively by α (1 \rightarrow 3) and β (1 \rightarrow 4) linkages (Raman & Doble, 2015). There are three mostly known carrageenan types, the κ - (kappa), ι - (iota), and λ - (lambda) carrageenans (Das, Sharma, Mondal, & Prasad, 2016), shown in Fig. 3, together with the μ - (mu), ν - (nu) carrageenan precursors. These carrageenans differ depending the number and position of sulphate groups and the content of 3,6-anhydro- β -galactose. However, the κ - and ι -are the most common carrageenan types applied to food products (Bui, Nguyen, Renou, & Nicolai, 2019). The applications of carrageenan is related to its type (ι , κ , λ) due to the variations in physico-chemical properties (Ganesan, Munisamy, & Bhat, 2018). For instance, the number of sulphate groups affects the water solubility and gel strength. The λ -carrageenan has three sulphate groups, and these chemical groups enhance the water solubility (it is water soluble, even at room temperature). In addition, λ -carrageenan has poor gelling properties and it is in general most used as thickener. On the other hand, κ - and ι -carrageenans have one and two sulphate groups, respectively, conferring excellent

Table 1
Researches including products, biological activities and molecules from *Kappaphycus alvarezii*.

Activities	Products and molecules	Authors
Anticancer activities		(Raman & Doble, 2015) and (Bakar, Tengku Ibrahim, Mohamad Shalan, & Mohamed, 2017)
Antioxidant activities		(Kumar, Ganesan, & Rao, 2008), (Gereniu, Saravana, Getachew, & Chun, 2017) and (Makkar & Chakraborty, 2017).
	Carrageenan	(Uy et al., 2005), (Montolalu, Tashiro, Matsukawa, & Ogawa, 2008), (Webber, De Carvalho, & Barreto, 2012), (Webber, De Carvalho, & Barreto, 2012; Webber, De Carvalho, Ogliari, Hayashi, & Barreto, 2012), (Vázquez-Delfín, Robledo, & Freile-Pelegri, 2014), (Rhein-Knudsen et al., 2015), (Das, Sharma, Mondal, & Prasad, 2016), (Manuhara, Praseptiangga, & Riyanto, 2016), (Usuldin et al., 2017), (Yousouf et al., 2017), (Gereniu et al., 2018) and (Bui et al., 2019).
	Carrageenan film	Ganesan et al. (2018).
	Chlorophylls and carotenoids	(Indriatmoko, Limantara, & Brotsudarmo, 2015) and (Baskararaj et al., 2019).
	Glucose and Ethanol	(Khambhaty et al., 2012), (Hargreaves, Barcelos, da Costa, & Pereira, 2013), (Masarin et al., 2016), (Roldán et al., 2017), (Meinita et al., 2019) and (Solorzano-Chavez et al., 2019)
	k-sap	(Mondal et al., 2013), (Das & Prasad, 2015) and (Mondal et al., 2015).
	Lectin homologous	Kawakubo, Makino, Ohnishi, Hirohara, & Hori, 1999.
	Medium density fibreboard (MDF)	Alamsjah et al. (2017).
	Protein concentrate	Kumar, Ganesan, Selvaraj, & Subba Rao, 2014.

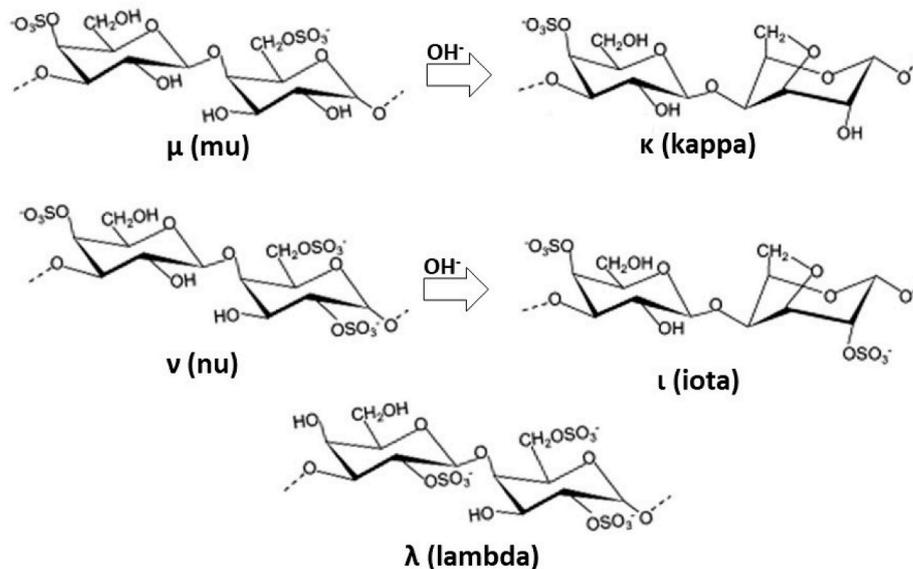


Fig. 3. Disaccharide repetitive structures of μ – (mu), ν – (nu), ι – (iota) κ – (kappa) and λ – (lambda) carrageenans. Repeated units of carrageenan can form polymers with only one type such as κ - or ι -carrageenan, just as they can form hybrid carrageenans (structures with more than one type of repeated unit forming a copolymer). Source: Adapted from Dyrby et al. (2004).

gelling properties, and are also partly water soluble at 60 °C, and totally water soluble at 80 °C (Campo, Kawano, da Silva, & Carvalho, 2009).

Carrageenan extraction can be carried out by thermal alkali methods and by other methods. Some works related to the extraction of carrageenan from KA are presented in Table 1. The presence of alkali promotes the transformation of μ e ν -carrageenan precursors in κ - and ι -carrageenan (Fig. 3), respectively (Rhein-Knudsen et al., 2015). However, green alternative extractions have been developed, for instance, using red algae solution (distilled water) and the methods ultrasound (Youssef et al., 2017) and microwave, with different solvents (acetone, ethanol, methanol, 2-propanol and water) (Uy, Easteal, Farid, Keam, & Conner, 2005; Vázquez-Delfín, Robledo, & Freile-Pelegrín, 2014), or with alternative solvents such as ionic liquids (Gereniu, Saravana, & Chun, 2018).

3.2. Pigments

The different types of seaweed contain a wide variety of photoprotective classes of components, such as polyphenols, mycosporine-like amino acids, sulphated polysaccharides, and carotenoids, among others. The concentration of the pigments present in each alga type depends on cultivation conditions such as solar incidence, medium composition, macroalgae specie, cultivation depth, among others (Pangestuti et al., 2018). For instance, higher KA cultivation depth results in algae with higher chlorophyll concentration (Indriatmoko, Limantara, & Brotosudarmo, 2015).

Pigments such as chlorophylls and carotenoids can be found in KA. According to Indriatmoko, Limantara, & Brotosudarmo, 2015, the major components found in brown and green KA variants are chlorophyll and β -carotene, respectively. Although, other pigments such as allophycocyanin, phycocyanin, and phycoerythrin can be also found (Schmidt, Nunes, Maraschin, & Bouzon, 2010; Sharmila Banu, Santhosh, Hemalatha, Venkatakrisnan, & Dhandapani, 2017).

3.3. Protein

A study of the amino acids profile present in KA was conducted by Naseri et al. (2019). From this study, 15 amino acids were quantified: lysine, arginine, alanine, cysteine, methionine, leucine, phenylalanine, proline, threonine, tyrosine, aspartic acid, serine, valine, glutamic acid,

histidine, tryptophan, isoleucine, and glycine. Thus, taking into account these 15 amino acids, 56.7% are non-essential and 43.3% are essential amino acids, then, KA is a potential source of essential amino acids. It is worth noting that aspartic acid (4.19 mg g⁻¹), glutamic acid (3.16 mg g⁻¹) and phenylalanine (3.02 mg g⁻¹), showed the highest amino acids concentrations.

The protein concentration in KA can reach up to 18 wt%. Kumar, Ganesan, Selvaraj, & Subba Rao, 2014 obtained protein concentrate from KA (essentially alkaline extraction pH 12 with NaOH 1 M). Moreover, the authors tested emulsifying properties with different oils (until 72 h) and foaming capacity and stability over a range of pH 2–10. The protein concentrate showed remarkably stable emulsions with Jatropha oil. Regarding foaming properties, the foaming capacity of protein concentrate is pH dependent; in which the highest foam capacity was at pH 4.0.

3.4. Phenolics compounds

Red seaweeds present phenolic molecules. Baskararaj et al. (2019), extracted phenolic compounds from KA biomass using microwave-assisted extraction with different solvents (acetone, n-propanol, ethyl acetate, n-hexane, methanol, ethanol and chloroform). The optimal extraction condition was methanol 80%, microwave power 20%, radiation induced temperature 45 °C and radiation exposure time 12.5–14.5 min. Four phenolics compounds were identified: chlorogenic, cinnamic, gallic and 3-hydroxy-benzoic acids.

Kumar, Ganesan, & Rao, 2008 tested different solvents for the recovery of extracts from KA and then evaluate the total phenolic compounds (TPC) from these extracts. The TPC was evaluated by Folin-Ciocalteu method and the extracts antioxidant activity was detected by 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free radical method, Ferrous ion-chelating activity, reductive potential and also by linoleic acid system with ferrothiocyanate reagent. The authors used Soxhlet method to obtain the extracts, and the results indicate better performances in antioxidant activities provided by extracts recovered by ethanol and methanol as solvents.

Naseri et al. (2019) found higher phenolic content in extract obtained from KA with water as solvent, compared with ethanol and methanol. Gereniu, Saravana, Getachew, & Chun, 2017 used subcritical water and evaluated the phenolic content of two strains of KA, brown

and red ones. The samples showed similar amount of phenolics, with the highest content obtained at 270 °C and 8 MPa. In addition, they found that water acidified at 1% with formic acid led to higher phenolic content, compare to non-acidified water.

3.5. Glucose and galactose

The KA seaweed cell wall is composed of cellulose and galactan, polysaccharides formed by repeated units of glucose and galactose, respectively, which could be converted into fermentable sugars (glucose and galactose, respectively). Roldán et al. (2017) and Meinita, Marhaeni, Jeong, and Hong (2019) studied the possibility of obtaining ethanol from the residue of carrageenan process. The waste, rich in glucan, can be hydrolyzed by enzymes, producing glucose that, after fermentation, generate ethanol. Roldán et al. (2017) found the glucan conversion to glucose was three times higher compared to sugarcane bagasse. For Meinita et al. (2019), more than 3000 tons of ethanol can be obtained per year, considering the production of 17,549 tons of carrageenan waste per year.

3.6. Anticancer and antioxidant activities

The soluble dietary fiber from KA could be a potential functional food, with properties that reduce or avoid colon carcinogenesis (Raman & Doble, 2015). The authors reported that low molecular weight carrageenan molecules may be associated with this anticancer activity. The study conducted by Bakar, Tengku Ibrahim, Mohamad Shalan, & Mohamed, 2017 detected, with the use of ethanolic extract from KA, the *in vivo* degeneration of breast cancer cells. Besides, KA has also been associated with various types of anticancer activity, as can be seen in a review recently published by Liu et al. (2019).

Some works presented in the literature also demonstrate the antioxidant potential of KA extracts (Gereniu, Saravana, Getachew, & Chun, 2017; K. Suresh; Kumar, Ganesan, & Rao, 2008; Makkar & Chakraborty, 2017). Kumar, Ganesan, & Rao, 2008 and Makkar & Chakraborty, 2017 evaluated the antioxidant activity of KA extracts by DPPH free radical method. The KA extracts were recovered by Soxhlet with different solvents and by exhaustive extraction with ethyl acetate:methanol mixture (1:1 v/v), respectively. The antioxidant activity from the KA extracts (Soxhlet and exhaustive method) was similar to synthetic antioxidant butylated hydroxytoluene (BHT).

3.7. Fertilizers

The liquid solution obtained from the fresh KA, mechanically crushed, is known as K-sap. It is a potent plant stimulant. This bio-stimulating action seems to be linked to four plant growth hormones (indole acetic acid, zeatin, kinetin and gibberellic acid (GA₃), in addition to inorganic micronutrients and potassium (Mondal et al., 2015).

Das & Prasad, 2015 studied the extraction of K-sap using ionic liquid. The authors tested three different ionic liquids and found that the ionic liquid [Bmim] [PF₆] can be used to obtain plant growth regulators.

4. Non-conventional methods of red algae extraction

The extraction of target compounds from red algae can be carried out by conventional or by non-conventional methods. Conventional procedures are well established methods, such as maceration, percolation, and Soxhlet, otherwise, PLE, SWE, SFE, MAE and UAE are within the non-conventional procedures. These alternative methods have several advantages over conventional ones such as high yield, restrictive use of organic solvent, fast process, and low temperature, selectivity and cost, which result mostly in environmentally friendly processes (Cikoš, Jokić, Šubarić, & Jerković, 2018; Kadam, Tiwari, & O'Donnell, 2013). Therefore, most non-conventional methods are aligned with the biorefinery concept. Despite the clear advantages of non-conventional techniques,

there are still a long way to spread worldwide their industrial applications, particularly when high pressures are associated, in methods such as SFE, SWE and PLE.

Regarding the red algae biorefinery, the biomass can provides products such as carrageenan, ethanol, biofertilizer, biogas, besides lipids-fertilizers-agar-bioethanol among others, as recently demonstrated by Álvarez-Viñas, Flórez-Fernández, Torres, & Domínguez, 2019. The biorefinery concept applied to KA by means of using conventional extraction techniques was already investigated (Ingle et al., 2018; Masarin et al., 2016; Meinita et al., 2019; D. Mondal et al., 2013; Roldán et al., 2017; Shanmugam & Seth, 2018). However, no studies have been found related to KA biorefinery using non-conventional extraction methods, and therefore, should be investigated. Some works involving non-conventional methods are shown in Table 2.

4.1. Supercritical fluid extraction

The red seaweed group, which includes KA, contain valuable polyunsaturated fatty acids (PUFA's) (Peñuela et al., 2018), which can be recovered from this type of biomass. In this sense Chen and Chou (2002) extracted PUFA's from 10 red algae species by SFE using CO₂ as solvent, and at 500 psi, 55 °C for 3 h. The crude lipid fraction in dry mass base (% wt/wt) ranged from 11.2 (*Porphyra dentate*) to 21.5 (*Liagora boergereseni*). In general, 16:0, 20:4ω6 and 20:5 ω3 (eicosapentaenoic acid - EPA) represented over 70% out of the total fatty acids. It is worth noting that 22:6ω3 (docosahexaenoic acid - DHA) was not detected. *Liagora boergereseni* had the highest concentration of EPA (6.78 mg/100 mg crude lipid), which is higher when compared to fish oil. Thus, red algae, in particular *Liagora boergereseni*, have a great potential to be used as a source of EPA for SFE at an industrial scale.

Cheung (1999) studied the SFE from the red algae *Hypnea charoides*, and evaluated the effect of temperature (from 40 to 50 °C) and pressure (from 24.1 to 37.9 MPa) on the recovery of fatty acids. The maximum yield of lipids was 67.1 mg g⁻¹ (on dry base of freeze-dried seaweed) at 37.9 MPa and 50 °C. The highest extraction yield of saturated fatty acids was obtained at 24.1 MPa and 50 °C (39.9% of total fatty acids). On the other side, regarding polyunsaturated fatty acids, the highest extraction yield was at 31.0 MPa and 40 °C (51.7% of total fatty acids).

The red seaweed *Gracilaria mammillaris* was studied by Ospina, Castro-Vargas, & Parada-Alfonso, 2017, which used SFE at different conditions. The authors evaluated the effect of temperature, pressure, and co-solvent concentration to obtain the best antioxidant sample. The extract recovered by SFE at 30 MPa, 60 °C and with 8% ethanol as co-solvent showed the highest total phenolic content of 3.791 mg (GAE/g), while the extract obtained at 30 MPa, 50 °C and 5% ethanol as co-solvent provided the highest carotenoid content of 5.038 mg carotenes per gram of seaweed in dry basis.

Extract of red alga *Gloiopeltis Tenax* was obtained by SFE with CO₂ at 30 MPa and 45 °C and ethanol as co-solvent. Antioxidant assays from the extract were carried out by DPPH, β-carotene/linoleic acid-coupled oxidation reaction and deoxyribose degradation by iron-dependent hydroxyl radical. From the recovered extracts 30 components were identified by gas chromatograph (GC) coupled with mass spectrometer, including six sesquiterpenes (14.39%), three ketones (5.02%), seven fatty acids and their esters (29.1%), two phenols (1.71%), and three sterols (12.81%). In addition, the extracts showed remarkable antioxidant activity (Zheng, Chen, Yao, Chen, & Shi, 2012).

Although technically feasible, and analogous to the above-mentioned studies for different red algae, no literature data, related to the extraction of molecules of interest from KA using the non-conventional method SFE, were found.

4.2. Pressurized liquid extraction and subcritical water extraction

Klejduš, Plaza, Šnoblóvá, and Lojková (2017) evaluated different extraction methods, individual or in combination, for the recovery of

Table 2
Non-conventional extraction methods used in *Kappaphycus alvarezii*.

Extraction Methods	Aim	Studied process Conditions	Authors
SWE	Monosaccharides and bioactive compounds	P: 1–10 MPa; R: 150 rpm; S: Water, formic acid (1%) and sodium hydroxide (1%); S/L: 1:40 (m/v); T: 150–300 °C and t: 5 min.	Gereniu, Saravana, Getachew, & Chun, 2017
	Carrageenan extraction using IL	P: 5 MPa; R: 200 rpm; S: Water and many different Ionic Liquids 1%. S/L: 1:80 (m/v); T: 60–180 °C and t: 5 min.	Gereniu et al. (2018)
MA	Carrageenan extraction	F: 2450 MHz; PW: 300 W; S: water, sodium hydroxide 6%, potassium hydroxide 6%, Methanol-water (45:55 wt%), ethanol-water (37–63 wt%), acetone-water (55–45 wt%) and 2-propanol-water (40–60 wt%); t: 30 min.	Uy et al. (2005)
	Process conditions that maximize biomass yield, antioxidant, chlorophyll and β-carotene content.	F: 2450 MHz; PW: 106–192 W; S: Acetone, n-propanol, ethyl-acetate, n-hexane, methanol, ethanol and chloroform (all in 70% v/v in aqueous). Besides, methanol 57.5–87.5% v/v in aqueous; S/L: 1:10 (m/v) T: 37.5 to 67.5 °C. t: 5–15 min.	Baskararaj et al. (2019)
	Study the effect of heating mechanism on the formation of products and their composition in Microwave-assisted pyrolysis	PW: 560 W; T: 500 °C. t: 15 min.	Gautam, Shyam, Reddy, Govindaraju, and Vinu (2019)
	Determine minerals and trace elements using microwave assisted digestion	S: nitric acid supra pure metal 65%; S/L: 1:10 (m/v); T: 200 °C. t: 15 min. pH: 7.0; PW: 150 W; S: Water; S/L: 1:100 (m/v); T: 90 °C and t: 15 e 30min.	Yoganandham et al. (2019)
UAE	Carrageenan extraction		Youssof et al. (2017)

UAE: Ultrasound assisted extraction; SWE: Subcritical water extraction; MA: Microwave assisted. F: Frequency; P: Pressure; PW: Power; R: Rotation; S: Solvent; S/L: Solid Liquid Ratio; T: Temperature; t: time.

phenolic compounds from four seaweeds: *Sargassum muticum*, *Undaria pinnatifida* and *Cystoseira abies-marina* (brown seaweeds) and *Chondrus crispus* (red seaweed). The authors carried out preliminary tests only using *Cystoseira abies-marina*. The analysis of the results indicated that sequential extraction method composed of UAE followed by PLE led to the highest phenolics recovery when compared to other four methods: (I) passive leaching extraction, (II) ultrasound-assisted extraction followed by passive leaching extraction, (III) Ika Ultra-Turrax® Tube Drive

and (IV) Ultrasound extraction followed by Ika Ultra-Turrax® tube. Then, the extraction method composed by UAE followed by PLE was applied to *Chondrus crispus* (red seaweed). The phenolic profile of the red seaweed *Chondrus crispus* was evaluated by rapid chromatography and MS/MS. The results demonstrated a presence of phenolic compounds such as vanillin (highest concentration), 3,4-dihydroxybenzaldehyde, *p*-hydroxybenzaldehyde, and, gallic, protocatechuic, *p*-hydroxybenzoic, chlorogenic, vanillic, caffeic, syringic, *p*-coumaric, ferulic, salicylic, and sinapic acids.

Gereniu, Saravana, Getachew, & Chun, 2017 evaluated subcritical water extraction for KA extracts. The authors used different solvents, pressures and temperatures (Table 2). The highest values of antioxidant activity, total phenolic, total flavonoids and protein contents were obtained at 270 °C/8 MPa. On the other hand, higher concentrations of reducing sugar and total reducing sugar was obtained at 150 °C/5 MPa. Whereas Pangestuti, Getachew, Siahaan, & Chun, 2019 evaluated the temperature and solid to liquid ratio influence on the hydrolization of red algae *Hypnea musciformis* by SWE. The authors founded that 210 °C is the optimum temperature to obtain an extract with better antioxidant activity, within the studied range between 120 and 270 °C. However, temperatures below 180 °C were better to obtain extracts enriched in sugar compounds.

Gereniu et al. (2018) tested κ-carrageenan extraction using ionic liquids (1%) in a subcritical water apparatus (extractions conditions as shown in Table 2). The authors tested seven different ionic liquids and compared with water under subcritical conditions and with an extraction method using an autoclave. The highest extraction yield of carrageenan was found for the ionic liquid 1-butyl-3-methylimidazolium acetate (BMIMAc) when compared with the other six tested solvents, in particular at higher temperatures from 120 to 180 °C.

4.3. Microwave assisted extraction

Vázquez-Delfín, Robledo, & Freile-Peigrín, 2014 evaluated the influence of time and temperature on the content and type of carrageenan obtained from *Hypnea musciformis*. The authors found that, when compared to conventional method (hydrothermal), which is costly (KOH solution 3%, at 85 °C for 3.5 h), MAE showed slightly lower carrageenan yield, 18.7% and 16.6%, respectively. However, MAE is dramatically faster (10 min).

Boulho et al. (2017) performed the extraction of carrageenan from the red algae *Solieria chordalis* by MAE and by the conventional method (KOH solution 1%, at 85 °C for 3.5 h). Then, the biological properties of both carrageenans were compared. The authors used animal cells - Vero cell lines (line no. ATCC CCL81) – to correlate the carrageenans with alterations in cell morphology, in particular swelling, shrinkage, granularity, and detachment, cytotoxicity, and also antiviral property against *Herpes simplex virus type 1* (HSV-1; family Herpesviridae). Conventional and MAE carrageenans showed similar chemical properties (protein, total sugar, sulphate, Fourier transform infrared spectra and ¹³C NMR spectra analysis). However, it should be emphasized that MAE has a clear advantage, it is faster, with 10–25 min, compared to 3.5 h from conventional method. In addition, MAE carrageenan showed higher antiviral activity against the HSV-1 virus (Peñuela et al., 2018).

Levulinic acid is considered a chemical platform because it is technically feasible to generate, from it, a wide range of derivatives, and consequently different products can be synthesized, such as plasticizers, polymers, pharmaceuticals, herbicides and fuel additives. Levulinic acid is obtained from rehydration under acidic conditions of the 5-(hydroxymethyl)furfural (HMF). HMF is produced by the dehydration of hexose. Hexoses are present in red algae biomass. Based on this, Cao et al. (2019) applied microwave assisted low-temperature to carried out the saccharification of red algae *Gracilaria lemaneiformis*. The optimal condition (180 °C, 20 min, 0.2 M H₂SO₄ and 5% (w/v) of solid/liquid ratio) achieved 16.3 wt% of levulinic acid. It is worth noting that similar levulinic acid yields were obtained from wheat straw (Chang, Cen, &

Ma, 2007), although microwave assisted low-temperature is significantly faster, 20 min process, when compared to conventional heating (2 h).

Microwave extraction can be enhanced by enzymes, Lee et al. (2016) evaluated the production of polysaccharides with antioxidant properties from red algae *Pyropia yezoensis* by MAE with carbohydrate hydrolytic enzymes: Viscozyme, Ultraflo, amyloglucosidase (AMG), Termarmyl and Celluclast. The authors investigated different extraction times (10 min to 2 h) and enzyme concentrations (10:1 and 100:1) with microwave operating at 400 W. AMG (10:1 and 2 h) showed the highest degree of hydrolysis (25%). In addition, it was observed a synergic effect between microwave and AMG, in which it doubled the degree of hydrolysis of the polysaccharides when compared to microwave hydrolysis or enzymatic hydrolysis.

Uy et al. (2005) performed the extraction of carrageenan from KA using a continuous microwave method with aqueous mixtures (extraction conditions as shown in Table 2). The authors showed that carrageenan can be extracted in high purity, with lower solvent consumption and extraction time compared to the traditional hot water extraction.

Regarding other biomolecules instead carrageenan, Baskararaj et al. (2019) optimized the extraction yield of β -carotene and chlorophyll from KA. The authors evaluated the influence of the solvent concentration using methanol-water mixtures, and also the extraction time, temperature, and microwave power (extraction conditions as shown in Table 2). The optimum condition for these responses was methanol-water concentration of 80%, 12.5–14.5 min of extraction time, 45 °C and 170 W.

4.4. Ultrasound assisted extraction

The UAE has also been used to obtain pigments from red macroalgae. Le Guillard et al. (2015) used an ultrasonic flow reactor to extract the pigment R-phycoerythrin from *Grateloupia turuturu*. The seaweed was cut in small pieces (5–7 mm²) and homogenized in tap water, with pH adjusted to 5.5. The UAE occurred assisted by different Enzymatic cocktails, Sumizyme TG, Sumizyme MC, Multifect® CX 15 L and Ultraflo® XL at 22 or 40 °C, 200 W or 340 W for 6 h. The authors found that UAE at 22 °C led to higher extraction (3.6 ± 0.3 mg g⁻¹) of the thermosensitive pigment R-phycoerythrin.

Subsequently, the same research group proved that the UAE of carbohydrates and amino acids from *Grateloupia turuturu* Yamada was enhanced by an enzymatic cocktail composed of Sumizyme TG, Sumizyme MC, Multifect® CX 15 L and Ultraflo® XL, that is, when compared to UAE, the ultrasound-assisted enzymatic extraction showed promising results (Le Guillard et al., 2016). All experiments were performed at 40 °C, pH 5.5 for 6 h with reaction mixture, composed of 20% wet and cut seaweed homogenized in tap water.

Similarly, Romarís-Hortas, Bermejo-Barrera, and Moreda-Piñeiro (2013) applied ultrasound-assisted enzymatic hydrolysis to enhance the extraction of iodinated amino acids from red seaweed *Palmaria palmate* and *Porphyra umbilicalis*. Pancreatin was the most feasible enzyme. The ultrasound-assisted enzymatic hydrolysis was carried out at 45 kHz, pH 8.0, at 50 °C for 12 h. It is worth noting that when compared to green and brown species, the authors found the lowest concentrations of iodine, 21 and 38 g g⁻¹, for the seaweed *Palmaria palmate* and *Porphyra umbilicalis*, respectively.

Topuz, Gokoglu, Yerlikaya, Ucak, & Gumus, 2016 optimized the UAE of phenolic compounds and antioxidant molecules, detected by ABTS method, from a red seaweed, the *Laurencia obtuse*. The optimal conditions obtained were: 1:30 (g.mL⁻¹), 50 °C and 42.8 min and 1:24 (g.mL⁻¹), 45 °C and 58 min for phenolics and antioxidant activity, respectively.

The UAE has also been used for the carrageenan extraction from red algae species KA and *Euchema denticulatum*. The carrageenan yield for both algae, recovered by ultrasound, was similar 50–55% (extraction conditions as shown in Table 2), but they were superior to the

conventional method (27%), while extraction times were 15 and 120 min, for UAE and conventional method, respectively (Youssof et al., 2017).

5. Process integration and biorefinery

Red algae have high content of polysaccharides, and also a considerable concentration of proteins, lipids, minerals, and phenolic compounds. Based on the variety of valuable compounds, red algae, in particular KA, are potential raw materials for biorefineries (Torres et al., 2019; Álvarez-Viñas, Flórez-Fernández, Torres, & Domínguez, 2019). Therefore, researches focused on macroalgae and combined with the biorefinery concept have been growing in recent years. The Scopus Database (www.scopus.com) was used to identify the scientific trends. The search was carried out on June 29, 2020 using the following keywords/booleans “macroalgae” OR “seaweed” (including all green, red and brown macroalgae) AND “biorefinery” OR “process combination” OR “cascade processing” OR “sequential process”. The search parameters were title, abstract, keywords, document type, and publication data, from 2010 to 2020. As a result, 194 documents were obtained (Fig. 4). According to Fig. 4, a significant increase in scientific documents was detected from 2013 to 2019, with 13 and 55, respectively. Regarding documents type, 128 (65.98%) are research articles, 29 (14.95%) review papers and 24 (12.37%) book chapters, whereas conference papers, conference reviews, notes, books, editorials and letters, represent 13 (6.70%). In order to narrow the subject, a second search was conducted including the term “red”, i.e., “red macroalgae” OR “red seaweed” AND “biorefinery” OR “process combination” OR “cascade processing” OR “sequential process”. As result, only 15 documents were found between the years 2010–2020, 12 (80.00%) research articles, 2 (13.33%) review papers and note 1 (6.67%).

As already mentioned, KA is an unexplored and valuable biomass for green biorefinery conversion, due to the presence of pigments (3.2), proteins (3.3), phenolic compounds (3.4), glucose/galactose (3.5) anticancer and antioxidant molecules (3.6)and, fertilizers (3.7). However, KA is essentially cultivated as carrageenan source, thus, KA exploitation is underestimated, generating large amounts of residues from the

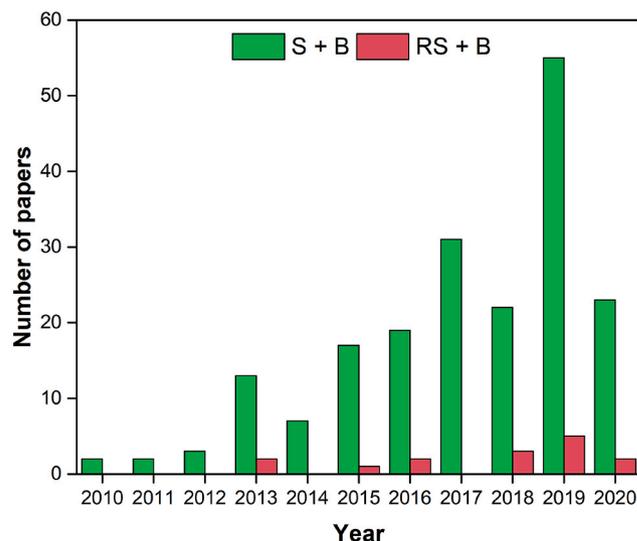


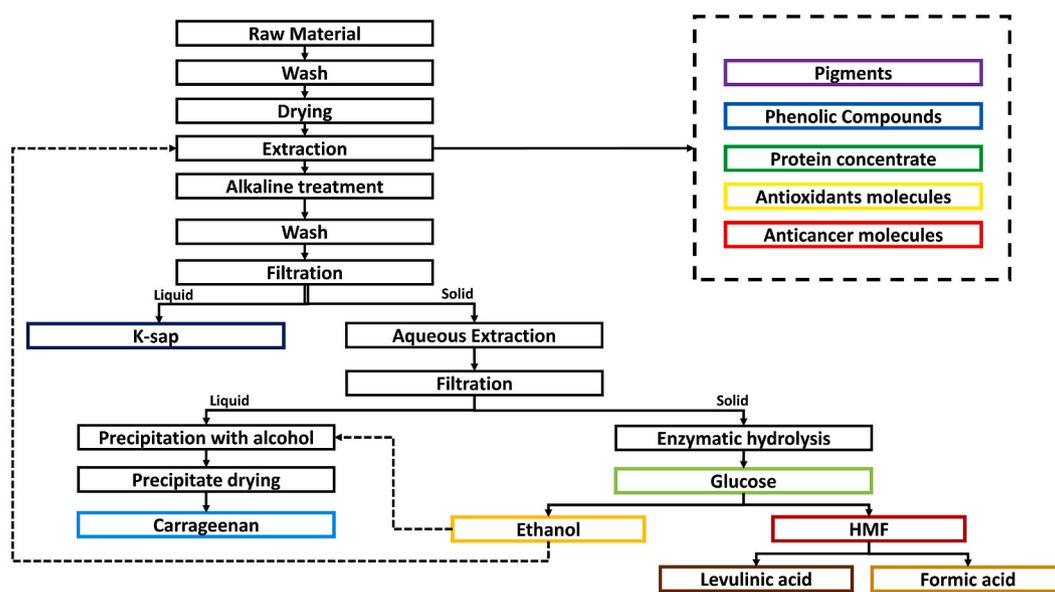
Fig. 4. Number of researches published from 2010 to 2020 (April 2020) according to the Scopus database platform. Where (S+B) refers to searches “Seaweed” OR “macroalgae” AND “biorefinery” OR “process combinations” OR “cascade processing” OR “sequential process”. Otherwise, (RS +B) refers to the searches of “Red seaweed” OR “red macroalgae” AND “biorefinery” OR “process combinations” OR “cascade processing” OR “sequential process”. The data show the results for all document types: Article, review, book chapters, among others.

carrageenan production. Therefore, the application of the biorefinery concept is an essential strategy to aggregate value to the production chain of KA carrageenan and should be deeply investigated.

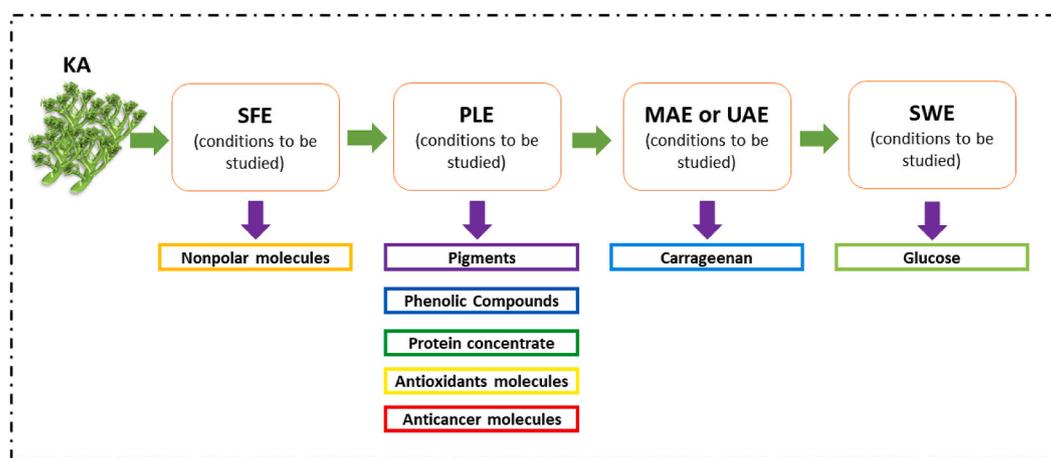
Fig. 5 presents the biorefinery concept applied in KA (flowchart and sequential processes), which was elaborated based on scientific literature (from previous sections) and our empirical research prospecting. This concept could be used to all red algae species with high content of carrageenan or agar, together with other compound(s) of interest, where only few fine adjustments in extraction methods and conditions should be considered in order to adapt for each biomass.

In this suggested biorefinery approach (Fig. 5a), the seaweed biomass is first washed with tap water to remove salt, sand, and debris. Then the biomass is dried and grounded, in order to minimize reactions (e.g microbial degradation and oxidation) and increase extraction efficiency, respectively. The grounded biomass is then submitted to extraction procedures with non-aqueous solvents, since it avoids the loss of carbohydrates. However, the experimental conditions must preserve the adequate recovery of carrageenan, as well as the extraction of other

valuable substances. In this case, sequential extractions with low nonpolar solvents such as hexane, and/or intermediate polar ones like ethanol could be performed to obtain fractions of this biomass. Then, in a sequence, an alkaline treatment could be used to increase the yield of carrageenan. In this step, the precursors μ - and ν -carrageenan are converted to κ - and ι -carrageenan, respectively, as described in section 3.1 (Rhein-Knudsen et al., 2015). After that, the biomass is water washed to remove the excess of alkali, and then filtered, separating in a liquid stream, which could be used to obtain K-sap, a fertilizer, and a solid material, that could be used in a sequential process, for instance, to obtain carrageenan (Hayashi et al., 2014) and cellulose. Thus, the solid material is used in hydrothermal extraction (the classical approach), with water at 80 °C, leading to the production of carrageenan (liquid phase) after precipitation with alcohol (Hayashi et al., 2014). It worth noting that carrageenan precipitates, while cellulose and galactan, from KA seaweed cell wall, remain in ethanol fraction (supernatant). The precipitate can be dried to obtain carrageenan, whereas the supernatant can be added to the hydrolyzed material to get glucose and galactose for



a)



b)

Fig. 5. Biorefinery concept applied in *Kappaphycus alvarezii*. a) Process flowchart b) Sequential process designed using recent extraction processes. Source: The authors

bioethanol production (Meinita et al., 2019). Therefore, we hypothesize a complex sequential process for the extraction of valuable substances from the red algae, and obtaining different products in a rational sequential extraction methodology, which may result in the recovery of lipids, pigments, carrageenan and glucose, as proposed in Fig. 5b.

No studies were found involving the extraction of KA by SFE, and it could be applied, prior to carrageenan extraction. This subject should be deeply investigated to detect the influence of the conditions of temperature and pressure of the supercritical fluid that affect the recovered fractions from KA. Also, pre-treatment conditions such as drying procedures, biomass gridding and others, prior to SFE, could affect the resulting product. It is worth mention that SFE was already applied to extract antioxidants and antimicrobial compounds from *Agaricus brasiliensis* (Mazzutti et al., 2012), carotenoids from pink shrimp (*Penaeus brasiliensis*) (Mezzomo, Maestri, Dos Santos, Maraschin, & Ferreira, 2011), antitumoral compounds from *Cordia verbenacea* (Parisotto et al., 2012), alkaloids such as piperine from *Piper nigrum* (Andrade, Trivellin, & Ferreira, 2017), among others.

Following the proposed biorefinery concept, the biomass residue of SFE could be used for PLE in order to recover antioxidant molecules (Gereniu, Saravana, Getachew, & Chun, 2017) or carrageenan (Gereniu et al., 2018) as presented in section 4.2. In this sense, other green methods for carrageenan extraction can be used, for instance ultrasound with distilled water (Youssouf et al., 2017); and microwave with ethanol and water (Vázquez-Delfín, Robledo, & Freile-Pelegrín, 2014). Then, mostly, cellulose and, very likely, few types of molecules remain in the KA (insoluble). Cellulose can be hydrolyzed to obtain glucose by either subcritical water or cellulases.

Then, the glucose can be used by yeasts to produce ethanol. The produced ethanol can be used for carrageenan extraction, for instance by microwave method (Vázquez-Delfín, Robledo, & Freile-Pelegrín, 2014).

The interactions among the different recovered products (from the various process steps) could be also investigated. For instance, since carrageenan is an encapsulating agent, the product from SFE could be encapsulated (complex coacervation process) by the carrageenan recovered from MAE or UAE (Bakry, Huang, Zhai, & Huang, 2019; Souza, Thomazini, Chaves, Ferro-Furtado, & Favaro-Trindade, 2020); or the KA extracts and the carrageenan could be used for the production of active biofilms (biopolymer) (Vijayakumar et al., 2020) or blended with other polymers, as chestnut starch, in order to improve the mechanical/drying properties of biofilms as detailed by Moreira et al. (2011).

Different extraction routes can be used to obtain high-value molecules from KA, such as the sequential recovery of bioactive compounds and carrageenan, in particular proteins/carrageenan or also K-sap/carrageenan, or pigments/proteins/carrageenan, or other combinations. In this sense, since there is no information about this strategy, the biorefinery concept involving KA should be investigated, and in fact it should be aligned to an economic feasibility study. Then, the best route can be scaled-up industrially. Similarly, the concept of circular economy could be also applied for it, since the wastes from carrageenan production can be converted into ethanol. Then, the ethanol, in turn, can be used as solvent for the recovery of phenolic compounds, or antioxidant molecules prior to the carrageenan extraction or for the carrageenan precipitation.

6. Conclusions

Currently, *Kappaphycus alvarezii* processing is mainly destined for the extraction of carrageenan. This review demonstrated the potential of this alga as a source to obtain different products such as proteins, phenolic compounds, fertilizers, pigments, glucose (as a basis for obtaining ethanol and other products such as formic acid and levulinic acid). Besides, we noticed that there is few information on non-conventional methods for the extraction of valuable molecules from this remarkable alga, the KA. The microwave is the recent technique used to obtain compounds of interest to KA and red algae. The PLE and

SWE are presented as mostly unused methods for KA, while no data were found, to the best of our knowledge, with SFE for valuing KA. In general, ultrasound is used as a pre-treatment for this biomass. Finally, based on literature information about the various different classes of relevant compounds from KA, we suggest that studies follow the newest concept of biorefinery to obtain different products from this red macroalgae, the KA. In the future, it is expected that the extraction of carrageenan from KA should be expanded to obtain ethanol, fertilizers, pigments, concentrates proteins, among other products that can be obtained from this biomass.

Conflicts of interest

The authors have declared no conflict of interest related to the present review.

CRediT authorship contribution statement

Adenilson Renato Rudke: Conceptualization, Data curation, Visualization, Investigation, Writing - original draft, Writing - review & editing. **Cristiano José de Andrade:** Conceptualization, Supervision, Resources, Project administration, Writing - review & editing, Funding acquisition. **Sandra Regina Salvador Ferreira:** Conceptualization, Supervision, Resources, Project administration, Writing - review & editing, Funding acquisition.

Acknowledgments

The authors wish to thank the Brazilian funding agencies for the financial support and fellowship. Specifically, we acknowledge CNPq (National Council of Technological and Scientific Development, Brazil), Project 404347/2016-9, and CAPES (Coordination for the Improvement of Higher-Level Personnel, Brazil), projects CAPES/PROEX-1624/2018 and CAPES/PRINT 88887.310560/2018-00. We also like to thank EPAGRI-Florianópolis.

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