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Review

Ulva Seaweed-Derived Ulvan: A Promising Marine Polysaccharide for Biomaterial Design

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Abstract: Currently, green seaweed is underutilized compared to other major seaweeds. Among green seaweeds, many scientists have reported the utilization of *Ulva* in various fields in recent years, which intrigues its potential as the next top candidate for biomass in industrial biorefineries. *Ulva* has unique polysaccharides called ulvan, which are considered for medicinal and pharmacological applications. Ulvan is a sulfated polysaccharide consisting of rhamnose, glucuronic acid, and sulfated sugar units, which offers a range of bioactive properties, including immunomodulation, antimicrobial activity, anticoagulant, and biocompatibility, making it a versatile candidate for biomaterial design. This review presents an in-depth analysis of the potential route for the application of ulvan, starting from extraction methods, structural and biological characterization to biomaterial design, highlighting its advantages over traditional polysaccharides such as agar, carrageenan, and alginate.

Keywords: green seaweed; marine biomaterial; ulvan; cellulose

1. Introduction

In recent years, seaweed, or macroalgae, has attracted significant attention for its potential as a sustainable source of food and non-food industries, such as food additives, animal feeds, pharmaceuticals, nutraceuticals, cosmetics, textiles, biostimulants, bioplastics, and biofuels [1–6]. Seaweed are simple aquatic plants that thrive in diverse environments, ranging from freshwater to highly saline oceans [7]. From an environmental point of view, seaweed is a highly autotrophic plant [8]. Through photosynthesis, seaweeds produce significantly more organic matter and consume CO_2. The photosynthetic efficiency of seaweeds was 3–5 times higher than terrestrial plants [7,9] making it highly effective in converting sunlight and CO_2 into biomass. The carbon uptake rates reach 8–20 tons per hectare/year [4,8,9] contributing to carbon sequestration and helping mitigate climate change. Furthermore, the biomass productivity of seaweed was greater than terrestrial biomass [10]. For instance, the yield of brown seaweed was 225 tons dry weight/Ha/year, 2.3 yield was 2.3 folds higher than sugarcane [9]. In addition, seaweed has lower lignin content than land plants [6,11–13] so the process of extracting seaweed components will be easier with lower energy input.

Based on the pigments contained in their thallus, seaweeds are classified into three major groups: red seaweeds (Rhodophyta), green seaweeds (Chlorophyta), and brown seaweeds

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(Phaeophyta) [4,7]. Currently, red, and brown seaweed are widely known both in terms of the number of species and their commercial production. Suntana et al. reported that the number of red and brown seaweed species reached 4000 and 1500 species respectively, while green seaweed only 900 species [14]. Apart from being obtained from the wild, several types of seaweed can also be cultivated well [15]. Seaweed cultivation offers several advantages over terrestrial plant farming, making it a sustainable and environmentally friendly choice. On seaweed cultivation, there is no need for arable land [15,16] and reduce competition with terrestrial agriculture which ends the need for arable land and reduces competition with terrestrial agriculture [6]. In addition, unlike terrestrial plants, seaweed does not require fresh water or chemical fertilizers [16], conserving valuable resources and minimizing pollution.

Green seaweed, especially *Ulva*, is one of the promising species in terms of availability, sustainability, and potential applications and uses. *Ulva* is commonly known as sea lettuce and is seen worldwide [17,18]. Remarkably, *Ulva* shows adaptability to various salinities, growing well in marine and brackish water and freshwater [19,20]. Some species of *Ulva* caused green tide bloom. Green tide blooms occur more global seawater eutrophication and temperature rise [21]. The largest *Ulva*-forming green tide happened in the Yellow Sea of China, covering 1746 km^2 and producing over 24 million tons of biomass [22]. *Ulva* thrives in diverse habitats, including tidal pools and rocky shores, and can grow optimally in water temperatures of 20 – 30 °C [17,23,24]. Daily growth rate (DGR) in the open sea was 20.1 ± 1.8 % day^{-1}. Interestingly, it was cultivated in the pond or tanks, the DGR reached 27.9 ± 4.4 % day^{-1} [18]. Studies have also shown that *Ulva* achieves higher growth rates than other seaweed massively cultivated such as *Porphyra umbilicalis*, *Chondrus crispus*, and *Laminaria saccharina* [25,26].

Ulva is composed of mainly carbohydrates (47 – 67 %) [27] consisting of starch (4 %), cellulose (9 – 10 %), hemicellulose (14 – 32 %) and Ulvan (13 – 39 %). The protein content of *Ulva* was (12 – 30 %) and fat (1 – 4 %). Like seaweed, *Ulva* also has ash (21 – 45 %) [27–30] consisting of macro and micro minerals. *Ulva* sp. as a nutraceutical agent can be used as food that shows beneficial physiological functions, improves well-being, and reduces the risk of certain diseases, including inflammatory disorders, cancer, bacterial infections, and viral infections; it also acts as an immunomodulating and hypolipidemic agent [31]. Generally, Ulvan is extracted from seaweed by conventional methods carried out separately. This process will produce waste and environmental problems. Through the concept of integrated biorefinery [6,29,30,32–35], the production of ulvan with various byproducts will be able to increase the added value of the *Ulva* seaweed industry. Through the biorefinery approach, process efficiency can be increased, for example increasing from 26% to 39%, as well as cellulose as a by-product increasing from 12% to 39% [28]. Although several papers have comprehensively reviewed ulvan [31,36], to the best of our knowledge, there are few reported concepts of biorefinery concept with green extraction ulvan which focuses on ulvan characteristics for biomaterial purposes. Moreover, there are no studies that have revealed its transition from resource-extraction understanding-based research to biomaterial design application-focused work while addressing the chemical and biological engineering aspects of its exploration. In line with this knowledge gap, this review further explores the comparative advantages of ulvan by comparing its properties in relation to other seaweed-derived polysaccharides and examining the challenges it faces in future applications for biomaterial design across various fields.

2. *Ulva*, Structural Characteristics, and Extraction of Ulvan

2.1. Ulva

As is generally observed in the seaweed, the entire body of *Ulva* is known as a thallus which is composed of hold fast, stipe, and blade standing for the function of root, stem, and leave in the higher plant such as seagrass. The size of the thallus reaches 100 cm. The color of the thallus ranges from bright green to dark green, depending on the species and environmental conditions. The dominance of chlorophyll pigments causes green color. The shapes of the thallus are thin, flat, and sheet-like

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resembling lettuce leaves. Some species may appear tubular or filamentous [15]. Examples of species, color and shape are presented in Figure 1.

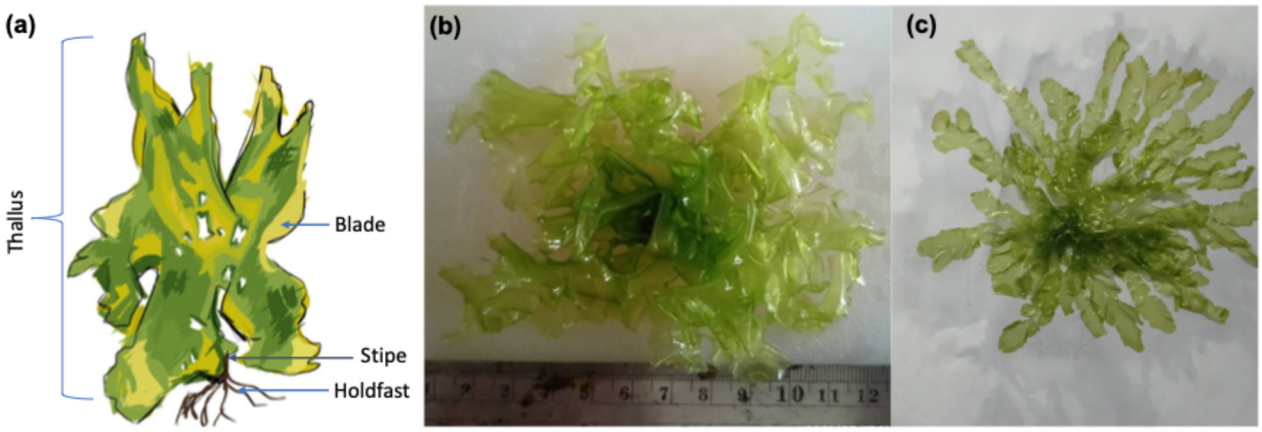

Figure 1. Morphological features illustration of *Ulva* (a) and photographic representations of *Ulva* species: *Ulva lactuca* (b) and *Ulva prolifera* (c).

2.2. Ulvan Chemical Structure characteristic

The chemical structure of ulvan polysaccharide consist of repeating sugar which unique to *Ulva* species (Figure 2). The major monosaccharide sugars are rhamnose, glucuronic acid, xylose, iduronic acid, and galactose. Sulfate group is attached in all rhamnose and some xylose [37]. Based on thallus morphology, Ulva divides into blade and filamentous. The nomenclature of repeating disaccharide is first initiated by Kidgell et al. [36]. The repeating sugar in ulvan polysaccharide of blade and filamentous *Ulva* are different, resulting different sugar composition. In their new study, it was found that in the filamentous *U. ralfsii* and *U. prolifera*, sulfate also found in glucuronic acid [38]. Besides sulfate, ulvan also have carboxyl group on uronic acid in the form of glucuronic acid and iduronic acid. A lot of hydroxyl group makes ulvan hydrophilic and water-soluble.

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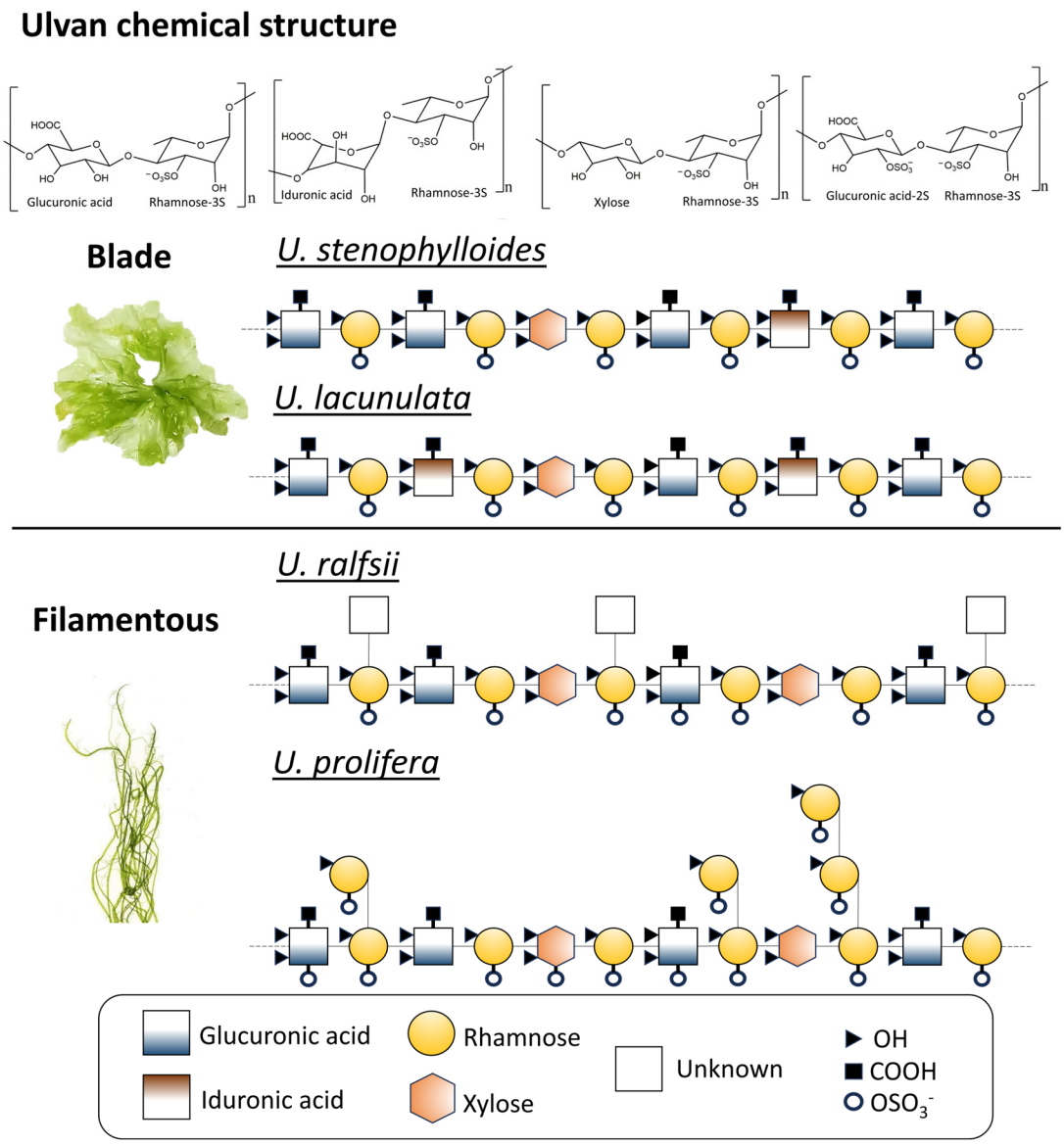

Figure 2. Chemical structure of ulvan.

2.3. Ulvan Extraction Strategy

In ulvan extraction, the quantity and quality of the extracted ulvan depend on the extraction method, purification process, and biomass sources. The ulvan polysaccharide extraction method is selected based on the properties of the ulvan molecule, its physicochemical characteristics, and its interactions with other components [39]. Broadly, ulvan extraction can be categorized into three approaches: physical, chemical, and enzymatic. The extraction process primarily focuses on ulvan due to its high abundance. However, co-extraction during the process often results in the presence of salts, proteins, pigments, and other polysaccharides, such as cellulose, glucuronan, xyloglucan, and starch. The intended final product plays a critical role in determining the specific steps of ulvan extraction. Figure 3 illustrates the schematic of ulvan extraction from *Ulva*. In this work, we will unravel the steps of ulvan extraction, emphasizing yield, strategies, and the management of side products in the context of *Ulva* biorefinery.

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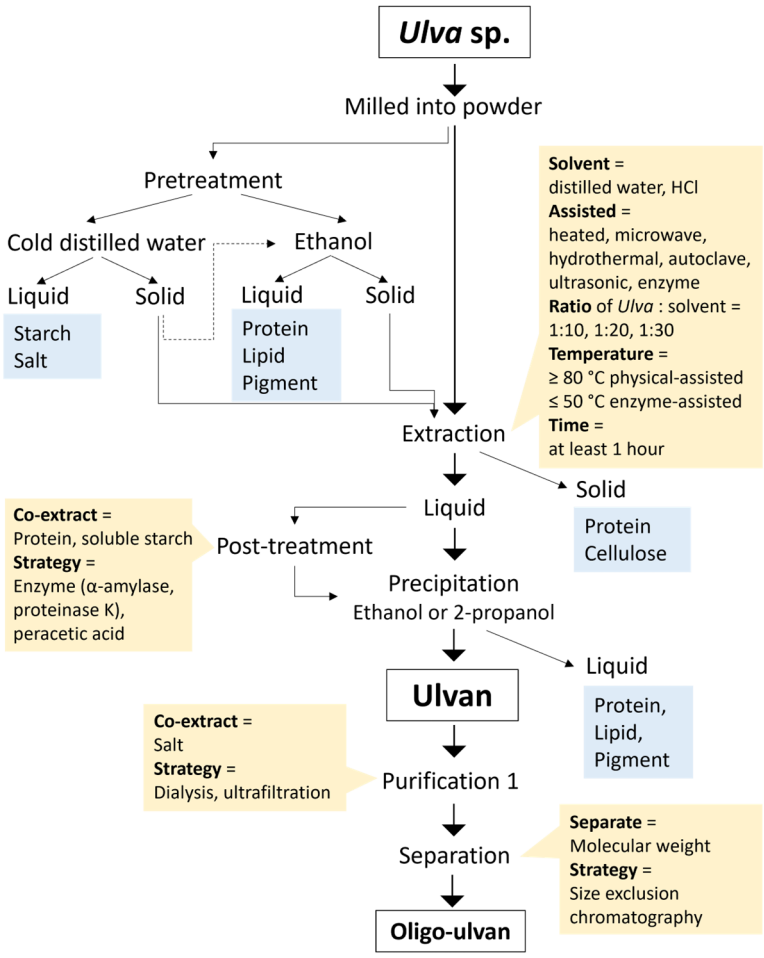

Figure 3. Schematic extraction steps of ulvan from *Ulva* sp.

In the biorefinery concept, the goal is to optimize the use of biomass resources by maximizing benefits and profitability while minimizing waste [40]. As previously mentioned, *Ulva* holds significant potential, with ulvan being its most unique and valuable component. Therefore, focusing on ulvan as the primary extraction target, while managing other potentials through sequential extraction, presents a highly attractive approach. In the context of ulvan biorefinery, side products can be categorized into co-products, ulvan itself, and residual products.

The co-products in *Ulva* include salts, pigments, lipids, and proteins. Extracting co-products helps reduce co-extracted impurities in ulvan, thereby increasing its yield. Since *Ulva* is harvested from the sea, it contains a high salt content, which can impact the extraction process. Reducing salt content enhances protein yield while decreasing the mineral content. For instance, extracting *Ulva* with distilled water at 25 °C for 2 hours or at 40 °C for 30 minutes removes 22 % of the salt without significantly affecting ulvan extraction [41]. In addition to salt, starch can be extracted using cold distilled water. Extraction of starch from *U. ohnoi* with cold distilled water and a homogenizer yields 7.33 % of the dry weight of *Ulva* [30].

Another valuable co-product is pigment, which can be extracted using ionic liquids or organic solvents [42]. Ethanol is the most commonly used solvent for pigment extraction from *Ulva*, yielding 3.6 mg/g of dry weight [43]. Cascading extraction, starting with salt removal, increased the ulvan yield from 3.7 % to 8.2 % of *Ulva* dry weight, while subsequent pigment extraction showed no significant impact on ulvan yield [44]. Besides pigments, ethanol also extracts lipids and proteins from *Ulva* [44,45]. The compounds extracted with an ethanol-to-water ratio of 70:30 exhibit bioactivity, with an IC50 of 1.2 g/mL of biomass in the solvent [46]. Although pigment removal at the beginning of the process has minimal effect on ulvan yield, pigments themselves have significant

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applications in fields such as cosmetics, food additives, and pharmaceuticals. Therefore, their early extraction holds considerable value on its own.

The extraction of ulvan requires careful optimization of solvents and conditions, as these not only influence ulvan yield but also affect the co-extraction of other materials. Table 1 summarizes the ulvan yields, molecular properties, and extraction conditions across various *Ulva* species. Solvents used for ulvan extraction are typically categorized as acidic, alkaline, or neutral. Among these, acidic solvents generally produce higher yields compared to alkaline solvents [45]. Interestingly, even hot distilled water, a neutral solvent, can achieve good ulvan yields with a wide range of molecular weights [36]. Acidic solvents likely enhance ulvan extraction by breaking down the cell wall matrix and disrupting ionic interactions between ulvan and other components, making the polysaccharide more accessible for solubilization. In contrast, alkaline solvents may lead to degradation or selective solubilization of other polysaccharides, reducing ulvan recovery.

In addition to solvent selection, an extraction temperature of at least 80 °C is recommended for optimal results. Assisted extraction strategies, such as microwave, ultrasonic, autoclave, hydrothermal, or enzymatic techniques, can further enhance ulvan yield. Enzymatic assistance using cellulase, for example, is energy-efficient and achieves higher yields compared to non-assisted methods [47]. While physical-assisted methods are highly effective in increasing yield, they tend to consume significantly more energy compared to enzymatic approaches. Physical-assisted methods, such as microwave and ultrasonic techniques, improve extraction by disrupting cell walls through rapid heating or mechanical vibrations [45,48]. Enzymatic approaches target specific bonds, like glycosidic linkages, to release ulvan with minimal structural damage and energy use [49].

The solid fraction generated during ulvan extraction constitutes a significant portion of the residual product. This solid fraction contains cellulose, protein, and minerals, with its composition varying based on the pretreatment and extraction processes used. For instance, the residual solid obtained from hydrothermal extraction combined with supercritical CO_2 and ethanol pretreatment is rich in cellulose and protein but has lower heavy metal and mineral content, making it a promising candidate for food or feed applications [50,51]. The cellulose derived from *Ulva* exhibits unique characteristics, which make it suitable for a wide range of applications. Separating protein and cellulose from the residual solid can yield more valuable side products, enhancing the overall economic and environmental sustainability of the ulvan biorefinery process.

Table 1. Ulvan yield, molecular properties, extraction conditions, and co-products across different Ulva species.

Species	Yield (% dw)	MW (kDa)	Sulfate (% dw)	Extraction Solvent	T (°C)	Assisted	Solvent for Co-product	Ref
U. ohnoi	3.50	105	17.60	HCl (pH2)		-	-	
U. tepida	3.90	313	21.60	HCl (pH2)	37	-	-	[52]
U. prolifera	6.70	246	16.60	HCl (pH2)		-	-	
U. lactuca	17.95	-	17.22	Distilled water	50	Cellulase	-	[47]
U. lactuca	16.90	265	53	NaOH	70	Ultrasonic		[48]
	14.50	280	58	HCl	70			
	12.50	304	39	Distilled water	70			
U. linza	17.00	-	-	Citric acid		-	-	[52]
	6.02	-	14.92	Distilled water	60	-	Ethanol-protein and pigment	[53]
U. fasciata	7.34	-	12.73	HCl		-		
	6.74	-	7.760	Na_2EDTA		-		
U. lactuca	14.22	-	16.82	HCl (pH2)		-	-	[47]
U. linza	29.33	16	13.78	Oxalic acid		-	Distilled water - Starch	[52]
	17.76	300	-	Distillled water	80	-	-	
U. intestinalis	23.21	88	-	Acidic water (pH3)		-	Ethanol-lipid and pigment	[45]

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Species	Yield (% dw)	MW (kDa)	Sulfate (% dw)	Extraction Solvent	T (°C)	Assisted	Solvent for Co-product	Ref
U. ohnoi	16.11	110	-	Alkaline water (pH10)	85	-	Distilled water – salt Ethanol – pigments	[44]
	20.41	-	-	Distillled water		Microwave		
	17.89	-	-	Distillled water		Autoclave 121 °C		
	23.73	-	-	Distillled water		Ultrasonic		
	8.20	10.5	12,5	HCl		-		
	7.00	16.3	12.4	HCl		-		
	8.10	10.8	12.5	HCl		-		
Ulva sp.	0.04	-	18.00	Citric acid		-	-	[54]
U. fenestrata, U. lactuca, U. compressa	18.00	-	17.80	HCl		-	-	[49, 55]
	18.00	-	17.80	HCl		-	-	
U. lactuca, U. compressa	11.00	-	14.30	Distilled water	90	Post-treatment α-amylase & proteinase K	Ethanol-protein and pigment	[55]
	11.00	-	9.30	Distilled water				
U. lactuca	41.96	-	23.20	ChCl-glycerol		Peracetic acid	-	[56]
U. lactuca	3.40	-	15.65	HCl (pH1.5)		-	-	[47]
U. pertusa	17.80	283	13.20	Distilled water		-	-	[57]
	20.60	352	9.20	Distilled water		Ultrasonic	-	
	25.30	404	6.80	HCl (pH4.5)		Pretreatment cellulase at 50 °C	-	
	26.70	300	3.90	HCl (pH4.5)			-	
Ulva sp.	30.36	-	-	HCl (pH2)	90	-	-	[58]
	30.48	-	31	Distilled water	120	Microwave hydrothermal	-	
	30.46	-	40	Distilled water	140		-	
	30.66	-	50	Distilled water	160		-	
	30.70	-	20	Distilled water	180		-	
	30.66	-	21	Distilled water	200		-	
Ulva sp.	11.00	-	11.02	Distilled water	120	Hydrothermal	Pretreatment supercritical CO_2 & ethanol - polyunsaturated rich lipids & phenolic content	[51]
	19.00	-	7.14	Distilled water	140			
	22.00	-	10.09	Distilled water	160			
	5.00	-	7.58	Distilled water	180			
	5.00	-	7.36	Distilled water	200			

During the extraction of ulvan, various other components are co-extracted, which are typically considered impurities. To obtain pure ulvan, these impurities must be effectively removed. Ulvan, a water-soluble polysaccharide, is insoluble in alcohol [5]. This property allows for its selective precipitation, while other soluble compounds remain in the liquid phase. Even with extended pretreatment strategies, the precipitation step remains critical for isolating pure ulvan [44]. This step separates ulvan from pigments, lipids, and proteins. Subsequent processes, such as centrifugation, evaporation, and ultrafiltration, are employed to further separate the liquid and solid phases following precipitation.

Alcohol precipitation is a convenient and widely used method; however, its effectiveness is limited by the insolubility of certain impurities, such as salts and starch. Post-treatment using

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enzymes or strong chemicals, such as peracetic acid, provides an effective means of minimizing co-extracted components [5]. For example, α-amylase can be used to reduce starch content, while proteinase K is effective for protein removal [59]. Dialysis and ultrafiltration are commonly used to remove salts from ulvan extracts. Before dialysis, the precipitated ulvan must be rehydrated using distilled water or an appropriate buffer solution. Dialysis typically employs membrane tubing with a molecular weight cut-off (MWCO) ranging from 12–14 kDa [60]. The choice of downstream processing steps for ulvan purification depends on its intended applications, as ulvan has a wide molecular weight range, spanning from over 400 kDa to less than 3.9 kDa [36]. Molecular weight-based purification is often performed using Size Exclusion Chromatography (SEC), which allows for precise separation based on size. The molecular weight of ulvan plays a crucial role in determining its rheological properties and bioactivity, with higher molecular weights favoring structural applications and lower molecular weights enhancing bioavailability in pharmaceutical uses.

SEC separates ulvan based on particle size, which is determined by the hydrodynamic volume of the molecules in solution. This separation can be used to estimate molecular weight by comparing the elution profile of ulvan to a calibration curve generated with standards of known molecular weight. High-performance SEC is typically performed using distilled water as the mobile phase and carried out on a High-Performance Liquid Chromatography system equipped with an Infrared detector [58]. Further separation may be required if the target product is a rare sugar, such as rhamnose. Rare sugars such as rhamnose are valuable for their applications in pharmaceuticals and as precursors in chemical synthesis, necessitating further refinement to achieve the desired purity and concentration.

3. Biological Properties of Ulvan

Ulvan holds significant potential as a biomaterial, largely due to its exceptional biological properties that are crucial for the functionality of biomaterials. This review highlights ulvan's biological activities, focusing on its role as a biomaterial with key attributes such as excellent biocompatibility, immunomodulatory effects, anticoagulant activity, and antimicrobial properties. These properties are essential for biomaterials, as they enable compatibility with biological systems and enhance therapeutic efficacy, making ulvan a promising candidate for various biomedical applications.

3.1. Biocompatibility Profile

Biomaterials must be compatible with biological tissues, meaning they should not provoke harmful immune responses or toxicity when introduced into the body. This is a critical characteristic for materials used in implants, drug delivery systems, and tissue engineering. The biocompatibility of ulvan has been assessed through various techniques, including cytotoxicity tests, haemolysis assays, and studies of cellular uptake and interactions.

Cytotoxicity testing has been performed both in vitro on cell cultures and in vivo using experimental animals [61,62]. Ulvan's cytotoxicity has been studied across a range of cell types, including fibroblast cells (e.g., mouse C3H [L929], 3T3) [63,64], macrophage cell lines (e.g., RAW 264.7, peritoneal, and J774A.1) [65–68], gut cells (e.g., IPEC-1) [69–71], myoblast cell (e.g. mammalian L6 cells) [72–74], HaCaT keratinocytes [75], Vero cells [76] and in animal models such as mice and rats [77]. T The most used method for cytotoxicity testing is the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, which measures cell viability by detecting the reduction of yellow MTT dye into purple formazan crystals by metabolically active cells, indicating mitochondrial activity.

Ulvan has generally been shown to be non-toxic, with several studies reporting high cell viability across various cell lines exposed to ulvan extracts. Fractions of ulvan from several spesies of *Ulva*, namely *U. pertusa* [65,66], *U. intestinalis* [68,78], *U. armoricana* [69,70], *U. lactuca* [63,77,79], *U. clathrata* [80], *U. compressa* [81], and *U. prolifera* [67,82], exhibited over 50 % cell viability at concentrations of ≥500 μg/mL. Furthermore, ulvan derived from *Ulva* sp. has been proven safe for mammalian L6 cells,

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showing no cytotoxic effects at concentrations under 90 mg/mL. Similarly, it did not show toxicity in 3T3 cells even at concentrations up to 10,000 mg/mL [83]. In human L929 cells, ulvan remained metabolically active after 72 hours of exposure, with no decrease in cell viability [64].

The hemolysis assay, which measures hemoglobin release from red blood cells, is a simple screening method for potential biocompatibility of a material. Ulvan extracted from *U. lactuca* demonstrated hemolytic activity, with a recorded hemolysis percentage of 12.38 % at a concentration of 100 μg/mL. The negatively charged oxygen groups on ulvan electrostatically interact with the positively charged phosphatidylcholine lipids on the outer surface of red blood cells, contributing to ulvan's hemolytic activity [84].

3.2. Immunomodulatory effect

Immunomodulatory properties are a key biological activity that can serve as an essential parameter in biomaterial characterization, especially in applications involving interactions with the immune system, such as tissue engineering, wound healing, implants, and drug delivery. The ability of a biomaterial to modulate immune responses in a controlled manner ensures safety, biocompatibility, and effectiveness in these medical applications [85,86]. Immunomodulation refers to the alteration of the immune system's response, either by enhancing immune responses (immunostimulatory) or reducing excessive immune activity (immunosuppressive). This process involves regulating immune cell functions (like macrophages, T cells, or natural killer cells), cytokine production, and overall immune system responsiveness. The primary goal of immunomodulation is to achieve a balanced immune response that supports effective defense against infections or tumours while preventing immune system overactivation, as seen in autoimmune diseases and allergies [85].

The immunomodulatory effects of ulvan have been widely investigated in various macrophage cell types, including RAW 264.7 cells (*Rat Adherent White blood cell* 264.7 cells), mouse peritoneal macrophages, J77A.1 cells, and fish head kidney cells [86–92]. Moreover, ulvan's impact on immune modulation has been explored in several models, such as fish [93,94], porcine intestinal epithelial cells (IPEC-1 cell line), rats [77,97], mice [77,78,95,96], and chickens [97]. A range of probes are commonly used to evaluate ulvan's effects on inflammation, including signalling molecules (e.g., cytokines like tumor necrosis factor-alpha (TNF-α) , interleukin, IL (IL1, IL2, IL6, IL10, IL12), C-X-C motif chemokine ligand (CXCL1, CXCL12, CXCL14), and C-C motif chemokine ligand), which are various types of interleukins and chemokines that play roles in immune regulation), active metabolites (e.g., Prostaglandin E2), nitric oxide (NO)), immunoglobulins (e.g. immunoglobulin M (IgM), Intercellular Adhesion Molecule, and Vascular Cell Adhesion Molecule-1), enzymes (e.g., cyclooxygenase-2 (COX-2) , inducible nitric oxide synthase-2 (iNOS-2) , Heme Oxygenase-1, and Myeloperoxidase), and transcription-related molecules (e.g., nuclear factor kappa-B (NF-κB) and mRNA) [65–67,78,82,94,95,98].

The immunomodulatory effects of ulvans are closely associated with the inflammatory response, which can be divided into four key stages: inducers, sensors, mediators, and target tissues, as shown in Figure 4. Inflammation begins with inducers, which can be classified as either exogenous or endogenous. Exogenous inducers, such as pathogen-associated molecular patterns, are recognized by specific receptors, while endogenous inducers include damage-associated molecular patterns released from damaged host cells. Other endogenous molecules, like advanced glycation end products and oxidized lipoproteins, are often linked to oxidative stress and can also trigger inflammation. Sensors, such as Toll-like receptors (TLRs), Nod-like receptors, and other pattern recognition receptors, identify these inducers and activate downstream signaling pathways like mitogen-activated protein kinase (MAPK), NF-κB, and SIRT1/FOXO1. These signaling pathways lead to the production of various inflammatory mediators, including chemokines, cytokines, vasoactive amines, eicosanoids, matrix metalloproteinases, nitric oxide, and free radicals. These mediators are involved in several processes, such as pain induction, immune modulation, and tissue repair. The target tissues affected by these mediators show responses such as increased vascular permeability,

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immune cell recruitment, and either tissue damage or repair. If this process is dysregulated, it may lead to chronic inflammation and associated disorders [65].

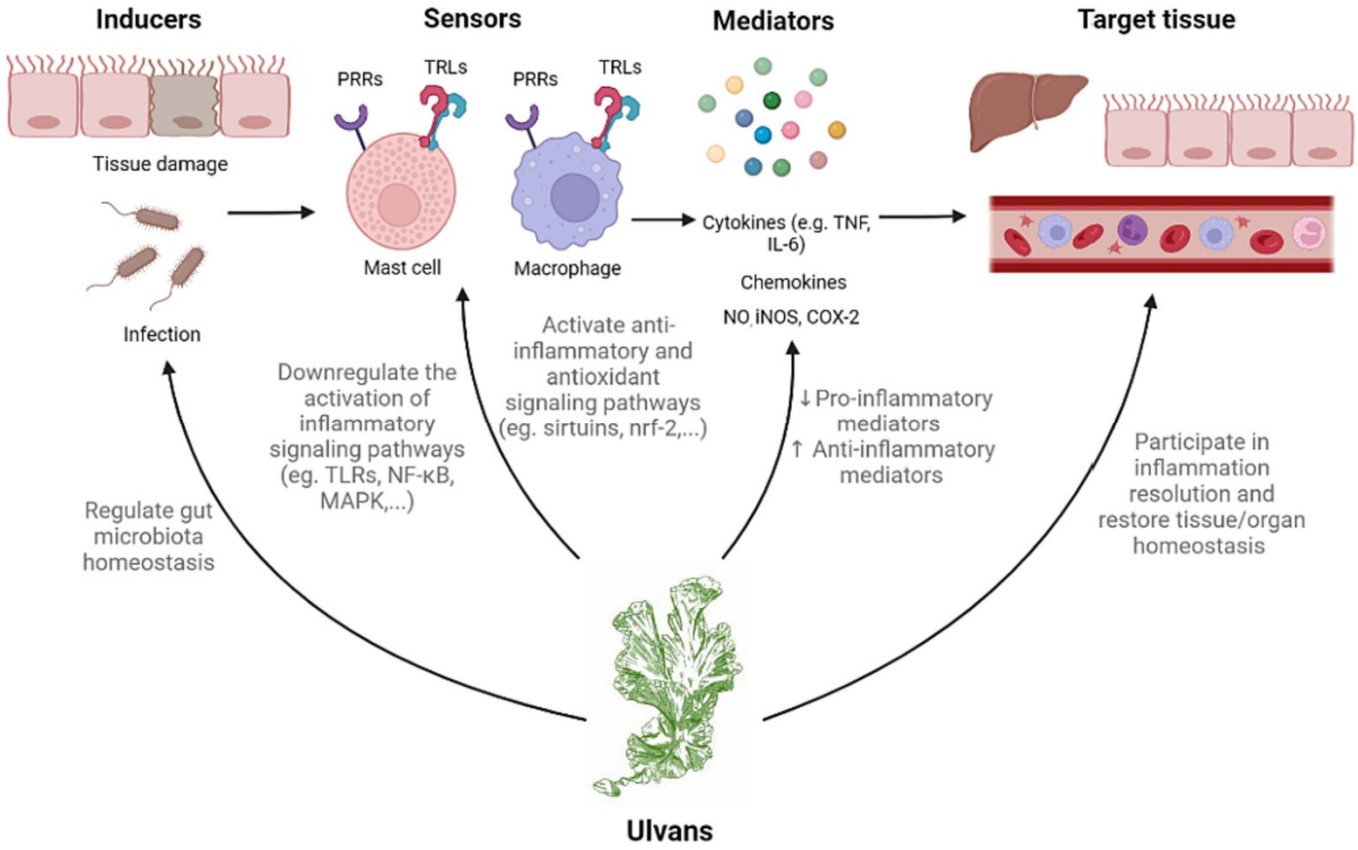

Figure 4. The Role of Ulvans in Modulating Inflammatory Pathways. Reproduced from Flórez-Fernández et al. [99] with permission. Copyright (2023) Elsevier.

Ulvans function as immunomodulatory agents through various mechanisms that influence the immune system, including the suppression of pro-inflammatory cytokine production, modulation of the NF-κB pathway, enhancement of anti-inflammatory cytokines, regulation of TLR signaling, and restoration of gut microbiota balance (Figure 4). The immunostimulatory properties of ulvan are largely determined by its structural features, such as monosaccharide composition, sulfate content, and molecular weight, as discussed by Kidgell (2019) [36]. One of the key mechanisms of ulvans is the regulation of cytokine production, particularly pro-inflammatory cytokines that are crucial in immune responses. Cytokines like TNF-α, IL-6, and IL-1β, which are commonly elevated in inflammatory conditions such as inflammatory bowel diseases (IBD) [100], can be modulated by ulvans. Additionally, ulvans regulate intestinal inflammation by inhibiting the NF-κB pathway. Ali et al. (2016) [101] demonstrated that ulvan from *U. pertusa* COMP reduces the production of pro-inflammatory cytokines (IL-12, p40, IL-6, TNF-α) by preventing the phosphorylation of IκBα, which inhibits its degradation and the nuclear translocation of NF-κB. This action suppresses the expression of inflammatory genes and helps maintain immune homeostasis.

Ulvans enhance the production of anti-inflammatory cytokines, such as IL-10. This cytokine is vital for suppressing inflammatory responses and promoting tissue repair. By increasing IL-10 levels, ulvans counteract the effects of pro-inflammatory cytokines, further contributing to an anti-inflammatory state [102,103]. Ulvans also play a role in regulating TLR signaling pathways, particularly TLR4. By modulating these pathways, ulvans can inhibit the activation of downstream inflammatory responses, including those mediated by NF-κB and MAPK pathways. This regulation is essential for preventing excessive immune activation and inflammation [102].

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The immunomodulatory effects of ulvan are partly attributed to its capacity to alter the gut microbiota. The gut microbiome plays a key role in immune system regulation, and ulvan's prebiotic properties support the growth of beneficial microbes, enhancing immune function and controlling inflammation [103–106]. Ulvans influence the gut microbiota by promoting beneficial bacteria and regulating immune responses, which is essential for gut health and preventing inflammation-related disorders. By restoring microbiota balance, ulvans help maintain immune homeostasis, promoting beneficial bacteria and suppressing harmful ones, which is important for preventing dysbiosis and reducing inflammation [107,108].

3.3. Anticoagulation Activity

Anticoagulant activity is a vital characteristic of biomaterials used in medical applications, especially those that come into direct contact with blood. This property ensures biocompatibility, functionality, and safety by preventing blood clot formation (thrombosis), minimizing inflammation, and maintaining proper blood flow, which collectively improve patient outcomes and extend the lifespan of medical devices [109]. The anticoagulant potential of a molecule is typically assessed through three primary tests: activated partial thromboplastin time, thrombin time, and prothrombin time. These tests evaluate how the material influences various pathways in the coagulation cascade, providing critical information about its hemocompatibility.

Studies have indicated that ulvan, a polysaccharide derived from various species of the seaweed genus *Ulva*, exhibits anticoagulant effects. Key species include *U. clathrata* [110], *U. lactuca* [111,112], *U. prolifera* [113], *U. fasciata* [112,114], *U. nematoidea* [115], *U. conglobata* [116], *U. linza* [117,118], and *U. reticulata* [112]. The anticoagulant potency of ulvan differs across species and is influenced by environmental and physiological factors. The anticoagulant activity of ulvan depends on the degree of sulfation and molecular weight, both of which are critical to its effectiveness [115–118]. Higher sulfation enhances its activity, while molecular weights below 200 kDa can diminish it [115].

Regarding its mechanism of action, ulvan primarily affects the intrinsic and/or common pathways of the coagulation cascade. The intrinsic pathway is triggered by the interaction of Factor XII with an anionic surface, while the extrinsic pathway is initiated when Factor VII binds to tissue factor, a receptor released from damaged cells. Both pathways converge at Factor X, activating the common pathway, which leads to the conversion of prothrombin into thrombin. Thrombin then catalyzes the transformation of soluble fibrinogen into insoluble fibrin, forming the structural framework of a clot [119].

3.4. Antimicrobial Activity

Antimicrobial activity is a crucial characteristic of biomaterials, particularly those used in medical applications, as it significantly enhances their safety and functionality. It helps prevent infections by reducing microbial colonization on the material's surface, which is especially vital for implants, wound dressings, and other medical devices. Additionally, antimicrobial properties protect biomaterials from degradation caused by microbial activity, thereby prolonging their lifespan and maintaining their performance [120].

Ulvan has been studied for its ability to combat various harmful microorganisms. Van Tran et al. [121] were the pioneers in demonstrating the antimicrobial properties of ulvan derived from *U. reticulata*, showing significant inhibitory effects against two pathogenic bacteria linked to skin diseases and inflammation. They reported inhibition zones of 20 mm against *Enterobacter cloacae* and 18 mm against *Escherichia coli*. Fournière et al. [122] also documented the biological activity of ulvan extracts from *Ulva* species against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Cutibacterium acnes*. In addition, Ibrahim et al. [123] emphasized the potent antimicrobial effects of partially purified ulvan from *U. lactuca* against certain fish and human pathogens, including *E. coli* ATCC 8739 and *C. albicans* ATCC 10,231. However, ulvan showed no antimicrobial activity against two Gram-positive bacteria (*S. aureus* ATCC 25,923 and *L. monocytogenes* ATCC 35,152), a Gram-negative bacterium (*B. pertussis* ATCC 8467), or fungal pathogens (*A. niger*, *P. notatum*, and *F. solani*). The antimicrobial

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effects of ulvan are attributed to its distinctive chemical structure, which is composed mainly of rhamnose, uronic acid, and sulfate groups [121].

4. Ulvan in Biomaterial Design

Due to its unique structural and functional properties, ulvan exhibits significant potential across fields. The unique structure come from its β-(1,4) backbone is composed of alternating glucuronic acid (GlcA) and rhamnose (Rha) units, which are often modified by varying patterns of sulfation. These sulfate groups are crucial because they enable intermolecular interactions, such as hydrogen bonding and electrostatic forces, which are essential for gelation [124]. Additionally, ulvan contains carboxyl groups that serve as active sites for synthesizing complexes with other molecules, further expanding its functional versatility. The natural origin of ulvan as a renewable and sustainable material further enhances its relevance in environmentally friendly biomaterial design.

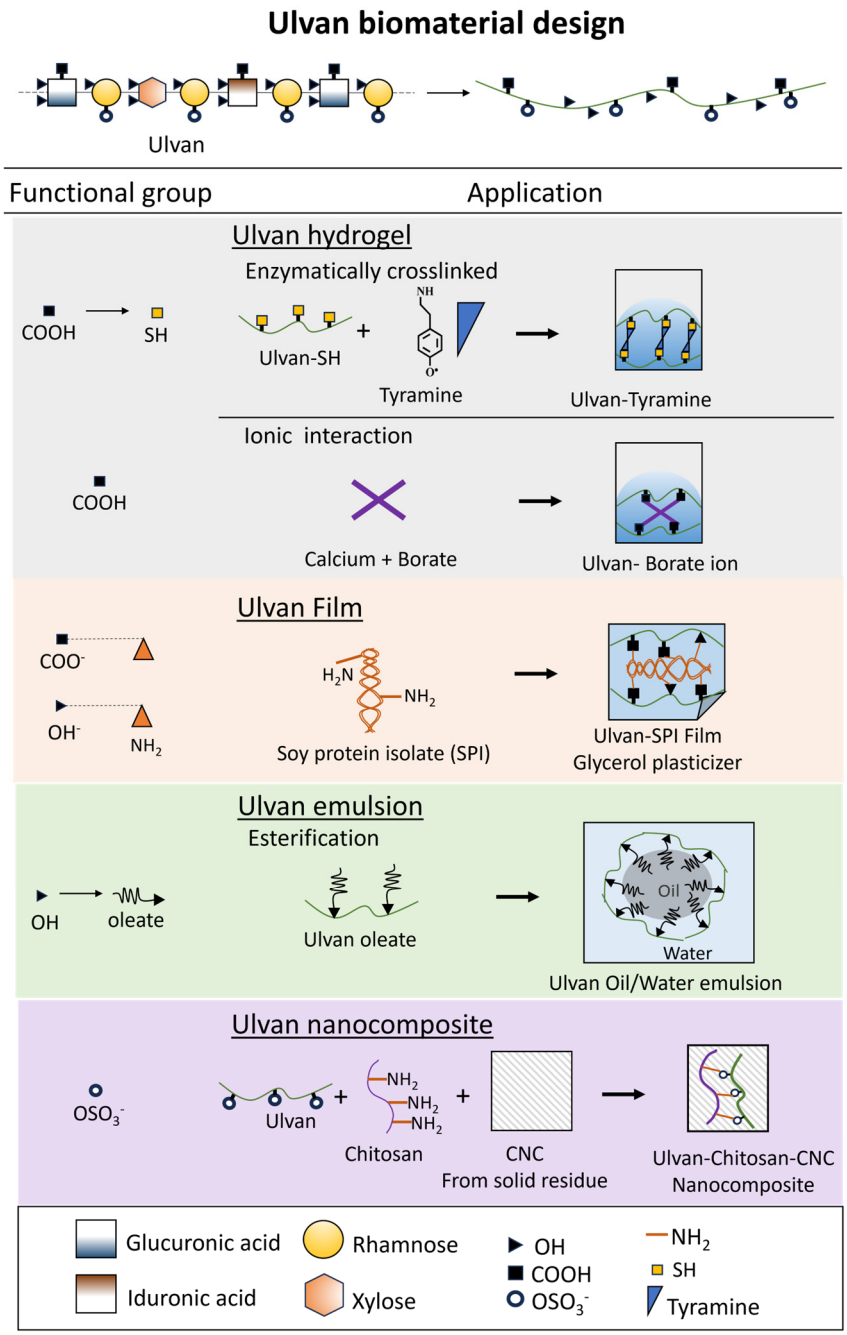

Figure 5. Illustration of ulvan biomaterial design strategy for hydrogel, film, emulsion and nanocomposite.

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Ulvan has the remarkable ability to transform liquids into semi-solid gels by forming network structures. This process occurs through hydrogen bonding, ionic interactions, or hydrophobic interactions. These properties make ulvan highly valuable in the food, cosmetics, and pharmaceutical industries, where it is used to improve the texture, stability, and consistency of products. We will discuss the ulvan in hydrogel, film, emulsion, and nanocomposite (Figure 5).

4.1. Ulvan-Based Hydrogel

Ulvan's carboxyl and sulfate groups play a pivotal role in its ability to form hydrogels through various crosslinking methods. One such method involves oxidizing ulvan with sodium periodate, which introduces aldehyde groups along the polysaccharide backbone [125]. These aldehyde groups react with gelatine's amine groups through Schiff-base reactions, forming covalent imine bonds. The Schiff-base reaction occurs when the aldehyde groups (−CHO) in ulvan dialdehyde interact with the primary amine groups (−NH2) in lysine residues of gelatine, resulting in stable C=N bonds [126]. Using phosphate-buffered saline (PBS), hydrogels with 80% gelatine and 20% ulvan showed the lowest swelling capacity (300%), while hydrogels with 40% gelatine and 60% ulvan reached the highest swelling capacity (900%). When deionized water was used, swelling capacity increased significantly, with 80% gelatine and 20% ulvan samples showing 1000% swelling, and 40% gelatine and 60% ulvan samples exhibiting an extraordinary swelling capacity of 2400% [50]. These results demonstrate the tunable properties of ulvan-based hydrogels depending on solvent composition and polymer ratios. This interaction not only creates a robust hydrogel network but also enhances its binding capacity for dyes and heavy metal ions, utilizing the free amine groups from gelatine and carboxyl groups in ulvan [45]. The Schiff-base strategy involving gelatin matrices is applicable for tissue engineering application [127] and bone tissue engineering [128].

Another advanced approach uses enzymatic crosslinking with horseradish peroxidase (HRP) and hydroxyphenyl compounds such as tyramine. Hydroxyphenyl compounds are particularly suitable substrates for HRP due to their reactivity in green chemistry processes [129]. Tyramine is the most commonly used hydroxyphenyl compound in enzymatic gelling systems, offering a safe profile and efficient conjugation via its terminal amine group [130]. In this system, ulvan-tetrahydroxyphenyl (UT) conjugates are synthesized by forming amide bonds between the carboxyl group of ulvan and the amine group of tyramine, facilitated by carbodiimide chemistry [131]. The carboxyl groups are first activated by reacting with EDC and sulfo-NHS in a slightly acidic environment, creating reactive sulfo-NHS esters optimized for polymer bonding. In the presence of hydrogen peroxide (H_2O_2), HRP catalyzes the oxidative coupling of hydroxyphenyl compounds through a radical mechanism [130]. Covalent bonds form between carbon atoms in the ortho position to the hydroxyl or oxygen atoms of phenol groups, creating a stable crosslinked network. These enzymatically crosslinked hydrogels achieve swelling degrees of approximately 2000%, classifying them as superabsorbent materials [128]. The enzymatic and H_2O_2 conditions can be adjusted to optimize gelation times for applications such as injectable hydrogels [132].

Ulvan's gelling potential is also being explored in the development of bioinks for 3D printing applications. A bio-ionic liquid derived from ulvan is formulated by mixing it with choline chloride and subjecting it to ethanol precipitation. This process results in a material with excellent viscoelastic strength, making it an ideal candidate for use in advanced 3D bioink formulations [53]. More details on its biocompatibility and specific cell interaction performance would further solidify its relevance in biomedical applications.

The exploration of ulvan hydrogels extends to food applications. When formulated with alginate, ulvan forms a scaffold suitable for probiotic encapsulation. While alginate is widely used as a scaffold for nutrient encapsulation [133] , it has limitations when applied to systems involving living organisms. In contrast, ulvan demonstrates strong prebiotic activity and supports cell proliferation [134] , effectively addressing alginate's limitations in microbial encapsulation. Ulvan-alginate hydrogel beads for probiotic immobilization have been shown to enhance the survival rate of

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probiotics in both simulated gastric and intestinal fluids [135] . This system offers significant potential for applications in the food and beverage industry.

4.2. Ulvan-Based Film

Ulvan-based film formulations utilize glycerol as a plasticizer to create hydrophilic films. These films are typically composed of ulvan, glycerol, distilled water, and boric acid. To enhance the material's characteristics, 10% carnauba wax and Tween-80 can be added, resulting in hydrophobic films ideal for food packaging. These hydrophobic films demonstrate impressive mechanical properties, with an average tensile strength of 1 MPa and an average elongation at break of 80% [56]. Further comparisons with conventional gelling agents could provide insight into ulvan's superior performance and sustainability.

4.3. Ulvan-Based Nanocomposite

Hybrid hydrogels that incorporate ulvan exhibit enhanced mechanical and functional properties. For instance, ulvan crosslinked with citric acid and hybridized with sodium carboxymethyl cellulose (Na-CMC) achieves a swelling degree of up to 387.5%, highlighting its improved mechanical stability. This hybrid hydrogel is synthesized using a single-pot heating method, where a fixed citric acid concentration of 20 wt% is used to crosslink ulvan and Na-CMC. The simplicity of this process enhances its applicability in scalable production methods. Comparatively, ulvan hydrogels without Na-CMC show a swelling capacity of 248.7%, demonstrating that hybridization significantly improves performance. [54]

Comprehensive utilization of Ulva is further demonstrated by Mariia et al. [136]. Ulvan is reacted with chitosan to form polyelectrolyte complexes involving anionic and cationic side chain interactions. The sulfate groups in ulvan carry a negative charge (anionic), while the amine groups in chitosan are positively charged (cationic). Combining chitosan/ulvan with cellulose nanocrystals (CNCs), extracted from the solid residue of ulvan extraction, results in nano-bio composite hydrogels designed for wound healing applications. Chitosan hydrogels incorporating 20% CNC show enhanced tensile strength of 1.2 MPa and a significant increase in swelling capacity, indicating improved mechanical properties. Furthermore, these nanocomposites exhibit excellent cell proliferation, remarkable biocompatibility, and non-toxicity. The sustained release of epidermal growth factors from these hydrogels accelerates wound healing, demonstrating their advanced therapeutic potential.

Further advancements in ulvan research include ulvan hybrid with carrageenan and polyvinyl alcohol (PVA). For ulvan hybrid carrageenan, the synthesis of ulvan-amide derivatives through carbodiimide chemistry. These derivatives enable the creation of ulvan-kappa-carrabiose hybrid polysaccharides, expanding the scope of ulvan-based materials [137]. For ulvan nanofiber fabrication with PVA, ulvan-polyvinyl alcohol (PVA) nanofibers, produced via electrospinning with a 1:2 ulvan/PVA ratio, demonstrate promising potential for advanced material applications, including biomedical and environmental uses [125]. Specific examples of these applications, such as filtration membranes or antimicrobial coatings, would add depth.

4.4. Ulvan-Based Emulsion

A detailed evaluation of ulvan highlights its significant potential in various industries, especially within food and cosmetic formulations. Ulvan's capacity to hold water and oil, quantified at 3.17 g water/g ulvan and 2.66 g oil/g ulvan respectively [45], makes it particularly useful for stabilizing emulsified products. This capability helps prevent liquid separation (syneresis) while enhancing viscosity and texture, ensuring consistency in complex formulations [138].

In emulsified systems, increasing ulvan concentrations from 1 % to 3 % enhances both emulsion activity and stability. At its peak concentration of 3 %, ulvan achieves an emulsion activity index of 69.66 m^2/g and a stability of 72.39 % [45]. While polysaccharides are typically recognized for their

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stabilizing rather than emulsifying roles, ulvan stands out due to its surface-active functional groups, such as carboxyl, sulfate, and hydroxyl, as well as hydrophobic protein-like elements [139]. The molecular structure of ulvan, which includes a high molecular weight and glucuronic acid content, significantly bolsters its ability to form stable emulsions by increasing solution viscosity and strengthening interfacial layers [140].

Ulvan also exhibits excellent foaming capabilities, achieving a foaming capacity of 75 % and a stability of 54 % at 3 % concentration [45]. These properties are crucial for developing consistent and appealing textures in food and cosmetic products [140]. As ulvan concentrations increase, its ability to stabilize foam improves, largely due to its high molecular weight. This allows it to create robust networks at the air-water interface, effectively delaying the merging of gas bubbles and prolonging foam integrity. Such characteristics are highly beneficial for applications in whipped desserts, aerated beverages, and cosmetic mousses, where stable foam structures are essential [139,140].

5. Comparative Advantages of Ulvan

One of the key advantages of ulvan is its potentially high yield due to the high and robust biomass of *Ulva* species, which can outperform other seaweed sources such as agar, carrageenan, alginate, laminaran, fucoidan, porphyran, floridean, and xylofucoglycan [141]. As mentioned in the previous section, ulvan extracted from *Ulva* is derived from an undesired seaweed, which can be produced 7 – 10 times faster and in higher quantities than other commercially available seaweed biomass in the current seaweed industry. This characteristic ensures a sustainable production pipeline, addressing scalability issues that often limit other polysaccharides.

The extraction of ulvan is also reported to be relatively easy and simple, making it a more accessible and cost-effective option compared to other marine polysaccharides. Compared to other marine polysaccharides, ulvan demonstrates superior yield potential, with up to ~41 % extraction efficiency from dry *Ulva* biomass [56,142]. This is higher than the yields typically reported for agar (10 – 15 %) or fucoidan (5 – 10 %). The ability of *Ulva* species to proliferate in eutrophic environments further enhances its suitability for large-scale production, reducing reliance on pristine ecosystems required for agarophytes or carrageenophytes. Chemically, with ulvan's unique properties, stands as an equally competitive seaweed polysaccharide alongside others such as agar, carrageenan, alginate, laminaran, fucoidan, porphyran, floridean starch, and xylofucoglycan, offering distinct advantages in yield, functionality, and bioactivity.

Notably, unlike agar or carrageenan, which require heat for gel formation, ulvan can form gels under non-thermal conditions through ionic cross-linking with $CaCl_2$ and H_3BO_3 [143]. This characteristic could position it as a potential alternative to alginate, a widely used marine polysaccharide This property is advantageous for applications requiring cold processing, such as in the pharmaceutical and food industries. For instance, ulvan-based hydrogels can encapsulate heat-sensitive bioactives, a limitation for thermally reliant gelling agents. Furthermore, the high sulfate content of ulvan has garnered interest in the biomedical field, as it may confer anticoagulant properties, similar to heparin, leading to it being referred to as the "vegan heparin" [144]. Compared to other seaweed polysaccharides, ulvan has also demonstrated versatility in its bioactive compounds, exhibiting a range of beneficial properties, such as antioxidant, immunomodulatory, anticancer, and antimicrobial activities [141,145]. The richness of sulfated moieties in ulvan's structure also favors its potential for engineering and modification, opening up opportunities for the development of innovative polymeric materials and applications [146]. The comprehensive comparison between ulvan and other marines' polysaccharide shows in Table 2.

Table 2. Comparison of chemical modifications, gelling mechanisms, yield, and applications in biomaterial design of marine polysaccharides.

Polysac-charide	Source Algae	Yield Range (%)	Gelling Mechanism	Existing Function in Current Market	Commercial Availability	Mechanical Properties	Cytocom-patibility	Thermal Stability	Cross-Linking Potential	Functionalization Potential	Common Modifications	Applications of Modifications	Challenges in Modifications
Ulvan	*Ulva* spp.	15-41	Ionic cross-linking with divalent cations (e.g., Ca2+; $CaCl_2$, H_3BO_3)	Emerging in tissue engineering, drug delivery, and bioadhesive development	Moderate, requires specialized extraction processes	Moderate elasticity, suitable for hydrogels	Excellent, supports cell adhesion and proliferation	Moderate, stable up to ~80°C under physiological conditions	High, forms strong ionic cross-links	High, easily modified with bioactive groups	Thiolated ulvan, sulfation, carboxymethylation, phosphorylation, hydrogel formation	Drug delivery, tissue engineering, bioadhesive development, antioxidant systems	Complexity in achieving uniform thiolation, scalability issues
Agar	*Gelidium* spp.	10-15	Thermal gelation via hydrogen bonding	Widely used in food industry (gels, thickeners), limited biomedical applications	High, widely available and established supply chain	Strong, brittle gels, limited elasticity	Good, limited applications in biomedical fields	High, retains gel pro-perties up to ~100°C	Moderate, limited chemical reactivity	Moderate, limited functionalization pathways	Thiolated agar, esterification, hydrogel formation, nanoparticle stabilization	Encapsulation, tissue scaffolding, bioadhesives, wound dressings	Low reactivity under mild conditions, batch variability
Carra-geenan	*Kappa-phycus* spp.	20-30	Thermal gelation via sulfate groups. Helical structures formed via 3,6-anhydro-galactose units and ion interactions	Predominantly in food as stabilizers and thickeners, some drug delivery systems	High, commercially available for various industries	Flexible gels, moderate strength	Moderate, may require modifications for biocompa-tibility	High, stable up to ~120°C	High, versatile cross-linking potential	High, supports diverse chemical modifications	Sulfation, hydrogel formation, derivatization for drug delivery	Drug release matrices, bioadhesive, biocompatible scaffolds	Control over sulfation levels, stability in physiological conditions
Alginate	*Macrocystis* spp.	15-35	Ionic cross-linking with Ca2+ or other divalent ions	Extensively in food, pharmaceuticals, and wound care products	High, extensively used and widely produced	High elasticity, robust structural integrity	Excellent, widely used in tissue engineering	High, stable across wide temperature ranges (~150°C)	High, readily cross-links with divalent ions	High, extensively modified for various uses	Calcium cross-linking, thiolation, carboxylation, hydrogel formation, esterification	Controlled release systems, wound care, tissue scaffolding	High dependency on cross-linking agents, cost of modification processes

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Polysac-charide	Source Algae	Yield Range (%)	Gelling Mechanism	Existing Function in Current Market	Commercial Availability	Mechanical Properties	Cytocom-patibility	Thermal Stability	Cross-Linking Potential	Functionalization Potential	Common Modifications	Applications of Modifications	Challenges in Modifications
Fucoidan	*Fucus* spp.	5-10	Not a primary gelling agent, interacts through sulfated domains	Limited use in niche biomedical applications (anticoagulants, drug carriers)	Low, niche market with limited availability	Weak mechanical properties, limited application	Variable, dependent on sulfation level	Moderate, sensitive to heat above ~70°C	Low, limited cross-linking capability	Moderate, functionalization depends on sulfate groups	Sulfation, desulfation, acetylation, hydrogel formation, anti-coagulant enhancement	Anti-inflammatory agents, drug carriers, heparin substitutes	Variability in biological activity, cost-intensive extraction and modification
Laminaran	*Laminaria* spp.	10-20	Weak hydrogen bonding and limited gel formation	Occasionally in nutraceuticals and research-grade biomaterials	Low, specialized production with limited supply	Low mechanical strength, not primary gelling agent	Moderate, limited data on cytocompatibility	Low, weak stability under heat, <60°C	Low, rarely used for cross-linking	Low, not typically functionalized extensively	Oxidation, acetylation, hydrogel formation, nanoparticle delivery systems	Nanoparticle stabilizers, immune enhancement, tissue scaffolds	Low stability under physiological conditions, complex modification processes
Porphyran	*Porphyra* spp.	10-15	Thermal gelation and hydrogen bonding	Emerging in antioxidant-rich supplements and basic drug delivery systems	Moderate, emerging commercial interest	Moderate strength, suitable for soft applications	Good, supports basic biomedical applications	Moderate, stable under mild thermal conditions (~80°C)	Moderate, potential for chemical derivatization	Moderate, supports basic functionalization	Sulfation, esterification, hydrogel formation, antioxidant enhancement	Antioxidant applications, drug delivery, immune modulation	Limited structural studies, stability in industrial applications

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Despite potential of ulvan discussed in the previous chapter, it faces certain challenges that could hinder its broader adoption in commercial and industrial needed. Key limitations include:

Extraction Complexity and Standardization. The extraction process for ulvan remains less standardized compared to traditional polysaccharides like agar or carrageenan. Variability in the chemical composition of Ulva biomass due to environmental factors affects the consistency and quality of ulvan. Green solvent and enzyme-assisted methods show promise for improving efficiency but require further optimization for industrial scalability.

Seasonal Yield Variability. Currently, most Ulva cultivation occurs in wild or semi-wild conditions, where environmental factors such as temperature, nutrient availability, and seasonal variations significantly affect the yield and quality of ulvan. This lack of controlled cultivation introduces variability and limits the scalability of ulvan production.

Functional Limitations. Although ulvan exhibits excellent gelling and bioactive properties, its mechanical strength in hydrogels is often lower compared to alginate or carrageenan. This limitation restricts its use in applications demanding high structural integrity, such as wound dressings or load-bearing scaffolds in tissue engineering.

Processing Costs. Specialized extraction methods, including green solvents and enzymatic approaches, increase production costs. The absence of well-established infrastructure for ulvan processing further compounds this issue, making it less competitive than agar or alginate in certain markets.

Future Directions. To overcome these limitations, research efforts should focus on:

- Enhanced Extraction Techniques: Developing cost-effective, standardized methods for high-purity ulvan production.
- Cross-Linking Strategies: Enhancing mechanical properties of ulvan-based materials through innovative cross-linking and composite formation.
- Sustainability Metrics: Incorporating life cycle assessments to establish ulvan as a green alternative to synthetic and traditional polysaccharides.
- Controlled Cultivation: Advancing aquaculture techniques for Ulva species to ensure stable and high-quality ulvan yields independent of seasonal and environmental variations.
- Establishing high-quality ulvan standards depends on its intended use, whether as feed, a food source, or a bioactive compound in the biomedical field.

By addressing these challenges, ulvan has the potential to surpass its current limitations and establish itself as a cornerstone versatile material in biomaterial science and industrial applications.

Lastly, the evaluation of Ulvan as a biomaterial emphasizes its potential across three key strategies: Bioactive Ingredient, Scaffold-Backbone Design and Dual Function Synergetic (Figure 6). While substantial progress has been made, critical gaps remain in integrated functionality, mechanical property optimization, and encapsulation stability. Addressing these challenges could unlock transformative applications for Ulvan in biomaterial design, particularly in biomedical and industrial fields.

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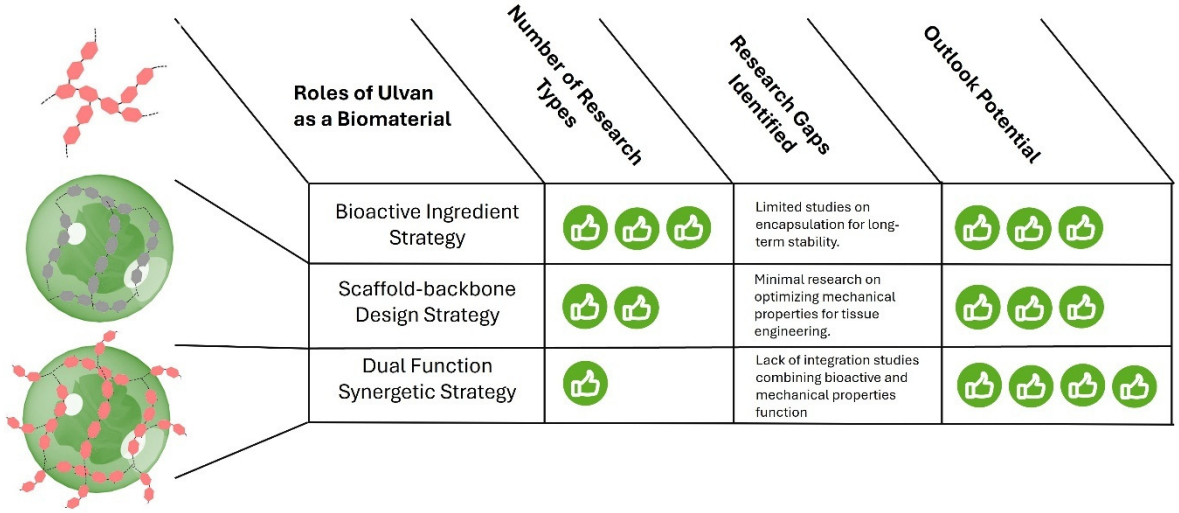

Figure 6. Summary of the roles of ulvan as a biomaterial and its rationale for outlook biomaterial design.

6. Conclusion

Ulva provide the potent as the versatile new generation of seaweed that more robust and sustainable. The cultivation of *Ulva* offers environmental benefits, including high carbon sequestration, rapid growth, and low resource requirements. Integrated green biorefinery of *Ulva* approaches enhance its polysaccharide extraction efficiency of ulvan as the main sugar. It enables the recovery of valuable co-products such as pigments, proteins, and cellulose, boosting sustainability. Ulvan's superior yield and scalability compared to other marine polysaccharides position it as an economically viable alternative.

Ulvan, a sulfated polysaccharide derived from *Ulva* seaweed, is a promising biomaterial due to its unique structure and exceptional bioactive properties, including immunomodulation, anticoagulant activity, antimicrobial effects, and biocompatibility. Its ability to form hydrogels, films, scaffolds, and nanocomposites makes it valuable for biomedical, food, and environmental applications. Unlike traditional polysaccharides, ulvan's non-thermal gelation and high sulfate content provide advantages for preserving heat-sensitive bioactives and mimicking heparin-like anticoagulant properties.

Despite its potential, challenges in extraction optimization and impurity management remain. Advancing green extraction methods and exploring innovative applications will unlock ulvan's full potential. With its sustainability, versatility, and scalability, ulvan is poised to play a vital role in advancing biomaterial design and addressing global challenges in healthcare, food security, and environmental sustainability.

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Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

DGR	Daily growth rate
MWCO	Molecular weight cut-off
SEC	Size Exclusion Chromatography
IPEC-1	porcine intestinal epithelial cells
TNF- α	tumor necrosis factor-alpha
IL	Interleukin
CXCL	C-X-C motif chemokine ligand
IgM	Immunoglobulin M
COX-2	Cyclooxygenase-2
iNOS-2	inducible nitric oxide synthase-2
NF-κB	nuclear factor kappa-B
MAPK	Mitogen-activated protein kinase
TLR	Toll-like receptors
HRP	Horseradish peroxidase
Na-CMC	Sodium carboxymethyl cellulose
CNC	Cellulose nanocrystals
PVA	Polyvinyl alcohol

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