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RESEARCH ARTICLE

Ulvan: A Comprehensive Review of Extraction, Structure, Biological Activities, and Applications in Food and Biomedicine

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Abstract: Marine green macroalgae of the genus Ulva (Chlorophyta) have gained increasing scientific interest due to their high nutritional profile and abundance of biologically active constituents. Among these, ulvan—a sulfated polysaccharide predominantly found in the cell walls of Ulva species—represents the principal water-soluble dietary fiber with extensive pharmacological relevance. Ulvan is recognized for its multifaceted bioactivities, including immunomodulatory, antioxidant, antiviral, anticancer, and antihyperlipidemic effects. These biological functions are largely attributed to its unique structural features, such as sulfate content, monosaccharide composition, and molecular conformation, which enable interactions with diverse molecular targets and modulation of cellular signaling pathways across plant and animal systems. In addition to its health-promoting properties, ulvan contributes significantly to gastrointestinal health by enhancing fiber intake, thereby playing a preventive role against chronic diseases such as cardiovascular disorders and metabolic syndromes. Owing to its broad bioactivity and favorable physicochemical characteristics, ulvan is considered a promising candidate for applications in nutraceuticals, pharmaceutical formulations, agricultural biostimulants, and sustainable biomaterials. This review presents a comprehensive analysis of recent advancements in extraction and purification strategies for ulvan, emphasizing the utility of acid-assisted methods, membrane filtration techniques, and advanced analytical platforms for profiling sugar composition and molecular weight. Furthermore, the review critically evaluates experimental evidence on the therapeutic and functional potential of ulvan, highlighting its versatility as a biopolymer with significant translational potential across multiple industrial domains.

Keywords: Ulvan, Sulfated Polysaccharides, Bioactivities, Structural Characterization, Bioapplication.

INTRODUCTION

Species of the green macroalgal genus Ulva exhibit rapid growth and high biomass productivity across a wide range of environmental conditions, attributed to their rich biochemical composition.

However, this prolific growth can also lead to environmental challenges, such as the occurrence of “green tides” in coastal regions [1]. Owing to their adaptability and nutrient uptake efficiency, Ulva species have been explored for large-scale cultivation, particularly for use in bioremediation of nutrient-enriched effluents from intensive aquaculture systems. Cultivated Ulva offers the advantage of producing a uniform and high-quality biomass suitable for downstream applications. Among the bioactive compounds derived from Ulva, ulvan—a sulfated polysaccharide located in the cell wall—has gained significant attention.

Ulvan can constitute 9–36% of the dry weight of Ulva biomass and is primarily composed of sulfated rhamnose, uronic acids (glucuronic and iduronic acids), and xylose [2]. In addition to ulvan, Ulva cell walls also contain cellulose, xyloglucan, and glucuronan, which collectively contribute up to 45% of the biomass dry weight. Notably, ulvan is unique among these polysaccharides in containing both rhamnose and iduronic acid [3]. Rhamnose has been linked to bioactivities related to skin regeneration and plant defense responses, while uronic acids and their sulfated derivatives are key components of glycosaminoglycans (GAGs) such as heparin and dermatan sulfate in mammalian systems. Structurally, ulvan resembles GAGs through its repeating disaccharide units of uronic acid and sulfated sugars, suggesting potential roles in modulating similar biological pathways [4].

Due to these structural features, ulvan shows promise for diverse applications, including use in biomaterials (e.g., wound healing, tissue scaffolds), nutraceuticals (e.g., antiviral, antioxidant, immunomodulatory, anticancer, and antihyperlipidemic agents), functional foods, and agriculture, as highlighted in recent reviews. Given that the bioactivity of ulvan is closely tied to its structural properties, it is essential to understand how extraction

and purification methods influence its chemical composition and, consequently, its biological efficacy. This review critically examines the literature on ulvan, focusing on extraction and purification techniques, structural features, and associated bioactivities.

Chemical Structure and Physicochemical Characteristics of Ulvans

Ulvans are complex, sulfated heteropolysaccharides primarily extracted from green macroalgae of the Ulva genus [5]. Their structural variability is shaped by species, environmental conditions, and extraction techniques. The main monosaccharides include L-rhamnose, D-glucuronic acid, L-iduronic acid, and D-xylose, with minor sugars such as D-glucose, D-galactose, D-arabinose, and D-mannose, whose roles remain unclear. Ulvans are composed mainly of alternating α- and β-(1→4)-glycosidic linkages forming repeating disaccharide units, notably ulvanobiuronic acid type A [β-D-glucuronic acid-(1→4)-α-L-rhamnose 3-sulfate], type B [α-L-iduronic acid-(1→4)-α-L-rhamnose 3-sulfate], and ulvanobiose type U [β-D-xylose-(1→4)-α-L-rhamnose 3-sulfate], occasionally sulfated at C-2 of xylose (Figure 1). Although (1→4) linkages predominate, minor (1→2) and (1→3) bonds and limited branching—especially at uronic acid residues—have been observed. Ulvan's conformation in aqueous media is sensitive to pH and ionic strength. At neutral to mildly acidic pH, rhamnose-driven hydrophobic interactions induce a compact, bead-like structure, while salt presence further restricts chain mobility, lowering viscosity. In contrast, alkaline conditions favor chain expansion and intermolecular interactions, enhancing gelation and viscosity [6]. Ulvan typically exhibits a molecular weight between 1 and >2000 kDa and a sulfation degree ranging from 2% to 40%, parameters that significantly affect its solubility, rheology, and bioactivity. Chemical and enzymatic modifications—including depolymerization, selective (de)sulfation, and derivatization of carboxylic acids (e.g., esterification, amidation, reduction)—enable structural tuning. Additionally, covalent cross-linking has been utilized to improve gel strength and mechanical stability, expanding ulvan's utility in biomedical and industrial applications [7].

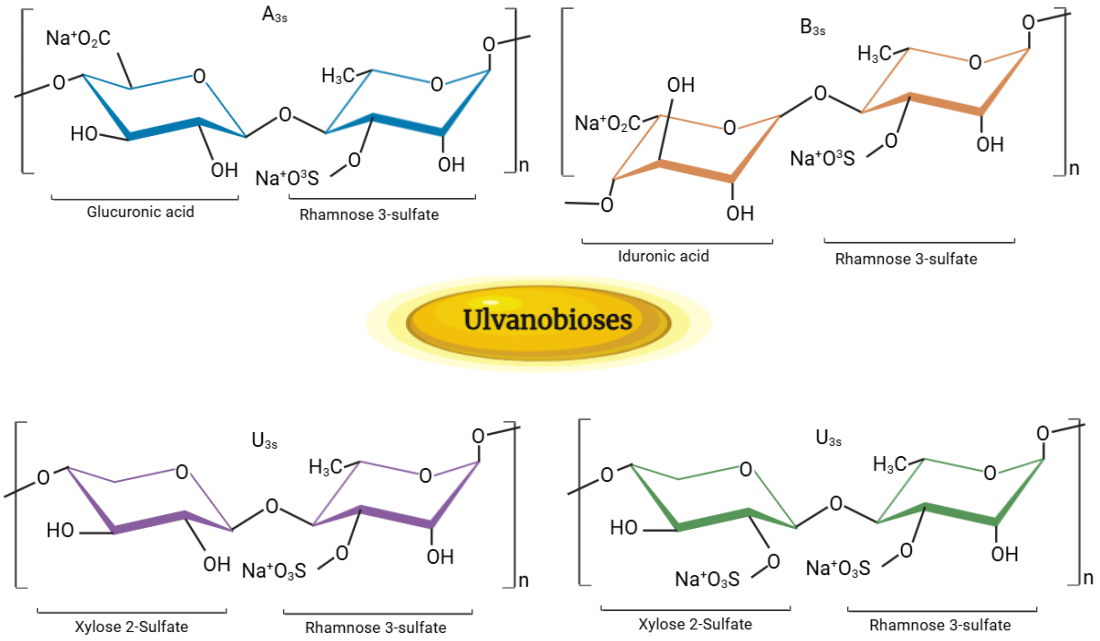

Figure 1. The structures of main disaccharide units in ulvan.

Extraction Strategies for Ulvan

The efficiency and purity of ulvan extraction are influenced by species-specific traits of Ulva, environmental and geographical factors, and biomass handling practices such as storage, milling, and pre-treatment (Figure 2). Its strong association with the cell wall via ionic interactions, hydrogen bonds, and borate diester cross-links limits its aqueous solubility. Hence, extraction protocols are tailored to disrupt these interactions while preserving ulvan's structural integrity. Key factors affecting extraction include particle size, solid-to-liquid ratio, extraction time, temperature, and solvent properties. Ulvan solubility increases under alkaline or mildly acidic conditions due to ionization of sulfate and uronic acid groups. However, solubility is often greater at lower pH due to disaggregation of polymer aggregates. Pre-treatment with warm water enhances extraction by removing salts through osmotic shock, while milling improves solvent accessibility. Acidic solutions, particularly dilute HCl (pH < 3), are effective in breaking ionic cross-links, yielding ulvan with high rhamnose content and minimal protein contamination compared to oxalate-based methods [8]. Protein removal is facilitated near its isoelectric point (pI ≈ 2.25 in Ulva). Nonetheless, harsh conditions can cause depolymerization, compromising biological activity [9]. Optimal extraction should balance yield and structural preservation. Moderate conditions (pH 2.0, 80 °C, 1 h) offer high efficiency with minimal degradation, while severe conditions (pH 1.5, 90 °C, 3 h) significantly reduce

polymer integrity. Recommended parameters for efficient ulvan extraction are temperature 80–90 °C, pH 2.0–4.5, and extraction time of 1–3 h, ensuring optimal yield, selectivity, and minimal structural loss.

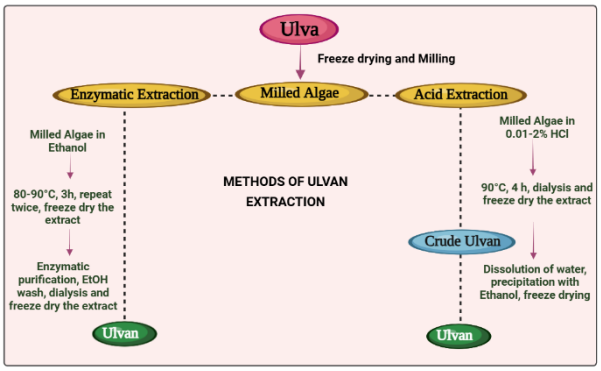

Figure 2. Diagrammatic representation of the extraction process of ulvan from Ulva species.

Isolation and Purification of Ulvan

Ulvan isolation and purification strategies differ based on study objectives and available resources. Isolation refers to separating ulvan from biomass and solvent, while purification removes co-extracted impurities such as salts, pigments, and proteins. These overlapping processes critically influence ulvan's physicochemical and biological properties. Post-extraction, biomass is typically removed by centrifugation or filtration, and the extract is concentrated via evaporation, ultrafiltration, or lyophilisation; spray drying is favored in industrial contexts. Ethanol precipitation (70–96%) is the most common lab-scale method, selectively precipitating ulvan while leaving smaller solutes in solution. However, it may co-precipitate salts or low molecular weight fractions, necessitating desalting to ensure accurate composition analysis. Desalting is commonly achieved through dialysis or ultrafiltration. Dialysis is preferred for analytical-grade samples with low ash content, whereas ultrafiltration—typically involving concentration and diafiltration is more suited for large volumes. Membranes with 3.6–12 kDa MWCO are used, with ~10 kDa offering optimal balance between retention and efficiency [10]. Despite high impurity levels in many extracts, chromatographic methods remain underused. Ulvan's polyanionic nature makes it amenable to anion-exchange chromatography (AEC) and size-exclusion chromatography (SEC). AEC, using DEAE or Q-anion exchangers, effectively removes proteins and neutral polysaccharides, while SEC (e.g., Sepharose CL-6B, Sephacryl S-400/HR, Sephadex G-200) is valuable for molecular weight analysis and bioactive fractionation. The extent of purification required is heavily influenced by the extraction method. Selective extraction reduces the need for intensive purification, although desalting and protein removal remain essential due to ulvan's similarity to co-extracted macromolecules.

Structural Characterization of Ulvan

The structural characterization of ulvan is inherently challenging due to its complex macromolecular nature, which includes diverse monosaccharide residues such as neutral, acidic, and amino sugars heterogeneous sulfation, variable glycosidic linkages, high molecular weight, and branching patterns. Furthermore, aggregation tendencies and contamination with co-extracted polysaccharides can obscure accurate analysis. As a result, the term "structural characterization" is preferred over "structural elucidation," as complete molecular resolution remains difficult to achieve. Accurate physicochemical and biological assessment of ulvan necessitates the use of highly purified samples and a comprehensive suite of analytical methodologies. Initial characterization typically involves determination of total carbohydrate, protein, and ash contents, followed by detailed analysis of monosaccharide composition, glycosidic linkages, and the degree of sulfation. Core sugars include rhamnose, xylose, glucuronic acid, and iduronic acid, with sulfation levels assessed through turbidimetry, ion chromatography, HPLC with conductivity detection, elemental analysis, or FTIR. Quantification of monosaccharides is primarily conducted via chromatographic techniques such as gas chromatography (GC), high-performance liquid chromatography (HPLC), and high-performance anion-exchange chromatography (HPAEC) [11]. Accurate profiling requires complete hydrolysis of ulvan; however, conventional acid hydrolysis methods often fail to cleave resistant aldobiuronic linkages and may degrade sensitive sugars. To address this, a sequential hydrolysis using methanolic HCl followed by aqueous trifluoroacetic acid (TFA) or a chemoenzymatic method incorporating β-D-glucuronidase is preferred. HPLC and HPAEC enable direct analysis of hydrolysates without derivatization, with HPAEC offering superior resolution for detecting neutral, acidic, and amino sugars. In contrast, GC requires monosaccharide derivatization—typically to alditol acetates or trimethylsilyl (TMS) ethers following reduction of the C1-aldehyde group. Uronic acids, which resist conversion to alditol acetates under standard conditions, can be quantified through prior reduction with sodium borodeuteride, producing 6,6′-dideuterio-aldoses for GC–MS analysis. Alternatively, uronic acids can be estimated using colorimetric assays. TMS derivatization enables the detection of both neutral and acidic sugars, although overlapping anomeric forms can complicate chromatograms; this can be mitigated by pre-reduction to alditols prior to derivatization [12]. HPAEC coupled with pulsed amperometric detection (HPAEC-PAD) remains the most comprehensive approach for

monosaccharide profiling. However, HPLC and GC also provide valuable information on hydrolysis efficiency and sugar composition. Beyond compositional data, the analysis of glycosidic linkages and substitution patterns is essential for understanding ulvan's functional properties. Linkage analysis via GC–MS of partially methylated alditol acetates requires prior reduction of uronic acids. Further structural insights including sugar sequence and anomeric configuration are obtained through two-dimensional NMR spectroscopy of oligosaccharide fragments, with characteristic ^{1}H and ^{13}C shifts used to identify repeating units and substitution sites, including sulfate esters. Molecular weight (MW) and molecular weight distribution (MWD) are critical parameters influencing ulvan's bioactivity. These are typically assessed via size-exclusion chromatography (SEC) using detectors such as refractive index (RI) or UV. However, due to the structural disparity between ulvan and conventional calibration standards, accurate MW determination often requires advanced detectors like multi-angle laser light scattering (MALLS) and viscometry, which also provide insight into aggregation behavior and conformational properties. While in-depth characterization is resource-intensive, high-throughput approaches are valuable for routine and industrial-scale applications. Colorimetric assays for uronic acids, rhamnose, xylose, sulfate, and protein content offer rapid screening, though enzymatic assays, while more specific, are less efficient in multiplexed formats. Spectroscopic methods such as FTIR, Raman, NIR, and NMR coupled with chemometric tools (e.g., partial least squares regression) enable rapid, non-destructive profiling of ulvan. Key FTIR absorption bands include regions corresponding to carboxylic acids (1650–1600 and 1425–1400 cm^{-1}), sulfate esters (1260–1215, 850–835, and 795–785 cm^{-1}), and glycosidic linkages (1055–1030 cm^{-1}) [13]. Though still under validation, these spectral methods hold promise for efficient, routine compositional assessment. To ensure clarity regarding ulvan's biological potential, at minimum, analyses should include sugar composition (neutral and acidic), MW and MWD profiling, and contaminant assessment (e.g., proteins and ash).

BIOLOGICAL ACTIVITIES OF ULVAN

Overview

Ulvan, a sulfated polysaccharide from Ulva species, exhibits diverse biological activities in both animal and plant systems. Its structural resemblance to glycosaminoglycans (GAGs) in animals suggests a potential to mimic these molecules, influencing various biological processes. In plants, despite the absence of sulfated polysaccharides, ulvan's similarity to rhamnogalacturonans and rhamnolipids may underlie its bioactivity [14]. Notably, ulvan's bioactivity is influenced by factors such as molecular weight, degree of sulfation, sugar composition, and branching, leading to variability across different Ulva species and environmental conditions. Ulva species are known for their diverse bioactive properties, exhibiting significant anticoagulant, immunomodulatory, anticancer, antioxidant, antiviral, and antihyperlipidemic activities, as highlighted in the table 1. This review focuses on ulvan's potential biomedical applications and its emerging roles in plant physiology, horticulture, and agriculture.

Cytotoxicity and Immunomodulating Activity

Assessing the cytotoxicity of ulvan is crucial for its development as a supplement or therapeutic agent. Studies involving various cell lines including macrophages (e.g., RAW 264.7, J774A.1), gut cells (e.g., IPEC-1), fibroblasts (e.g., L929), and Vero cells, and animal models like Swiss mice and Wistar rats [15] have demonstrated that ulvan is largely non-toxic. For instance, ulvan fractions from species such as *U. pertusa*, *U. intestinalis*, *U. armoricana*, *U. lactuca*, *U. clathrata*, *U. compressa*, and *U. prolifera* have shown >50% cell viability at concentrations ≥500 µg/mL. Ulvan's influence on the immune system has been explored through in vitro studies using macrophage cell lines (e.g., RAW 264.7, J774A.1) [16], tissues like intestinal epithelial cells, and in vivo studies in animal models (e.g., Wistar rats, mice, chickens). Inflammatory responses are mediated by cytokine production, often triggered by the activation of NF-κB via toll-like receptors (TLRs). Ulvan has been observed to modulate this pathway, affecting the expression of various cytokines and enzymes. For example, RAW 264.7 cells treated with ulvan from *U. intestinalis* exhibited increased production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12) and anti-inflammatory cytokine IL-10, along with enzymes like iNOS and COX-2 [17]. This suggests ulvan's potential as a non-specific immunostimulant. However, its immunomodulatory activity varies significantly between studies and species, influenced by factors such as molecular weight and degree of sulfation. Further research is needed to elucidate these structure-activity relationships.

Table 1. Reported bioactive properties of ulva species based on literature evidence.

Ulva Species	Bioactive properties					
	Anticoagulant	Immunomodulation	Anticancer	Antioxidant	Antiviral	Antihyperlipidemic
U. arasakii	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. armoricana	-N/D-	2	-N/D-	1	1	-N/D-
U. clathrata	3	1	-N/D-	-N/D-	1	-N/D-
U. compressa	1	-N/D-	-N/D-	-N/D-	1	-N/D-

U. conglobata	1	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. fasciata	3	2	2	5	-N/D-	3
U. flexuosa	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. gigantea	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. intestinalis	-N/D-	5	4	3	2	1
U. lactuca	3	3	5	10	3	2
U. linza	1	1	-N/D-	3	-N/D-	-N/D-
U. meridionalis	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. nematoidea	1	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. ohnoi	-N/D-	1	-N/D-	-N/D-	-N/D-	-N/D-
U. olivascens	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. pertusa	-N/D-	2	1	4	1	6
U. prolifera	-N/D-	2	1	4	-N/D-	2
U. reticulata	1	-N/D-	1	-N/D-	-N/D-	-N/D-
U. rigida	-N/D-	2	-N/D-	1	-N/D-	1
U. rotundata	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-
U. scandinavica	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-	-N/D-

(-N/D-) indicates information not documented, while numbers from 1 to 10 represent the count of studies or researchers that have reported the respective bioactive properties.

Antioxidant Activity

Ulvan demonstrates antioxidant properties by scavenging reactive oxygen and nitrogen species and enhancing the activity of endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) [18]. In vitro assays, including DPPH radical scavenging and lipid peroxidation inhibition, have shown that ulvan's antioxidant capacity is influenced by its sulfate content and molecular weight (Figure. 3). Chemically oversulfated ulvan exhibits enhanced radical scavenging activity compared to its native form. In vivo studies further reveal that ulvan can reduce oxidative stress markers, such as malondialdehyde (MDA), and boost antioxidant enzyme activities. For instance, ulvan from *U. pertusa* administered to hyperlipidemic mice resulted in decreased MDA levels and increased SOD and CAT activities. These findings suggest that ulvan's antioxidant effects may be mediated through the activation of signaling pathways that regulate antioxidant enzyme expression, though the precise mechanisms require further investigation.

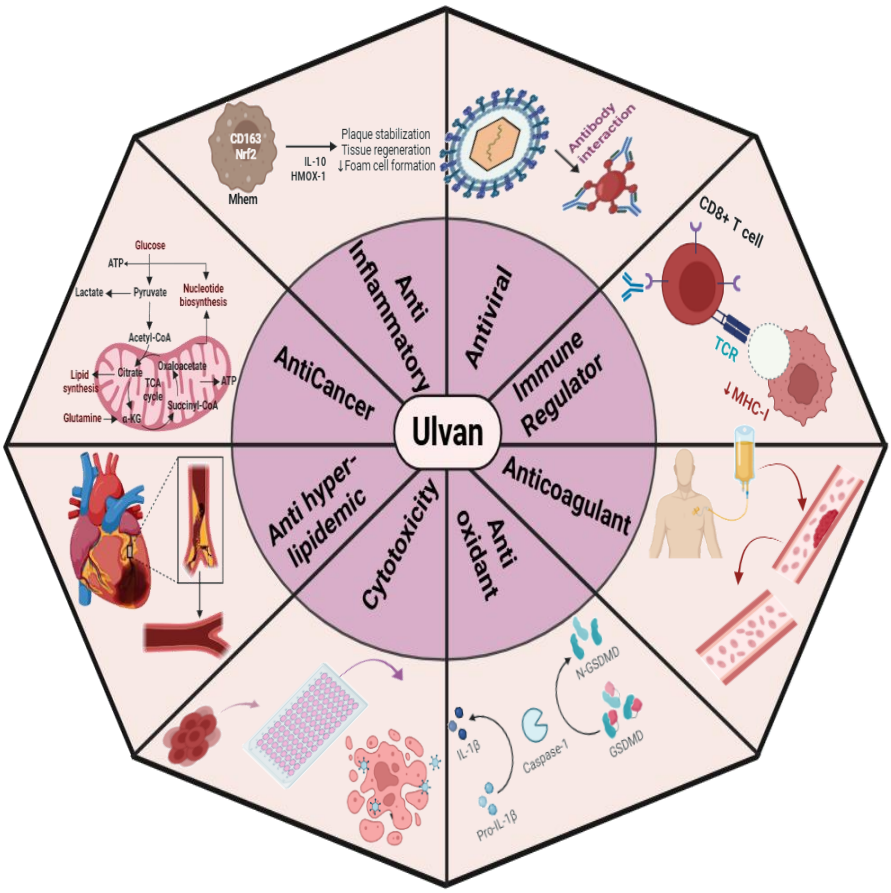

Figure 3. Overview of the biological activities exhibited by ulvan extracted from various Ulva species.

Anticancer Activity

Cancer progression is a multistep process driven by both internal and external factors that induce oxidative DNA damage, leading to mutations and disruptions in cell cycle regulation, differentiation, and apoptosis [19]. Several studies have reported the anticancer potential of ulvan, a sulfated polysaccharide from Ulva spp (Figure. 3)., through its antiproliferative and pro-apoptotic effects on various cancer models. Ulvan derived from *U. lactuca*, *U. intestinalis*, *U. pertusa*, *U. prolifera*, *U. tubulosa*, and *U. fasciata* has demonstrated inhibitory activity against diverse cancer cell lines, including murine sarcoma (S180), hepatocellular carcinoma (HepG2), breast cancer (MCF-7), cervical cancer (HeLa) [20], gastric carcinoma (AGS, MKN45), and colon cancer (HT-29, HCT-116, Caco-2, DLD1) [21]. In vivo studies in rat and mouse models have also confirmed antitumor effects, though no clinical trials have yet been conducted. Notably, ulvan from *U. lactuca* exhibited strong cytotoxic effects at 100 µg/mL, reducing HepG2, MCF-7, and HeLa cell viability to zero. While the exact mechanism remains unclear, upregulation of p53 and downregulation of Bcl-2 indicate apoptosis induction. Additionally, decreased levels of proliferating cell nuclear antigen (PCNA) in rat liver cells suggest reduced DNA synthesis and cell proliferation [22]. However, not all ulvan fractions show high efficacy. For instance, ulvan from *U. prolifera* and *U. intestinalis* demonstrated only mild or negligible cytotoxicity in vitro, with inhibition rates of 10–26% against AGS cells at 200–1000 µg/mL. Despite this, in vivo administration of *U. intestinalis* ulvan significantly reduced tumor burden in mice (61–71% reduction at 100–400 mg/kg), likely through immunostimulatory mechanisms, as indicated by increased spleen and thymus weights. Ulvan's anticancer effects appear to involve multiple pathways, including apoptosis induction, suppression of cell proliferation, and modulation of immune responses. These effects are influenced by the structural characteristics of ulvan, particularly molecular weight and sulfation degree. However, clear structure activity relationships remain to be elucidated. Due to its generally modest cytotoxicity compared to conventional chemotherapeutics, ulvan may serve better as an adjunct agent offering complementary benefits such as antioxidant and immunomodulatory effects. Emerging applications include its use in nanoparticle-based drug delivery systems for poorly soluble anticancer drugs, selenium-polysaccharide protein conjugates, and pH-sensitive nanosystems targeting tumor angiogenesis [23]. Further research is needed to evaluate ulvan's bioavailability and its synergistic potential in combination therapies.

Anticoagulant Activity

The coagulation cascade is regulated via intrinsic and extrinsic pathways, both converging into a final common pathway that leads to thrombin generation and fibrin clot

formation. This process involves sequential activation of clotting factors (e.g., XIII, XII, XI, IX, X, VII), which are primarily serine proteases and glycoproteins. The intrinsic pathway is triggered by the activation of factor XII upon contact with negatively charged surfaces, while the extrinsic pathway is initiated when tissue factor from injured cells binds to factor VII. Both routes culminate in the activation of factor X, which then converts prothrombin into thrombin and fibrinogen into fibrin. Anticoagulant agents may inhibit one or more of these pathways. Ulvan, a sulfated polysaccharide, primarily interferes with the intrinsic and/or common pathways, as demonstrated by several species including *Ulva clathrata*, *U. lactuca*, *U. prolifera*, *U. fasciata*, *U. nematoidea*, *U. conglobata*, *U. linza*, and *Capsosiphon fulvescens* [24]. Anticoagulant potential is typically assessed using activated partial thromboplastin time (aPTT), thrombin time (TT), and prothrombin time (PT) assays, which reveal the pathway specificity of the inhibition. For instance, ulvan from *U. linza* increased aPTT by 3.3–6.2-fold, with activity positively correlated with both degrees of sulfation and molecular weight [25]. A hydrolysed ulvan (MW = 11 kDa, SO_3^- = 20.1%) showed a 63% increase in aPTT compared to its native form (MW = 108 kDa, SO_3^- = 21.3%), and further oversulfation (SO_3^- = 34.4%) enhanced this effect by an additional 20%. Similar trends were noted for TT, while PT effects remained minimal. Notably, enzymatic extraction studies from *U. prolifera* suggested that high sulfation enhances anticoagulant activity, though efficacy declines when molecular weight exceeds ~200 kDa. Overall, the anticoagulant efficacy of ulvan is primarily influenced by its sulfation level and molecular weight. Although its activity is generally lower than that of heparin (approximately 2–40-fold less), ulvan fractions such as that from *U. conglobata* (SO_3^- = 35.2%) achieved a 2.5-fold increase in aPTT at 2 µg/mL, compared to 6.2-fold by heparin at the same concentration. While ulvan does not target all three coagulation pathways, its selective action on the intrinsic pathway which is linked to inflammation, coagulation, and immune modulation suggests potential therapeutic relevance [26]. Species-specific differences and environmental factors further contribute to the structural variability and bioactivity of ulvan.

Antihyperlipidemic Activity

The human lipoprotein transport system regulates lipid metabolism, with VLDL delivering triglycerides to tissues and generating LDL-C, which distributes cholesterol for membrane and hormone synthesis. In contrast, HDL-C removes excess cholesterol to the liver for elimination [27]. Disruption of this system, commonly seen in metabolic syndrome, leads to hyperlipidemia and increases cardiovascular risks. Sulfated polysaccharides from macroalgae, particularly ulvan, have shown promising antihyperlipidemic effects in animal studies, as evidenced by improvements in lipid profiles reducing TC, TG, and LDL-C while elevating HDL-C. The efficacy of ulvan depends on its structural features, especially molecular weight and degree of sulfation. For example, native ulvan from *Ulva pertusa* (151.6 kDa) significantly lowered TC and LDL-C in hyperlipidemic rats, whereas low molecular weight ulvan (28.2 kDa) had minimal effect on cholesterol but markedly reduced TG and increased HDL-C. A higher sulfation degree (40.6%) further enhanced cholesterol reduction compared to native ulvan (22.5% sulfation) [28]. Structural modifications, such as acetylation, also influence lipid-lowering potential, though the interactions between molecular weight and chemical substitution remain under investigation. Mechanistically, ulvan appears to enhance bile acid synthesis from LDL-C, as indicated by increased fecal bile acids, and modulate hepatic gene expression [29]. Polysaccharides from Monostroma nitidum and *U. prolifera* suppressed key genes involved in cholesterol and lipid synthesis (e.g., HMG-CoA reductase, SREBP-1c/2, ACC), while promoting cholesterol catabolism (e.g., CYP7A1) and LDL receptor activity [30]. These regulatory effects may vary depending on ulvan's structure. Additionally, its antioxidant capacity may support lipid regulation by preventing oxidative lipid damage.

Antiviral Activity

Ulvans have demonstrated potential antiviral activity by targeting various stages of viral replication, including entry, replication, and shedding (Figure. 3). Several Ulva species *U. compressa* [199,266*]*, *U. lactuca*, *U. clathrata*, *U. intestinalis*, *U. armoricana*, and *U. pertusa* have shown inhibitory effects against a range of enveloped viruses, such as herpes simplex virus (HSV), Newcastle disease virus (NDV), Japanese encephalitis virus (JEV), dengue virus (DENV), yellow fever virus (YFV), and West Nile virus (WNV), as well as influenza A (H1N1), avian influenza virus (AIV-H9N2), and measles virus (MeV). Antiviral assessments have been conducted using various in vitro systems, including Hep-2 cells, Vero cells, and MDCK cells as well as in vivo mouse models [31, 32]. The half-maximal inhibitory concentration (IC_{50}) of ulvan varies significantly, ranging from >150 µg/mL (weak activity) to as low as 0.1 µg/mL (strong activity) [33]. For instance, ulvan from *U. clathrata* exhibited potent NDV inhibition (IC_{50} = 0.1 µg/mL) by targeting the viral fusion protein. Although *U. pertusa*-derived ulvan displayed moderate inhibition against AIV-H9N2 (~40% at 100 µg/mL), co-administration with the AIV vaccine significantly enhanced antibody titers (~100% increase), indicating ulvan's immunostimulatory role [31]. Differences in antiviral efficacy among ulvan sources suggest structural dependencies. High molecular weight (~34 kDa) and elevated sulfation levels (up to 22%) are associated with enhanced antiviral activity. Notably, a highly sulfated ulvan fraction from *U. compressa* achieved complete HSV inhibition at 100 µg/mL (IC_{50} = 28.2 µg/mL), markedly outperforming the native form (IC_{50} = 153 µg/mL) [34]. However, comprehensive studies exploring structure–activity relationships remain limited. Current findings suggest ulvan's promise both as a direct

antiviral agent and as a vaccine adjuvant through immunomodulatory mechanisms.

Plant Defense

Recent studies have shown that ulvans modulate signaling pathways involved in plant immunity. Investigations using both in vitro (e.g., rice and wheat cell cultures) and in vivo systems (e.g., Arabidopsis thaliana, apple, bean, wheat, and barley) demonstrated ulvan's ability to activate plant defenses (Figure. 3). Ulvan derived from *U. fasciata*, *U. lactuca*, and *U. armoricana* has been identified as a potent priming agent, enhancing inducible defense responses [35]. Plant defense is primarily triggered through pattern recognition receptors (PRRs) that detect microbe- or pathogen-associated molecular patterns (MAMPs/PAMPs), initiating MAMP-triggered immunity (MTI) or PAMP-triggered immunity (PTI). Pathogens may suppress these defenses through effectors, which are counteracted by resistance (R) genes in plants, leading to effector-triggered immunity (ETI). Downstream defense responses include the production of pathogenesis-related proteins, cell wall fortification via lignin and callose, and biosynthesis of antimicrobial metabolites [36]. ETI additionally induces a hypersensitive response (HR), characterized by reactive oxygen species (ROS)-mediated cell death at infection sites. Both MTI/PTI and ETI contribute to systemic acquired resistance (SAR), enhancing defense readiness in distant tissues [37]. Phytohormones such as salicylic acid, jasmonic acid, ethylene, abscisic acid, cytokinins, auxins, brassinosteroids, and gibberellins tightly regulate these immune responses, with the outcome influenced by pathogen lifestyle (biotrophic vs. necrotrophic). Ulvan's impact on these signaling cascades has been evaluated via plant health indicators, disease severity, and molecular analyses. Ulvan from *U. fasciata* disrupted appressoria formation in *Colletotrichum gloeosporioides*, an anthracnose-causing pathogen. Pre-treatment of apple leaves reduced disease severity by approximately 50%, while Arabidopsis thaliana treated with ulvan exhibited resistance against *Alternaria brassicicola* and *Colletotrichum higginsianum* [38]. Although sulfation had no clear influence in some studies, desulfated ulvan from *U. lactuca* exhibited reduced phenylalanine ammonia-lyase (PAL) activity, while ulvan oligomers significantly enhanced PAL levels (>2-fold) and elevated salicylic acid, suggesting SAR activation. In contrast, ulvan from *U. armoricana* activated the jasmonic acid pathway in *Medicago truncatula*, *Nicotiana tabacum*, and *A. thaliana*, without affecting salicylic acid levels. This was supported by the upregulation of jasmonic acid-responsive genes (e.g., PDF1.2, NtLOX1) and the lack of expression of salicylic acid-dependent markers (PR1a, PR5). Ulvan's elicitor activity likely stems from its recognition by PRRs during PTI or ETI, implying structural similarity to MAMPs/PAMPs. Structurally related compounds such as rhamnogalacturonan I and bacterial rhamnolipids also activate plant defenses [39]. The presence of rhamnose in ulvan appears essential for immune activation in tomato, while glucuronic acid showed no effect. Ulvan oligomers also induced higher PAL activity than native polysaccharides. However, the role of sulfation remains inconclusive, with some evidence indicating its necessity and others showing no correlation.

CONCLUSIONS

Compared to other marine-derived sulfated polysaccharides such as carrageenan and fucoidan, the exploration of ulvan's structural characteristics and biological functions is still in its nascent stages. Despite this, ulvan exhibits considerable promise for applications spanning agriculture, biomedicine, and the development of functional biomaterials. Current understanding of the relationship between ulvan's structural attributes and its physicochemical and biological activities remains limited, primarily due to a lack of comprehensive and systematic studies employing highly purified and well-characterized ulvan preparations against clearly defined biological targets. Moreover, the complexity of ulvan's molecular structure necessitates detailed investigation into its pharmacokinetic properties and bioavailability prior to its advancement for therapeutic use. The inherent structural variability of ulvan, influenced by differences in algal species and extraction or purification methods, further contributes to inconsistencies across studies. Therefore, future research should prioritize the use of refined ulvan from a single, well-defined source or standardized extraction protocol. Such an approach will facilitate the identification of structure–activity relationships, thereby enabling more accurate comparisons across studies and paving the way for the rational design of ulvan-based therapeutic or functional applications.

Data availability

All relevant data can be found within the manuscript.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

Ganesh Sankaralingam and **Kanimozhi Subramaniyan**: Investigation and writing original draft; review and editing; **Sakthivel Muthu**: Supervision, Project administration, Methodology, Validation, Writing – original draft, review, and editing.

Competing interests

The authors declare no conflict of interest.

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