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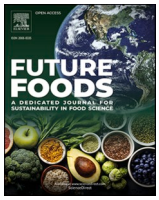

Bioactive metabolites from algae: occurrence, extraction techniques, functional properties, food applications and therapeutic prospects

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ABSTRACT

This review critically summarizes the major algal-derived bioactive compounds, including phenolics compounds (e.g., phlorotannins, bromophenols, phenolic acids), sterols (e.g., fucosterol, β-sitosterol), and polysaccharides (e.g., carrageenan, fucoidan, ulvan), as well as key pigments such as astaxanthin, β-carotene, lutein, violaxanthin, zeaxanthin, and chlorophylls. In addition, state-of-the-art extraction technologies including supercritical fluid extraction, pressurized liquid extraction, ultrasound assisted, microwave assisted, surfactant assisted, and enzyme assisted extractions, and carbon dioxide-expanded liquids) were systematically compared considering key parameters such as yield, versatility, compound selectivity, extract quality, cost-effectiveness, technical complexity, operational conditions, and sustainability principles. Based on this comparative evaluation, ultrasound assisted extraction emerged as the most versatile among advanced technologies, same as enzyme assisted extraction within ulterior techniques. The potential incorporation of these bioactive compounds into novel algae-based food systems, either as functional ingredients or texturizing agents, was also discussed. Moreover, their relevance in alternative therapeutic applications was also highlighted, with a proof-of-concept focused on the antiviral potential of sulfated polysaccharides (carrageenan, fucoidan, and ulvan). Overall, algae-based ingredients were found to be promising biofunctional agents for innovative food products, nutraceutical formulations, and therapeutic alternatives.

1. Introduction

Oceans cover approximately 70 % of the Earth's surface and contain an extensive diversity of marine organisms, which are estimated to comprise nearly half of the planet's biodiversity. This vast biological collection positions marine ecosystems as promising sources of natural products, due to their wide array of structurally diverse bioactive compounds (Wan et al., 2021). Among marine organisms, algae warrant special attention. These key components of marine ecosystem are prominent for their high availability, taxonomic diversity, and remarkable productivity. Marine algae are classified into two main groups: macroalgae (commonly referred to as seaweeds) and microalgae. Seaweeds inhabit the littoral zone and are traditionally classified into three major groups - brown algae (*Phaeophyta*), green algae (*Chlorophyta*), and red algae (*Rhodophyta*); blue-green algae (*Cyanophyta*), which are technically classified as cyanobacteria, are also noteworthy (Cotas et al., 2023).

Brown algae represent approximately 59 % of the total macroalgae cultivated worldwide, while red algae accounts for around 40 % of all cultivated production; in contrast, green algae comprise <1 % of harvested macroalgae (Rahikainen et al., 2021).

Microalgae are unicellular or simple multicellular organisms characterized by high grow rates and remarkable resilience to extreme environmental conditions, such as extreme temperatures, anaerobic environments, high salinity, photo-oxidative stress, osmotic fluctuation, and ultra-violet radiation (Wu et al., 2021), allowing them to inhabit both benthic and littoral zones, besides being distributed throughout the ocean as part of the phytoplankton community (Cotas et al., 2023).

In general, macroalgae and microalgae contain bioactive compounds such as sulphated polysaccharides (including fucoidan, carrageenan,

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and ulvan), phenolic compounds (e.g., phenolic acids, phlorotannins, bromophenols), and pigments (for instance, carotenoids and chlorophylls), which enable their wide range of biological activities, (antioxidant, antimicrobial, antiviral, anti-allergic, anti-inflammatory, antitumor, and anti-coagulant capacity), already evaluated using both in vitro and in vivo assays (Bouafir et al., 2025; Menaa et al., 2021).

However, it is important to note that the metabolic profiles of these organisms are highly responsive to environmental stimuli, which can influence the qualitative and quantitative production of bioactive metabolites (Lau et al., 2022). Despite this limitation, the recent interest in the biological and pharmacological activities of seaweeds and their secondary metabolites has been increasing widely (Choudhary et al., 2021).

In this context, and as observed with other natural sources of bioactive compounds, the selection of appropriate extraction methodologies is critical, demanding considering factors such as matrix effects, solvent type, temperature, pressure, and extraction duration, alongside fulfilling sustainability and green chemistry principles. Besides collectively determining the efficiency and selectivity of bioactive compounds recovery, these parameters are essential to characterize and validate specific biological activities (Tsegay et al., 2024).

The presented comparative analysis contributes to develop multipurpose sustainable processing strategies to support a more efficient utilization of algae-derived compounds in food formulations and nutraceutical/pharmaceutical formulations.

In the present review, the literature screening was conducted using Scopus and Web of Science as primary databases, covering works published between 2019 and 2025 (due to their relevance some works from 2018 were also included in Table 2). The search strategy included combinations of predefined keywords and Boolean operators, such as bioactive compounds, algae, phenolics, sterols, polysaccharides, and advanced extraction techniques (SFE, PLE, UAE, MAE, SAE, EAE, GXE). Only peer-reviewed articles written in English and reporting relevant experimental, analytical, or technological outcomes were considered. Titles, abstracts, and full texts were screened to ensure relevance to the scope of this review, and non-scientific sources, duplicated records, and publications with limited methodological clarity were excluded.

2. Bioactive compounds from algae

Metabolites represent a diverse group of compounds that, despite their wide-ranging physicochemical properties, are generally classified into two categories: hydrophilic polar molecules - such as amino acids, carbohydrates, organic acids, and phosphorylated compounds - and hydrophobic non-polar molecules, including fatty acids, sterols, lipophilic vitamins, and membrane lipids. According to the most recent data from the Human Metabolome Database (2020), over 8000 endogenous metabolites have been identified in humans, while nearly 35,000 exogenous metabolites - originating from foods, pharmaceuticals, or microbial sources - are estimated to exist (Belhaj et al., 2021).

Biological metabolites are further categorized into primary metabolites (such as carbohydrates, amino acids, polyamines, and lipids), which are essential for cellular maintenance, growth, and development, and secondary metabolites, including low-molecular-weight compounds - such as phenolic acids, terpenoids, sterols, and alkaloids (synthesized for adaptive purposes, including defense against pathogens, or resistance to abiotic stressors) (Yeshi et al., 2022). Although not directly involved in primary physiological functions such as growth or reproduction, secondary metabolites play a pivotal role in enhancing organism survival and resilience. The biosynthesis of these compounds is highly species-specific and influenced by both intrinsic developmental factors and extrinsic environmental conditions. A notable example is the elevated antioxidant production observed in species inhabiting extreme environments (Reshi et al., 2023).

Despite their functional differences, both primary and secondary metabolites contribute to the production of bioactive compounds that extend beyond basic nutritional value, offering health-promoting effects (Srivastava et al., 2020). Algae are known to synthesize a wide array of these biologically active compounds, including polysaccharides, bromophenols, lipids, proteins, and vitamins (Kammler et al., 2024). In terms of polysaccharide composition, brown algae primarily produce alginates, laminarins, fucans, and cellulose; red algae are rich in agars and carrageenans, while green algae predominantly contain ulvan (Moreira et al., 2023). Moreover, algae produce >250 different pigments, such as fucoxanthin (the carotenoid pigment that primarily provides the characteristic brown coloration of Phaeophyceae), phycoerythrin and phycocyanin, responsible for the red and purplish hues of red algae, or chlorophyl a and chlorophyl b, which give green algae their characteristic color, (Z. Chen et al., 2023; Manzoor et al., 2024), being also found in microalgae (Sun et al., 2024).

Besides their profile in bioactive compounds, there is increasing epidemiological evidence supporting the role of algae-derived components in lowering the risk of chronic diseases, including diabetes, cancer, hyperlipidemia, and neurodegenerative disorders (Yang et al., 2023b).

The next sections provide a detailed overview of the most relevant bioactive compounds found in seaweeds, with a focus on phenolic compounds, sterols, and sulfated polysaccharides.

2.1. Phenolic compounds

Algae produce a diverse array of phenolic compounds that belong to four main groups: phenolic acids (e.g., gallic, protocatechuic, caffeic, chlorogenic, vanillic, *p*-hydroxybenzoic, and salicylic acids), flavonoids (mostly found in green and red macroalgae and in microalgae), bromophenols (predominantly found in red algae), and phlorotannins (primarily present in brown algae).

The biosynthesis of these compounds is often induced by exposure to ultraviolet (UV) radiation and various environmental stressors, which increase the formation of reactive oxygen species (ROS). The bioactivity of seaweed-derived phenolics has been validated both in vitro and in vivo (cell culture studies), contributing to their growing application in pharmaceutical and cosmeceutical formulations, as well as their increasing consumption worldwide (Subbiah et al., 2023). In microalgae, the most common flavonoids are flavonols, flavones, flavanones, and isoflavones. However, the concentration of polyphenols in algal biomass is highly variable and depends on factors including species, season, UV exposure, light intensity, nutrient availability, and salinity (Cichoński and Chrzanowski, 2022).

2.1.1. Structural diversity of algal phenolic compounds

In algae, phenolic compounds are synthesized via two primary biosynthetic pathways: the shikimic acid pathway (which originates phenylpropanoids) and the acetic acid pathway (which produces simple phenols) (Del Mondo et al., 2022). Their most important group of simple phenolic compounds is represented by phenolic acids, which consist of a benzene ring bearing hydroxyl and/or methoxyl substituents and a carboxylic acid group; these are further divided into benzoic acids (C_6—C_1) and hydroxycinnamic acids (C_6—C_3) (Koşar et al., 2022). Algae also present several flavonoids, the phenylpropanoid derivatives that consist of a 15-carbon skeleton (C_6—C_3—C_6) arranged in two benzene rings connected by a heterocyclic pyran ring. Some of the forms identified in several algal species include quercetin, kaempferol, apigenin, luteolin, rutin, and naringenin (Dias et al., 2021b; Fernando et al., 2022; Mutha et al., 2021).

Bromophenols (Table 1) include simple brominated derivatives such as 2- and 4-bromophenol, 2,4- and 2,6-dibromophenol, and 2,4,6-tribromophenol. These metabolites are mainly present in red algae, although they can also be found in green and brown macroalgae (Jacobtorweihen and Spiegler, 2023).

In turn, phlorotannins (Fig. 1), the hydrophilic dehydro-polymers of phloroglucinol (1,3,5-trihydroxybenzene), are only found in brown algae. They are classified in six types based on their polymerization and

linkage patterns:

i. phloroethols (*ortho*-ether linkages)
ii. fuhalols (*para*-ether bonds with hydroxylated rings)
iii. fucophloroethols (ether and phenyl bonds)
iv. fucols (phenyl bonds)
v. eckols (with dibenzodioxin moities)
vi. carmalols (dibenzo-1,4-dioxin linkages) (L. R. G. Kumar et al., 2022).

Phlorotannin content can reach up to 25 % of seaweed dry weight and is influenced by species, tissue type, maturity, and environmental factors such as season, salinity, nutrient levels, light intensity, and temperature (Catarino et al., 2022).

2.1.2. Bioactivity of algal phenolic compounds

Phenolic compounds exhibit antioxidant activity, primarily through electron or hydrogen donation and formation of stable radical intermediates that mitigate the oxidative damage to cellular biomolecules (Charlton et al., 2023). In addition to their antioxidant, anti-inflammatory, and analgesic properties validated in vivo, these metabolites display a wide range of in vitro bioactivities, including antibacterial, antiviral, hepatoprotective, and antitumor activities (Mihaylova et al., 2024). Such properties are influenced by structural characteristics such as the degree of methylation, hydrogenation, or hydroxylation (Shahidi and Dissanayaka, 2023).

Among algae-derived phenolics, phlorotannins are the most extensively studied in relation to human health (Erpel et al., 2020). Their antioxidant capacity can exceed that of simpler phenolics by 15–30-fold, depending on the polymerization degree (Gisbert et al., 2023). Industrially produced phlorotannin-rich extracts are already available on the market, often incorporated into dietary supplements targeting cardiovascular health, particularly through modulation of high-density lipoprotein cholesterol (HDL-c) levels (Zheng et al., 2022). Other validated properties include in vitro evidence of UV protection (Hermund et al., 2022), antiviral activity against human immunodeficiency virus (HIV) (Harb and Chow, 2022; Serna-Arbeláez et al., 2021), antiadipogenic (Dayarathne et al., 2024), neuroprotective (Meshalkina et al., 2023), antitumor, bactericidal, and radioprotective effects (Serna-Arbeláez et al., 2021), as well as in vivo antiallergic responses (Serna-Arbeláez et al., 2021; Sugiura et al., 2021).

2.2. Sterols

Sterols found in algae are collectively termed phytosterols, encompassing both sterols and stanols. These metabolites have garnered substantial scientific attention due to their demonstrated health-promoting effects. Phytosterols belong to the triterpene family and serve as essential structural components of cellular membranes, where they stabilize phospholipid bilayers, similarly to the effect of cholesterol in animal cell membranes (X. Li et al., 2022).

In algae, phytosterols are present either as free molecules or conjugated with fatty acids (most commonly) or sugars (Evtyugin et al., 2023). The C29 forms predominate, but the sterol profile can be modulated by ecological conditions, geographic origin, developmental stage, or the algae species itself. For instance, fucosterol (Fig. 2) is the major sterol in brown algae, whereas isofucosterol is more characteristic of green algae species (Voshall et al., 2021).

2.2.1. Structural diversity of algal sterols

Phytosterols share a high degree of structural similarity with cholesterol, including a tetracyclic cyclopent[α]phenanthrene nucleus, a hydroxyl group at C3, methyl substituents at C10 and C13, and an aliphatic chain attached at C17. They generally contain 28 or 29 carbon atoms and one or two C—C double bonds (most commonly, one within the sterol nucleus, and, in some cases, an additional bond in the side chain. The primary structural distinction from cholesterol lies in the side chain at the C24 position (Fig. 2); whereas cholesterol carries an eight-carbon side chain, it contains nine or ten carbon atoms in most phytosterols (Feng et al., 2020). Moreover, the stereochemistry at C24 differentiates phytosterols according to their sources; plant sterols predominantly exhibit the α-configuration, whereas algal sterols are more commonly arranged in the β-configuration. The analytical characterization of algal sterols is technically challenging because these metabolites occur in both free and conjugated forms, most commonly as fatty acid esters or glycosides linked to the 3-OH position on ring A (Evtyugin et al., 2023).

Among algal species, and although the general sterol composition is preserved, specific profiles are modulated by environmental factors, geographic origin, and developmental stage (Voshall et al., 2021).

Importantly, these compounds are not synthetized endogenously in humans, are poorly absorbed, and are excreted more rapidly than cholesterol (M. Shen et al., 2024).

2.2.2. Bioactivity of algal sterols

Phytosterols have been associated with several health benefits, most notably their hypocholesterolemic effect, which may enable their incorporation into functional foods designed to prevent and manage hypercholesterolemia. Microalgae are particularly appealing as phytosterol sources due to their rapid growth, high biomass productivity, and elevated concentrations of these bioactive metabolites (Sañé et al., 2023).

Among algal phytosterols, fucosterol and saringasterol - particularly abundant in species such as *Sargassum fusiforme* - have been shown to reduce low-density lipoprotein cholesterol (LDL-c) without affecting HDL-c levels (Poli et al., 2021). Fucosterol showed other biological properties (the species from which it was isolated are indicated for each activity):

i. antibacterial (*Sargassum longifolium* and *Turbinaria conoides*);
ii. anticholinesterase (*Ecklonia stolonifera, Panida australis*, and *Sargassum horridum*);
iii. antidiabetic (*E. stolonifera, Eisenia bicyclis*, and *Pelvetia siliquosa*);
iv. anti-inflammatory (*Hizikia fusiformis, P. australis*, and *U. pinnatifida*);
v. antioxidant (*E. stolonifera, E. bicyclis*, and *P. siliquosa*);
vi. antitumor (*Nannochloropsis oculata, Porphyra dentata*, and *Sargassum oligocystum*);
vii. cytotoxic (*Sargassum carpophyllum* and *Sargassum thunbergii*);
viii. neuroprotective (*E. stolonifera* and *P. australis*) (Hannan et al., 2020; Sañé et al., 2023).

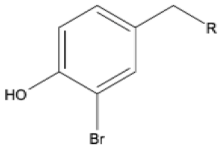
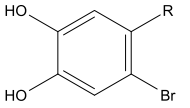
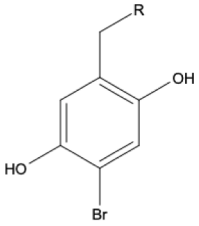
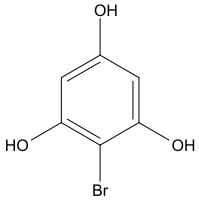
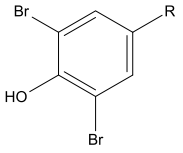
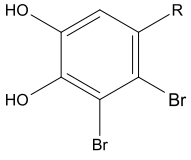
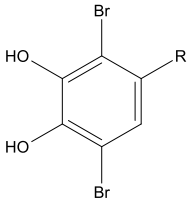
Despite these health benefits, phytosterols may interfere with the absorption of fat-soluble vitamins and antioxidants, which should be carefully considered when evaluating their use in food and pharmaceutical applications (Miszczuk et al., 2024).

2.3. Sulfated polysaccharides

Algae are increasingly recognized as a valuable and sustainable source of bioactive compounds, particularly structurally complex polysaccharides with promising functional and technological properties. These macromolecules exhibit unique physicochemical, rheological, and biological characteristics that support their incorporation into functional foods, pharmaceuticals, and cosmetic formulations (Otero et al., 2023).

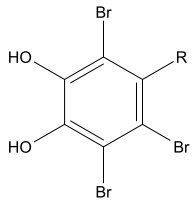
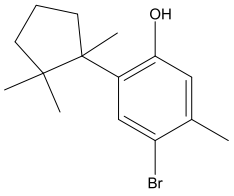
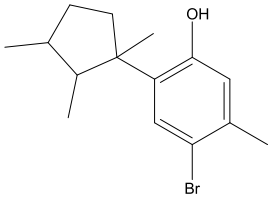
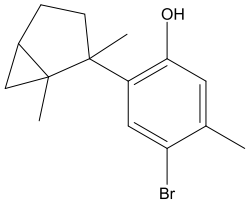
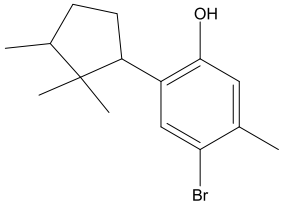
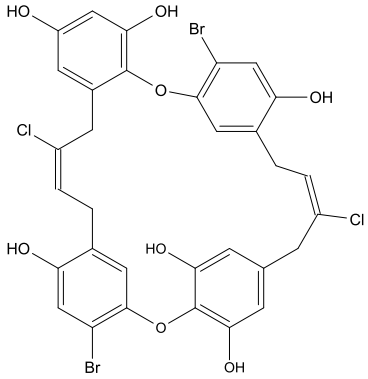
Among algal polysaccharides, sulfated forms such as fucoidan, ulvan, agar, carrageenan, phorphyran, and furcellaran, are of particular interest due to their abundance, broad spectrum of bioactivities, lack of acute toxicity, cost-effectiveness, biodegradability, and biocompatibility. These attributes have enabled their extensive utilization across the food, pharmaceutical, and cosmetic industries. Additionally, non-

Table 1
Representative bromophenol structures organized by substitution pattern and structural class and corresponding algal source (Fakee et al., 2023; Jacobtorweihen and Spiegler, 2023).

Bromophenol type	Basic structure	Genera
3-Bromo-4-hydroxybenzyl		*Avrainvillea* (green) *Bostrychia* (red) *Halopythis* (red) *Odonthalia* (red) *Polysiphonia* (red) *Rhodomeia* (red) *Vertebrata* (red)
2-Bromo-4,5-dihydroxybenzyl		*Polysiphonia* (red) *Rhodomela* (red)
4-Bromo-2,5-dihydroxybenzyl		*Cymopolia* (green)
2-Bromo-phloroglucinol		*Cystophora* (brown) *Eisenia* (brown) *Grateloupia* (red) *Rhabdonia* (red) *Rytiphlaea* (red)
3,5-Dibromo-4-hydroxybenzyl		*Leathesia* (brown) *Neorhodomela* (red) *Odonthalia* (red) *Polysiphonia* (red) *Vertebrata* (red)
Lanosol		*Leathesia* (brown) *Carradoriella* (red) *Leptosiphonia* (red) *Melanothamnus* (red) *Neorhodomela* (red) *Odonthalia* (red) *Osmundaria* (red) *Polyopes* (red) *Rhodomela* (red) *Vertebrata* (red) *Vidalia* (red)
3,6-Dibromo-4,5-dihydroxybenzyl		*Neorhodomela* (red) *Symphyocladia* (red)

(*continued on next page*)

Table 1 (*continued*)

2,3,6-Tribromo-4,5-dihydroxybenzyl		*Symphyocladia* (red) *Pterosiphonia* (red) *Rhodomela* (red) *Vertebrata* (red)
Cuparane		*Laurencia* (red)
Laurane		*Laurencia* (red) *Corallina* (red) *Osmundea* (red)
Cyclolaurane		*Laurencia* (red) *Corallina* (red)
Laurokamurane		*Laurencia* (red)
Chrysophaentin (note: the B configuration is showed)		*Chrysophaeum*

sulfated polysaccharides like laminarin have also been reported as bioactive constituents with emerging applications in these sectors (Nagahawatta et al., 2023).

2.3.1. *Structural diversity of algal sulfated polysaccharides*

Algal polysaccharides can be categorized into hydrocolloid and non-hydrocolloid types. Hydrocolloids, particularly phycocolloids, are widely valued for their rheological properties, being extensively used as thickeners, gelling agents, and stabilizers across food industrial applications. Current estimates suggest that more than one million metric tons of brown and red seaweeds are processed annually for phycocolloid production (Tomadoni et al., 2022).

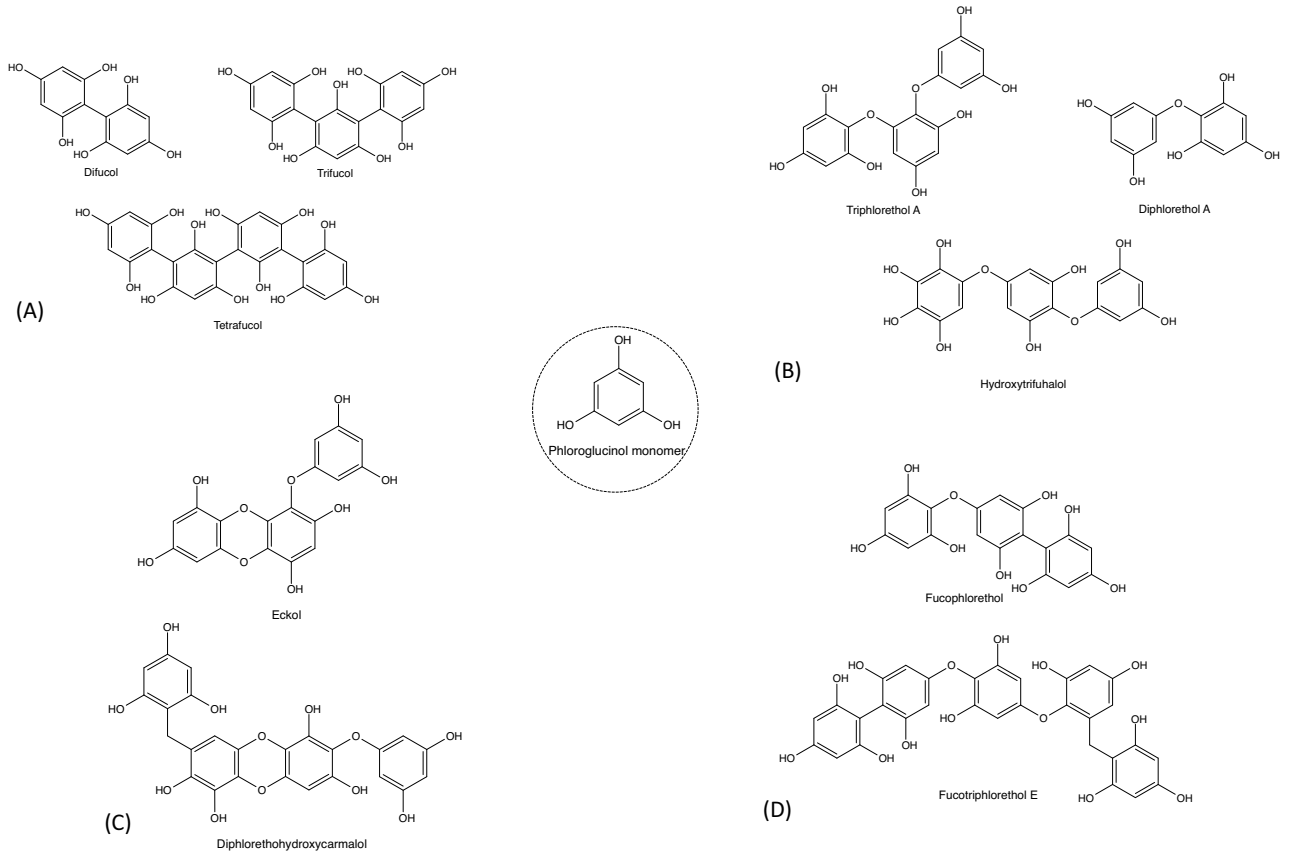


Fig. 1. Representative classes of phlorotannins: (A) - fucols; (B) - phlorethols and fuhalols; (C) - carmalols and eckols; (D) - Fucophlorethols.

Brown seaweeds are the exclusive source of fucoidan and fucan. Fucoidan primarily refers to homopolysaccharides composed predominantly of α-L-fucose and sulfate ester groups, whereas fucans are more complex heteropolysaccharides based on sulfated fucose, potentially containing other monosaccharides (e.g., mannose, galactose, glucose, xylose), uronic acids, acetyl groups, proteins, and amino sugars (Usov et al., 2022).

In red seaweeds, carrageenan and agar (collectively known as sulfated galactans) are the predominant sulfated polysaccharides. Carrageenan, named after *Chondrus crispus* (commonly known as carrageen moss or Irish moss), consists of repeating disaccharide units (carrabiose) composed of D-galactose and 3,6-anhydro-D-galactose, linked by alternating β-(1,3)- and α-(1,4)-glycosidic bonds (Kravchenko et al., 2023; S. J. Park et al., 2024). Structural variations in carrageenan (Fig. 3), including the number and position of sulfate groups, the presence of 3,6-anhydro-D-galactose units, and the conformation of the pyranose ring, define the three main commercial types: kappa (κ), iota (ι), and lambda (λ) (Elmarhoum et al., 2023; Mokhtari et al., 2021).

Agars (or agarans) are linear polysaccharides composed of repeating agarobiose units made up of D-galactose, L-galactose, and/or 3,6-anhydro-L-galactose, also connected by alternating β-(1,3)- and α-(1,4)-glycosidic bonds (Ciancia et al., 2020). Agar is predominantly found in *Gelidium, Gracilaria, Porphyra*, and *Ahnfeltia* species, showing high variability in the sulfation patterns among these taxa (Chumsook et al., 2023).

Ulvan refers to the main sulfated polysaccharides in green algae of the order Ulvales (mainly *Ulva* and *Enteromorpha* species). These highly charged polyelectrolytes are composed of variable proportions of rhamnose, xylose, and uronic acids (glucuronic and iduronic) (Fig. 3) (Kidgell et al., 2019; Z. Wang et al., 2024).

2.3.2. *Bioactivity of algal sulfated polysaccharides*

In marine macroalgae, sulfated polysaccharides and their lower molecular weight oligosaccharide derivatives have demonstrated different biological activities (Otero et al., 2023). Reported effects, demonstrated in vitro and in animal models, include antidiabetic, antiadipogenic, anticoagulant, antithrombotic, antioxidant, antiviral, antimicrobial, antitumor, antiproliferative, anti-inflammatory, and immunomodulatory effects. The presence, density, and position of sulfate groups are widely recognized as key determinants of these bioactivities (Carpena et al., 2023; Carvajal-Barriga and Fields, 2023; Pradhan et al., 2023; S. M. Qiu et al., 2022; Wijesekara et al., 2024; Xie et al., 2023). Additional physiological effects reported for these polysaccharides include prebiotic activity and potential benefits against atherosclerosis, hepatopathies, uropathies, and nephropathies (Lomartire and Gonçalves, 2022).

Carrageenan is widely utilized in controlled drug release, biomacromolecules transport, and tissue regeneration due to its viscosity, film-forming properties, negative charge, and high gelling capacity (Daei et al., 2022).

Agar, in addition to sharing the typical bioactivities of sulfated polysaccharides, exhibits UV-protective, prebiotic, and anti-aggregation effects (X. Chen et al., 2021; Lomartire and Gonçalves, 2022; Praiboon et al., 2023). In the food industry, agar functions as a key solidifying and stabilizing agent (S. H. Park et al., 2020). Agarose and its derivatives have also been applied in regenerative medicine, promoting angiogenesis, osteogenesis, chondrogenesis, and neurogenesis (X. Chen et al., 2021; Jiang et al., 2023; Ortiz-Arrabal et al., 2023; Revete et al., 2022; Salati et al., 2020).

Ulvan has been utilized in wound dressing, tissue engineering, drug delivery systems, food packaging materials, pest management, and wastewater treatment (Anisha et al., 2023). Ulvans also exhibit structural, physicochemical, and biological properties beneficial to maintain

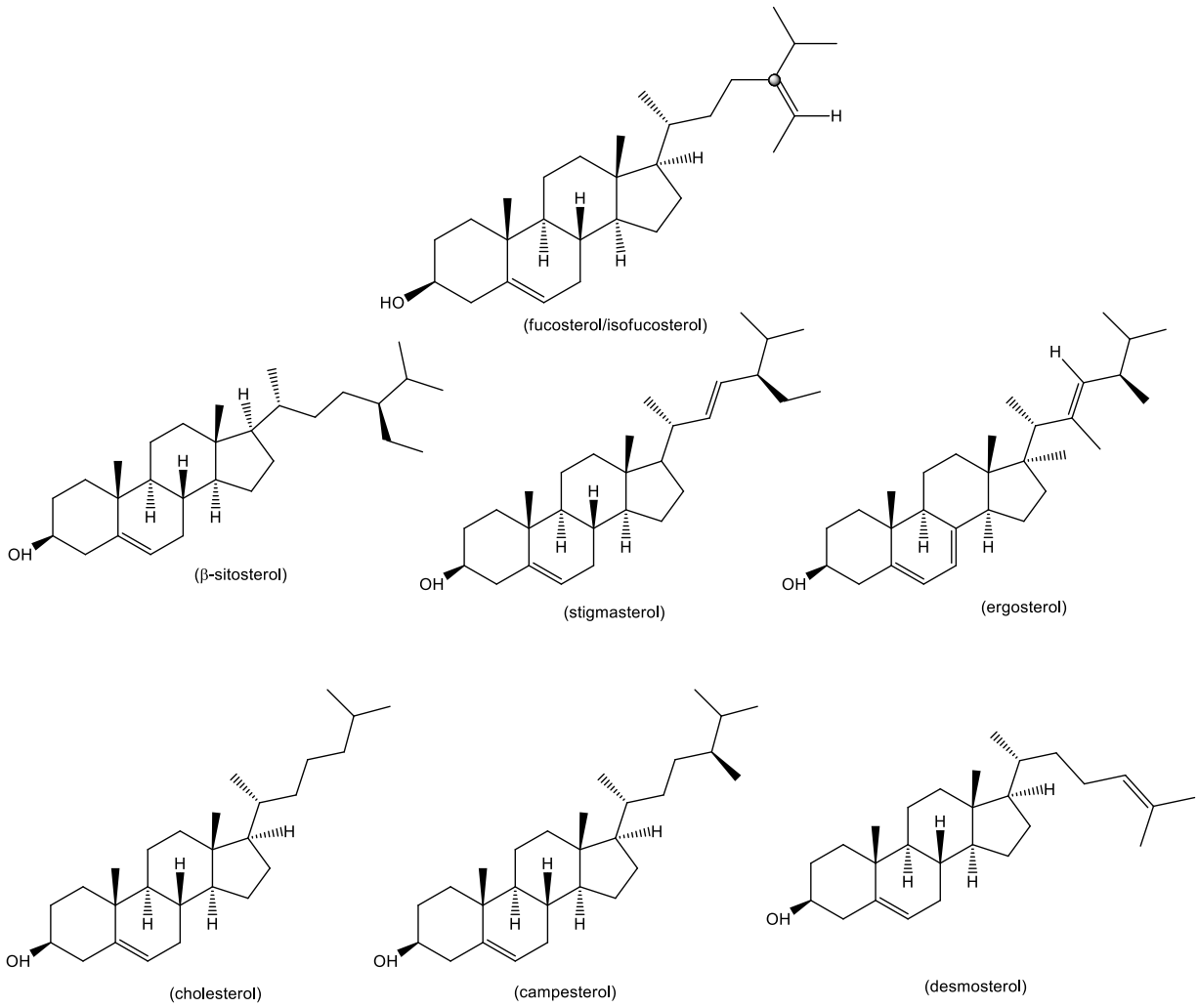


Fig. 2. Chemical structures of the predominant sterols identified in algae. Fucosterol (*E*-isomer) and isofucosterol (*Z*-isomer) differ in the C24 configuration (highlighted with a sphere).

intestinal health (C. Li et al., 2023).

Overall, sulfated polysaccharides represent valuable sources of rare sugar precursors and bioactive oligosaccharides, particularly as novel biomaterials for drug delivery applications and as multifunctional texturizing agents in gel-based formulations.

3. Extraction of bioactive compounds from algae

Given the extensive algae biodiversity and the structural complexity of their bioactive compounds, the selection of an optimal extraction method represents a critical step in the analytical workflow. In fact, the efficiency and reliability of subsequent steps - separation, identification and characterization of bioactive compounds - are highly dependent on the applied extraction technique (Arias et al., 2023). Moreover, implementing suitable extraction protocols is essential not only to achieve higher concentrations of the target bioactive compounds, but also to obtain extracts free from potentially harmful substances (such as heavy metals) that could pose risks to human health (Cannavacciuolo et al., 2024).

Traditional extraction techniques, such as Soxhlet extraction and conventional solid-liquid extraction, are generally associated with prolonged processing times and substantial solvent consumption, which contribute to an elevated environmental impact, besides presenting limited reproducibility. Therefore, the following sections will focus exclusively on advanced and emerging extraction technologies, which generally offer improved efficiency, selectivity, and environmental sustainability.

3.1. Advanced extraction techniques

Recent advancements in extraction technologies have driven the development of several innovative methodologies, including microwave assisted extraction (MAE), ultrasound assisted extraction (UAE), supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE). These techniques offer enhanced selectivity, improved process efficiency, and a higher degree of automation, while also fulfilling the principles of green chemistry (Cannavacciuolo et al., 2024). Collectively, these technologies are designed to improve the detection and purification of bioactive compounds, thereby improving the selectivity of analytical methods and the sensitivity and reliability of subsequent bioassays. In this way, such approaches support the implementation of robust, reproducible, and scalable biorefining protocols (Sabotič et al., 2024).

3.1.1. Supercritical fluid extraction (SFE)

SFE explores the physicochemical properties of fluids in their supercritical state to extract soluble analytes from solid matrices. Supercritical carbon dioxide is frequently used due to its favorable critical conditions (304.25 K, 7.38 MPa), low toxicity, non-flammability, chemical inertness, and availability in high purity. This technique

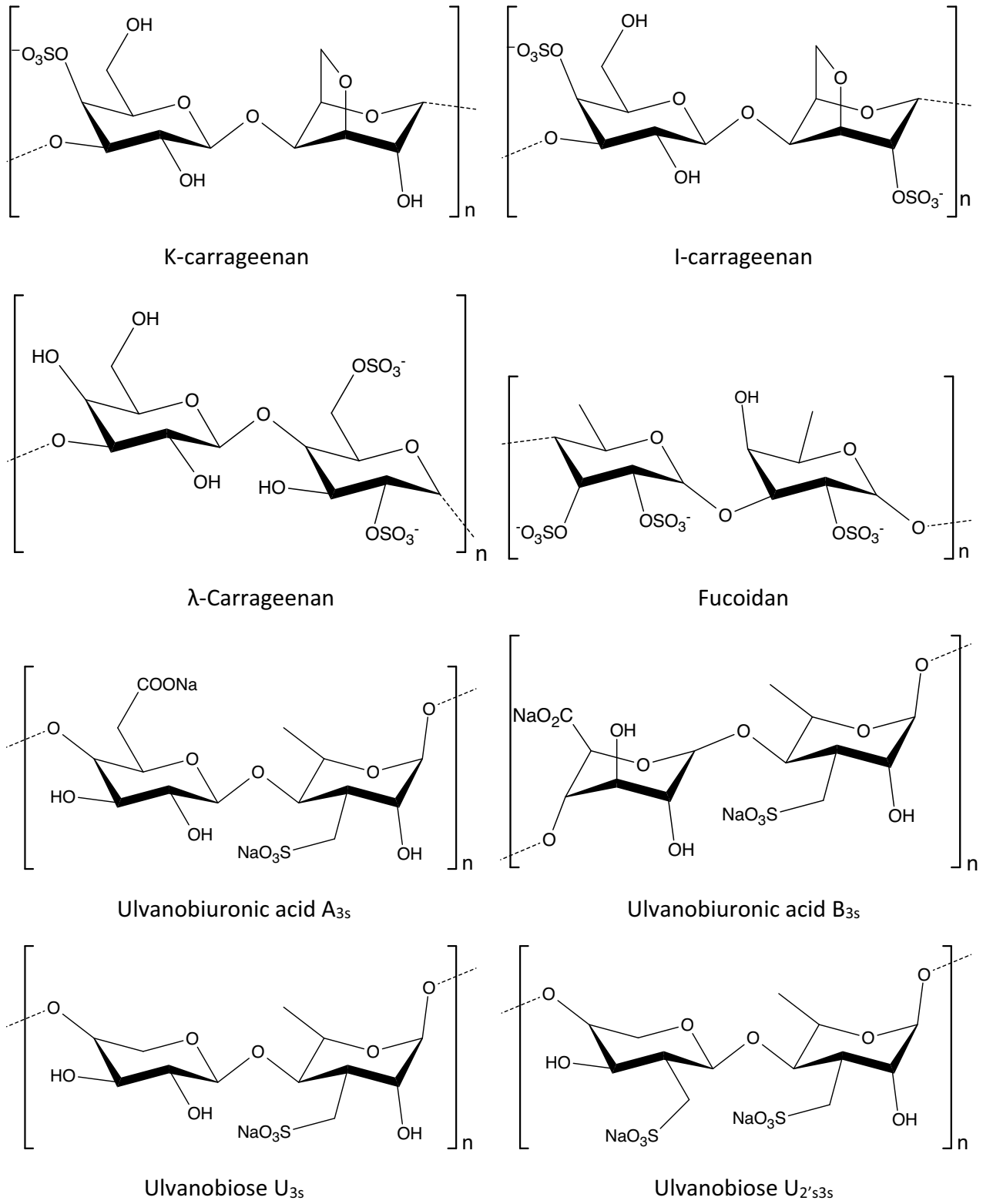


Fig. 3. Representative chemical structures of major carrageenan, fucoidan, and ulvan components. Ulvanobiuronic acid A_{3s} contains a glucuronic acid residue linked to rhamnose-3-sulfate; ulvanobiuronic acid B_{3s} contains an iduronic acid linked to rhamnose-3-sulfate; ulvanobiose U_{3s} contains a xylose residue linked to rhamnose-3-sulfate; ulvanobiose $U_{2's3s}$ contains a xylose-2-sulfate linked to rhamnose-3-sulfate.

provides high selectivity, reduced solvent consumption, short extraction times, and compatibility with automation. However, its efficiency is influenced by key operational parameters such as pressure, temperature, solubility of target compounds, and extraction duration (Fraguela-Meissimilly et al., 2023; Hu et al., 2025).

The general SFE procedure involves loading the sample onto a sorbent within the extraction cartridge, which is inserted into the SFE extraction cell and further brought into contact with supercritical CO_2. The target analytes are subsequently trapped using a suitable solvent - typically ethanol - at room temperature (facilitated by the cooling effect

Table 2
Overview of selected advanced (SFE, PLE, UAE, MAE) and emerging (SAE, EAE, GXE) extraction techniques applied to algal biomass; representative algal sources, key operational conditions, and main classes of extracted bioactive compounds are summarized.

Extraction technique	Algal sources	Extraction conditions	Extracted compounds	References
Advanced techniques				
SFE	*Aurantiochytrium* sp.	40 °C; 30 MPa	Omega-3 fatty acids, phenolic compounds	(De Melo et al., 2020)
	Chlorella saccharophila	73 °C; 24 MPa	Fatty acids	(Alhattab et al., 2019)
	Chlorella sorokiniana	50 °C; 20 MPa	β-carotene, lutein, violaxanthin, zeaxanthin, chlorophylls	(Morcelli et al., 2021)
	Chlorella vulgaris	60 °C; 25 MPa	Carotenoids (e.g., astaxanthin, β-carotene, lutein), chlorophylls, phenolics	(Georgiopoulou et al., 2022)
	Coccomyxa onubensis	70 °C; 40 MPa	Lutein, total phenols, antioxidant compounds	(Ruiz-Domínguez et al., 2022a)
	Dunaliella salina	45 °C; 20 MPa	β-carotene	(Tirado and Calvo, 2019)
	Haematococcus pluvialis	50 °C; 55 MPa	Astaxanthin, lutein, fatty acids	(Di Sanzo et al., 2018)
	Nannochloropsis sp.	60 °C; 30 MPa	EPA	(Jiménez Callejón et al., 2022)
	Phaeodactylum tricornutum	30 °C; 30 MPa	Fucoxanthin	(Ruiz-Domínguez et al., 2022b)
	Pseudostautosira trainorii	60 °C; 30 MPa	Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)	(Sprynskyy et al., 2022)
	Schizochytrium sp.,	76 °C; 47 MPa	DHA	(Rodríguez-España et al., 2022)
	Spirulina platensis	50 °C; 25 MPa	Phycocyanin, chlorophyll a, carotenoids, minerals, fatty acids	(Martí-Quijal et al., 2023)
PLE	*Cystoseira barbata, Fucus virsoides*	H_2O, 0.1 M H_2SO_4; 60, 100, 140 °C	Sulfated polysaccharides	(Dobrinčić et al., 2021)
	Cystoseira mediterranea, Ceramium virgatum, Halopteris scoparia, Padina pavonica, Ulva lactuca, Ulva intestinalis	EtOH:H_2O 75:25; 120 °C	Carotenoids, phlorotannins	(Keramane et al., 2023)
	Eisenia bicyclis	H_2O; 90–250 °C	Melanoidins, phlorotannins	(Gomes et al., 2022)
	Fucus vesiculosus	Hexane, EtOH, ethyl acetate, acetone, and EtOH at 50 %; 80, 120, 160 °C	Fatty acids	(Otero et al., 2018)
	Fucus vesiculosus	Ethanol at 59 %; 137 °C	Phenolic antioxidants (gallic, protocatechuic, and gentisic acids)	(Sumampouw et al., 2021)
	Fucus vesiculosus	Low polarity water; 120–200 °C	Phenolic compounds, alginate, fucoidan	(Getachew et al., 2022)
	Himanthalia elongata	EtOH:H_2O 50:50	Fatty acids	(Otero et al., 2018)
	Kappaphycus alvarezii	H_2O; 150 °C	Carrageenan	(Gereniu et al., 2018)
	Laminaria ochroleuca	Hexane, EtOH, ethyl acetate, ethanol, and EtOH at 50 %; 120 °C	Fatty acids, phenolic compounds	(Otero et al., 2019)
	Sargassum cristaelefolium	H_2O; 121 °C	Fucoidan	(Lin et al., 2022)
	Sargassum muticum	EtOH:H_2O 95:5, 75:25, and 25:75; 120, 160 °C	Phlorotannins	(Jagirani and Soylak, 2022)
	Sargassum serratifolium	EtOH; 100 °C	Phenolic compounds, meroterpenoids (sargahydroquinoic acid and sargachromenol)	(Baek et al., 2024)
	Sargassum thumbergii	H_2O; 180 °C	Phlorotannins	(J. S. Park et al., 2022)
	Ulva intestinalis, Ulva lactuca	EtOH:H_2O 50:50	Fatty acids	(Otero et al., 2018)
UAE	*Ascophyllum nodosum, Fucus distichus, Fucus serratus, Fucus vesiculosus*	EtOH; 22 kHz	Fucoidan	(Obluchinskaya et al., 2025)
	Arthrospira platensis, Scenedesmus obliquus	EtOH, ionic liquids [1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMIM-BF4), 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM-PF6), 1-butyl-3-methylimidazolium chloride (BMIM-Cl), 1-hexyl-3-methylimidazolium chloride (HMIM-Cl)]; 20 kHz	Carotenoids, chlorophyll	(Fernandes et al., 2024)
	Chlamydomonas reinhardtii, Chlorella sp., *Nostoc commune*	H_2O, 500 W	Carbohydrates	(Ooi et al., 2025)
	Chlorella sp.	EtOH, dimethylcarbonate, cyclopentyl methylether, 2-methyltetrahydrofuran; 40 kHz	Polyunsaturated fatty acids	(Hui et al., 2023)
	Chlorella vulgaris	Ectoin, panthenol; 100 W	Polysaccharides	(Lu et al., 2024)
	Chlorella vulgaris	Ethanol; 130 W	Polar lipids	(Couto et al., 2022)
	Chromochloris zofingiensis	DES; 40 kHz	Canthaxanthin	(Yang et al., 2023a)
	Cystoseira indica	MeOH, acetone, MeOH:acetone; 150 W	Fucoxanthin	(Oliyaei and Moosavi-Nasab, 2021)
	Dunaliella salina	H_2O; 200 W	Protein, polyphenols	(Ferreira et al., 2023)
	Fucus vesiculosus	Sodium bicarbonate (0.1 M); 26 kHz	Alginate	(Ummat et al., 2024)

(*continued on next page*)

Table 2 (*continued*)

Extraction technique	Algal sources	Extraction conditions	Extracted compounds	References
Advanced techniques				
	Fucus vesiculosus, Pelvetia canaliculata	EtOH:H_2O 50:50; 26 kHz	Phlorotannins, flavonoids, sugars	(Garcia-Vaquero et al., 2021)
	Gracilaria edulis, Sargassum wightii, Ulva rigida	MeOH; 40 kHz	Fucoxanthin, phloroglucinol, gallic acid, quercetin, ferulic acid, vanillin	(Y. Kumar et al., 2020)
	Hypnea flagelliformis	NADES; 37 kHz	Catechin gallate, epigallocatechin, epigallocatechin gallate, epicatechin, epicatechin gallate, gallic acid	(Olfat et al., 2024)
	Kappaphycus alvarezii, Kappaphycus denticulatum, Kappaphycus striatum	EtOH:H_2O 50:50; 26 kHz	Phenolic compounds	(Putra et al., 2022)
	Nannochloropsis sp.	Hexane/isopropanol; 20 kHz	Fatty acids, pigments	(Mienis et al., 2024)
	Phaedoactylum tricornutum	H_2O; 100 W	Carbohydrates, carotenoids, polyphenols	(Al Khawli et al., 2021)
	Porphyra haitanensis	EtOH; 40 kHz	Phenolic acids, flavonoids, organic acids	(Xu et al., 2022)
	Sargassum fusiforme	Ethyl lactate; 40 kHz	Fucoxanthin	(Nie et al., 2021)
	Sargassum muticum	DES; 10, 20 W	Gallic acid, 3,4-dihydroxibenzoic acid, syringic acid, salicylic acid, caffeic acid, ferulic acid, *p*-coumaric acid, catechin, quercetin	(B. C. Jesus et al., 2023)
	Undaria pinnatifida	EtOH; probe-type ultrasonic cell pulverizer	Fucoxanthin	(C. Wang et al., 2023)
MAE	*Ascophyllum nodosum*	EtOH; 1400 W	Fucoxanthin, polyphenols	(Cassani et al., 2024)
	Ascophyllum nodosum, Laminaria hyperborea	DES	Phenolic compounds	(M. Jesus et al., 2025)
	Chlorella vulgaris	EtOH:H_2O 90:10; 40, 60 °C	Carotenoids, chlorophylls, phenolic compounds	(Georgiopoulou et al., 2023)
	Cystoseira barbata, Fucus virsoides	H_2O, 0.1 M HCl, 0.1 M H_2SO_4; 60, 80, 100 °C	Sulfated polysaccharides	(Dobrinčić et al., 2021)
	Codium tomentosum, Eiseinia bicyclis, Fucus vesiculosus, Gracilaria gracilis, Himanthalia elongata	EtOH, acetone; 1000 W	Carotenoids, chlorophylls	(Lopes et al., 2024)
	Fucus spiralis, Fucus vesiculosus, Laminaria saccharina	0.1 M HCl; 800 W	Fucoidan, alginate	(Zayed et al., 2023)
	Fucus vesiculosus	EtOH (0, 20, 40, 60, 80, 100 %); 25, 50, 75, 100, 125, 150 °C	Phlorotannins	(Amarante et al., 2020)
	Fucus vesiculosus, Pelvetia canaliculata	EtOH 50 %; 250 W	Phlorotannins, tannins, phenolic compounds, flavonoids, sugars	(Garcia-Vaquero et al., 2021)
	Kappaphycus alvarezii	EtOH; 60 °C	Carrageenan	(Rudke et al., 2022)
	Phaeodactylum tricornutum	EtOH (0, 50, 100 %); 30, 100, 170 °C	Phenolic compounds, chlorophylls, fucoxanthin	(Gilbert-López et al., 2017)
	Porphyridium purpureum	H_2O; 30, 65, 100 °C	B-phycoerythrin	(Huschek et al., 2022)
	Sargassum muticum	Proline:propylene glycol (1:4), proline:1,4-butanediol (1:4), choline chloride:citric acid; 800 W	Gallic acid, 3,4-dihydroxybenzoic acid, caffeic acid, *p*-coumaric acid, syringic acid, ferulic acid, salicylic acid, catechin and quercetin	(B. C. Jesus et al., 2023)
	Sargassum swartzii	EtOH; 100–800 W	Phlorotannins	(Toan et al., 2021)
	Tetradesmus obliquus	EtOH:H_2O 50:50; 400, 600, 800 W	Aliphatic hydrocarbons, alkylated hydrocarbons, ketones, phenols, and esters	(Gouveia et al., 2021)
	Undaria pinnatifida	EtOH (20, 36, 60, 84, 100 %); 2, 4, 7, 10, 12 Bar	Fucoxanthin	(Lourenço-Lopes et al., 2023)
Ulterior techniques				
SAE	*Acutodesmus obliquus*	ROKAnolNL5; peristaltic pump in countercurrent mode	Lipophilic bioactives compounds	(Fellechner et al., 2019)
	Chlorella saccharophila	Hexadecyltrimethylammonium bromide (CTAB); 24 h	Fatty acids	(Alhattab et al., 2019)
	Chlorella sorokiniana	CTAB, myristyltrimethylammonium bromide (MTAB); 6000 rpm, 10 min	Polysaccharides, proteins	(Taghavijeloudar et al., 2021)
	Chlorella vulgaris	Anionic [sodiumdodecylbenzene sulfonate (SDBS) and sodium dodecyl sulfate (SDS)], cationic [CTAB and methylbenzethonium chloride (MBC)], and non-ionic (polyoxyethylene-2-isooctylphenyl ether (IGEPAL CA-210) and polyethyleneglycol sorbitan monostearate (Tween 60)] surfactants; 120 °C	Fatty acids	(J. Y. Park et al., 2021)
	Dunaliella salina	Tergitol NP10 aqueous solution (30 %); stirring for 48 h	Carotenoids	(Pinheiro et al., 2019)
	Synechocystis sp.	CTAB, dodecyltrimethylammonium bromide (DTAB); 5 h	Lipids and nonpolar pigments, carotenoids and chlorophyll a	(Lai et al., 2018)
EAE	*Arthrospira platensis*	Lysozyme; 27 °C, 4 h	Allophycocyanin, carotenoids	(Tavanandi et al., 2019)
	Arthrospira platensis	Alcalase®, Flavourzyme®, Ultraflo® L, Vinoflow® Max; 30–50 °C, 24 h	Peptides and aminoacids	(Verdasco-Martín et al., 2019)
	Ascophyllum nodosum	Celluclast; 50 °C, 6, 24 h	Carotenoids, polyphenols, polysaccharides, protein	(Periaswamy Sivagnanam et al., 2024)

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Table 2 (*continued*)

Extraction technique Advanced techniques	Algal sources	Extraction conditions	Extracted compounds	References
	Canistrocarpus cervicornis, Colpomenia sinuosa, Feldmannia irregularis, Iyengaria stellata, Padina gymnospora, Sargassum angustifolium, Sargassum boveanum	Novozyme; 50–60 °C, 20 h	Phenolic compounds	(Sabeena et al., 2020)
	Chondracanthus chamissoi, Macrocystis pyrifera	Cellulase (Cellic CTec3); 50 °C, 16 h	Proteins	(Vásquez et al., 2019)
	Ecklonia maxima	Cellulase, Cellic® CTec2, Cellic® HTec2, Viscozyme® L; 50 °C, 24 h	Phlorotannins, fucoidan, sodium alginate	(Mabate and Pletschke, 2024)
	Fucus evanescens, Saccharina latissima	Cellulase, alginate lyase; 40 °C, 24 h	Fucoidan	(Nguyen et al., 2020)
	Haematococcus pluvialis	Cellulase, pectinase; 40 °C, 1 h	Astaxanthin	(X. Zhao et al., 2019)
	Nannochloropsis oceania	Cellulase, laccase; 40 °C, 24 h	Fatty acids, EPA-containing lipid	(Zhao et al., 2022)
	Nannochloropsis sp.	Cellulase; 70 °C, 1000 rpm, 1 h	Fatty acids	(C. Qiu et al., 2019)
	Saccharina latissima	Alcalase; 50 °C, 3 h	Fucoidan, laminarin	(Herrera Barragán et al., 2022)
	Sargassum dupplicatum	Cellulase, Termamyl, and Viscozyme; 25 °C, 3 h	Phlorotannins	(Boi et al., 2020)
	Solieria chordalis	Protamex®, Neutrase®; 50 °C, 3 h	Carrageenans, oligosaccharides, phenolic compounds, proteins	(Spain et al., 2024)
	Ulva fenestrata	Cellulases (Viscozyme L and Cellulysin) and proteases (Neutrase 0.8 L and Flavourzyme); 40–60 °C, 3, 6, 17, 20 h	Ulvan	(Malvis Romero et al., 2023)
	Ulva latuca	Agarases, alginate lyases, arylsulfatases, cellulases, cellobiohydrolases, fucosidases, mannosidases, pectate lyases, ulvan lyase, xylanases; 160 rpm, overnight	Proteins, chlorophylls, carotenoids, fatty acids	(Costa et al., 2022)
	Ulva sp.	Protamex®; 50 °C, 3 h	Carbohydrates, monosaccharides, uronic acids, proteins	(Fournière et al., 2019)
GXE	*Botryococcus braunii, Chlorella vulgaris, Isochrysis galbana, Scenedesmus obliquus,*	Carbon dioxide expanded ethanol; 275 Bar	Lipophilic compounds, chlorophylls	(Mendiola, 2020)
	Phormidium autumnale	Carbon dioxide expanded ethanol; 50 °C	Sterols	(Fagundes et al., 2021)
	Schizochytrium sp.	Carbon dioxide expanded ethanol; 50 °C	Triacylglycerols, phospholipids, glycolipids, fatty acids	(P. L. Li et al., 2019)

generated during CO_2 expansion). The resulting extracts are further subjected to chromatographic analysis (Tzima et al., 2023).

SFE has been extensively applied to extract bioactive constituents, including carotenoids (e.g., astaxanthin, β-carotene, fucoxanthin, lutein, violaxanthin, zeaxanthin), fatty acids (particularly, eicosapentaenoic acid and docosahexaenoic acid), chlorophylls, minerals and phenolic compounds, from several algae species (Tzima et al., 2023; Vo et al., 2024; Zhou et al., 2022), as reviewed in Table 2. Besides enabling the selective recovery of target biomolecules, SFE avoids thermal degradation and solvent residues, while offering tunable operational parameters for scalability.

3.1.2. Pressurized liquid extraction (PLE)

PLE employs organic solvents at elevated pressure and temperature, typically above their boiling points, to maintain a liquid state and enhance solute diffusion. This approach improves analyte recovery by facilitating matrix disruption and increasing solvent penetration due to reduced viscosity and surface tension under high-temperature conditions (Barp et al., 2023).

The method involves packing a solid sample into a stainless-steel extraction cell, followed by solvent treatment under controlled conditions (40–200 °C and 3.45–20.68 MPa) for short time intervals (5–15 min). The resulting extract is purged into a collecting vial using compressed gas. This method offers some key advantages such as minimal solvent consumption, enhanced extraction efficiency and selectivity, short processing times, high automation, and suitability for processing fresh biomass (Quitério et al., 2022).

PLE has been predominantly employed to extract sulfated polysaccharides, phlorotannins, carotenoids, and fatty acids from a variety of algae species including *Ascophyllum nodosum, Eisenia bicyclis, Fucus serratus, Himanthalia elongata, Laminaria ochroleuca, Sargassum muticum* or *Ulva latuca* (Perez-Vazquez et al., 2023). When coupled with mass spectroscopy, PLE has demonstrated improved efficiencies for isolating C29 and diene sterols, but achieving optimal performance requires careful tuning of operational parameters, including temperature and pressure (Abou Mrad et al., 2020). In either case, the addition of antioxidants before the extraction process is recommended to minimize oxidative degradation (Oubannin et al., 2024).

Other bioactive compounds extracted using PLE, such as carotenoids, phlorotannins, fatty acids, phenolic acids, polysaccharides (alginate, carrageenan, fucoidan), or meroterpenoids are summarized in Table 2, along with their corresponding algae sources and operational parameters.

3.1.3. Ultrasound assisted extraction (UAE)

UAE utilizes ultrasonic waves (20 kHz to 1 MHz) to enhance solvent penetration and mass transfer from solid matrices during extraction. This technique is particularly effective in accelerating the pre-treatment steps, besides being compatible with diverse solvents (L. Shen et al., 2023). Its primary mechanism involves acoustic cavitation, in which microbubbles rapidly form and collapse, generating localized extreme conditions (temperatures up to 4800 °C and pressure increase of about 1000 atm) that substantially increase extraction kinetics (K. Kumar et al., 2021). The extraction efficiency depends on several operational parameters, including solvent type, pH, particle size, temperature, pressure, ultrasonic frequency, and sonication duration. In addition, UAE is mostly conducted as a batch process, and the obtained extracts often require further purification (K. Kumar et al., 2021; L. Shen et al., 2023).

UAE has been demonstrated as an efficient technique to extract phenolic compounds (including, polyphenols, phlorotannins, flavonoids, phenolic acids), organic acids, sulphated polysaccharides (specifically alginate, fucoidan), carotenoids (such as canthaxanthin and fucoxanthin), chlorophylls, polyunsaturated fatty acids, polar lipids, and

proteins from numerous algae species, as detailed in Table 2.

3.1.4. Microwave assisted extraction (MAE)

MAE integrates microwave energy with conventional solvent extraction to accelerate mass transfer by rapidly heating the solvent and sample matrix. Microwaves (0.3–2.5 GHz) generate internal heating, enhancing extraction kinetics and efficiency (Patrice Didion et al., 2023).

Typically, solvent is continuously circulated through a pressurized extraction cell to maintain the liquid state at an elevated temperature (López-Salazar et al., 2023). This configuration allows for reduced solvent use (up to 90 % less than traditional methods) and rapid processing (15–30 min). The technique offers high throughput, reproducibility, and efficient analyte recoveries (A. Kumar et al., 2023). On the other hand, MAE may yield impure extracts, generally requiring post-extraction clean-up due to limited selectivity (Quitério et al., 2022).

Recent innovations in MAE include techniques such as compressed air microwave distillation, microwave accelerated steam distillation, solvent-free microwave extraction, and vacuum microwave hydrodistillation (Nisca et al., 2022).

MAE has emerged as a rapid and energy-efficient technique to recover diverse bioactive compounds from algae (Table 2). Its advantages include enhanced extraction yield and kinetics (Toan et al., 2021), higher recovery and improved pigment stability (Lopes et al., 2024), shorter processing times with preservation of functional integrity (Zayed et al., 2023), uniform heating, and efficient cell disruption (Huschek et al., 2022). Collectively, these features classify MAE as a scalable and environmentally friendly extraction strategy for the sustainable recovery of high-value algal metabolites.

MAE has been demonstrated as being particularly efficient to extract phenolic compounds due to the high moisture content of algal tissues, which promotes rapid heating, cell disruption, and efficient analyte release into a cold solvent system (Pôjo et al., 2021; Sadeghi et al., 2024). MAE also operates under mild, non-photolytic conditions that help preserving the structural integrity of phenols and improve extraction efficiency (Gil-Martín et al., 2022). However, phenolics bearing multiple hydroxyl substituents may be more susceptible to degradation during extraction (Alara et al., 2021).

Besides phenolic compounds (including phenolic acids, flavonoids, phlorotannins), other compounds such as carotenoids (e.g., fucoxanthin), chlorophylls, and polysaccharides (such as alginate, carrageenan, fucoidan), were extracted from several algal species, as summarized in Table 2.

3.2. Ulterior techniques

This section provides a concise overview of some emerging extraction methodologies, highlighting their underlying principles and applications in the extraction of bioactive compounds from algal species.

3.2.1. Surfactant-assisted extraction (SAE)

SAE employs surfactants (such as polyoxyethylenated sorbitan monooleate (Tween 80), glucoside alkyl ethers, or polypropylene alkyl ethers) as additives to enhance solvent performance. By reducing interfacial tension between the liquid and solid phases, surfactants improve solvent penetration and mass transfer. Their amphiphilic structure facilitates the solubilization of hydrophobic and hydrophilic compounds embedded within biological membranes in aqueous media (Bjerk et al., 2021).

SAE has emerged as a promising and sustainable approach for valorizing algal biomass for next-generation food applications. This technique improves the extraction efficiency while minimizing reliance on hazardous organic solvents. Recent studies (Table 2) have demonstrated that SAE has predominantly been employed to recover lipophilic compounds (e.g., carotenoids, fatty acids, and chlorophylls), although it has also demonstrated effectiveness in extracting hydrophilic constituents, such as polysaccharides and proteins, from both microalgae and macroalgae (Qin et al., 2022).

Moreover, the tunability of surfactant type and concentration offers opportunities for process optimization and integration with green downstream technologies. Moving forward, the development of biodegradable or food-grade surfactants, coupled with techno-economic and life-cycle assessments, will be essential to establish SAE as a scalable and food-safe strategy for sustainable ingredient production from algae (Miao et al., 2024).

3.2.2. Enzyme-assisted extraction (EAE)

EAE involves the application of specific enzymes to degrade structural polysaccharides within the algal cell wall, thereby improving the accessibility and release of intracellular bioactive compounds. The main advantage of EAE is the possibility of working under mild conditions, which helps preserving the structural integrity of sensitive target molecules. However, it often requires an additional purification stage to remove residual enzymes and impurities (Łubek-Nguyen et al., 2022).

This method has been applied to extract several classes of bioactive compounds from seaweeds and microalgae, including phenolics (e.g., polyphenols, phlorotannins), polysaccharides (such as carrageenan, fucoidan, laminarin, sodium alginate, and ulvan), amino acids, peptides, proteins, fatty acids, carotenoids (astaxanthin), and other pigments (allophycocyanin) (Table 2), although further research is needed to optimize the operational conditions and determine the most effective enzyme combinations for targeting specific compounds (Sanjeewa et al., 2023).

Overall, EAE represents a key enabling technology for the sustainable production of functional ingredients and nutraceuticals for food and feed applications.

3.2.3. Gas-expanded extraction (GXE)

GXE works with solvent systems modified by the dissolution of a compressible gas, typically CO_2, due to its non-toxicity, and ease of removal. The incorporation of CO_2 results in carbon dioxide-expanded liquids (CXL), which exhibit lower viscosity and higher diffusivity compared to conventional solvents (Pilařová et al., 2022). Additionally, the solvation environment is altered - often decreasing polarity and generating acidic species - facilitating the selective extraction of targeted compounds (Amador-Luna et al., 2023; Yang et al., 2022).

By modulating solvent composition and operational conditions, GXE enable the selective extraction of non-polar to moderately polar metabolites, including carotenoids, lipids, and phenolics. GXE have been experimentally applied to algae (Table 2), particularly to extract chlorophylls, sterols, triacylglycerols, phospholipids, glycolipids and fatty acids), although in less extent when compared to other extraction technologies. Nonetheless, GXE represent a promising green and scalable technology for producing functional ingredients and nutraceuticals within sustainable food systems (Dias et al., 2021a).

3.2.4. Hyphenated techniques

While individual extraction techniques have advanced considerably, their limitations - particularly regarding selectivity and extract purity - still require attention. Hyphenated extraction techniques, which integrate an extraction step with an in-line clean-up or fractionation stage, offer enhanced selectivity and process efficiency. For example, combining SFE with SPE has enabled the targeted recovery of trace phenolic compounds from microalgae by incorporating SPE cartridges directly within the SFE setup (Souza et al., 2021).

Furthermore, the synergistic application of high-pressure extraction with hydrolysis (enzymatic or non-enzymatic), or the sequential use of ultrasound and microwave-assisted techniques, has shown great potential in maximizing bioactive compounds recovery from seaweeds (Quitério et al., 2022).

For the recovery of multiple compound classes, sequential or hierarchical extraction methods (e.g., SC—CO_2 for lipids followed by EAE +

PLE for polysaccharides and proteins) can maximize valorization but raise, though they increase process complexity and costs, which must be justified by the value of the final product.

Molecularly imprinted polymer (MIPs), widely recognized for their molecular recognition capabilities, represent a promising solution for selective extraction. Although predominantly employed in terrestrial plant matrices and biological samples, recent studies suggest the potential of coupling MIPs with algal extraction systems to improve specificity and reduce matrix interferences (Baker and Sardari, 2021; Kamaruzaman et al., 2021; Suzaei et al., 2023; Zuo et al., 2023).

3.3. Comparison of different extraction techniques

As discussed in the previous sections, the advanced and ulterior extraction techniques reviewed herein demonstrated to be efficient to recover bioactive compounds from seaweeds and microalgae, generally enabling rapid and sustainable processing times, and high reproducibility (Fig. 4).

Overall, extraction methods based on compressed fluids, such as SFE and PLE, demonstrate high selectivity, which can be further optimized by adjusting operational parameters such as pressure, temperature, and solvent composition (Quitério et al., 2022). On the other hand, cell wall disruption techniques, such as MAE, UAE, SAE, and EAE, are influenced by several critical factors, including operating temperature, pre-treatment conditions, solid-to-solvent ratio (SSR), input energy (e.g., microwave or ultrasound power), and enzyme specificity. Despite the clear advantages associated with these innovative extraction methodologies, their industrial-scale implementation may still face practical constraints, some of which associated to inherent structural and biochemical characteristics of algal biomass, as explained in the next sections.

3.3.1. Method-specific limitations of working with algal biomass

Algal biomass comprises great potential as a source of different bioactive compounds, but their utilization in green extraction technologies may result challenging. The major drawbacks arise from i. their complex and variable cell-wall composition (including the sulfated and non-sulfated polysaccharides that form dense, gel-like matrices); ii. seasonal and species heterogeneity, and iii. the co-existence of targets with widely different polarity and stability, hindering the choice of solvents and operational conditions (Bogdan et al., 2025).

These limitations manifest differently accross each extraction technology.

For SFE, which is especially adequate for lipophilic molecules, and offers solvent-free extracts, minimal thermal degradation, and straightforward solvent recovery for scale-up, the main limitations are its low efficacy for polar compounds (when polar co-solvents are not used), high operational costs, and the need for pre-disruption of cell walls to access intracellular lipids in many macroalgae and microalgae. The addition of ethanol or other generally recognized as safe co-solvents can broaden the polarity range; however, it also reintroduces challenges related to solvent handling and potential residue issues (Amador-Luna et al., 2023; Uwineza and Waśkiewicz, 2020).

In turn, PLE enhances solvent penetration and can selectively hydrolyze glycosidic linkages under controlled temperature and pressure, making it suitable for extracting mid-polarity compounds and less polar polysaccharides. However, the application of high temperatures may lead to the depolymerization and degradation of heat-sensitive constituents (e.g., some pigments and proteins), while also increasing the co-extraction of salts and low-molecular impurities, particularly when desalting is incomplete. Therefore, careful optimization of temperature, extraction time, and solvent composition is essential to balance selectivity, yield, and product integrity (Amador-Luna et al., 2023).

UAE, while effective in reducing extraction time and improving

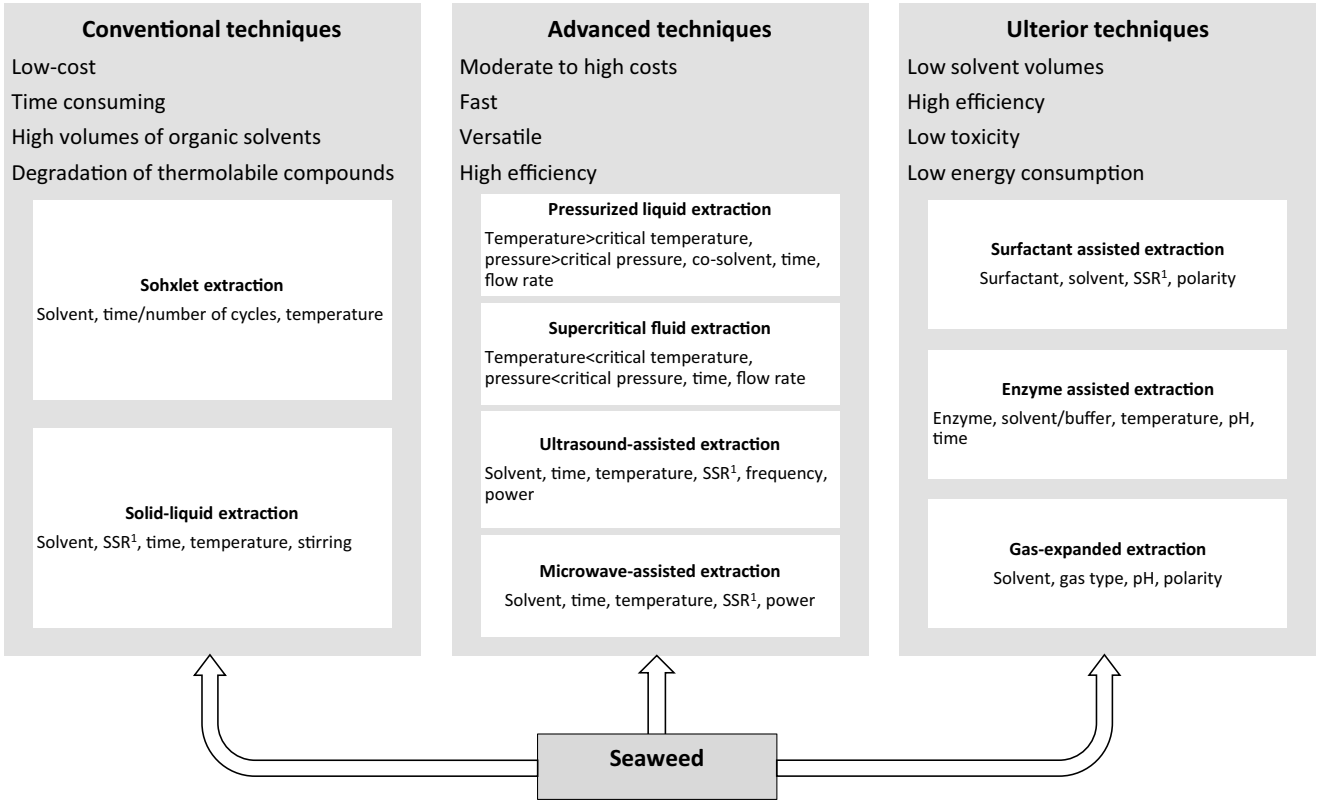

Fig. 4. Schematic overview of principal extraction technologies (categorized as conventional, advanced, and ulterior methods) applied for the recovery of bioactive compounds from algae. Key operational characteristics, advantages, and representative techniques are highlighted for each group. [1]SSR: solid-to-solvent (Pattnaik et al., 2021; Quitério et al., 2022).

yields for many target compounds (such as polysaccharides, phenolics, and pigments), is usually limited by non-uniform energy distribution in larger reactors (scale-up challenge), potential local overheating and oxidation near cavitation sites, and the risk of molecular fragmentation of sensitive bioactives under excessive intensity. Its full potential is often realized when applied as a pretreatment, for example prior to PLE, to facilitate subsequent extraction (Kumar et al., 2021).

Regarding MAE, which allows rapid heating and improved solvent penetration, this technique can be applied to extract both polar and non-polar compounds when an appropriate solvent system is selected. Its main limitations are associated with thermal effects: localized hotspots may lead to protein denaturation and algal pigments oxidation, while penetration depth is ruled by the dielectric properties of both the solvent and the biomass. Although optimized duty cycles, tailored solvent selection, and adequate temperature control can reduce these risks, they are not possible to be fully eliminated. Additionally, MAE requires reactor configurations capable of safely processing the heterogenous and high-moisture algal biomass without arcing or uncontrolled thermal escalation (Díaz-de-Cerio and Trigueros, 2025).

SAE, while using food-grade surfactants or micellar systems to solubilize polar and amphipathic molecules, can be highly effective for recovering proteins, phycobiliproteins and some glycoproteins. However, its major drawbacks include the need for downstream surfactant removal to meet food-grade specifications, potential regulatory barriers depending on the surfactant used, and possible alterations in analytical performance due to matrix effects (e.g., colorimetric interferences). Consequently, SAE is highly promising for lab-scale and targeted extractions, but its successful industrial application will require robust and validated purification workflows (Kopp and Lauritano, 2025).

EAE is conceptually attractive for algal bioprocessing because tailored enzymes (e.g., agarases, alginate and ulvan lyases, cellulases, carrageenases, fucosidases) can selectively hydrolyze structural matrix components and release entrapped molecules under mild conditions. However, several limitations must be considered, including enzyme cost, the need for food-grade enzyme preparations, the need to optimize enzyme cocktails and reaction conditions for each algal species, and potential downstream complications due to the presence of released oligosaccharides that can hinder purification. In turn, studies indicate that EAE can be advantageous when targeting high-value compounds, though scale-up feasibility and efficient enzyme recycling remain unsolved challenges (Costa et al., 2022; Herrera Barragán et al., 2022).

Finally, GXE enable tunable solvent polarity and improved mass transfer under moderate pressure conditions, making them appealing for the selective extraction of non-polar to moderately polar metabolites. However, applications in algal systems remain limited compared to terrestrial plant matrices, making the technique promising but insufficiently validated for algal biomass. Current challenges include the need for specialized reactor designs capable of handling mixed gas-liquid phases, precise process control to maintain extraction selectivity, and a lack of industrial case studies demonstrating techno-economic competitiveness (Sánchez-Camargo et al., 2018).

Overall, mass transfer limitations imposed by gel matrices, co-extraction of salts (affecting taste and stability), seasonal variability in composition, and the need to preserve labile functional groups represent key challenges in algal biomass processing. Practical mitigation strategies reported in the literature include combining physical disruption techniques (e.g., UAE, MAE, bead milling) with EAE to weaken matrices before targeted extraction, desalting or chelation steps to reduce Ca^{2+} mediated crosslinking in alginates, and using low-temperature, short-duration extractions or mild solvents (such as SC—CO_2) to protect thermo-labile compounds (Table 3).

4. Therapeutic prospects of seaweed extracts and isolated compounds: focus on antiviral activity

Sulfated polysaccharides have gained substantial attention as multifunctional bioactive ingredients with translational relevance across food, nutraceutical, and biomedical sectors. Their diverse therapeutic attributes, combined with favorable safety profiles, position them as promising candidates for next-generation functional foods and health-promoting ingredients. Furthermore, their anionic character, charge density, and structural flexibility, might be of particular interest for antiviral activity purposes, as those attributes enable interactions with viral surface proteins, host cell receptors, and immune pathways, providing multiple mechanisms through which they may inhibit viral attachment, replication, and propagation (Pereira et al., 2025).

Among the diverse bioactive metabolites identified in marine algae, sulfated polysaccharides, and their low-molecular weight oligosaccharides, have, indeed, emerged as the most extensively studied compounds in the scope of antiviral applications (Otero et al., 2023). Their antiviral efficacy is primarily attributed to their affinity for specific viral surface epitopes, mediated by the negatively charged sulfate groups (Carvajal-Barriga and Fields, 2023). This physicochemical characteristic enables direct interactions with viral particles, thereby obstructing key steps of the viral life cycle (Liyanage et al., 2023). Beyond direct virucidal actions, sulfated polysaccharides can block viral infections through three principal mechanisms:

a) **Inhibition of viral adsorption and invasion** - viral infection is initiated by the recognition and attachment of viral particles to host cell receptors, often sulfated proteoglycans structurally analogous to heparin. Sulfated polysaccharides can competitively bind to these receptors or to the viral surface proteins, forming non-infectious polysaccharide-virus complexes. These electrostatic interactions prevent viral adsorption and block subsequent cellular invasion (Yoshida, 2021).
b) **Inhibition of viral transcription and replication** - sulfated polysaccharides may interfere with viral replication by competing with RNA template-primer complexes for enzyme-binding sites, thereby inhibiting essential viral polymerases and other replication-associated enzymes. Compounds such as ulvan and carrageenan have been shown to disrupt viral transcription and replication pathways through these competitive interactions (Liyanage et al., 2023).
c) **Inhibition of viral release** - these polysaccharides can modify the biophysical properties of the host cell membrane, reducing its flexibility and impairing the release of newly formed viral particles. This effect has been demonstrated, for instance, in the inhibition of human metapneumovirus (hMPV) release by carrageenan (Ciejka et al., 2019). Moreover, sulfated polysaccharides may interfere with host signaling pathways by binding to neuroaminidase and disrupting the activation of key regulatory proteins such as the epidermal growth factor receptor, nuclear factor kappa B, and serine/threonine kinases, thereby further constraining viral penetration and propagation (Liyanage et al., 2023)

4.1. Carrageenan

Carrageenan has been shown to form stable complexes with viral particles by binding to envelope domains essential for host cell attachment, thereby blocking viral entry and subsequent infection (Liyanage et al., 2023). Beyond the variability associated with virus strain and polysaccharide type, its antiviral efficacy is modulated by the degree of polymerization and sulfation. The negatively charged carrageenan molecules enable electrostatic interactions with positively charged regions on viral surfaces, interrupting the attachment process and thus preventing host-cell infection (Kalsi et al., 2025).

The three principal carrageenan types - κ-, ι-, and λ-carrageenan - exhibit antiviral activity through distinct but complementary mechanisms:

Table 3
Key classes of algal bioactives, typical extraction constraints, and recommended green processing approaches.

Compound class	Representative targets	Typical extraction challenges from algae	Recommended extraction approaches/pretreatments
Polysaccharides (sulfated and non-sulfated)	Alginate, fucoidan, carrageenan, agar, ulvan, laminarin	Dense gel matrix, Ca^{2+} cross-linking, high viscosity, seasonal variability	EAE (alginate and ulvan lyases, carrageenases) plus mild heat; subcritical/pressurized water for selective hydrolysis; desalting/chelation pretreatment (Costa et al., 2022; Herrera Barragán et al., 2022; Lomartire and Gonçalves, 2022).
Pigments (lipophilic and hydrophilic)	Chlorophylls, carotenoids (astaxanthin, β-carotene, fucoxanthin), phycobiliproteins	Lipophilic pigments sequestered in membranes; phycobiliproteins are water-soluble but labile	SFE (CO_2 plus co-solvent) or GXE for carotenoids; cold aqueous or buffer extraction for phycobiliproteins; protection from oxidation/light; combination with cell disruption (UAE or MAE) (Amador-Luna et al., 2023; Periaswamy Sivagnanam et al., 2024).
Lipids	TAG, glycolipids, phospholipids, EPA, DHA, sterols, tocopherols	Intracellular storage; oxidation; co-extraction of pigments	SFE (CO_2 plus co-solvent) or GXE to tune polarity; prior mechanical disruption (bead milling, sonication) (Amador-Luna et al., 2023).
Proteins and peptides	Total protein, bioactive peptides	Co-extraction with polysaccharides; denaturation; solubility changes	Aqueous extraction with pH shift, enzyme-assisted release (cellulases/proteases), mild MAE or UAE as pretreatment; desalting (Herrera Barragán et al., 2022).
Phenolics compounds	Phlorotannins, phenolic acids, flavonoids, bromophenols	Strong binding to matrix; oxidation; variable polarity	Hydroalcoholic PLE, UAE or MAE to enhance mass transfer, controlled temperature to avoid oxidation (Mittal and Ranade, 2023).

a) **κ-carrageenan** primarily inhibits viral adsorption to the host-cell surface and suppresses subsequent viral protein expression. It has demonstrated inhibitory effects against multiple viruses, including H1N1 influenza virus, SARS-CoV-2, herpes simplex virus (HSV)-2, and human papillomavirus (HPV) (Jang et al., 2021; Wei et al., 2022).
b) **ι-carrageenan** acts mainly by preventing viral protein aggregation on the host-cell surfaces. This form has shown antiviral activity against human rhinovirus, HPV, multiple influenza strains (H1N1, H3N2, H5N1, H7N7), and SARS-CoV-2 (Frediansyah, 2021; Henríquez et al., 2023; Morokutti-Kurz et al., 2021; Wei et al., 2022).
c) **λ-carrageenan** inhibits viral internalization by interacting with host-cell receptors and binding to viral envelope proteins. Reported antiviral effects include activity against influenza virus, rabies virus, and dengue virus (DENV) serotype 3 (Jang et al., 2021).

4.2. Fucoidan

Fucoidan has been widely studied for its antiviral properties. It has been shown to inhibit reverse transcriptase and neuraminidase, interfere with viral adsorption and penetration, and suppress intracellular viral replication. These mechanisms have been documented across a wide spectrum of viruses, including SARS-CoV-2, influenza A viruses (H1N1, H3N2, H5N3), HSV-1 and HSV-2, hepatitis B and hepatitis C viruses, HIV, respiratory syncytial virus, human cytomegalovirus, HPV, and Newcastle disease virus (NDV) (Liyanage et al., 2023; Oliyaei et al., 2022; Wei et al., 2022).

In human norovirus models, fucoidan effectively blocked the binding of GII-4 virus-like particle and inhibited viral replication in vivo. It also upregulated the expression of interferon-stimulated genes, thereby encoding antiviral effector pathways (Mensah et al., 2023). Beyond direct antiviral action, fucoidan exhibits immunomodulatory effects, including enhancement of natural killer cell activity, promotion of dendritic cell maturation, and enabling memory T-cell development. Comparable antiviral effects have also been reported for agar, which showed activity against HSV-1, HSV-2, influenza A and B viruses, NDV and Japanese encephalitis virus (JEV) (Panggabean et al., 2022).

Moreover, fucoidan has shown potential as a dietary supplement capable of mitigating respiratory damage following viral infections by supporting innate immune responses and reducing inflammation (Pradhan et al., 2022).

4.3. Ulvan

Ulvan also demonstrated diverse antiviral activities. It has been shown to reduce syncytia formation in measles virus (MeV) infections, inhibit cell-to-cell fusion in NDV, downregulate HSV protein synthesis, and prevent infection and replication of vesicular stomatitis virus and JEV (Wei et al., 2022). Furthermore, ulvan exhibited antiviral effects against hepatitis A virus and adenovirus by blocking viral internalization, specifically by interfering with virus-host receptor interactions (Maray et al., 2023).

Ulvan has also been reported to be active against several other viruses, including MeV, NDV, DENV, yellow fever virus, West Nile virus, H1N1, avian influenza virus and HSV (Wei et al., 2022). Recent studies further demonstrated its virucidal activity and its capacity to inhibit viral replication and absorption, particularly against SARS-CoV-2 (Binsuwaidan et al., 2024). Ulvans have also been reported for being capable of entering host cells via an energy-dependent process and subsequently activate the stimulation of interferon genes signaling pathway, leading to the induction of type I interferons and downstream interferon-stimulated genes (Zhang et al., 2025). Beyond its direct antiviral action, ulvan also showed immunomodulatory effects, such as downregulating of pro-inflammatory cytokines production (Wei et al., 2022).

Overall, the multifaceted antiviral mechanisms of sulfated polysaccharides highlight their potential as natural, food-compatible therapeutic agents for the prevention and mitigation of viral infections.

5. Conclusions

Algae constitute a highly valuable and versatile source of bioactive compounds with well-established health-promoting properties, highlighting the importance of developing extraction strategies that are not only efficient, selective, and scalable, but also aligned with environmental sustainability processes. In this context, novel green extraction approaches such as SFE, PLE, MAE, and UAE, together with using alternative solvent systems like ionic liquids, deep eutectic solvents (DES), and natural deep eutectic solvents (NADES), offer promising approaches to enhance yield, purity, and compound integrity, while reducing environmental impact.

As an essential upstream step, extraction plays a pivotal role in the feasibility and functional performance of algae-derived bioactive compounds in emerging natural-based food formulations and nutraceutical and biomedical applications.

In the scope of biomedical applications, sulfated polysaccharides (e.g., carrageenan, ulvan, and fucoidan) stand out as particularly promising agents due to their broad spectrum of documented biological properties, as exemplified by their multipurpose antiviral effects.

Considering their natural abundance, biocompatibility, low toxicity, and comparatively fewer regulatory constraints compared to synthetic analogues, algal-derived ingredients can be incorporated in next-

generation functional foods or innovative therapeutic alternatives. Continued interdisciplinary research integrating bioprocess optimization, mechanistic bioactivity evaluation, and application-driven formulation design will be essential to fully translate their potential into commercial value.

Ethical statement

All authors agree there's nothing to declare.

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CRediT authorship contribution statement

Cláudia S.G.P. Pereira: Writing – original draft, Investigation, Conceptualization, Writing – review & editing. **M. Carpena:** Writing – original draft, Investigation, Conceptualization. **João C.M. Barreira:** Writing – review & editing, Formal analysis, Conceptualization. **Cristiana F.C. Silva:** Writing – original draft, Investigation. **M.A. Prieto:** Writing – review & editing, Supervision. **M.Beatriz P.P. Oliveira:** Writing – review & editing, Supervision.

Declaration of competing interest

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

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Data availability

All used data is available in the current version of the manuscript.

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