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Review

Anti-inflammatory potential of ulvan

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ABSTRACT

Green seaweeds are a widespread group of marine macroalgae that could be regarded as biorenewable source of valuable compounds, in particular sulfated polysaccharides like ulvans with interesting biological properties. Among them, anti-inflammatory activity represents an interesting target, since ulvans could potentially avoid side effects of conventional therapies. However, a great variability in ulvan content, composition, structure and properties occurs depending on seaweed specie and growth and processing conditions. All these aspects should be carefully considered in order to have reproducible and well characterized products. This review presents some concise ideas on ulvan composition and general concepts on inflammation mechanisms. Then, the main focus is on the importance of adequate selection of extraction, depolymerization and purification technologies followed by an updated survey on anti-inflammatory properties of ulvans through modulation of different signaling pathways. The potential application in a number of diseases, with special emphasis on inflammaging, gut microbiota dysbiosis, wound repair, and metabolic diseases is also discussed. This multidisciplinary overview tries to present the potential of ulvans considering not only mechanistic, but also processing and applications aspects, trusting that it can aid in the development and application of this widely available and renewable resource as an efficient and versatile anti-inflammatory agent.

1. Introduction

Ulvales (Chlorophyta) are a group of marine macroalgae world widely distributed; between 88 and 400 *Ulva* species (and formerly *Enteromorpha*) have been recognized taxonomically [1–3]. *Ulva* sp. is cultivated and collected for food consumption, the biomass from cultivation being of higher quality and homogeneity than that from natural harvesting. The underexploited low-cost biomass associated with proliferations in eutrophicated waters also represents a potential feedstock that adequately valorized could reduce the economic impact derived from its management.

Cell wall polysaccharides are the major components of seaweeds, accounting for 38-54 % of the dry weight in green ones. In *Ulva* sp. the major polysaccharide is ulvan, cellulose, a linear xyloglucan and a

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glucuronan are present [4,5]. Starch is also found, in contents fluctuating seasonally or with environmental or cultivation conditions, reaching up to 32 % of the dry weight in *Ulva rigida* [6,7]. Ulvans are sulfated cell-wall matrix polysaccharides, mainly composed of rhamnose, uronic acids (D-glucuronic and its epimer L-iduronic), and xylose. Ulvans shares chemical analogy with mammalian glycosaminoglycans (heparan sulfate, chondroitin sulfate, dermatan sulfate and hyaluronan) found in human skin. This high biocompatibility, biodegradability and low toxicity have recently attracted considerable attention for the preparation of novel biomaterials for biomedical and pharmaceutical applications, especially in tissue regeneration or wound healing [5,8] as a better alternative to synthetic materials [9]. A number of ulvan-based structures have been developed, including membranes and films, nano- and microparticles, hydrogels, 3D porous structures and nanofibers [8,10]. Ulvans are also valuable due to their gelling properties and varied biological properties, such as antioxidant, anticoagulant, anti-inflammatory, immunomodulating, antimicrobial, antiviral, anti-hyperlipidemic, antitumor and healing [8,11–13].

Inflammation is an adaptive response triggered by noxious conditions and stimuli, such as infections and tissue damage [14], that has a central role in the host defense system. Inflammation is highly regulated in order to restrict its action to the time and place where it is necessary, because loss of control can lead to tissue damage and lead to number of diseases, including rheumatoid arthritis, chronic inflammatory bowel diseases, neurodegenerative disorders, and septic shock syndrome [15–17]. Interestingly, ulvans have gained a great interest as an alternative and complementary treatment of different diseases characterized by an inflammation-driven pathogenesis, on the basis of its previously mentioned biological properties. Likewise, research regarding the specific mechanisms activated by ulvan underling its anti-inflammatory actions has deserved attention in the last years [12,18,19]. Thus, to the date several cellular signaling pathways have been proposed to carry out the biological activities of ulvans [12,18–22].

Recent reviews on ulvan can be found. Among them, Kidgell et al. (2019) published a comprehensive overview on the extraction, purification and properties of ulvan [5]. Tziveleka et al. (2019) [8] surveyed the chemical composition and structure, extraction processes, physicochemical and biological properties as well as the potential of ulvan from different genus in the design of different biomaterials. Liu et al. (2022) [12] compiled the various functions of *Ulva* polysaccharides aiding in a healthy aging, such as regulation of immune cells and aging-related genes, promoting tumor senescence and mitochondrial function, maintaining liver balance, and protecting gut microbiome from inflammation. Shah et al. (2023) focused on the therapeutic potential of ulvan and the associated molecular mechanisms and the challenges associated with clinical translation and Anisha et al. (2023) focused on ulvan applications [20,23].

In this review, some general ideas on the ulvan occurrence and chemical, functional and biological characteristics are summarized and then the relevance of the different extraction and purification technologies and their influence on the ulvan composition and activity is discussed. After summarizing key aspects on anti-inflammatory mechanisms of ulvan, a number of examples of potential application of ulvan in different diseases are presented. Therefore, this work offers an updated overview of the role of ulvans on inflammation, addressing both chemical, engineering and pharmaceutical aspects.

2. Ulvan composition and structure

The *Ulva* species contain 31-80 % carbohydrates, 2-13 % protein, 13-26 % ash and around 4 % lipid [5,24,25]. Ulvans are the major water-soluble polysaccharides accounting from 8 to 36 % dry weight [5,26]. They play a structural role, being located in the intercellular space of the cell wall, bound to cellulose, proteins and other polysaccharides.

These sulphated hetero-polysaccharides are mainly composed of rhamnose (16.8–45.0 %), glucuronic acid (6.5-22.5 %), xylose (2.1–12.0 %), iduronic acid (0.7–9.1 %) and glucose (0.5–6.8 %). The sulfate content (14-32 %) was lower but the uronic acid content (12-27 %) was higher than in the sulfated polysaccharides from other green seaweeds [9,11,25]. The presence of other monosaccharides, such as galactose, arabinose and mannose in variable amounts as a component or as a contaminant in ulvan is not clear and their adscription belonging to ulvan is uncertain [5,8,9].

Ulvan structure is unique regarding the presence of sulfated L-rhamnose and iduronic acid. The structure is slightly branched and complex with two main repeating disaccharides, the most abundant being aldobiuronic acids (ulvanobiuronic acids, types A and B) and minor aldobioses (ulvanobioses, type U). The ulvanobiuronic acid type A3s is formed by β-D-glucuronic acid (1,4)-linked to α-L-rhamnose 3-sulfate and the type B3s is formed by α-L-iduronic acid (1,4)-linked to α-L-rhamnose 3-sulfate. Ulvanobioses U3s consists of β-D-xylose (1,4)-linked to α-L-rhamnose 3-sulfate, and ulvanobioses type U2's,3s consists of β-D-xylose 2-sulfate (1,4)-linked to α-L-rhamnose 3-sulfate. The structure of the main repeating ulvan disaccharides is presented in Fig. 1, their occurrence and the biological activity have been compiled in different reviews [8]. Sulfation is mainly found on C-3, on both C-2 and C-3 or at C-4 of rhamnose, and partially sulfated xylose at O-2 can occur; branching on O-2 of rhamnose, and on O-2 of uronic acids [8,25].

The composition, especially the monosaccharide profile, sulfate content and the molecular weight, as well as the structural features of ulvan determine the bioactivities. They differ depending on the species, life cycle, origin and season of collection but the extraction conditions may also affect the yield and characteristics of the resulting ulvan. The proportions of cell wall polysaccharides and glycoproteins coextracted with ulvan are highly variable.

Sulfate content is a key characteristic since sulfated polysaccharides exhibit better antiradical capacity [27] and stronger chelating ability towards Fe, Zn, Cu, and other metal ions improving the antioxidant and immunomodulatory properties compared to the non-sulfated one [28].

The different molecular weights of ulvan have been reported to range from 55 to 3600 kDa [9,11,25,29–31]. Usually, ulvans show two broad macromolecular fractions, at 775 kDa, at 150 kDa and a third intense peak at 1.5 kDa, which could also be attributed to *co*-extracted saccharides with low polymerization degree. However, the reported values depend on the extraction conditions, separation and determination method [8].

In addition, the gelation conditions and the tendency of ulvan to form microaggregates in dilute solutions in the presence of salts may contribute to the wide variability in the reported values [5,9,26,32]. Ulvan presents physico-chemical and biological properties with increasing interest for a variety of applications. Ulvan solutions exhibit low viscosities, corresponding to the presence of high proportions of short-chain polysaccharides and slightly branched structure [26], but can form gels with borate and divalent cations. The conformation of ulvan in solution is pH dependent and is influenced by the presence of counter-ions. Under neutral and low pH aqueous solutions, ulvan is found in beads conformation, and in the presence of salts the beads are aggregated [32]. The bead conformation of ulvan reduces the intermolecular interactions resulting in the low viscosity of its solutions. In contrast, in high pH solutions ulvan has a more open conformation increasing the intermolecular interactions that lead to higher viscosities and greater gel strengths.

3. Extraction and depolymerization

The technological and biological properties of ulvan are defined by their chemical composition and molecular structure, being both determined by the species, culture conditions, collection, conservation, and the extraction and purification methods [5,8,11,12,32,33]. In addition, due to the key importance of the molecular weight and sulfate content on the technological and biological properties of ulvan, a further depolymerization stage could be needed, in case the extraction stage

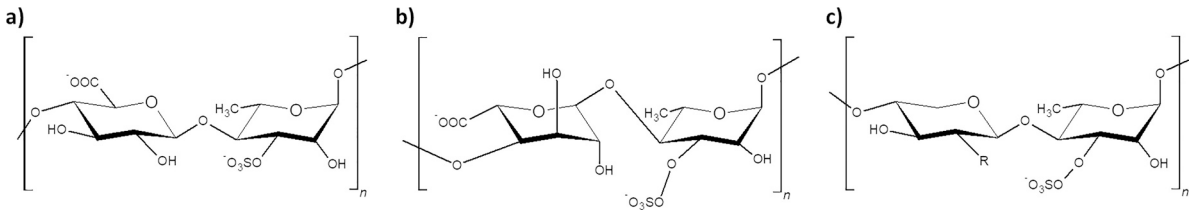

Fig. 1. Major constituents of ulvan, aldobiouronic acids, a) ulvanobiuronic acid 3-sulphate type A (A3s) and b) type B (B3s), and c) ulvanobioses type U3S (with either xylose or xylose 2-sulfate).

does not provide the desirable values.

Therefore, a rational selection of these conditions is needed and may also contribute to the development of more efficient and safer novel products. Before ulvan extraction, seaweeds are washed to remove sand, salts and epiphytes. Other pretreatment stages, such as drying and grinding, can influence the extraction performance. Drying is required when the feedstock has to be stored or transported before use [8,29], but could be unnecessary when processing the seaweeds near the collection area or if the objective is to separate the salts and to extract the polysaccharidic fractions. However, drying is a priority if the objective is to obtain the lipophilic fraction. The dried seaweeds are usually crushed and ground to a particle size from 0.3 to 3 mm diameter [13,21] to facilitate cell wall breakage and release of cytoplasmic and cell wall materials [11,32]. These are general considerations valid for the extraction of the different seaweed polysaccharides. However, in the case of ulvans, additional effects should be taken into account because the pH and salt concentration have important effects on ulvan aggregation, thus influencing not only extractability but also functional properties. Seaweed conditioning stages, such as freezing, freeze-drying, hot-air drying, brining and dry salting can influence the yield, physicochemical characteristics and rheological properties of ulvan. Robic et al. (2008) found that air drying at 70 °C provided higher ulvan yields, whereas brining at room temperature induced ulvan degradation and also poorer rheological properties than those from fresh algae [29]. Brining and salting favored the extraction of polysaccharides, but decreased the rhamnose content, due probably to the consumption of the organic matter by the microflora. In this context, another pretreatment stage could be aimed at extracting the salts from the algal biomass, using water at mild temperature [30]. This pretreatment enhances the extraction yield by reducing the aggregation of ulvan and by facilitating the cell wall content exposure to the solvent due to the osmotic shock.

Before ulvan extraction, the removal of colored matter can be addressed using organic solvents and mixtures, such as ethanol [31,32], dichloromethane and ethanol [9] or methanol:chloroform:water (4:2:1) [11]. However, the impact of this stage cannot be noticed on the yield and quality and has been suggested to be non-necessary [5]. Therefore, the need and configuration of the pretreatment stages should be defined case by case.

3.1. Extraction

The extraction yield is greatly determined by the extraction method, data in Fig. 2 shows some examples of ulvan extraction yields values attained with different technologies. A recent comprehensive presentation of the influence of the extraction conditions on yield, and molecular weight can be found [5].

Ulvans are traditionally extracted by hot-water at 80-90 °C for 2-4 h under stirred conditions [35], followed by an ethanolic precipitation. Due to the importance of the interactions of ulvan with other cell wall components, the addition of acid and chelating agents, usually EDTA, ammonium oxalate [26,29] or sodium oxalate [29,30,32] have been proposed to enhance the ulvan yields. Low pH improves the selectivity for ulvan. Additional extraction stages of the solid can be carried out with the same solvent or with water [32,35].

Acidic water extraction and with acidified ammonium oxalate provided higher ulvan yields than extraction with sodium chlorite or with

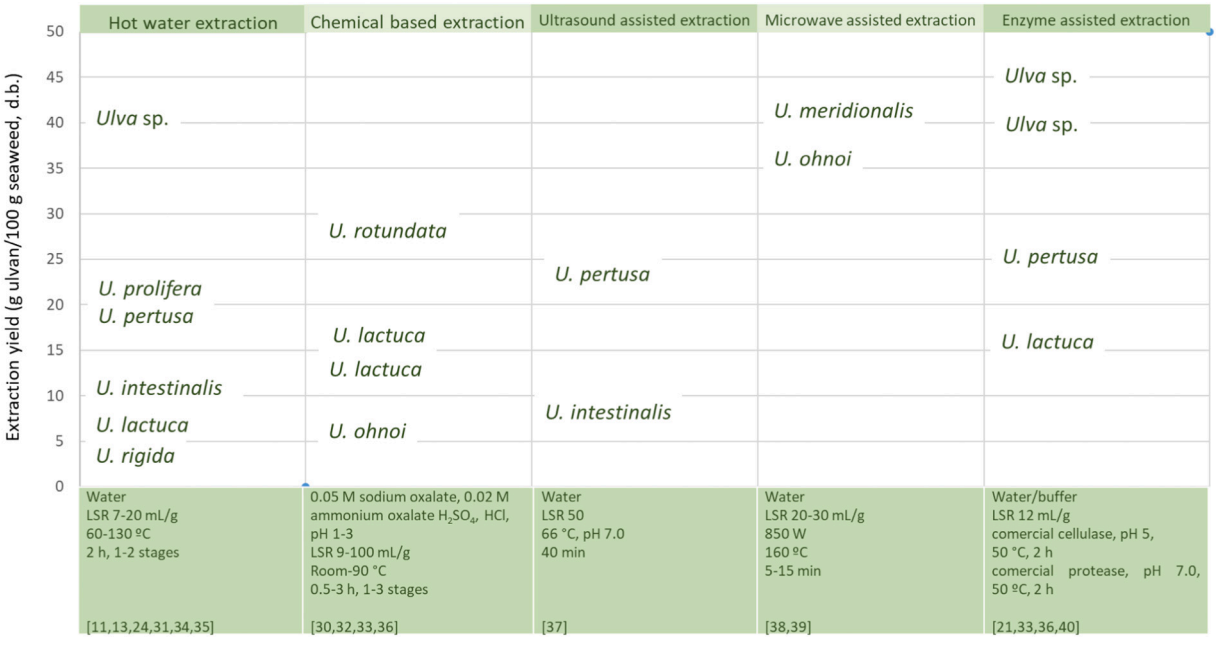

Fig. 2. Examples of ulvan extraction yields with different extraction strategies. LSR: liquid solid ratio.

DMSO. The subsequent reextraction increased the glucose and protein whereas the sulfate content was decreased. The type of extractant influences the macromolecular distribution, HCl and DMSO extracts were composed by low molecular weight oligomers, the oxalate extract was mainly composed by high molecular weight ones, and the chlorite extract contained a low content of HMW molecules and a small proportion of LMW molecules [32].

Higher extraction temperature and time can enhance the yield but could lower purity and promote degradation by causing depolymerisation and desulfation [5,32]. Adequate selection of the extraction conditions is required to achieve the compromise between yield, selectivity and integrity of the ulvan structure, and is usually achieved at 80-90 °C, pH 2-4.5 during 1-3 h [5,33]. However, despite repeated 30 min extractions with hot dilute HCl improve the extraction efficiency, they were less selective than a single 1 h extraction, due to coextraction of other components, such as starch [32].

The extraction conditions, pH value and the presence and types of cations [33], show a great impact on the rheological properties of ulvan solutions, which exhibit low viscosity and pseudoplastic behavior [32]. Increased temperature can cause degradation of the polysaccharide. The pH affects both the yield and purity, a low pH improves the selectivity for ulvan [5]. The extraction efficiency and selectivity could be benefited at pH below the pKa of uronic acids, due to the dispersion of ulvan aggregates and to the minimized solubilization of glucuronan, xyloglucan, and soluble protein [5,32].

Apart from hot water and chemical based extraction, more efficient, sustainable and selective technologies are desirable. Ultrasounds aid in the extraction of ulvans based on both physical and chemical effects, the first aiding in cell wall breakage and mass transfer and the second in some radical based reactions. Different examples can be found, Liu et al. (2019) applied an ultrasound-assisted hot water method to obtain ulvans from *E. prolifera* and *U. lactuca* [41]. Chen et al. (2021) reported enhanced ulvan yields and higher antiradical capacity by ultrasound assisted extraction than that extracted with hot water, but the viscosity was lowered [34]. Rahimi et al. (2016) applied ultrasound to aid in the extraction of ulvan from *U. intestinalis*, obtaining a product with reducing properties and antiradical and macrophage-stimulating capacity [37]. Alternatively, this technology has been proposed for the protein extraction from *U. rigida* under alkaline conditions assisted by ultrasonication [42].

Microwave-assisted extraction offers advantages derived from the rapid heating caused by molecular rotation of dipoles and electrolytes under oscillating electromagnetic fields. In addition, structural cell wall damage associated to rapid water vaporization inside cells, favor mass transfer. Tsubaki et al. (2016) applied microwave-assisted hydrothermal extraction of ulvan with higher yields and shorter times than in conventional extraction [38]. Values up to 40 % could be attained in a rapid process with 4 min of come-up time and 10 min at 160 °C. Whereas those ulvans extracted at 100-140 °C showed peaks at 400 kDa and 800 kDa, at 160 °C and higher they started to decompose. Therefore, selectivity towards ulvan and rhamnan sulfate were higher at lower temperatures, but at higher temperatures also starch and protein were solubilized and hydrolyzed. André et al. (2023) used a microwave-assisted hydrothermal processing at 160 °C, to maximize ulvan yields and sulfate content, although also the protein content was also the highest [39]. They also found that the addition of chlorine chloride enhanced the viscoelastic properties compared to those of ulvans precipitated with ethanol.

Enzyme-assisted extraction with commercial formulation of different activities have been tried. Since proteins are responsible for entrapping ulvan and other wall polysaccharides, the addition of endoproteases has been tried [21,43]. The higher protein extraction yields obtained by this technology led to a product with superior protein content than that obtained by maceration. The amyloglucosidase treatment before extraction did not succeed in facilitating the ulvan extraction, probably because resistant starch may have been inaccessible to the enzyme [44].

Combined strategies can be preferred. Chen et al. (2021) confirmed that the combination of enzymatic hydrolysis with a commercial cellulase and the further hot water extraction assisted by ultrasound for 30 min provided better yields than each of the treatments alone [34]. The molecular weight distribution of ulvan was more markedly reduced when obtained by hot water extraction, than by ultrasonic-assisted extraction or by enzyme-assisted extraction. The enzyme assisted technology was the most efficient to liberate larger molecular weight polysaccharide chains. Also, the further ultrasound treatment after enzyme assisted extraction caused additional polysaccharide cleavage.

In order to aid in the determination of ulvan composition combined enzymatic and chemical extraction of powdered alga with commercial cellulases and proteases was addressed [40,45] to provide high ulvan yield and could be mainly composed of high peak molecular weight polysaccharides [33]. The operation conditions also determine the textural characteristics (firmness, springiness and adhesiveness) of ulvan gels. Sequential extraction by hot oxalate and hot dilute acid was used to extract different pools of ulvan and the insoluble material remaining was mainly composed of cellulose and hemicelluloses with residual proteins [32].

Moawad et al. (2022) isolated ulvan from *Ulva fasciata* by a sequential extraction using distilled water, HCl or Na_2EDTA and an alkaline extraction of the residual solids [13]. Whereas the highest polysaccharides yield was attained for water extraction, the sulfate content was higher in HCl extracts and the protein content was higher after the alkaline extraction of the EDTA extracted solids, which also showed the highest anti-inflammatory activity. However, the alkaline extracts from the residue from water extraction exhibited the highest antifouling and antioxidant activity.

3.2. Depolymerization

The high average molecular weight of ulvan, up to 2000 kDa [5] limits its solubility and biological absorption compared to lower molecular weight oligomers, which also show enhanced bioactivities [35]. Depolymerization strategies can be based on physical (thermal, ultrasound, microwave, γ-irradiation), chemical (acid, alkaline conditions, depolymerization) or enzymatic processes, i.e. using ulvan lyases. The structural degradation occurring during this process may affect the ulvan functionality, mainly regarding the molecular weight and the sulfation degree [5]. The yields and sulfate content were strongly different depending on the seaweed. When Liu et al. (2019) applied acid depolymerization with 0.05 M H_2SO_4 and HCl for 1.5 h at 100 °C the oligomers from *U. lactuca* contained 9 % sulfate, whereas those from *E. prolifera* contained 5 % sulfate [41].

Time, temperature and acid concentration favored the decrease in MW. Microwave-assistance highly accelerated the reaction rate. Li et al. (2013) applied microwave-assistance to accelerate the reaction rate during acid hydrolysis of *Enteromorpha prolifera* polysaccharides and reported the cleavage of only glycosidic linkages without breaking significant structural units [35]. Compared with conventional heating, the reaction time to prepare products with same MWs was reduced by 2-3 times with microwave assistance. Enhanced chelating capacity and hydroxyl radical scavenging for 3.1 kDa and better superoxide scavenging for 247-446 kDa were observed for samples with similar sulfate content and monosaccharide composition.

Enzyme degradation can be performed under milder conditions (pH 5.5, 37°C) than those needed for chemical degradation, with high efficiency and specificity, and could be beneficial to preserve bioactivity. Li et al. (2017) extracted ulvans of 147.8 kDa from *E. prolifera* using hot-water extraction and low Mw polysaccharide (44.8 kDa) were obtained by enzymatic depolymerization [27]. The enzyme degradation has been also used for analytical purposes, to aid in the elucidation of ulvan structure [32,34], i.e. Lahaye and Robic (2007) used an extracellular ulvan-lyase from a marine Gram-negative bacterium, acting by cleaving the (1 → 4) linkage between rhamnose 3-sulfate and glucuronic acid to produce di-, tetra-, and pentasaccharides [26]. The potential of

the oligomers produced have been reviewed [46]. Li et al. (2020) prepared a 2.56 kDa ulvan, by an enzymatic method using an ulvan lyase of the PL25 family, which cleaves the (1 → 4) glycosidic bond between 3-O-sulfated Rha and GlcA [47]. This ulvan protected on dextran sulfate sodium induced colitis and reduced the disease index, colon shortening, and colonic tissue damage, and reduced the inflammatory infiltration and damage. LMW-ulvan reduced the level of IL-1β in the colon and serum, which indicated its possibility to suppress NLRP3 inflammasome activation. LMW-ulvan could inhibit the Th1 cell response and improve the Th2 cell response. The activity of enzymes was different depending on the seaweed species due to structural differences between their polysaccharides. Chen et al. (2021) found that the ulvan-lyase was limited by iduronic acid and whereas high molecular weight oligosaccharides were produced from *U. armoricana*, lower degradation was achieved on other species [34].

A depolymerization procedure valid for continuous processing of an ulvan solution, using a commercial resin as immobilized catalyst in a column has been reported [48]. This strategy (80 °C, 24 h) generated low molecular weight ulvans (1.5 kDa) with low polydispersity index from a crude ulvan (3000 kDa) [21]. This alternative avoided the degradation reactions leading to monosaccharides and byproducts, that could occur during acid hydrolysis with hydrochloric, sulfuric, trifluoroacetic, formic, or nitrous acids. Resin depolymerization (4 mL/g, 80 °C, 24 h) retained 8 % [21] or more [48] sulfate. Depolymerization with hydrogen peroxide in 24 h at 50 °C led to the formation of 8 kDa oligomers. Sulfate groups were partially cleaved during both radical depolymerization by H_2O_2 and by ion-exchange resin depolymerization [21]. Proteins were abundant in both depolymerized fractions (13-17 %).

Free radical depolymerization using H_2O_2 treatment can be controlled by adequate selection of time and temperature, and products with low molecular weight (8 kDa) could be obtained. However, the process may present lower reproducibility and severe conditions could lead to degradation products. Hydrogen peroxide depolymerization retained only 6 % sulfates despite mild conditions selected (8 %, *v*/v, 35 or 50 °C). Both high and low molecular weight fractions exhibited anti-inflammatory activity as determined by LOX inhibition. Ion-exchange resin depolymerization with desulfated lowest molecular weight led to a reduction in inhibition activity.

Kidgell et al. (2020) depolymerized purified ulvan from *U. ohnoi* to obtain fractions with 7, 9, 13, 21 and 209 kDa and observed low dispersity of the ulvans [49]. The 209 kDa fractions showed anti-inflammatory effect on LPS-stimulated RAW264.7 murine macrophages by secreted interleukin-10 and prostaglandin E2 and also enhanced the LPS-induced inflammation by minor increases of IL-1β and IL-6. However, the highest molecular fractions increased the levels of IL-1β, IL-6, IL-10 and IL-12 from RAW264.7 cells and elicited a greater immunomodulatory response than lower molecular weight fractions.

3.3. Purification

Following the extraction of ulvan, the extract is separated from the residual biomass by filtration and/or centrifugation. In some cases, filtration by siliceous earth after vacuum filtration was proposed [25,30,35]. The combined extracts can be dialyzed and concentrated or directly treated with ethanol to precipitate a crude ulvan or with a quaternary ammonium salt to recover proteins [21,26,33]. Precipitation is a widely used methods but it is limited by the higher solubility of low molecular weight ulvan, the difficulties in replication of results and the further need of dialysis to lower salt content. After further purification and concentration stages can be addressed using membrane technology, by ultrafiltration or dialysis (12–14 kDa), or by anion-exchange chromatography to remove proteins and neutral polysaccharide impurities, or by size-exclusion chromatography, also valid for characterization purposes [30–33]. After air-, spray- or freeze-drying a purified ulvan can be obtained [8]. In addition, adsorption of contaminants onto activated charcoal, and enzymatic hydrolysis to remove starch and proteins [9,41] has been tried. A discussion on the commonly used isolation and purification methods can be found [5]. A general scheme of the possible stages needs is summarized in Fig. 3.

However, crude extracts contain other components that could contribute to bioactivity. Several studies confirm the potential of the phenolic fraction. Pradhan et al. (2021) found that the crude methanol and ethanol extracts from *Enteromorpha intestinalis* showed anti-inflammatory effect, determined by hemolysis, and by proteinase and lipoxygenase inhibitory activities, comparable to that of acetylsalicylic acid [50]. Among others, radical scavenging and antidiabetic properties (α-amylase, α-glucosidase inhibition), were observed. Ibrahim et al. (2021) confirmed the possibility to ameliorate hyperthyroidism-mediated cardiovascular inflammations and related oxidative stress in hyperthyroid rats fed *Ulva fasciata* methanolic extract containing phenolics and flavonoids [51]. A reduction in serum levels of the thyroid hormones T3 and T4, proinflammatory cytokines (TNF-α, MPO, and CRP), triglycerides and total cholesterol, as well as the cardiac biomarkers CK-MB, LDH, and troponin comparable to those of a standard drug. Interleukin 10 was significantly upregulated. Nabil-Adam et al. (2021) reported that *Ulva lactuca* polyphenolic extracts showed oxidative/antioxidant and inflammatory effects, protecting against heavy metal induced cardiovascular diseases in rats, by reducing the levels of MPO and NO [52].

Yan et al. (2019) confirmed that a water-ethanol extract of *Enteromorpha prolifera* and its flavonoid-rich fraction <3 kDa decreased fasting blood glucose, improved oral glucose tolerance, and protected against liver and kidney injury with reduced inflammation in mice [53]. Other bioactive compounds such as pheophorbide a and chlorophyll *a* showed antioxidant and anti-inflammatory properties. The protein fraction has also positive influence, Cian et al. (2018) reported that peptides from *Ulva* sp. attenuated the TNF and IFN-γ production in lipopolysaccharide or concanavalin A immune stimulated cells. Inhibitors for the activation of NFκB, MAPK p38 and JNK inhibited IL-10 induction in rat splenocytes and exerted anti-inflammatory effects in immune cells mediated by TLR4 and NFκB [54]. Lipids from *Ulva ohnoi* showed physiological activity in the state of inflammation in a mouse model as well as the antioxidant and antibacterial activity. The amount of NO produced, the expression of TNF-α, IL-6, and IL-1β as well as the crypt loss and inflammatory cell infiltration were decreased compared to the control group. The presence of phenolics could also contribute to this action [55]. Other compounds can exhibit this activity. The norisoprenoid (3-hydroxy-4,7-megastigmadien-9-one) isolated from *U. pertusa* inhibited interleukin (IL)-12 p40, IL-6 and TNF-α cytokine production by blocking MAPKs and NF-κB pathways by inhibiting the phosphorylation of ERK1/2, JNK1/2, p38 and IκBα, and also inhibited the transcriptional activity of AP-1 and NF-κB [56].

4. Mechanisms of ulvans actions on inflammation

Inflammatory pathway can be divided into four steps: inducers, sensors, mediators, and target tissues that are affected by the inflammatory mediators. Therefore, inflammatory response can be controlled at these four levels [57].

Firstly, inducers are the signals that initiate the inflammatory response, and they can be classified in exogenous or endogenous. Exogenous inducers involve pathogen-associated molecular patterns (PAMPs), having specific set of receptors to recognize them. Endogenous inducers of inflammation may be molecules released from damaged cells of the host, known as damage-associated molecular patterns (DAMPs). There are also compounds associated with oxidative stress such as AGEs (advanced glycation end products) and oxidized lipoproteins that cause an inflammatory response [14,58]. Sensors are specific receptors for host cells, e.g., macrophages and tissue-resident mast cells. Sensors are activated when they specifically recognize inductors, subsequently triggering the production of mediators [14]. Toll-like receptors (TLRs)

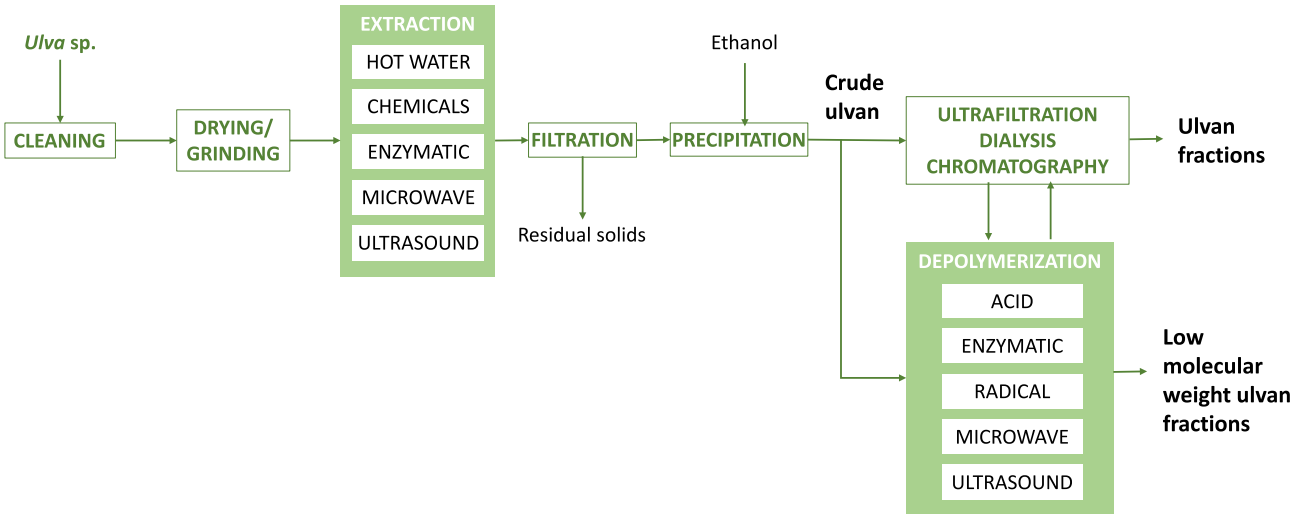

Fig. 3. Processes for a) enzyme assisted extraction and radical depolymerization poly- and oligosaccharide *Ulva* sp.

and NOD (nucleotide-binding oligomerization-domain protein)-like receptors (NLRs), and Pathogen recognition receptors (PRRs) are the main of them. The main intracellular signaling pathways involved in inflammation are mitogen-activated protein kinases (MAPKs), transcription factor nuclear factor kappa B (NF-κB) and SIRT1/FOXO1 [15], which regulate the production of inflammatory mediators [14,15]. Finally, inflammatory mediators produced during the inflammatory response are endogenous chemicals including chemokines, cytokines, vasoactive amines, eicosanoids, matrix metalloproteinases, and toxic molecules such as nitric oxide or free radicals. Besides, these mediators can induce pain and promote or inhibit inflammation and tissue repair [14,15,57–59].

There are mainly two different types of inflammation: acute and chronic. Initially, the inflammatory response is acute. This acute response may resolve or evolve into a chronic response if it is not adequately resolved or the immune cells remain active [14,60]. Overall, controlled inflammatory response is beneficial to the host as inflammation is about restoring homeostasis. Conversely, alteration of inflammatory pathways involved in its resolution is implicated in the development of acute and chronic inflammatory disorders, such as autoimmune diseases including atherosclerosis, Inflammatory Bowel Disease, and Rheumatoid Arthritis [12,18,34]. With the aim of controlling these processes, there are currently different therapies available to treat inflammatory diseases, including drugs such as Non-Steroidal Anti-Inflammatory Drugs, which can cause small bowel mucosal injury and occult bleeding [37]. Besides, clinical anti-inflammatory therapeutics have some limitations such as aqueous insolubility, low bioavailability, off-target effects, and poor accessibility to subcellular

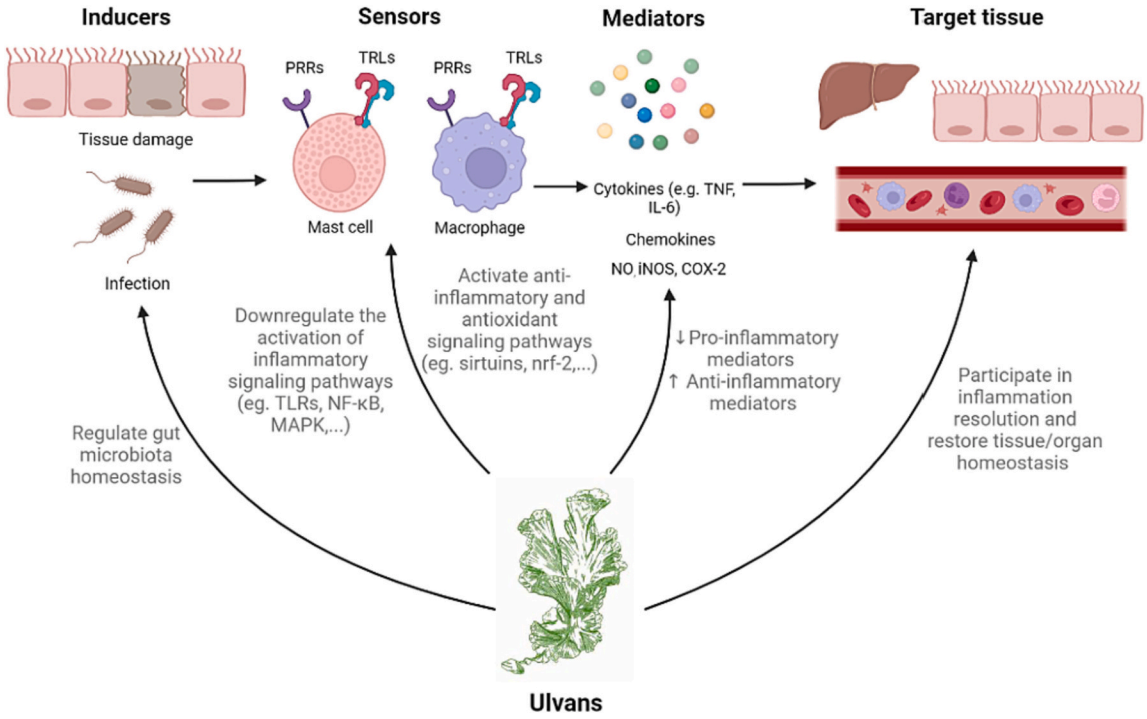

Fig. 4. Mechanisms of ulvans actions on inflammatory process. COX-2, cyclooxygenase-2; IL, Interleukin; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NF-κB, nuclear factor kap-pa-B; nrf-2, nuclear factor-erythroid 2-related factor-2; PPRs, pathogen recognition receptors TLR, toll-like receptor; and TNF, tumor necrosis factor. Figure was created with Biorender (https://biorender.com/).

compartments [34]. Therefore, there is still ongoing a search for new compounds that replace classical anti-inflammatory drugs having fewer adverse effects. In the pursuit of novel, better, and safer products, and the promising characteristics of ulvans (biocompatibility, biodegradability, economic, availability and low toxicity), they have gained much attention as bioactive compounds with therapeutic activities [42].

Ulvans have demonstrated *in vitro* and *In vivo* biological activities such as immunomodulation, antioxidant, anticancer, anticoagulant, antihyperlipidemic, antidiabetic or anti-viral, including also cosmeceutical applications [61]. Ulvans act modulating several cellular signaling pathways to carry out their biological activities [12,19,21,22,41]. The main signaling pathways that ulvans act on to regulate inflammation are summarized below and in Fig. 4. Ulvans carry out these anti-inflammatory actions by blocking and regulating different points of the intracellular signaling pathways, preventing apoptosis, inhibiting multiple enzymes, or modulating activity of transcription factors and in turn expression of inflammation-related genes [12,19,21,41].

4.1. NF-κB pathway

One of the most important inflammatory transcription factors are NF-κB, which is a pleiotropic regulator of a variety of damage response genes and inflammation [16,62]. Prior to activation, NF-κB is complexed with IκBα, an inhibitory protein keeping NF-κB in inactive state in the cytoplasm. The canonical NF-κB pathway is triggered by signals from a large variety of immune receptors, which bind inducers such as lipopolysaccharide (LPS) and proinflammatory factors like TNF [63]. When NF-κB pathway is activated, IκBα is phosphorylated, polyubiquitinated and its subsequently degraded by the 26S proteasome, so NF-κB dimers is released and translocate from cytoplasm into the nucleus [64]. Once in the nucleus, canonical NF κB family members (in the form of various dimeric complexes, including RELA–p50, c REL–p50, and p50–p50) bind to specific DNA elements and activate transcription of genes encoding chemokines, cytokines, adhesion molecules (intercellular adhesion molecule 1, vascular cell adhesion molecule-1 and endothelial–leukocyte adhesion molecule 1) enzymes that produce secondary pro-inflammatory mediators, and inhibitors of apoptosis [63,65]. Different studies have described that ulvans modulate inflammatory responses thought inhibition of NF-κB pathway at different steps. For instance, ulvan extracted from *Ulva pertusa* containing a norisoprenoid 3-hydroxy-4,7-megastigmadien-9-one (COMP) and selenium nanoparticles coated with an *Ulva lactuca* polysaccharide attenuate expression of pro-inflammatory cytokines such as IL-6, TNF-α, iNOS, and COX-2 by inhibiting phosphorylation of IκBα, and thus blocking NF-κB activation [56,64]. In addition, a sulfated glucuronorhamnoxylan of the green alga *Capsosiphon fulvescens* whose backbone consists of alternating sequences of 4-linked L-rhamnose-3-sulfate and D-xylose residues, a typical ulvan-type polysaccharide of green alga, ameliorates osteoporotic bone resorption by dampening receptor activator of NF-κB ligand (RANKL)-induced osteoclastogenesis [66].

4.2. Toll-like receptors

TLRs are PRRs that are expressed on most immune cells. They are the first line of defense against microbes, considering that TLRs are activated when recognize PAMPs [67,68]. Two different pathways are involved in TLRs signaling transduction: the myeloid differentiation primary response 88 and TIR-domain-containing adaptor inducing IFN-β pathway. Depending on the nature of the transducer that is used, various kinases (IRAK4, IRAK1, IRAK2, TBK1, and IKKε) and ubiquitin ligases are recruited and activated, culminating in the engagement of the NF-κB, type I interferon, p38-MAPK or JNK-MAPK pathways [67]. At last, both pathways lead to induction of gene expression of immune stimulatory cytokines and chemokines via activation of transcription factors, such as NF-κB, activating protein (AP)-1, or interferon response factor [68]. There are ten TLR subtypes with their specific ligands, expression profiles, and cellular localization [68]. For instance, TLR4 is involved in activation of LPS-induced NF-κB pathway and stimulation of MAPK cascades in monocyte and macrophage [15,69,70]. Different studies revealed that ulvans could modulate inflammation induced from pathogenic microorganisms through blockage of this pathway. For instance, *Enteromorpha prolifera* polysaccharide–zinc (EP–Zn) attenuated intestinal inflammation via inhibiting the TLR4/NF-κB signaling pathway and in turn the production of inflammatory cytokines such as TNF-α, IL-6 and IL-1β [28]. Conversely, it has been also described that ulvans could regulate heterophil activation through TLR2 and TLR4, being involved in the protection of innate host defense against invasive pathogens [71].

4.3. Mitogen-activated protein kinases (MAPK) signaling pathways

MAPKs are a highly conserved group of serine/threonine kinases regulated by phosphorylation cascades, which are expressed in different cell types and regulate cellular activities as gene expression, mitosis, movement, metabolism, and programmed cell death. In addition, MAPKs are a key signaling pathways that promote inflammation inducing NF-κB activation and secretion of pro-inflammatory cytokines [16,72–74]. These pathways are activated by different stimuli and intricately associated with transcription factor phosphorylation in downstream TLRs signaling, which leads to expression of target genes resulting in a biological response [75]. The multiple interactions between the different MAPK cascades serve to integrate the responses and activate separate sets of genes [15,74]. The three conventional families of MAPKs in mammals are JUN N-terminal kinases (JNK1), p38 kinases, and extracellular signal-regulated kinases (ERK1/2). p38 has a central role in regulation of inflammatory cytokine expression to initiate leucocyte recruitment and activation [16,74]. Its activation can be triggered by IL-1β, TNF-α or bacterial LPS, regulating expression of many pro-inflammatory cytokines [15]. ERK pathway is activated through Receptor tyrosine kinases and associated with cell proliferation, differentiation, migration, senescence, and apoptosis [73,74,76]. ERK1/2 primarily phosphorylates c-Fos for inflammatory cytokine production. Besides, ERK1/2 can play a role in NF-κB regulation in response to other inflammatory mediators [15]. Finally, JNKs are stress-activated protein kinases, which bind and phosphorylate the DNA binding protein c-Jun and increase its transcriptional activity. c-Jun is also a component of the AP-1 transcription complex, which is an important inflammatory transcription factors [62] that contributes to the control of many cytokines' expression [74,77]. Interestingly, it has been recently described that ulvan extracted from *Ulva pertusa* containing COMP blocks MAPKs pathways by inhibiting the phosphorylation of ERK1/2, JNK1/2, p38 [56]. Similarly, *Ulva* spp. hydrolysates and their peptide fractions regulate cytokine production in macrophages and lymphocytes via modulation of MAPK pathway, and specifically through p38 and JNK but not ERK signaling [54]. Thus, several studies confirmed the immunomodulatory actions of ulvans by inhibition of MAPK signaling cascades.

4.4. Signaling pathways involved in anti-inflammatory and anti-oxidant effects

Sirtuins are a class III histone deacetylases that can catalyze the deacetylation of both histone and non-histone proteins, consuming one molecule of NAD^+ during each deacetylation cycle. There are seven mammalian sirtuins, SIRT1–7, being SIRT1 the most studied sirtuin. SIRT1 is involved in DNA repair, apoptosis, inflammation, aging, and other biological processes [78]. Sirtuins regulate metabolism in major metabolic tissues such as the liver, heart, white adipose tissue and skeletal muscle and have anti-aging functions conserved in mammals [79]. Besides, Sirt1 can affect organism homeostasis at body's oxidation and inflammatory level through the deacetylation to some transcription

factors such as nuclear factor E2-related factor 2 (Nrf2), NF-κB, p53 and Forkhead box transcription factor O1 (FOXO1) [80,81]. In this regard, Nrf2 is a transcription factor related to the aging process caused by oxidative stress. The activation of Nrf2 can induce the expression of various genes associated to cell protection and cellular detoxification, protecting cells against oxidative damage and inflammation [81–83]. Whereas, FOXO1 transcription factor is an evolutionarily conserved regulator of cell metabolism, oxidative stress, inflammation, and apoptosis [84]. Interestingly, SIRT1, FOXO1 and Nrf2 are regulated by ulvans [12]. For instance, Ardizzone et al. (2022), demonstrated that ulvans from *Ulva pertusa* enhanced antioxidant response and modulated the apoptosis, regulating the expression of p53, Bax, Bcl-2 and caspases, modulating SIRT1/Nrf2/NF-κB axis [85]. Moreover, Lui et al. (2019) demonstrated oxidative action of ulvans from *Ulva lactuca* and *Enteromorpha prolifera* in senescence accelerated mice by promoting the expression of Sirt1, which modulates the expression of the FOXO1 and p53 [41].

In summary, ulvans can regulate inflammation and oxidative stress through modulation of different signaling pathways, i.e., NF-κB, TLRs, MAPKs, and sirtuins among others. In general, ulvans modulate inflammatory cascade inhibiting its activation at different points. Nonetheless, they could also activate pro-inflammatory responses in order to reinforce the protection of host immune system against pathogen invasion or tissue damage [54,71].

5. Potential of ulvan in inflammation

Among the most explored biological activities of ulvans on human health, antioxidant/radical scavenger activity [37,43,86] anti-hyperlipidemic [87,88], anti-inflammatory/immunomodulatory [89–91], anticoagulant [11,92], anticancer/antitumor [11,36,90], antibacterial [93,94], antiviral [43,95,96], and tissue engineering [97–99] are widely mentioned. Thus, the therapeutic use of ulvans has gained a great interest as an alternative and complementary therapy for the treatment of different diseases characterized by an inflammation-driven pathogenesis. Some examples of these effects are shown in the Table 1. Noteworthy, different studies have confirmed the lack of toxicity of ulvan without affecting cell growth, or even in some cases cell growth stimulation was observed [31]. The different cell lines evaluated have been overviewed by Kidgell et al. (2019) [5]. Also, studies with rats have confirmed the non-toxic character [47,100].

5.1. Ulvans in age-associated chronic inflammation (inflammaging)

Aging is related to many physiological processes, including energy metabolism, oxidative stress, cell apoptosis, and inflammation. During aging, multiples lesions and mutations in the DNA take place, and telomere shortening occurs in somatic tissues at each cell division. DNA lesions and critically short telomeres are known to trigger a persistent DNA damage response that can lead the cell into a senescent state and mitochondrial dysfunction. In addition, aging contributes to age-associated tissue dysfunction [83,101]. Human aging is characterized by a chronic, low-grade inflammation, a phenomenon that has been termed as “inflammaging” [102], which is a sterile inflammation associated with aging [103], so many tissues could be in a state of chronic inflammation, even without signs of infection.

There are different sources of age-related inflammation underlying pathological processes, which has been described to be modulated by ulvans in different studies [12,20]. One source of inflammaging could be the accumulation of dysfunctional cells and damaged macromolecules that increase with age due to their augmented production and/or inadequate elimination. The damaged molecules can act as DAMPs activating innate immunity [102]. Ulvans regulate the inflammatory response associated with age by modulating levels of pro-inflammatory mediators such as IFN-γ, TNF-α, and IL-6 [104]. In addition, in a recent study of Liu et al. (2019) it was observed that polysaccharides from *Ulva lactuca* and *Enteromorpha prolifera* can increase levels of regulatory cytokine IL-2, promoting production of regulatory and antigen-activated T lymphocytes, differentiation of natural killer cells, and suppressing unwanted immune responses, such as those that occur in autoimmune disease or transplant rejection reactions [41,105]. Moreover, ulvan from *Ulva* spp. has also been showed to exhibit anti-inflammatory activity by inhibition of enzymes involved in production of pro-inflammatory mediators like lipoxygenases [21], which are implicated in the synthesis of leukotrienes [21].

Another source of inflammaging could be the overproduction of harmful products by the microbial constituents of the human body that are released into surrounding tissues and blood circulation [102]. The gut microbiota is affected by the aging process in terms of composition and functionality, for instance, Firmicutes/Bacteroides, Bifidobacterium and lactic acid bacteria decrease [83,106], and families associated with aging as *Verrucomicrobiaceae*, *Streptococcaceae*, *Christensenellaceae*, *Pseudomonadaceae* and *Lachnospiraceae* increase. This age-associated gut dysbiosis is negatively associated with the levels of glutathione peroxidase (GSH), superoxide dismutase (SOD), catalase (CAT) and telomerase levels [41] and contributes to several age-associated processes such as immunosenescence and inflammaging, leading eventually to chronic low-grade inflammation [107]. Moreover, acute inflammatory responses to PAMPs may be impaired during aging, favoring an increased susceptibility to infection [102]. Interestingly, several studies have shown that ulvans are able to increase or decrease certain microorganisms associated with dysbiosis caused by aging. Thus, oligosaccharides from *Ulva lactuca* significantly decreased the abundance of *Desulfovibrio* to the normal level in accelerated senescence mice [41]. In addition, EP–Zn decreased the abundance of *Coriobacteriaceae* and *Brachybacterium* genera, which are potentially associated with intestinal inflammatory response [28,108]. EP–Zn also enhanced relative abundances of *Lachnospiraceae* belonging to the *Firmicutes phylum*, whose low abundance levels has been disclosed to increase the intestinal sensitivity to inflammation [28]. Finally, *Enteromorpha clathrata* sulfated polysaccharide promoted in gut microbiota the growth of beneficial microbes, such as *Akkermansia muciniphila*, *Bifidobacterium* spp., and *Lactobacillus* spp. as well as increased abundance of short chain fatty acids (SCFAs)-producing bacteria including *Bacteroides* spp., *Prevotella* spp., *Alloprevotella* spp., *Butyricimonas* spp., *Eubacterium* spp. and *Odoribacter* spp. These bacteria produced SCFAs, which play a beneficial role in modulation of host physiology and contribute to the treatment of dysbiosis-associated diseases [109].

One of the most important sources of inflammaging is oxidative stress. It could be caused by a decline in the production and activity of antioxidant enzymes involved in the clearance of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are accumulated in the cell affecting its functions [101]. Some of antioxidant enzymes decreased in the aging are CAT, SOD, GSH, glutathione peroxidase (GPX) and glutathione reductase (GR), which play a key role in the defense of the organism against ROS and RNS [12]. It has been shown that ulvans can protect the body against oxidative stress. For instance, Cai et al. (2016), demonstrated that *Ulva prolifera* polysaccharide can protect human skin fibroblast from being injured by hydrogen peroxide (H_2O_2). This polysaccharide decreased the oxidative stress in cells through stabilization of the Nrf2/Keap1 signaling system and regulation of cytoprotective genes involving the MAPK and mitochondria-mediated pathways [110]. Abd-Ellatef et al. (2017) demonstrated that ulvan from *Ulva fasciata* promotes the expression of genes encoding antioxidant enzymes, including SOD, GPX, GR and CAT, downregulating the levels of inflammatory cytokines TNF-α and nitric oxide (NO). It also reduces the content of malondialdehyde (products in lipid peroxidation) and advanced oxidation protein products, preventing lipid peroxidation and reducing DNA fragmentation in a model of oxidative stress in Wistar rat [100]. Besides, this ulvan regulates apoptosis by increasing the expression of pro-apoptotic protein p53, and decreasing the elevated levels of anti-apoptotic marker bcl2 in breast tissue [12,100]. Ulvans can also

Table 1
Some examples of ulvan, crude, fractions and derived products anti-inflammatory action.

Species	Extraction	Composition	Properties	Ref.
U. fasciata Delile	D Preext: 80 % E, LSR 100, 20 °C, A rinsing Ext: W, 0.2 N HCl or 0.1 M Na_2EDTA LSR 10, 60 °C, 2 h + 1 h, 2 stages, filtr., conc. E pptn, centr., D Residue reextracted with 0.1 M NaOH, LSR 10, 60 °C, 2 h Wash., D, pulveriz.	11.9-76.6 % carboh.; 03-2.4 % prot.; 7.7-21.4 % sulf	Anti-inflammatory activity, inhibition of albumin denaturation Fraction extracted with EDTA-NaOH exhibited the highest activity, followed by that extracted with HCl. Antioxidant and antifouling	[13]
U. intestinalis	PreExt: 80 % E, A rinsing, D, room temp. Extr: W, LSR 20, 65 °C, 2 h, centr., conc. 99 % E pptn, wash, D, 99 % E, A, D Fractionation: Chrom.	39.1 % rha, 39,0 % glu, 6.2 % sulf., 3.2 % prot. 194 kDa	Ulvan fraction stimulate macrophage cells, producing NO, release of IL-10	[31]
U. lactuca	Preextr.: soaking 80 % alcohol, 18 h + 70 °C, 4 h Extr: W, LSR 30; 100 °C, 1 h, filtr, centr., conc., 95 % E pptn; FD	52.6 % carbohydr. 45.3 % Rha 891.25 kDa	D-galactose induced kidney injury in mice Decreased levels of serum creatinine, urea nitrogen, cystatin C, and lipid peroxidation, protein carbonylation, and DNA oxidative damage. Improved kidney glutathione content. Increased superoxide dismutase, glutathione peroxidase and total antioxidant activity. Decreased TNF-α and IL-6 levels and expression of caspase-3	[132]
U. lactuca	Extr: LSR 25; enzymatic digestion papain (10 %), 60 °C, 6 h Purif: ion exchange chromatography on DEAE-cellulose	15.1 % sugars, 12.1 % free sulfate, no protein	Swiss mice: Decreased antinociception in response to acetic acid or formalin, Wistar rats: reduced dextran-elicited edema, UP acts on bradykinin pathway in its antinociceptive and anti-inflammatory responses	[169]
U. lactuca	Washed (sea, tap and dW), D Air D, cut Extr: W, LSR 10, 100 °C, 3 h, filtr, Dl, conc, 95 % E pptn, D		*In vitro* breast carcinoma cells (MCF-7) *In vivo* induced breast carcinogenesis in Wistar female rats Oxidative stress, antioxidant defense system, apoptosis, and inflammation Ameliorated the elevated levels of inflammatory cytokines TNF -α and NO	[100]
U. ohnoi	Commercial Depol: 2 g/L in water, 1 % *w/v*) H_2O_2 to 2.5 %, 50 °C, 1-7 h, vac. Filtr., Dl (10 kDa), FD	7, 9, 13, 21, 209 kDa	The inflammatory response of RAW264.7 murine macrophages	[49]
U. pertusa	Extr: *W, LSR 30,* 100 °C, 2 h, Filtr., 95 % E pptn, centr., deproteiniz by Sevag, chromat., Dl, FD Depol.: ulvan lyase Nanofiltration (1-5 kDa), Chromatography; Dl; FD	2.56 kDa 57.2 % Rha, 28.8 % Xyl, 7.4 % Gluc Ac, 1.8 % Glu	LMW-ulvan relieve intestinal inflammation and oxidative damage caused by DSS. Increased mRNA levels of claudin, favoring intestinal mucosal permeability	[47]
U. prolifera	Depol: cellulase (1 %), 37 °C, 24 h, filtr.; washing; 75 % E pptn.; FD	Rha: Glu Ac: Glu: Xyl: Gal molar ratio 4.16: 3.60: 2.07: 1.00: 0.46. Polysaccharide content is 71.35 %, 4431 Da.	Diabetic mice. Suppressive effect of EPO on inflammation and apoptosis of pancreatic cells	[129]
U. prolifera	Washed, dried, crushed, Extr: DW, LSR 10, enzymes,1.5 h; filtr., conc., 80 % E pptn; D Purif: Sephacryl S-100 EP–Zn complexation with $ZnCl_2$	Zn-ulvan: 71.3 % polysac., 10.1 % Zn DP > 85 % Rha: GluA: Xyl: Gal: Man 1: 1.25: 0.06: 0.02: 0.01	LPS induced intestinal inflammation in mice. Polysaccharide-Zn complex pre-treatment alleviated the decrease of colon length, prevented the enhanced MPO and DAO serum activities and the lost and sloughed shape of ileal villi. Prevented the enhanced expression levels of TLR4, phosphorylated NF-κB and IL-1β, IL-6, and IL-17	[28]
U. prolifera	Comercial ulvan (Purity 95 %) Digestion, filtr., conc., Dl, steriliz., D Polyvinylalcohol nanofiber		Suppressed secretion of TNF-α and IL-6. Regulate the inflammatory response in early stage of wound healing and further promote skin repair	[147]
U. prolifera	Crude polysaccharide 1340 kDa 95 % E, FD Depol: laboratory prepared enzyme (20 U/g), 35 °C, 3 h Ulvan-iron(III) preparation Purif: Chromat.; FD	178 kDa 56.4 % Rha, 18.5 % Glu, 15.4 % Gluc Ac., 9.7 % Xyl, 20.3 % iron content	Iron deficiency anemia rat model Alleviated inflammatory damage caused by Iron deficiency anemia. Decreased IL-4 concentration, the IFN-γ/IL-4 ration returned to the normal level, inhibit Th2 cell response. Mild-to-moderate gastrointestinal tract effects	[25]
U. lactuca	D, micronized Extr: US, 50 Hz, W, LSR 40, 60 °C, 1 h, centr. 95 % E pptn Purif: Protein removal by alkaline protease, $2.0 \cdot 10^5$ U/g, 50 °C, 2 h, Dl Depol: 0.05 M H_2SO_4 and HCl, 100 °C, 1.5 h, UF	8.99 % sulf. 29.9 % <1 kDa, 13.2 % 1–3 kDa, 19.% >3 kDa	*In vivo*: male senescence accelerated prone Decreased levels of IFN-γ, TNF-α, and IL-6; increased BDNF and ChAT levels Protection of hippocampal neurons Downregulation of the p53 and FOXO1 genes, upregulation of Sirt1 gene	[41]
E. prolifera	D, micronized Extr.: US, 50 Hz, W, LSR 40, 60 °C, 1 h, centr. 95 % E pptn Purif: Protein removal by alkaline protease, $2.0 \cdot 10^5$ U/g, 50 °C, 2 h, Dl Depol: 0.05 M H_2SO_4 and HCl, 100 °C, 1.5 h, UF	32.6 % <1 kDa 6.3 % 1-3 kDa 20.9 % > 3 kDa 4.66 % sulf	*In vivo*: male senescence accelerated prone Decreased levels of IFN-γ, TNF-α, and IL-6; increased BDNF and ChAT levels Protection of hippocampal neurons Downregulation of the p53 and FOXO1 genes, upregulation of Sirt1 gene	[41]
E. prolifera	Extr. Enz.: 20 U/g, 35 °C, 3 h, 95 % E pptn; centr.; desalting; FD	178 kDa 57.9 % Rha, 12.1 % Glu, 16.3 % Glc.	*In vivo*: male Wistar rats in an IDA model Return hemoglobin, red blood cells, serum iron, and	[25]

(*continued on next page*)

Table 1 (*continued*)

Species	Extraction	Composition	Properties	Ref.
	95 % E pptn; FD Depol: enzyme, 20 U/g, 35 °C, 3 h, 95 % E pptn., desalt, FD Purif: Chromat., FD Complex with iron (III)	ac., 13.7 % Xyl. 23.7 % sulf., 14.4 % uronic acid, Polys.-Fe (III) 20.3 % Fe. 43.3 % carboh.	erythropoietin to normal levels. Alleviation of inflammatory damage Decreased IL-4 concentration and the IFN-γ/IL-4 ratio returned to the normal level, maintained balance of Th1/Th2 (IFN-γ/IL-4 ratio) STZ-induced diabetic mice	
E. prolifera commercial polysac.	Depol.: LSR 20, cellulase 1 %, pH 5.5, 37 °C, 24 h 75 % E pptn., FD	44.1 kDa Rha: Glu. Ac: Glu: Xyl: Gal molar ratio 4.16: 3.60: 2.07: 1.00: 0.46.	Inhibited expression of caspase-1 and proinflammatory cytokines, IL-1β, IL-6, MCP-1 Alleviated pancreatic injury by suppression of inflammation and apoptosis	[129]
U. rigida	Cleaned, rinsed, D, Gr Extract: dist W, LSR 20, 121 °C, 20 min, filtr., E pptn, filtr., washed, sonicated, 1 h, filtr., FD	1000 kDa; 48.3 % sulf., 39.8 % carbohydr. 26.2 % Rha, 17.6 % UA.	Healing of ulvan and gelatin in nonwoven patches Restoration similar to normal skin. Faster wound contraction in early stages of the burn wound healing, suppressing inflammation, uniform wound closure	[146]
U. rigida	Washing (seawater and fresh water), D Ext.: LSR 12/0.6, 121 °C, 20 min, filtr., 96 % E pptn., filtr., E wash., sonicat. 1 h, filt., FD Electrospinning Ulvan/ polyethylene oxide	1150 kDa; 40.4 % carbohydr., 25.9 % rham., 17.9 % UA, 47.5 % sulf.	Elimination of skin inflammation, Anti-inflammatory activity of the ulvan/PEO patch	[167]
Ulva sp.	Wash, Gr (3 mm), FD Extr: *endo*-protease (6 %), 50 °C, 3 h, E pptn. Purif.: Dl (12–14 kDa) Depol: Radical hydrolysis (H_2O_2), 50 °C, 24 h, Or Acid hydrolysis (ion-exchange resin (10 mL equivalent), 80 °C, 24 h, filtr.; neutr.; Dl (0,5-1 kDa), FD	Polysacch. (> 670 kDa, 23–37 % carboh., 50 % Rha, 12 % Glu Ac, 3 % Xyl), 18–37 % UA, 30-49 % sulf) Oligosacch. (8 kDa, 1.5 kDa), 24-30 % carboh. 45–55 % Rha, 7–11 % Glu Ac, 22–31 % UA., 6.6 % sulf.	Decreased release of IL-8 by keratinocytes induced by *C. acnes* cultured in the presence of polysaccharide. Binding of ulvan rhamnose residues to bacterial lectins and the inhibition of the bacterial adhesion to keratinocytes Depolymerization associated with weakest anti-inflammatory activity	[170]
Enteromorpha	Wash, D, Crushed Extr. dW, 50 g/mL, 50 °C, 4 h TCA prot. Pptn, neutr., centrif, evap., E pptn, centr., wash, FD	97.6 % polysacc., 1.98 % prot.	*In vivo* mice model of constipation Decreased serum NO concentration Recovery intestinal microecology, enhancing the intestinal motility, alleviating constipation associated intestinal inflammation	[171]

dW: distilled water; E: ethanol; TCA: trichloroacetic acid; Centr: centrifugation; Conc: concentration; Cr: Crushing; Chromat: chromatographic fractionation; D: Drying; Evap: evaporation; Filtr: filtration; FD: freeze-drying; LSR: Liquid to solid ratio; Neutr.: neutralization; Pptn: precipitation; Preext: preextraction; Sonicat: sonication; Steriliz: sterilization; Wash: washing; UA: uronic acid

regulate oxidative stress through activation of the Sirt1 pathway, as demonstrated by Liu et al. (2019) in their study. *Ulva lactuca* oligosaccharides (ULO) and *Enteromorpha prolifera* oligosaccharides (EPO) polysaccharides promote the expression of Sirt1 and subsequently inhibit oxidative stress induced by H_2O_2 by suppressing the expression of FOXO1 in senescent mice [41]. Authors also demonstrated that ULO and EPO have an important antioxidant effect by enhancing the expression of glutathione, SOD, CAT, and telomerase, and attenuating AGEs and malondialdehyde levels, so that oligosaccharides boost total antioxidant capacity, which is likely comprised during aging [41]. Another cause of oxidative stress is the increment in the production of free radicals, such as highly reactive substance having unpaired electrons, for example, hydrogen and chlorine with one unpaired electron (H· and Cl·) and transition metal ions (Fe^{2+}, Cu^{2+} and Mn^{2+}), among others [41]. It has been described that sulphated polysaccharides from green seaweed present hydroxyl radical scavenging activities [111], which result from chelating ions such as Fe^{2+} and Cu^{+}, a Fenton reaction, that may be responsible for the inhibition of deoxyribose oxidation [112,113]. Similarly, ulvans from species like *Ulva intestinalis* exhibit 1,1-diphenyl-2-picrylhydrazyl radical-scavenging activity [113].

Cognitive function is reduced in a large number of diseases associated with aging due to loss of neurons [41]. Ulvans have also demonstrated neuroprotective properties due to their antioxidant and anti-inflammatory actions [20]. Their mechanisms of neuroprotection mainly reside in their ability to inhibit amyloid β (Aβ) fibrillation, its abnormal folding and aggregation, which is the main reason for the occurrence and development of Alzheimer's disease [114], as well as to alleviate ROS production and senescence in neurons [20]. Likewise, ULO and EPO can delay cellular senescence via downregulation of p53 and FOXO1, through the regulation of Sirt1 [41], and protect neurons via increment of levels of Brain-derived neurotrophic factor (a factor associated with the survival and development of neurons) and choline acetyl transferase (manipulates the activity of neurotransmitter-related enzymes) [41].

5.2. Ulvans in anemia-associated inflammation

Iron deficiency anemia (IDA) is the world's most common nutritional deficiency. The traditional oral iron agents are gradually becoming unsuitable for many patients because of their side effects, including gastrointestinal irritancy, low bioavailability, interfering absorption factors, and lipid peroxidation. It is for that reason that it is important to develop new iron supplements with non or minimum side effects. Among the iron (III) complexes, polysaccharide-iron complex has been found to show positive effects due to its bioactivity such as regulation of blood sugar, lowering of blood pressure, and promotion of blood circulation. Besides, polysaccharide-iron complex shows perfect stability, water-solubility and fewer side effects [25].

Ulvans can affect hematological indices. Some studies describe the impact of iron (III)-complexed ulvans on hematological parameters and intestinal iron absorption. For instance, Li et al. (2019) prepared sulphated *Ulva prolifera* polysaccharide (SUE)- iron (III) complex. SUE-iron (III) recovers hemoglobin, red blood cells, serum iron, and erythropoietin to the normal levels [25]. Similarly, Gao et al. (2019) obtained *Ulva pertusa* polysaccharide iron (III) complex, which increases levels of red blood cell, hemoglobin, and hematocrit, and enhances oxygen transportation and acid-base balance in tissues [115]. In addition, SUE-iron (III) complex prepared from Li et al. (2019) show anti-inflammatory effects, as it decreases IL-4 levels and recovers ~~the~~ IFN-γ/IL-4 ratio to the normal level. This study also indicated that SUE-iron (III) could inhibit Th2 cell response alleviating inflammatory damage caused by IDA [25].

5.3. Ulvans in intestinal inflammation

Inflammatory bowel diseases IBD, including Crohn's disease and ulcerative colitis, are a complex chronic inflammatory disorder of the gastrointestinal tract [116] that are associated with diverse responses to microbial and environmental agents [85]. Several molecules related with the development of intestinal inflammation, e.g., TNF, IFN, IL-1β, JAK/STAT, and proliferator-activated receptor (PPAR) [116], have been described to be regulated by the ulvans.

The interaction between NF-κB pathway activation and the accumulation of ROS and RNS results in intestinal inflammation and oxidative stress. Besides, these factors are also involved in the apoptosis and activation of pathological signaling pathways, so that their regulations play a key role in the treatment against IBD [85]. In this regard, ulvans are able to regulate intestinal inflammation by inhibiting the NF-κB pathway, as demonstrated by Ali et al. (2016) in their study, where an ulvan extracted from *Ulva pertusa* COMP alleviates pro-inflammatory cytokine production (i.e., interleukin IL-12, p40, IL-6, and TNF-α) via inhibition of IκBα phosphorylation. As previously mentioned, blockage of IκBα phosphorylation prevents its proteasomal degradation and in turn release and nuclear translocation of NF-κB do not occurs [56]. Similarly, Zhu et al. (2019) constructed selenium nanoparticles coated with an *Ulva lactuca* polysaccharide (ULP-SeNPs), showing that this polysaccharide modulates gastrointestinal inflammation through inhibition of NF-κB activation in macrophages by suppressing the phosphorylation of IκBα.ULP-SeNPs also decreased CD68 level. This implies that it reduces macrophage infiltration into colonic tissue and production of pro-inflammatory cytokines such as IL-6, TNF-α, iNOS, and COX-2 [64]. Another study using selenized polysaccharides from *Ulva pertusa* (ulvan-Se) shows that ulvan-Se has protective effects on the intestinal mechanical barrier, as it increases immunoglobulin A and immunoglobulin M, upregulates levels of IL-1β, interferon-γ and IL-4, and suppresses TNF-α, IL-1β, IL-6 and COX-2 mRNA expression mediated via activation of NF-κB pathway. Besides, ulvan-Se promotes the expression of tight junction proteins (such as zonula occludens protein 1, occludin and claudin-1) [117]. Ardizzone et al. (2022) evaluated the effect of oral daily administration of *Ulva pertusa* extracts in a murine model of induced colitis. They found that treatment significantly reduces tissue damage and the blocks inflammatory cascade via NF-κB inhibition, reducing pro-inflammatory cytokines production and increasing levels of anti-inflammatory cytokines [85].

Moreover, ulvans also regulates intestinal inflammation via modulation of another pathways. For instance, *Ulva pertusa* extracts attenuate inflammation related to ulcerative colitis damage by activation of SIRT1/Nrf2 pathway [85]. SIRT1/Nrf2 signaling alleviates oxidative stress and inflammation through its crosstalk with the NF-κB pathway, modulating the production of the anti- and pro-inflammatory cytokines as well as mediators like COX-2 and iNOS. In addition, *Ulva pertusa* has an anti-apoptotic effect on UC intestinal epithelial cells by inhibition of apoptotic pathways (increases Bcl-2 levels and decreases p53 levels), control of cell death process (reduction of caspase 3, caspase 8, and caspase-9 levels), maintaining in turn homeostasis of intestinal epithelial cell [85]. Finally, ulvan extracted from *Ulva pertusa* containing COMP inhibits MAPKs pathways by blocking phosphorylation of ERK1/2, JNK1/2, p38. The inhibition of this pathway, downregulates TLR9-dependent AP-1 activation, which is involved in the transcription of gene encoding pro-inflammatory cytokines [56].

Ulvans are also capable of modulating TLR-dependent signaling pathways. Cian et al. (2018) described the anti-inflammatory effect of hydrolysates obtained from *Ulva* spp. These peptides regulate TLR4-dependent NFκB/p38/JNK pathway and induce the production of the anti-inflammatory cytokine IL-10 in splenocytes, in splenic macrophages and lymphocytes. Although, they also induce TNF production, which could lead to an inflammatory response perhaps to enhance the immune response [54]. It has also described that EP–Zn inhibits TLR4/NF-κB signaling pathway [28]. It is related to improved intestinal physical barrier function by modulating mucosal structure, and attenuating intestinal inflammation in an *In vivo* model of gut inflammation. Thus, the levels of TNF-α, IL-1β and IL-6 induced by macrophages are decreased, whereas the levels of anti-inflammatory cytokines IL-10 secreted by Th2 cells is increased [28].

Finally, ulvans could also have a beneficial effect on intestinal inflammation through modulation of gut microbiota and the gut response to microbiota mismatches. The bacterial phyla of the human intestinal microbiota are mainly Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria [118]. Variations in the composition of the gut microbiota can lead to a state of dysbiosis. Dysbiosis is a hallmark of IBD, but also metabolic disorders, and neurological disorders [119,120]. For this reason, another key to the treatment of intestinal inflammation is to combat dysbiosis. Several studies have confirmed the immunomodulatory effect on gut microbiota of ulvans, and even its potential as an alternative to antibiotics in weaned livestock animals [28,121], as well as its participation in humoral immune response and regulation o anti-inflammatory processes within the gut epithelial tissue [122]. Thus, Berri et al. (2016) study used sulphated polysaccharide from *Ulva armoricana* (MSP) as a farm animals feed additive. MSP exhibits selective inhibition of the growth of pathogen microorganisms in intestine, such as *Pasteurella multocida*, *Staphylococcus aureus*, *Mannheimia haemolytica*, *Erysipelothrix rhusiopathiae*, *Streptococcus suis*, and *Enterococcus cecorum* [122]. Besides, MSP induces an upregulation of cytokines (including IL-1α, IL-1β, IL-6, IL-8, and TNFα) that suggests that polysaccharide might activate intestinal epithelial cells to initiate immune responses of the host [122,123]. Likewise, Zhang et al. (2022) using EP-Zn in mice found that compound exhibits an immunomodulatory effect on gut microbiota dysbiosis by enhancing relative abundances of *Lachnospiraceae*, *Atopostipes*, and *Ruminococcaceae* genera in the intestinal microbiota [28]. Atopostipes may possess immunomodulatory activity [124]; Ruminococcaceae was associated with intestinal inflammation induced by a high-fat diet in mice [124]. In addition, EP–Zn decreased the abundance of *Coriobacteriaceae*, *Brevibacterium*, *Brachybacterium*, *Dietzia*, *Microbacteriaceae*, and *Parasutterella genera* [28]. *Coriobacteriaceae* and *Brachybacterium* belonging to the *Actinobacteria phylum*, are potentially associated with inflammatory responses [108]. Another study performed by Xie et al. (2021) also used EP-Zn as an alternative to antibiotics in weaned piglet, observing that EP-Zn reduces the level of cytokines related to intestinal inflammation, such as IL-6, IL-8, IL-12 and TNF-α, and inhibits the phosphorylation of NF-kB in the jejunal mucosa of weaned piglets. In addition, weaned piglets supplemented with EP-Zn showed a significant increment in plasma antioxidant levels compared to the antibiotic treated group [121].

All together, these results reveal that ulvans from different *Ulva* spp. could be used as a potential alternative supplement for reducing intestinal inflammation in IBD.

5.4. Ulvans in inflammation related to metabolic disorders

Among the most common metabolic disorders are diabetes mellitus (DM), obesity, and hyperlipidemia. DM is characterized by endocrine-induced metabolic disorders with complex etiology [125]. Besides, it is linked with a low-grade inflammation state that reflects the activation of innate immunity where metabolic, environmental and genetic factors are implicated [126]. Some features of diabetes are high blood glucose levels, hyperinsulinemia (in the early stages), and low insulin sensitivity. Impaired glucose tolerance occurs in the early stages of this disease and may be associated with insulin resistance (IR) and impaired islet β-cell function [127]. Commercially available anti-diabetic drugs have a number of adverse side effects, so that search for new natural drugs to replace these drugs is still active [50].

Several studies have confirmed the potential of ulvans as anti-diabetic compounds due to their capacity to regulate different enzymes, proteins and processes related to this pathology. BelHadj et al. (2012) evaluated the effect of alga *Ulva lactuca* polysaccharides (ULPS)

on key enzymes related to diabetes and obesity and the results demonstrated that ULPS significantly improve glucose levels by reducing the abundance of α-amylase, maltase, and sucrose and regulate lipid homeostasis in diabetes by delaying carbohydrate and lipid digestion and absorption [127]. Lin et al. (2015) investigated the effects of polysaccharides from *Enteromorpha prolifera* on glucose metabolism in a rat model of DM. They measured fasting blood glucose and insulin levels and calculated the insulin sensitivity index, observing that PEP improve glucose metabolism via regulation of insulin receptor (InsR), glucokinase (GCK), and glucose transporter type 4 (GLUT-4) mRNA levels in liver and adipose tissue [128].

Destruction of pancreatic β-cell provokes insufficient insulin secretion which causes development of type 1 diabetes mellitus (T1DM). Destruction of pancreatic β-cell triggers an inflammatory response usually mediated by autoreactive T cells and macrophages. Elicited inflammasome activates caspase-1 and promotes the expression of pro-inflammatory cytokines such as IL-1β, IL-6 and MCP-1, which can induce local inflammation by downregulation of TNF [129]. Yuan et al. (2019) prepared *Enteromorpha prolifera* oligosaccharide (EPO), observing that these polysaccharides inhibit the expression of pro-inflammatory mediators in a murine model of T1DM. EPO also shows a hypoglycemic effect likely due to blockage of inflammation and apoptosis in islet beta cells. Thus, the increased secretion of insulin in these cells could lower blood glucose and improve the diabetic symptoms [129]. Similarly, PEPs reduce fasting blood glucose and blood insulin levels and increase the insulin sensitivity index in diabetic rats. In addition, PEP significantly increase the number of islets β-cells and repair the pancreas damage from diabetic rats [128]. They also reverse IR by increasing the mRNA expressions of InsR, adiponectin (protective factor for IR), GLUT-4, and GCK in the liver and adipose tissue of diabetic rats via activation of AMP-activated protein kinase [128]. Noteworthy, this protein kinase is known to play a crucial role in cellular energy homeostasis and insulin sensitivity [130].

Diabetic nephropathy (DN) is the second most frequent and prevalent complication of DM. DN is characterized by the appearance of persistent clinical albuminuria and a reduction in the glomerular filtration rate [131]. BelHadj et al. (2012) also found that *U. lactuca* polysaccharides (ULP) can revert the levels of plasma creatinine, urea, and albumin, protecting the kidney in diabetic rats [127]. Yang et al. (2021) reported the protective effect of ULP on kidney injury induced by D-galactose [132]. ULP decrease levels of serum creatinine, blood urea nitrogen, serum cystatin C, lipid peroxidation, protein carbonylation, and DNA oxidative damage and improve kidney glutathione content. They also decrease the levels of inflammatory cytokines TNF-α and IL-6 and apoptotic protein caspase-3. In addition, a significant increase in the activities of superoxide dismutase and glutathione peroxidase and total antioxidant activity are observed. These results demonstrated the involvement of antioxidant activity and anti-inflammatory actions of ulvans on their effects against oxidative stress in damaged kidney [132].

Moreover, the chronic hyperglycemic state triggers an increment in AGEs that interact through cellular receptors to favor activation of transcription factor NF-κB and protein kinase C (PKC) system, eventually leading to the appearance of inflammation [131]. Interestingly, ULO and EPO decreases AGEs levels [41]. Another metabolic disorder is hyperlipidemia. This pathological event is characterized by an abnormal elevation of lipids and lipoproteins, such as serum triglyceride (TG), total cholesterol (TC), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). There is a strong association between the levels of lipid parameters and hyperlipidemia, since LDL transfers cholesterol towards extrahepatic organs as its major carrier and HDL transports cholesterol from the periphery tissues to the liver for its catabolism. A decrease of serum HDL and increment of LDL and triglyceride are considered risk factors in metabolic disease related with coronary artery disease, so the reduction of cholesterol levels is essential for treatment of these pathologies [133,134]. Hyperlipidemia could also cause a low-grade inflammation [126] and weaken the antioxidant enzyme system via inhibition of CAT, SOD, GSH and GPX activity and elevation of lipid peroxide levels [135]. In this regard, Li et al. (2018) observed antioxidant and anti-hyperlipidemic activities of ulvan extracted from *Ulva pertusa*, showing higher effects in high sulphate-content derivatives. Rats fed with purified ulvan shows reduced levels of TC, TG, and LDL-cholesterol, whereas HDL-cholesterol is increased. Moreover, ulvan attenuates malondialdehyde levels, and enhances SOD and CAT expression. Thus, the ulvan could be potential sources of natural antioxidants to protect against oxidative stress damage induced by a high-cholesterol diet [135]. Teng, Qian & Zhou (2013) obtained PEPs and determined their hypolipidemic activity in rats. PEPs addition decreases plasma TC, TG and LDL-C levels and increased the HDL-C level, and reduced the liver weight and lipid content [22]. Pengzhan et al. (2003) and Jiang et al. (2020) obtained the same result for the effect of *Ulva pertusa*-ulvan on lipid profile. They concluded ulvan and all obtained fractions exhibit anti-hyperlipidemic properties in a model of hyperlipidemia associated with diabetes [88,136]. To further elucidate the mechanism by which ulvan effectively lowers serum cholesterol levels, Pengzhan et al. (2003) suggested that ulvans could favor cholesterol breakdown into bile acid facilitating its metabolism [88].

The importance of sulphate content in anti-hyperlipidemic activity of ulvans was highlighted by Qi & Sheng (2015) [137]. They prepared ulvan derivatives with normal (U) or high sulphate content ulvan (HU) from *Ulva pertusa* and then evaluated the expression of lipid metabolism-associated genes in a murine model. They found that HU has stronger hyperlipidemic activity than U, indicating that the high sulphate content of polysaccharide could improve the anti-hyperlipidemic properties. This effect may be due to HU has the capacity to inhibit the enterohepatic cycle of bile acids and to enhance the metabolism and decomposition of cholesterols through upregulation of the expression of ileum Farnesoid X receptor (FXR) and hepatic cholesterol 7 alpha-hydroxylase, but downregulation of hepatic FXR expression. In addition, an underlying mechanism of the lipid lowering of HU could also be the upregulation of PPAR-γ expression, which leads to the reduction of fat synthesis rate and increment of the fat hydrolysis rate, thus accelerating the metabolism and decomposition of triglyceride [137]. Nonetheless, further studies are warranted to elucidate these findings.

Roach et al. (2022) reported in two clinical studies in obese participants the beneficial effects of a dietary xylorhamnoglucuronan from *Ulva* sp. administered at 2 g/day or 4 g/day for six weeks. One of these studies showed improvement in the plasma lipids and in the atherogenic and two-hour insulin indexes. The prebiotic potential was also confirmed by the change in composition and abundance of microbiota. In both studies a reduction in inflammatory markers was also observed as well as C-reactive protein in one of them [138].

Xue et al. (2022) proposed an *Ulva prolifera* polysaccharide chelated-Mn for the treatment of dextran sulfate sodium (DSS)-induced colitis in C57BL/6 male mice for 7 days [139]. This compound helped the body to retrieve the weight loss, alleviated intestinal morphology damage and apoptosis, and decreased intestinal infiltration and inflammatory responses, decreased expression of inflammatory cytokines of IL-1β, IL-6 and TNF-α in the colon and lowered expression of IL-10 gene and also avoided the edema and shedding in colon and. Regulation of microbiota composition could show beneficial roles in colon inflammation, particularly the increased *Firmicutes* and the decreased *Bacteroidetes* counts.

Pung et al. (2022) found that enzymatic extracted *Ulva prolifera* polysaccharide (UPP) may present anti-obesogenic effects in high fat diet (HFD)-fed mice [140]. The results showed that UPP considerably slowed down the weight gain and improved metabolic disorders in HFD-fed mice. Notably, the effects were associated with lower body weight gain, reduced adipose tissue hypertrophy, triglyceride concentration in liver and systemic low-grade inflammation, and improved fasting blood glucose. Besides, changes in microbiota by ulvans may have a positively correlated effect on improving obesity and metabolic abnormalities.

5.5. Ulvans in skin care applications

The skin is a complex mesenchymal and epithelial tissue, combining various tissue elements (nervous, vascular, muscular, epithelial and connective), composed of multilayers organized in three major components: epidermis, dermis and hypodermis. It is the largest organ of the human body and is a complex and dynamic ecosystem. Dermatology and cosmetics field represent an important part of economic and due to the potential of algal extract bioactivities (i.e. ulvans), many studies were conducted the last years [37,43,89,93].

These bioactivities concern the skin care: cutaneous homeostasis and microorganisms equilibrium [94,141,142] anti-inflammatory effect due to external environment [86,143,144], anti-aging process [142,145] and wound-healing [10,146,147].

5.5.1. Skin care

Dermatological and cosmetics fields have recently started to focus on the human skin microbiome and microbiota. Human microbiota, mainly established on the skin, oral and vaginal mucosa, respiratory, urinary and gastrointestinal tracts, have fundamental roles in health and diseases.

The outer epidermal layer of the skin, the stratum corneum, is the first physical barrier that prevents chemical substances or pathogenic microorganisms' entrance, fluid evaporation and body heat loss. The stratum corneum is composed of 75-80 % proteins, 5-15 % lipids and 5-10 % unidentified coumpounds [142,148]. Skin microbiota is strongly linked to this stratum corneum and made of millions of comensal microorganisms, e.g., 1 million/cm^2 [149]. The scientific studies into skin microbiote led to the emergence of related studies in the cosmetic industry. Skin microbiota is involved in the maintenance of a healthy cutaneaous barrier, the immune system and limit pathogenic growth [150,151]. A dysbiosis, imbalance in this microbiota is correlated with skin pathological diseases, such as acne, sensitive and dry skins [152,153]. Fournière et al. (2020) exhibits the fundamental role of *Staphilococcus epidermidis* and *Cutibacterium acnes* in the skin system as two skin microbiota sentinels [142]. They can protect against and prevent pathogens, and in other way participate in skin equilibrium in their commensal form with the secretion of beneficial metabolites. However, when a skin microenvironment perturbation appears, their metabolism can be modulated, and their pathogenic form can disturb skin microbiota homeostasis with biofilm organization especially with the organization of inflammatory burst. For example, in acne inflammation, virulent *C. acnes* type IA activates mainly toll-like recepor 2 (TLR2) in keratinocytes, sebocytes and macrophages which induce an inflammatory response with activation of nuclear factor kappa B (Nf-kB) pathway and reactive oxygen species production (ROS) [154]. Finally, the study of these two bacteria and the effects of bioactive compounds appear to be relevant for skin care application. Actually, only few studies have focused on effect of ulvan extract on skin microbiota. Principally Fournière et al. (2021) showed for the first time the biological activity of ulvan extracts from *Ulva* sp. on *S. aureus*, *S. epidermidis* and *C. acnes* [94]. Poly and oligosaccharides were obtained from enzyme-assisted extraction and depolymerization. At 1000 μg/mL these fractions induced a decrease in the inflammatory potential (Interleukine 8 release, a cytokine involved in inflammatory pathway) of both acneic and non-acneic *C. acnes* strains on keratinocytes of up to 40 %. The strongest effect occurring when the bacteria were grown in the presence of polysaccharide fractions, and other components, such as proteins and peptides could also contribute to the activity of the extracts. No effect on the growth of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Cutibacterium acnes* RT4 (acneic strain) and RT6 (non-acneic strain) was observed. Polysaccharide did not alter the bacterial biofilm formation, whereas oligosaccharide fractions modified *S. epidermidis* and *C. acnes* biofilm structures.

The inflammatory response is also a key aspect of the tissue response to infections, but the prolonged inflammation leads to chronic disease and tissue damage. Various active compounds contained in *Ulva* species, such as alkaloids, triterpenoids, steroids, saponins, and flavonoids, exhibit multiple antibacterial and anti-inflammatory properties that can overcome the Methicillin-resistant *Staphylococcus aureus* antimicrobial resistance and accelerate tissue growth in the wound healing of nosocomial infections [141].

Another study shows that ulvan extract from *Ulva reticulata* have not any antibacterial effect against *Staphylococcus aureus* but have a significance against *Enterobacter cloace* and *Escherichia coli* two pathogenic bacteria responsible of potential inflammation and diseases on cutaneous system [93].

5.5.2. Antioxidant/antiradical activity

Approximately 95 % of oxygen is consumed as energy and ultimately becomes water; however, the remaining 5 % produces metabolites called activated oxygen or reactive oxygen species (ROS), which are extremely reactive. Skin, the largest organ in the human body, is exposed to air pollutants, ultraviolet rays, xenobiotics, and cosmetics, which promote the production of ROS. ROS exacerbate skin aging and inflammation [155,156] (Fig. 5), but also function as regulators of homeostasis in the human body, including epidermal keratinocyte proliferation. There are four ROS: superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), the hydroxyl radical ($^{\bullet}OH$), and singlet oxygen ($^1O_2$). Nitric oxide ($^{\bullet}NO$) and peroxynitrite ($ONOO^-$) are also included as ROS. These ROS are involved in complex and diverse reaction pathways. Oxidative stress is defined as an increase in the production of ROS and other oxidants that exceeds the antioxidant capacity [157]. Since ROS and free radicals are highly reactive and unstable, their direct roles in skin remain unclear. However, ROS produce relatively stable oxidants *In vivo*, including 4-hydroxy-2-nonenal and MDA. These oxidants change the structures of proteins, induce cell apoptosis, and regulate the release of inflammatory cytokines [155,157]. ROS also trigger various biological responses through the activation of transcription factors, such as mitogen-activated protein kinase (MAPK) which cause the increase of the response of activator protein 1 (AP-1), which increase the production of metalloproteinases (MMP), and decrease the type I and III collagen production [158–160]. ROS activate also Nf-kB way which is responsible for MMP and pro-inflammatory cytokines (IL-1 et-6, TNF α) increase production [155,159].

The exogenous antioxidant capacity of ulvan has been extensively assessed with *in vitro* assays using 1,1-diphenyl-2-picryl hydrazil (DPPH) radical scavenging, superoxide scavenging, ferric reducing antioxidant power (FRAP), hydroxyl radical scavenging, and lipid peroxide inhibition [5].

Hardouin et al. (2016) demonstrated than ulvan extract using enzyme assisted extraction (EAE) exhibits an antioxidant capacity. Specifically, they used a neutral *endo*-protease, a multiple-mix carbohydrase, a mix of neutral and alkaline endo-protease, to extract ulvan and antioxidant activity was assayed using DPPH scavenging activity assay. DPPH is widely used as a free radical to evaluate antioxidant compounds that have the capability to reduce DPPH radicals by donating hydrogen and produce a stable form. The standards BHA and BHT present an inhibiting concentration (IC_{50}) of 4.8 and 6.8 μg/mL, respectively. Samples obtained with EAE extraction presented positive results with an IC_{50} comprised between 1.8 and 12.5 mg/mL. Likewise, it was supposed that antiradical effect could be due to its contain in rich phenolic compounds [43].

Rahimi et al. (2016) have demonstrated sulfated polysaccharides from *Ulva intestinalis* extracted with ultrasonication exhibited dose-dependent DPPH radical scavenging capacities at concentrations ranging from 0.5 to 5.0 mg/mL. The highest scavenging activity was found to be 74 % at the maximum concentration of 5.0 mg/mL [37]. Authors explain that sulfated polysaccharides with higher molecular weights and sulfate contents exhibit potent antioxidant activities. In the same way, a study led on *Enteromorpha linza* highlighted oversulfated and acetylated derivative of polysaccharide has a strong antioxidant

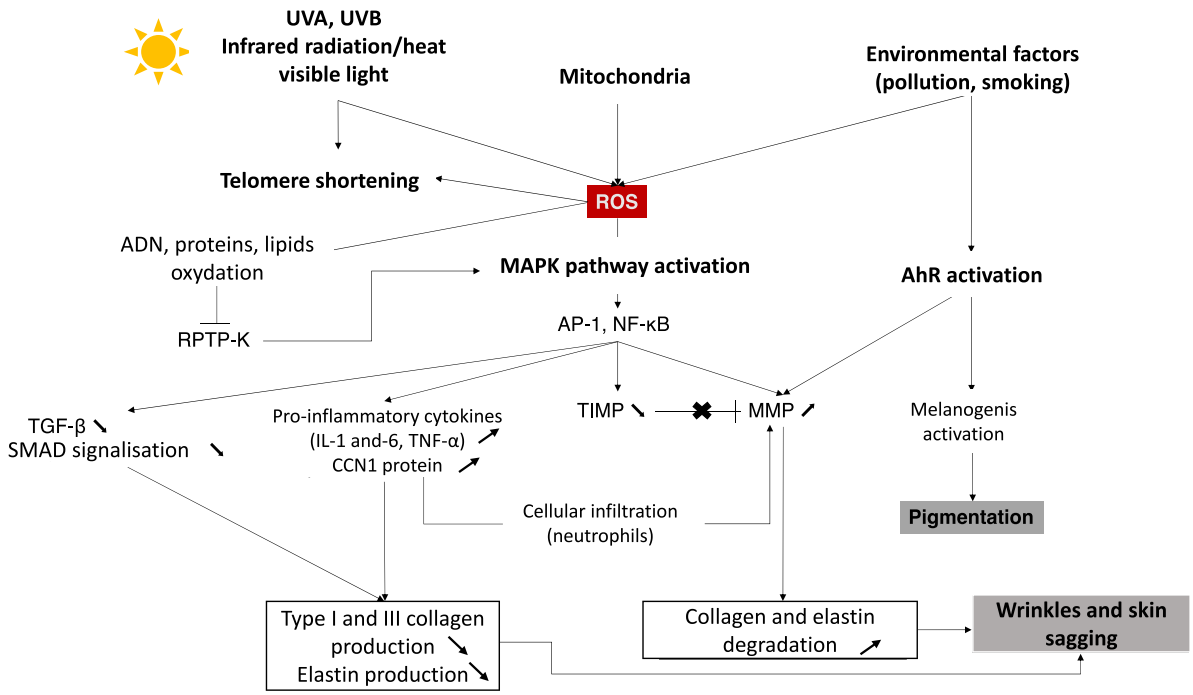

Fig. 5. Schematic representation of the pathogenesis of intrinsic and extrinsic skin aging: Role of ROS in inflammation. AP-1: « Activator Protein-1 »; NF-κB: « Nuclear Factor-kappa B »; AhR: « Arylhydrocarbon Receptor »; SMAD: « S-Mother Against Ddp »; RPTP-κ: « Receptor Type Protein-Tyrosinase Phosphatase κ »; TIMP: « Tissue Inhibitors of MetalloProteinases »; MMP: Matrix Metalloproteinases; TGF-β: « Transforming Growth Factor-β »; IL: InterLeukine; TNF-α: « Tumor Necrosis Factor α »; CCN1: « Cysteine-rich angiogenic protein 61 ». Modified according to [155,156].

activity. DPPH radical was scavenged by antioxidant through donation of hydrogen to form a stable DPPH–H molecule. The effect of antioxidant was due to their hydrogen-donating ability. For the authors the presence of acetyl and sulfate groups in the ulvan molecule could activate the hydrogen atom of the anomeric carbon. The higher activated capacity of the group, the stronger hydrogen atom-donating capacity. Thus, the sulfate and acetyl groups have an impact in ulvan antioxidant activities [161].

Another study performed on *Ulva lactuca* shows that sulfated polysaccharide has an antioxidant activity. In this study, the extract characterized by a highest weight-average molecular weight (Mw) value (2.79×10^3 kDa) has the strongest antioxidant activity with 75 % scavenging effect at 400 mg/mL compared to extract 1.32×10^3 kDa with 59 % scavenging effect. The results of this study showed that the antioxidant activities of ulvan from *Ulva lactuca* depend on the molecular weight, sulphate content and carbohydrate composition [143].

Conversely, Qi et al. (2005) have proved low molecular weight sulfated polysaccharides from *Ulva pertusa* promoted the higher antioxidant capacity. Indeed, 28.2 kDa extract have a better antioxidant activity compare to the native polysaccharide extract (151.7 kDa) or a degraded ulvan with a high molecular weight (64.5 kDa) [144].

In conclusion, the antioxidant activity of ulvan depend on many factors. It is clear the molecular weight plays an important role in this activity but it is necessary to bind this with other parameters such as the sulfate group, the contribution of the monosaccharides with a variable content of hydroxy and carboxyl groups, as well as the hydrogen donation capability. The antioxidant activity of polysaccharides depends on the degree of substitutions, monosaccharides, and glycosidic linkages [86,143].

5.5.3. Wound healing

A wound is the loss of the normal integrity, structure, and functions of the skin due to a physical, chemical, or mechanical agent. Wound repair consists of an orderly and complex process divided into four phases: coagulation, inflammation, proliferation, and remodeling [162,163]. Wound healing is a complex and dynamic biological process that involves cells platelets, macrophages, fibroblasts, epithelial and endothelial cells, mediators, growth factors, and cytokines [163,164]. A suitable inflammatory microenvironment plays a vital role in wound healing and tissue regeneration because inflammation is the second stage of wound healing. But if the inflammation phase in chronic wounds is prolonged leads to the delay of the transition into the proliferation phase [147]. Even when a moderate presence of ROS facilitates wound healing, an excess exacerbates the inflammatory response making difficult the healing.

Ulvans can fulfill different requirements of wound dressings, among them acting as a barrier to microbial invasion, ensure a certain degree of moisture, low adhesion to the wound, good elasticity and gas permeability, biocompatible, non-toxic and non-allergenic [165]. The excellent wound healing properties of these polysaccharides can be favored by other bioactivities such as antibacterial, anti-inflammatory, hemostatic, … and by the good biocompatibility and biodegradability. They can be combined with copolymers and bioactives to prepare various dressings, including nanofibers, smart hydrogels and injectable hydrogels [165].

Chen et al. (2019) prepared a sulfated and rhamnose-rich, xylo-rhamno-uronic acid extract from the cell wall of a cultivated ulvacean macroalgae. It is therefore a strong candidate for applications in wound healing and tissue regeneration. This study targets the development of polysaccharide modification for fabrication of 3D scaffolds for skin cell (fibroblast) culture. The extract was modified by methacrylation and UV-crosslinked to produce hydrogels with tunable mechanical properties. The hydrogels demonstrate high cytocompatibility in human dermal fibroblasts and support cell proliferation over 14 days, more functional than alginate gels. An XRU-based bioink was developed for extrusion printing 3D and the resulting printed hydrogel scaffolds showed excellent cytocompatibility and also good shear-thinning properties, desirable for an ink for extrusion printing [166].

Terezaki et al. (2022) developed electrospun nanofibrous matrices composed of ulvan and marine gelatin in appropriate ratio to prevent

wound infection and to improve the healing process on the burn-inflamed skin of SKH-1 female hairless mice. The patches promoted faster wound contraction during the early stages of the healing process and suppressed inflammation. Histopathological analysis showed a restoration similar to normal skin, with only mild inflammation observed in the reticular dermis. In addition, the potential synergistic effect of either hydrolyzed collagen or silver nanoparticles incorporated in ulvan-based nanofibers was evaluated [146].

Using an electrospinning technique, Guo et al. (2022) manufactured a scaffold blend consisting of an *Enteromorpha* polysaccharide and polyvinyl alcohol and the biocompatible nanofibrous wound dressing materials loaded with anti-inflammatory ingredients were used for treating diabetic wounds. The efficacy was confirmed in both *in vitro* and *In vivo* studies. This scaffold accelerated the repair of skin wounds in diabetic mice, by regulating the inflammatory response in the early stage of wound healing and further promoting skin regeneration. It suppressed the secretion of TNF-α and IL-6, thus inducing the transformation of wound from inflammation to proliferation [147].

Kikionis et al. (2022) prepared nonwoven nanofibrous patches composed of ulvan and polyethylene oxide through electrospinning. The uniform structure favored the homogeneous distribution of ulvan in the fibrous matrix as well as its diffusion onto the wounded skin. The patches, applied to volunteers after cryosurgery of keloids, showed higher performance than a reference product in wound healing, elimination of skin inflammation, restoration of biophysical parameters similar to normal values and significant decrease in hemoglobin concentration, skin texture and volume, without discomfort or adverse reaction. In contrast, the reference product showed inferior performance in all evaluated parameters [167].

Kesavan et al. (2021) prepared a mannose-decorated chitosan-functionalized graphene oxide carrier loaded with ulvan from *U. lactuca* as drug delivery system for glioblastoma cancer with human cell line (U87). The carrier showed high ulvan entrapment and biocompatibility. Red blood cells stabilization by hypotonic solution higher than 90 % was observed, and this can be an *in vitro* measurement of anti-inflammatory activity of nanocarriers, since these cells can be regarded as an analog of lysosomal layers, and lysosomal membrane stabilization is considered key for drug delivery applications [168].

6. Conclusions

Ulvan, sulphated polysaccharide exhibiting different rheological and biological properties, can be found in the cell walls of *Ulva* sp., a widely available and abundant marine resource. The processing conditions can influence the chemical, physical and biological properties of ulvan. A compilation of different conditions valid to extract active ulvans and ulvan fractions is presented. Anti-inflammatory properties of ulvans are based on their ability to regulate inflammation and oxidative stress through modulation of different signaling pathways, giving them the potential to protect from inflammation in a number of diseases. Nonetheless, to the date studies on the biological effects of ulvans have been carried out employing extracts from different species of *Ulva* as well as extraction and purification methodology. Therefore, future experiments will need to clearly specify the composition of ulvans and unravel the structure/activity relationship in order to elucidate and better define the anti-inflammatory effects observed by ulvans in the context of their therapeutic applications.

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CRediT authorship contribution statement

Conceptualization, N.B., C.V-G. and H.D.; resources, N.F.-F., N.B., C. V-G., M.D.T., R.M.-F., F.J.B. and H.D.; writing—original draft preparation, T.L., AN.B., C.V-G. and H.D.; writing—review and editing, N.F.-F., A.R.-C., T.L., N.B., C.V-G., M.D.T., M. B:, A.M., A.M., M.J.L-V., R.M.-F., F.J.B. and H.D.; visualization, N.F.-F., A.R.-C., T.L., N.B., C.V-G., M.D.T., M. B:, A.M., A.M., M.J.L-V., R.M.-F., F.J.B. and H.D.; project administration, N.F.-F., A.R.-C., T.L., N.B., C.V-G., M.D.T., M. B:, A.M., A.M., M. J.L-V., R.M.-F., F.J.B. and H.D.; funding acquisition, N.F.F., N.B., C.V-G., M.D.T., R.M.-F., F.J.B. and H.D. All authors have read and agreed to the published version of the manuscript.

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.

Data availability

No data was used for the research described in the article.

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