

Review

Fucoidan–Alginate Composite Nanogels and Hydrogels: Design Strategies, Gelation Mechanisms and Sustainable Applications

Kamran ^{1,†}, Tie-Zheng Ma ^{2,†} , Qiu-Yu Xia ¹ , Kit-Leong Cheong ¹ , Shoaib Younas ³, Ukasha Arqam ³, Malik Abdul Rahim ⁴, Sai-Yi Zhong ^{1,5,*} and Rui Li ^{1,*} 

- ¹ College of Food Science and Technology, Guangdong Ocean University, Guangdong Provincial Key Laboratory of Aquatic Product Processing and Safety, Guangdong Province Engineering Laboratory for Marine Biological Products, Guangdong Provincial Engineering Technology Research Center of Seafood, Guangdong Provincial Engineering Technology Research Center of Prefabricated Seafood Processing and Quality Control, Guangdong Provincial Science and Technology Innovation Center for Subtropical Fruit and Vegetable Processing, Zhanjiang 524088, China; kamranniamatali@outlook.com (K.); qiuyuxia@163.com (Q.-Y.X.); klcheong@gdou.edu.cn (K.-L.C.)
- ² School of Food and Health, Beijing Technology & Business University, Beijing 100048, China; matiezheng@btbu.edu.cn
- ³ School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China; shoaibfsn@yahoo.com (S.Y.); ukasha.arqam@ucp.edu.pk (U.A.)
- ⁴ Department of Basic & Applied Chemistry, University of Central Punjab, Lahore 54782, Pakistan; mabdul.rahim@ucp.edu.pk
- ⁵ Shenzhen Research Institute, Guangdong Ocean University, Shenzhen 518120, China
- * Correspondence: zhongsy@gdou.edu.cn (S.-Y.Z.); lirui@gdou.edu.cn (R.L.)
- † These two authors contributed equally to this work.

Abstract

Fucoidan and alginate, two marine-derived polysaccharides, have recently attracted considerable interest in both biomedical and food applications due to their unique structural characteristics and multifunctional bioactivity. However, few studies have examined fucoidan–alginate composite nanogels and hydrogels, and a comprehensive review covering formulation strategies, gelation mechanisms and other aspects of these composite systems is still lacking. Therefore, this narrative review provides a critical overview of recent progress in fucoidan–alginate composite nanogels and hydrogels, especially in terms of formulation strategies, gelation mechanisms and their potential applications in food and biomedical fields. In these composite systems, alginate can be ionically cross-linked with divalent cations (e.g., Ca^{2+}) to form three-dimensional networks that retain water and can encapsulate and release bioactive cargo, whereas fucoidan is proposed to modulate network structure and bioactivity. Combining sulfated, fucose-rich fucoidan with guluronic acid-rich alginate has been reported to produce complementary effects on mechanical properties, structural stability and bioactivity; however, whether these effects are genuinely synergistic has rarely been tested directly, and the level of evidence is therefore explicitly distinguished throughout this review. These properties suggest potential applications in drug delivery, wound healing and tissue engineering, although most available evidence is in vitro or preclinical. Key barriers to translation include the source-dependent variability of fucoidan, incomplete mechanistic understanding of the composites, safety considerations such as anticoagulant activity, limited in vivo and clinical evidence, and unresolved issues related to scalability and regulatory standardization.

Keywords: marine polysaccharides; hydrogel; green formulation; bioactive delivery; sustainable application; controlled release



Academic Editor: Sik Yoon

Received: 8 September 2026

Revised: 17 October 2026

Accepted: 19 October 2026

Published: 22 October 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and

conditions of the [Creative Commons](https://creativecommons.org/licenses/by/4.0/)

[Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Marine habitats provide an abundant array of bioactive polysaccharides, which are a broad group of biopolymers with complex structures, found in marine organisms such as algae, bacteria, and marine invertebrates [1]; they are particularly abundant in algae [2]. These polysaccharides have attracted much attention because of their broad range of biological activities, which can be exploited in numerous industrial applications. The structural diversity of marine polysaccharides plays a key role in determining their biological functions, conferring upon them a range of bioactivities, including antioxidant, anticoagulant, immunomodulatory, anti-inflammatory, and antimicrobial effects. This structural heterogeneity derives mainly from differences in monosaccharide composition, molecular weight, and modifications such as glycosidic linkages and sulfation patterns, all of which contribute to their biological activities [3,4]. Their structure is a unique feature that determines their rheological properties, bioactivity, and potential uses in food or health applications [5]. The algal polysaccharides include alginate (from *Laminaria* and *Ascophyllum*), fucoidan (from *Fucus vesiculosus* and *Undaria pinnatifida*), and ulvan (from *Ulva*). Among these, fucoidan and ulvan are heavily sulfated, which confers on them considerable bioactivity that is exploitable in biomedical applications [6].

Marine polysaccharide-derived hydrogels have been developed as promising biomaterials, offering advantages including biocompatibility, biodegradability, and adjustable mechanical properties [7]. Due to their hydrophilic nature, marine polysaccharides can generate 3D networks capable of holding large amounts of water and can therefore be efficiently utilized in the development of hydrogels [8]. The mechanical properties of such hydrogels are tunable through blending or cross-linking, enabling adjustable stiffness and elasticity, which are key aspects for specific applications in load-bearing biological soft tissues [8]. These hydrogels have also been shown to display various biological activities including immunomodulation, angiogenesis and antimicrobial activity, following molecular modifications such as sulfation and acetylation [9].

Beyond fucoidan and alginate, several other marine polysaccharide pairs have been explored as composite hydrogel platforms, including carrageenan–chitosan and alginate–chitosan polyelectrolyte complexes, which rely on analogous electrostatic and ionic cross-linking mechanisms to generate tunable three-dimensional (3D) networks [10]. These precedents suggest that some design principles of polysaccharide composite gelation—such as charge complementarity between oppositely charged partners, divalent-cation bridging, and hydrogen bonding—may be transferable across marine polysaccharide pairs, even though functional groups, charge densities and gelation kinetics differ. An important difference, however, is that carrageenan–chitosan and alginate–chitosan pairs are oppositely charged, whereas fucoidan and alginate are both anionic; therefore, the mechanisms cannot simply be carried over. Because fucoidan has been reported to exhibit anticoagulant, antiviral, antioxidant and immunomodulatory activities typical of sulfated fucans, and alginate has well-characterized gelling chemistry, the fucoidan–alginate composite is a potentially instructive model system in which to dissect these transferable design rules while also addressing bioactivity requirements unique to sulfated, fucose-rich polysaccharides.

As a class of recently developed marine polysaccharide-based composites, fucoidan–alginate hydrogels have attracted substantial attention due to their promising applications in both biomedical and food-related fields [11]. Although the number of publications has increased, most studies focus on individual polymers, providing limited insight into the mechanisms behind composite gelation and structure–function relationships [12,13]. Therefore, there remains a need for a comprehensive and critical review that covers design strategies, intermolecular interactions, processing methods, and sustainable applications of fucoidan–alginate composite hydrogels.

To substantiate the claimed gap in the literature, we explicitly compared the scope of this review with the most closely related recent reviews. Reviews focusing on fucoidan-based hydrogels [13] discuss fucoidan cross-linking and bioactivity in depth but treat alginate, when mentioned at all, as one of several possible copolymers rather than analyzing the fucoidan–alginate pair specifically. Reviews focusing on alginate [14] similarly mention fucoidan and sulfated polysaccharides more generally only in passing. Broader reviews of marine-polysaccharide biomaterials [7] and of seaweed polysaccharide extraction/modification [6] cover many polysaccharide types at a higher level of generality but do not specifically analyze the M/G ratio-sulfation interplay in fucoidan–alginate systems. A review of hydrogels based on seaweed-derived sulfated polysaccharides (carrageenan, fucoidan and ulvan) [15] comes closest in spirit to the present review. However, it likewise does not focus on alginate as the pairing partner, nor does it address the sulfation-pattern/M-G ratio relationship that is the specific focus of this review. To our knowledge, no existing review has specifically analyzed fucoidan–alginate composite gelation mechanisms, cross-linking quantification, and structure–function relationships as an integrated topic. Accordingly, compared with two parallel summaries of the individual polymers, a combined analysis provides additional insight at the level of interaction—namely, how the two polymers influence each other’s ion binding, network structure and bioactivity—an aspect that cannot be inferred from either polymer alone.

To address this gap, this review uses the following working framework as its organizing principle: extraction and processing conditions-polymer structure (fucoidan molecular weight, sulfate content and charge density; alginate M/G ratio and molecular weight) → cross-linking conditions and ionic environment (Ca^{2+} concentration, pH, ionic strength, fucoidan: alginate ratio) → network architecture (cross-linking density, mesh size, heterogeneity) → physicochemical properties (swelling, mechanics, and release) → biological and application performance. Although each link has been studied separately for alginate or fucoidan, direct experimental evidence for the complete chain in fucoidan–alginate composites remain limited. Within this framework, the review relates fucoidan sulfation and alginate M/G composition to composite network structure where data are available, connects green extraction routes to the structural features that matter for composite gelation, and compares the requirements of biomedical and food-grade applications of these composites. Throughout, we distinguish three levels of evidentiary support: relationships directly demonstrated experimentally in fucoidan–alginate composite systems; relationships established separately for fucoidan or alginate individually, which we extrapolate to the composite only through explicitly flagged analogies; and mechanistically plausible hypotheses that, to our knowledge, have not yet been directly tested in the composite system and that we present explicitly as hypotheses requiring future validation. We reserve the term “synergy” for cases in which a direct interactive effect between fucoidan sulfation pattern and alginate M/G ratio has actually been reported in a composite system; where such direct composite-level evidence is currently unavailable, we describe the relationship as a plausible design hypothesis rather than an established synergy.

In line with this framework, this review is organized to progressively build from polymer source to application. It introduces the structural characteristics of fucoidan and alginate, critically compares sustainable, green extraction technologies used to recover these polysaccharides from brown seaweed biomass, summarizes the analytical methods used for their structural characterization, examines the intermolecular interactions and cross-linking mechanisms that govern fucoidan–alginate network formation, and discusses advanced design strategies for hydrogels, nanogels and stimuli-responsive systems, as well as applications in tissue engineering, drug delivery and regenerative medicine, and addresses safety, regulatory and scalability considerations together with future directions.

Each section states, where possible, how the information presented bears on the design or performance of the composite, and sections on extraction and characterization are kept to the aspects that affect composite gelation.

In terms of methodology, this is a narrative (critical) review; it was not conducted as a formal systematic review (e.g., following PRISMA), and no quantitative meta-analysis was performed. Literature for this narrative review was identified through structured searches of Web of Science, Scopus, PubMed, and Google Scholar, covering publications from approximately 2021 to 2026 (with earlier foundational literature, e.g., on the alginate egg-box model, included where mechanistically relevant regardless of date). Search terms combined “fucoidan”, “alginate”, “sulfated polysaccharide”, and “brown seaweed/brown algae” with “hydrogel”, “nanogel”, “nanoparticle”, “composite”, “cross-linking”, “extraction”, “characterization”, “drug delivery”, and “tissue engineering”, using Boolean AND/OR operators, together with citation chaining (forward and backward) from key reviews and primary research articles. Studies were included if they reported primary experimental or computational data, or review/synthesis content relevant to fucoidan and/or alginate structure, extraction, characterization, gelation mechanisms, or hydrogel/nanogel applications. Studies explicitly involving a fucoidan–alginate composite system (i.e., reporting both polymers combined in a single formulation) were distinguished from single-polymer studies and are flagged as such throughout the text; single-polymer studies are cited to support general polysaccharide principles or to provide mechanistic context, and conclusions drawn from single-polymer data are explicitly not presented as composite-system findings. Non-English-language publications, conference abstracts without peer-reviewed full text, and patents were generally excluded, except where no peer-reviewed equivalent was available for an important point.

2. Structural Characteristics of Fucoidan and Alginate

2.1. Fucoidan

Fucoidan is a fucose-rich and sulfated polysaccharide, mainly present in the cell wall and extracellular matrix of brown seaweeds. Major brown algae such as *Fucus*, *Sargassum*, *Laminaria* and *Turbinaria* are the main sources, with a lesser quantity being found in marine invertebrates such as sea cucumbers and sea urchins. The structural diversity of fucoidan is related to the differences in glycosidic linkage, monosaccharide composition and degree of sulfation, e.g., fucoidan from *F. vesiculosus* and *Ascophyllum nodosum* has alternating α -1,4 and α -1,3 linkages, while that from *Laminaria saccharina* are predominantly composed of α -1,3 linkages [16]. The structure of fucoidan is heterogeneous and source-dependent, so the unit drawn is only one representative example. The figure shows chemical structures only; it does not show experimentally observed interactions. Because carboxylate and sulfate groups are both negatively charged, direct attraction between them is not expected; however, hydrogen bonding and cation-mediated association between the two polymers have been proposed.

The monosaccharide composition, sulfate content, and molecular weight of fucoidan are influenced significantly by environmental factors such as geographical location, season, and habitat, and the physicochemical and biological properties of fucoidan are similarly affected [17]. The extraction of fucoidan usually involves pretreatments and can be carried out using solvents, such as ethanol or quaternary ammonium salts [18]. Fractionation methods such as solvent precipitation, membrane filtration or ion-exchange chromatography produce fractions of different molecular sizes. The molecular weight of fucoidan is typically between 13 and 950 kDa and the polymer can be categorized as low, medium or high-molecular weight with each form demonstrating different biological and rheological characteristics. Molecular weights and distributions are frequently characterized using

size-exclusion chromatography coupled with light-scattering methods, enabling accurate molecular characterization [19] (Figure 1A).

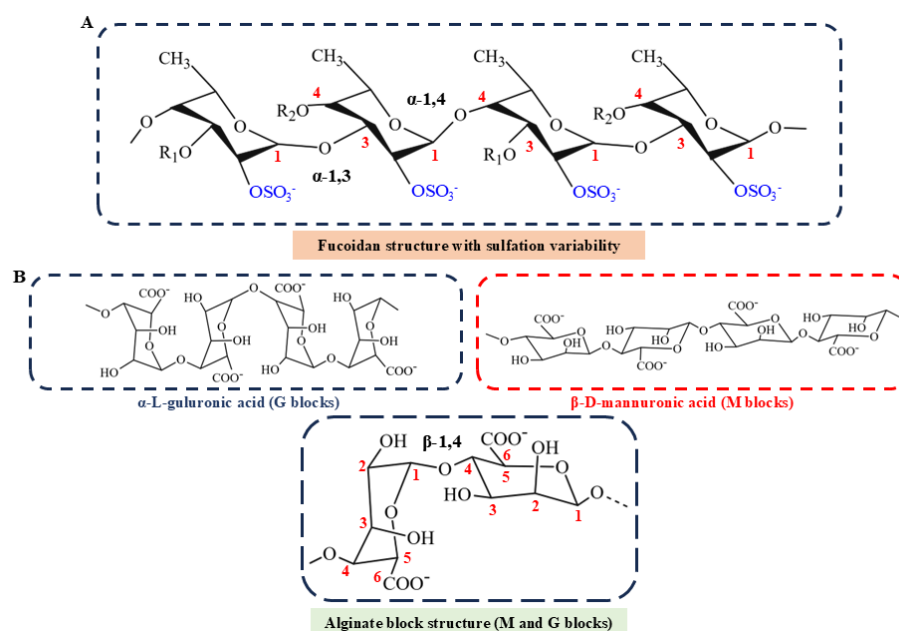


Figure 1. Schematic representative structures of the fucoidan and alginate. (A) Fucoidan consists of sulfated α -L-fucopyranose units with alternating α -1,3 and α -1,4 linkages and variable sulfation at C-2 and/or C-4 positions [20]; (B) alginate is composed of β -D-mannuronate (M) and α -L-guluronate (G) residues bearing carboxylate groups [21].

2.2. Alginate

Alginate, a linear polysaccharide found in the cell walls of brown algae, is widely used in food, pharmaceutical and biomedical fields. It is composed of 1,4-linked β -D-mannuronic acid (M) and α -L-guluronic acid (G), which are arranged in three types of blocks: M-blocks, G-blocks, and alternating M/G-blocks (Figure 1B). The M/G ratio, molecular weight and gelation behavior significantly affect the gelling properties of alginate hydrogels [14].

Common alginate sources include *Saccharina latissima*, *Laminaria digitata*, *Sacchoriza polyschides*, and *Himanthalia* spp., while commercial production often utilizes *Laminaria*, *Macrocystis*, and *Ascophyllum*. Green reagents have been developed to enable more sustainable extraction strategies. Examples include organic acids such as citric acid and lactic acid, which have increasingly been adopted as alternatives to traditional formaldehyde-based approaches. Another promising class comprises choline chloride-based deep eutectic solvents (DESs, e.g., choline chloride: urea), which are biodegradable and low-toxicity media that can achieve alginate yields comparable to, or even higher than those obtained by conventional alkaline extraction [22]. The procedure generally includes the following steps: acidifying the seaweed biomass; solubilizing the alginate in such biomass with sodium carbonate; centrifuging to separate the soluble portion; precipitating using ethanol; and drying the recovered product. Extraction efficiencies vary between algal species and process scales, with higher efficiency observed at smaller scales [23].

The M/G ratio critically influences the mechanical properties of the alginate gels. A higher M/G ratio produces relatively flexible elastic gels, while a lower ratio generates more rigid and brittle structures [14]. Gelation occurs through cross-linking with divalent cations, especially calcium, which preferentially binds to G-block regions and forms a 3D network in the solution. Additionally, molecular weight and block distribution also affect transparency, swelling, and mechanical strength, allowing alginate to be optimized for various applications, including wound dressing systems and functional food matrices.

Fucoidan–alginate hybrid hydrogels have been proposed for biomedical and nutritional applications [24]; the way in which fucoidan modifies the properties of alginate gels depends on the composition and Ca^{2+} conditions.

3. Sustainable Extraction Strategies of Brown Seaweed Polysaccharides

3.1. Green Sequential Extraction

Producing high-quality carbohydrate polymers through economically and environmentally sustainable routes is a central objective for both academic and industrial research, since extraction and processing conditions directly determine the molecular weight, sulfation pattern and purity—and therefore the downstream bioactivity and gelling performance—of the resulting polysaccharides [19]. Marine polysaccharides, such as those present in marine algae, particularly alginate and fucoidan from brown seaweeds, are already emerging as components of a circular bio-based economy, notably owing to their renewable character coupled with biodegradability and low competition for food and freshwater. Nevertheless, the performances of these polysaccharides are highly dependent on their extraction and processing procedures. Therefore, the development of green extraction technologies that preserve the structure of the polymer and are potentially lower impact has become highly desirable in current polysaccharide research.

Brown seaweeds (Phaeophyceae), such as *Laminaria*, *Fucus*, *Ascophyllum* and *Sargassum*, are abundant and renewable biomass sources for various high-value products including alginate, fucoidan, laminarin, polyphenols and minerals. Green extraction approaches are aimed at exploiting this biomass through combined processing routes that optimize resource efficiency and reduce waste generation. Sequential cascade extractions are a conceptual approach within brown seaweed biorefineries to obtain structurally and functionally diverse products. In this framework, fucoidan is usually the first component extracted, under a mild manner to preserve its sulfate groups that carry biological activity, and this is followed by alginate, which becomes available under alkaline conditions. This kind of sequential methodology increases the overall yield and minimizes structural degradation of target components caused by harsh non-selective treatments. This control is particularly important for fucoidan–alginate composites, where reproducibility and the ability to determine structure–property relationships are vital. Whether such processes are compatible with industrial-scale production and with regulatory requirements for biomass-based materials has still to be demonstrated for fucoidan–alginate materials of the required grade [25].

The following two clarifications apply throughout this section. First, we use “green” and “sustainable” in the qualified sense used by the cited primary literature—i.e., reduced solvent volume, energy input or processing time relative to conventional hot acid/alkali extraction—rather than as a claim of demonstrated overall environmental sustainability; formal life-cycle assessment (LCA) or techno-economic analysis data are rarely available for these extraction methods; and, where they exist, they are noted explicitly. In the absence of such data, a more accurate framing is that these methods are “potentially lower-impact” alternatives whose full sustainability (including energy demand, solvent recovery, water consumption, waste treatment, and scale-up behavior) remains to be formally quantified. Second, the extraction conditions discussed below should not be treated as an isolated topic: they can strongly influence the molecular weight, sulfation pattern/degree, and M/G composition of the recovered polysaccharides, with sulfation relating primarily to fucoidan and M/G composition to alginate, which in turn govern their rheological behavior and cross-linking capacity, the resulting composite network architecture, and ultimately the performance of the material in its target application. This extraction-to-application chain is referenced explicitly at several points below to connect processing choices to downstream

composite performance, rather than treating extraction as a self-contained topic. We therefore distinguish green-processing characteristics (e.g., lower solvent or energy use per extraction) from demonstrated sustainability outcomes (e.g., those quantified by life-cycle assessment); most studies discussed below support only the former.

3.2. Green Extraction Technologies

3.2.1. Ultrasound-Assisted Extraction (UAE)

Traditional alginate or fucoidan extraction processes generally suffer from depolymerization, desulfation, and a reduction in bioactivity due to prolonged heating and exposure to strong acids and alkalis. In contrast, green extraction methods aim to reduce solvent usage and energy input while preserving the integrity of the polymer structures [26]. UAE (Figure 2A) represents one of the major advances in the extraction of marine polysaccharides, such as fucoidan and alginate from brown seaweeds, offering a potentially lower-impact and more efficient alternative to conventional hot acid/alkali extraction and prolonged solvent-based maceration, which typically require higher chemical and energy inputs and cause greater structural degradation of the target polysaccharides [19]. In marine organisms, these polysaccharides serve various biological functions, including structural support and cell-wall organization [1]. For instance, alginate comprises M-blocks, G-blocks, and alternating M/G-blocks, and its properties are determined by the relative properties and sequential arrangement of these blocks [27].

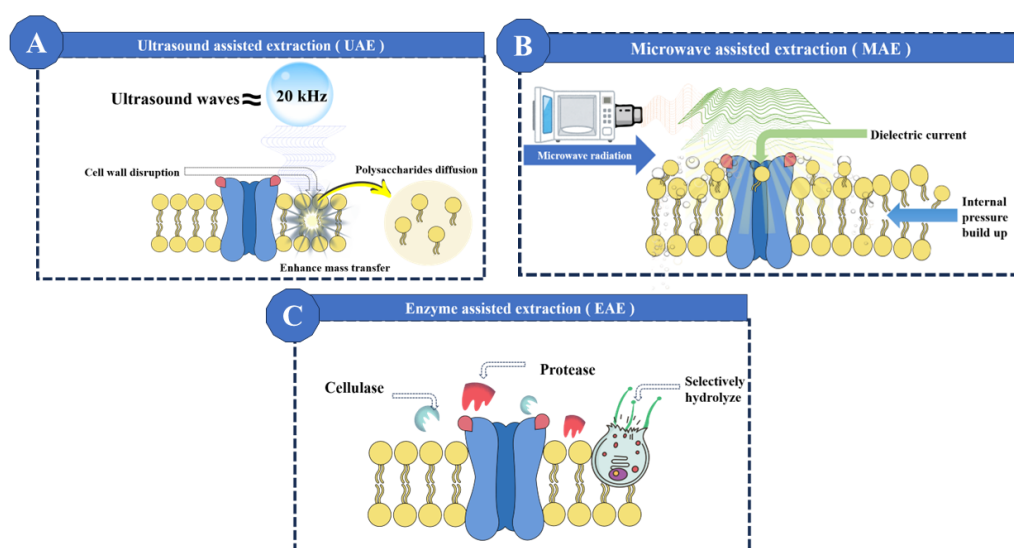


Figure 2. Green extraction technologies for polysaccharide recovery from biological matrices. (A) UAE uses high-frequency ultrasound waves (20 kHz) to break cell walls, thereby improving mass transfer and polysaccharide diffusion. (B) MAE relies on microwave radiation for dielectric heating, which induces pressure build-up and releases compounds from within cells. (C) EAE employs specific enzymes to hydrolyze cell wall components selectively and efficiently, enabling the targeted recovery of desired biomolecules. The panels are schematic illustrations of the working principle of each method and do not show experimental data.

By increasing mass transfer via acoustic cavitation, UAE has become an effective and potentially lower-impact method for recovering brown seaweed polysaccharides, especially fucoidan and alginate. Ultrasound waves (usually at 20 kHz) induce the formation of microscopic cavitation bubbles through alternating compression and rarefaction cycles. When these bubbles collapse violently, they generate localized hotspots (high temperature and pressure), micro-jets, shear forces, and shockwaves that disrupt the viscous hydrocolloid matrices and cellulose–hemicellulose networks found in algal cell walls. This structural

decomposition enhances the diffusion of uronic acid-containing alginates and intracellular sulfated fucans into the extraction medium, while also improving solvent penetration. In a direct comparison between dynamic maceration (60 °C) and probe ultrasound (22 kHz, 2 × 20 min, room temperature) applied to four Barents Sea brown algae (*F. vesiculosus*, *F. serratus*, *F. distichus*, and *A. nodosum*), UAE increased the mean fucoidan yield by about 43% and the uronic acid content by about 22%; however, the fucoidans obtained by UAE had a lower molecular weight, and there in vitro antioxidant and anticancer activities were reduced [28]. These are mean values for four species under one set of conditions and should not be generalized. For alginate, UAE (20 kHz, 20–91% amplitude, 6–34 min) recovered alginate within minutes from the solid by-product remaining after fucoidan extraction, compared with 24 h of stirred extraction at 60 °C in the reference procedure [29]. Together, these studies show that ultrasonic power and time must be balanced against chain integrity: intense cavitation can reduce molecular weight and may alter sulfate content, and response surface methodology (RSM) is commonly used to optimize this trade-off. For fucoidan–alginate composites this matters because lower-molecular-weight alginate generally forms weaker Ca²⁺ gels [14], and fucoidans with different molecular weights and sulfate contents may interact differently with the alginate network and differ in bioactivity; ultrasound conditions should therefore be reported together with the resulting molecular weight and sulfate content. UAE is an effective, potentially lower-impact route, but its energy demand, scalability and life-cycle impact for polysaccharide extraction have not been quantitatively compared with those of conventional methods.

3.2.2. Microwave-Assisted Extraction (MAE)

Marine polysaccharides, such as alginate and fucoidan (Figure 2B), can be extracted from brown seaweeds using microwave-assisted extraction (MAE), a rapid technology with potentially lower solvent and energy use. MAE is based on dielectric heating, whereby polar molecules and ions in the biomass-solvent system undergo dipole rotation and ionic conduction, respectively, under microwave radiation. This induces instantaneous volumetric heating and the development of internal pressure. This localized thermal stress markedly enhances mass-transfer kinetics, solvent penetration, and cell-wall disruption in comparison with traditional extraction methods. In a study on *Nizamuddinina zanardinii* processing residues, microwave-assisted extraction alone gave a higher alginate yield (15.36%, w/w) than conventional alkaline extraction (11.88%), suggesting that this technology may be beneficial [30]. Extraction performance is greatly influenced by microwave power, exposure time, temperature, and solvent polarity; overly high-power levels can lead to chain scission, reduced molecular weight, or partial degradation of the polymer structure. On mechanistic principles, MAE is effective, although there are very limited studies on its applicability to fucoidan, since it also requires precise optimization of the parameters to preserve sulfate ester groups and molecular integrity. The incorporation of MAE into sequential biorefinery processes, particularly for alginate recovery from fucoidan-extracted residues, further enhances biomass valorization and process sustainability. A detailed structural characterization using high-performance size-exclusion chromatography, NMR and FTIR is essential to elucidate the effect of microwave processing on the sulfation pattern, molecular weight distribution and functional properties. In particular, FTIR provides a rapid means of tracking microwave-induced structural changes: retention of the sulfate ester band near 1220–1260 cm^{−1} (fucoidan) or the carboxylate stretch near 1590–1620 cm^{−1} (alginate), together with the absence of new carbonyl or oxidation-related bands, indicates that the polysaccharide backbone and its bioactive substituents have been preserved, whereas band broadening or intensity loss may signal partial desulfation or depolymerization under excessive microwave power. In conclusion, MAE may be a

promising intensification method, but its scalability and its effects on sulfate retention and molecular weight must be demonstrated for each polysaccharide. For composite gels, the relevant question is whether the extracted fucoidan and alginate retain the key features on which network formation depends—sulfate content (fucoidan), carboxylate groups (alginate), and molecular weight.

3.2.3. Enzyme-Assisted Extraction (EAE)

EAE is a highly selective and potentially lower-impact method for recovering high-value marine polysaccharides, such as fucoidan and alginate, from brown seaweed biomass. Unlike conventional acid-alkali processes, EAE relies on the enzymatic hydrolysis of structural components such as cellulose, hemicellulose, and proteins in the cell-wall matrix, catalyzed by specific proteases and carbohydrases, including cellulases, hemicellulases, and pectinases (Figure 2C).

This hydrolysis increases cell-wall accessibility and facilitates the release of cell-wall-bound as well as intracellular and extracellular polysaccharides under controlled conditions. This approach is generally reported to preserve the mannuronic (M) and guluronic (G) blocks of alginate and the sulfate groups of fucoidan better than harsh chemical extraction, although this claim should be verified for each enzyme preparation. Preserving the sulfation pattern and polymeric structure of fucoidan is critical for its functional performance, including antibacterial, anti-inflammatory, anticancer, antidiabetic, and antioxidant properties. Therefore, the optimization of enzyme type, dosage, pH, incubation temperature, and time is essential to ensure efficient extraction while preventing excessive hydrolysis. Despite relatively high enzyme costs and longer processing times, EAE is a promising, potentially lower-impact technology for valorizing marine biopolymers, owing to its selectivity [31]. For composite gels, the key questions are whether enzymatic treatment changes the M/G ratio or block distribution, molecular weight, or sulfate content, and whether residual enzymes or proteins remain in the product. A critical comparison of these green extraction technologies is presented in Table 1.

Table 1. Comparison of Green Extraction Technologies for Marine Polysaccharides.

Parameter	UAE	MAE	EAE	References
Principle	Acoustic cavitation: micro-jets, shear forces and shock waves disrupt cell walls	Dielectric heating (dipole rotation, ionic conduction) causes internal pressure and cell-wall disruption	Enzymatic hydrolysis of cell-wall polymers (e.g., cellulases, pectinases)	[19,32]
Operating conditions (examples from cited studies)	Fucoidan: 22 kHz, 2 × 20 min, room temperature. Alginate: 20 kHz, 20–91% amplitude, 6–34 min [30]	Typically, minutes at elevated temperature and controlled power; conditions vary widely between studies	Mild temperature, extraction time of hours, controlled pH; exact conditions depend on enzyme type, dosage, substrate, and target polysaccharide	[28,29]
Example evidence (not directly comparable)	Fucoidan, four <i>Fucus</i> / <i>Ascophyllum</i> species vs. dynamic maceration: mean +43% yield, +22% uronic acid. Alginate, <i>F. vesiculosus</i> by-product vs. 24 h stirred extraction	Alginate, <i>N. zanardinii</i> by-products, microwave vs. alkaline: 15.36% vs. 11.88% (<i>w/w</i>)	No single quantitative comparison is given here; yields depend on species and enzyme	[28,30]
Effect on molecular integrity and sulfation	Lower fucoidan molecular weight and reduced in vitro activity after UAE in; over-sonication may depolymerize or desulfate	Excess power may cause chain scission; sulfate retention must be verified	Generally reported to preserve structure better than harsh chemical extraction; residual enzyme activity must be excluded	[28,33]
Main advantages	Short time, low temperature, simple equipment	Rapid volumetric heating	Selectivity, mild conditions	[19,32]

Table 1. Cont.

Parameter	UAE	MAE	EAE	References
Main limitations	Molecular-weight reduction; uneven energy distribution at scale	Thermal degradation at high power; limited data for fucoidan; uniform heating at scale	Enzyme cost, long processing time, enzyme and protein removal	[19,32]
Scalability (current evidence)	Considered closer to scale-up; no techno-economic or life-cycle data for these polysaccharides	Less mature; higher capital cost; no comparative life-cycle data	Considered closer to scale-up; enzyme cost is limiting; no life-cycle data	[25]
Relevance to hydrogel preparation	Lower alginate molecular weight generally gives weaker Ca^{2+} gels; report molecular weight and sulfate content with the extraction conditions	Verify sulfate and carboxylate integrity (FTIR, NMR) before gel formulation	Co-extracted protein or enzyme residues may affect gelation and safety	[14]

4. Characterization of Fucoidan and Alginate

4.1. Monosaccharide Profiling

Structural elucidation of marine polysaccharides (e.g., fucoidan, alginate) is essential for determining their composition, including monosaccharide composition, sulfation pattern, molecular weight, and functional properties. Chromatographic, spectroscopic, and rheological methods are commonly applied to study structure–bioactivity correlations [33]. For example, monosaccharide composition can be obtained via high-performance anion-exchange chromatography (HPAEC); sulfation positions and glycosidic linkages can be determined by both proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectroscopy, often complemented by two-dimensional experiments (e.g., HSQC, HMBC) for unambiguous signal assignment; and size-exclusion chromatography (SEC) helps determine the molecular weight distribution, which may correlate with the mechanical properties of the materials. Rheological studies are performed to investigate the viscosity and shear-thinning characteristics that reflect the functionality of polysaccharides, especially in gel formation and drug delivery (Figure 3). These techniques are frequently used in combination [33]. In addition, Fourier-transform infrared (FTIR) spectroscopy is frequently used as a rapid, complementary screening tool alongside NMR, since characteristic absorption bands (e.g., sulfate ester vibrations near $1220\text{--}1260\text{ cm}^{-1}$ in fucoidan and carboxylate stretching near $1590\text{--}1620\text{ cm}^{-1}$ in alginate) can help rapidly confirm the presence of key functional groups before more time-consuming NMR analysis is undertaken.

The first step in elucidating the structural framework of fucoidan and alginate is monosaccharide composition analysis. Acid hydrolysis of the polysaccharide chains to liberate individual monosaccharide units is typically the first step in this analysis. To efficiently cleave glycosidic bonds while minimizing the degradation of sensitive sugars, hydrolysis is typically performed using approximately 2 M trifluoroacetic acid at temperatures between 100 and 120 °C for 2–4 h. After hydrolysis, monosaccharides are separated and quantified using advanced chromatographic techniques. Because it allows for the simultaneous detection of neutral and acidic sugars without the need for derivatization, high-performance anion-exchange chromatography coupled with pulsed amperometric detection (HPAEC-PAD) is frequently used [34]. The most common constituents of fucoidan are fucose, galactose, xylose, mannose, glucose and uronic acids, which are easily detected by this method. Fucoidan typically contains a high proportion of L-fucose, accounting for 40–90% of the total monosaccharide content, depending on the algal source. Galactose, mannose and xylose are present in smaller amounts. Another approach involves reverse phase HPLC after precolumn derivatization with 1-phenyl-3-methyl-5-pyrazolone (PMP).

This method enhances the chromatographic resolution and detection sensitivity for complex monosaccharide mixtures.

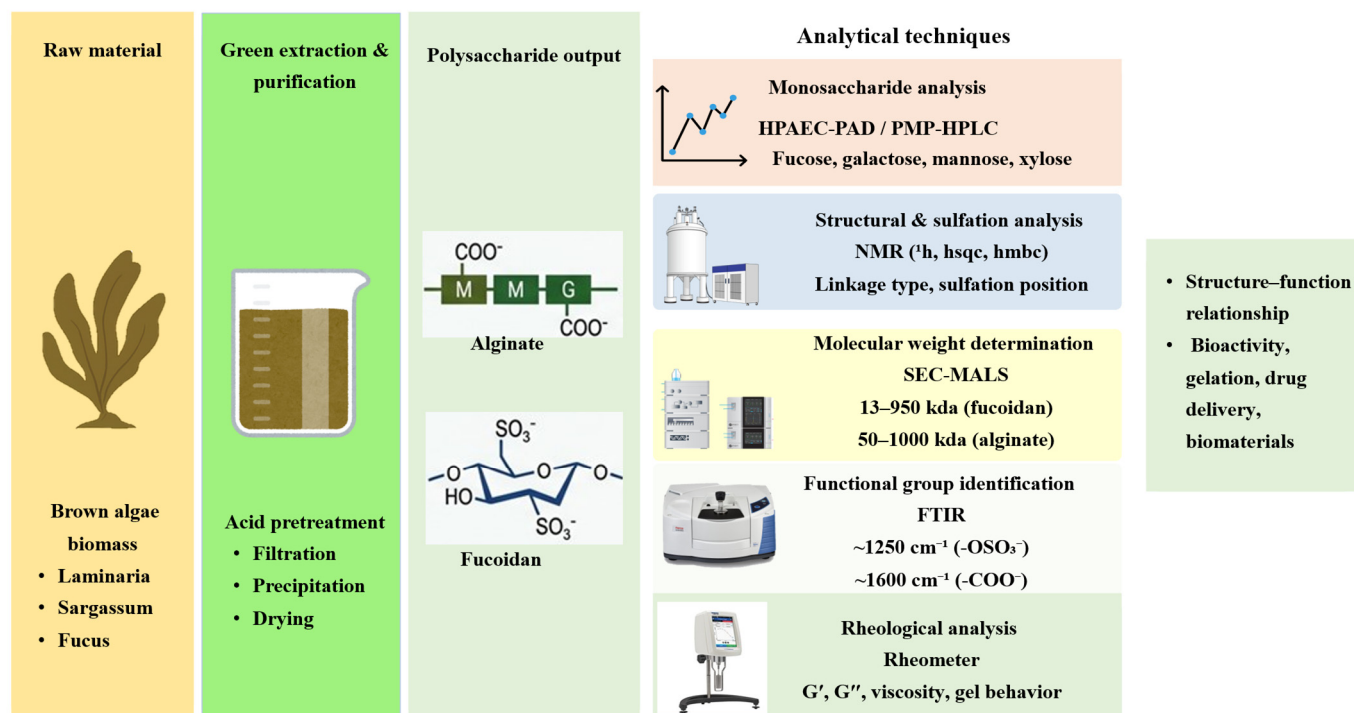


Figure 3. Analytical workflow for characterizing fucoidan and alginate from brown seaweeds. The scheme is a schematic workflow; molecular-weight ranges and band positions shown in the figure are literature ranges for the individual polymers, not measurements on a fucoidan–alginate composite.

One of the most important structural parameters of alginate is the proportion of M and G residues in the polymer chain. This M/G ratio has a significant effect on the mechanical strength and gelation properties of alginate hydrogels. The most precise method for determining this ratio is proton nuclear magnetic resonance (^1H -NMR) spectroscopy, which directly quantifies the block distribution within the polymer backbone, since the anomeric position signals of M and G residues appear at distinct chemical shifts [35]. Alginates typically have M/G ratios ranging from 0.4 to 1.6, but these values vary widely among brown algal species. Capillary zone electrophoresis has also been employed as an ancillary analytical method owing to its high separation efficiency, short analysis time, and low sample consumption [33,36].

4.2. Sulfation Analysis

Fucoidan's distinctive structural characteristic is its sulfate ester groups, which are intimately linked to its biological activities, such as anticoagulant, antiviral, and anti-inflammatory effects. Thus, it is essential to accurately determine the sulfate content and sulfation position to understand the function of fucoidan. The barium chloride-gelatin turbidimetric assay is a common colorimetric method for quantifying sulfate anions by forming insoluble precipitates of barium sulfate, and is therefore employed to quantify the total sulfate content of fucoidan. Ion chromatography is an alternative method that provides more accurate determination of sulfate [16]. Typically, sulfate groups account for 10–35% of the total fucoidan mass in most brown algal species, but this percentage can vary depending on species and extraction conditions [37].

Although the total amount of sulfate in the sugar backbone is important for quantitative information, the exact position of sulfate groups is more critical for the biological activ-

ity. The sulfation positions of fucoidan are frequently determined using two-dimensional nuclear magnetic resonance techniques, such as heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC). Sulfation typically occurs at the C2 and C4 positions of L-fucose residues, and such sulfation causes characteristic downfield shifts in proton and carbon NMR signals [16]. Methylation analysis, combined with gas chromatography–mass spectrometry (GC-MS) can provide additional structural information. The locations of glycosidic linkages in the polysaccharide chain can be determined by methylation analysis prior to hydrolysis [38]. Electrospray ionization tandem mass spectrometry (ESI-MS/MS) has been successfully applied to partially hydrolyzed fucoidan fragments, enabling oligosaccharide sequencing and revealing both the sequence of oligosaccharides and the positions of sulfate groups [33].

4.3. Molecular Weight and Chain Structure

The molecular weight and chain structure of fucoidan and alginate have a major impact on their physicochemical characteristics, such as viscosity, gelation behavior, and biological activity. These parameters are the most frequently measured using size-exclusion chromatography coupled with multi-angle laser light scattering (MALS) and refractive index (RI) detection. MALS enables absolute molecular weight measurements without the need for calibration standards, whereas size-exclusion chromatography separates polysaccharide molecules according to their hydrodynamic volume. This combination can also be used to determine the radius of gyration and solution chain conformation. Alginate typically has a MW ranging from 50 to 1000 kDa, depending on the algal species and extraction method, whereas fucoidan typically exhibits MW values ranging from 13 to 950 kDa [14,26]. As complementary or alternative approaches, gel permeation chromatography (GPC, essentially equivalent to SEC and typically coupled with conventional RI/UV detection and calibration with appropriate standards) and dilute-solution viscometry are also widely used to estimate molecular weight. In viscometry, the intrinsic viscosity of the polysaccharide is measured across a dilution series and converted to a viscosity-average molecular weight via the Mark–Houwink–Sakurada equation; although less precise than light-scattering methods for absolute molecular weight determination, viscometry is inexpensive, requires only simple, widely available instrumentation, and is well established for sodium alginate [39,40].

FTIR can be used to rapidly identify the functional groups of these polysaccharides. Carboxylate groups in alginate exhibit strong stretching bands in the range $1590\text{--}1620\text{ cm}^{-1}$, whereas sulfate ester vibrations characteristic of fucoidan appear in the range of $1220\text{--}1260\text{ cm}^{-1}$. In the $1020\text{--}1080\text{ cm}^{-1}$ region, additional peaks are observed corresponding to glycosidic C–O–C linkages. NMR spectroscopy provides further structural detail, as it reveals the anomeric configuration of sugar residues, the type of glycosidic linkages, and the sequence distribution in the polymer backbone. Together, these spectroscopic methods offer a comprehensive understanding of the molecular structure of alginate and fucoidan [41].

4.4. Rheological Analysis

Rheological analysis offers important physical information on the behavior of polysaccharide solutions and hydrogels. The viscosity of these polymer systems is influenced by molecular weight, concentration, sulfate content, pH, and temperature. Fucoidan and alginate typically exhibit a trend of increasing viscosity with concentration, which also varies as a function of algae source and ionic strength in general [42]. Therefore, rheological measurements are vital for the formulating materials with targeted mechanical and functional properties [43].

Rheological analysis characterizes the flow and deformation behavior of marine polysaccharides gels and solutions, which is important for applications in pharmaceutical, food, and biomaterials. Alginate has the ability to form ionotropic gels in the presence of divalent cations like Ca^{2+} ; this process is controlled by the egg-box model, in which the G-blocks cooperatively bind cations [44]. The rheological profile of alginate is thus quite different from that of fucoidan. Fucoidan generally behaves as a viscous polymer solution rather than forming strong gels, although its rheological properties are influenced by its molecular weight, ionic strength and branching. Oscillatory shear measurements, including frequency sweeps and amplitude sweeps, are used to determine the viscoelastic moduli (storage modulus G' and loss modulus G''), which describe the elastic (solid-like) and viscous (liquid-like) components of the material, respectively. Flow curves provide the steady-state viscosity as a function of shear rate, revealing whether the solution is Newtonian or exhibits shear-thinning behavior—a common property of many polysaccharides solutions [45]. These measurements are most informative when reported for the polymers actually used in a composite (fucoidan molecular weight and sulfate content; alginate M/G ratio and molecular weight) together with gel rheology, because only such paired datasets allow structure–property relationships in fucoidan–alginate gels to be tested directly.

5. Molecular Interaction Mechanisms in Fucoidan–Alginate Composite Systems

5.1. Charge Density

The molecular interaction mechanisms in the fucoidan–alginate composite system arise from a complex interplay of electrostatic forces, hydrogen bonding, ion binding and pH-dependent ionization. All these interactions are essential for structural stability, physicochemical properties, and applications in the food and biomedical sectors. Many of the mechanisms below were established for alginate or for polyelectrolyte systems in general; where direct evidence for fucoidan–alginate composites is limited, this is stated explicitly, and Table 2 indicates the evidence base for each mechanism.

Table 2. Proposed Interactions and Network Effects in Alginate and Fucoidan–Alginate Hydrogels.

Interaction Mechanism	Functional Groups/Components	Mechanistic Description	Structural/Functional Effects	Analytical Evidence	References
Charge density balance	Alginate ($-\text{COO}^-$), Fucoidan ($-\text{OSO}_3^-$, OH)	Difference in ionization behavior (pK_a alginate ≈ 3.4 – 4.4 ; fucoidan <1.5) controls electrostatic environment and polymer association. Protonation at low pH disrupts charge balance.	Determines polymer interaction strength, gel stability, permeability, and network density.	FTIR and rheology of fucoidan–alginate solutions (direct; suggestive)	[46]
Sulfate-carboxyl electrostatic interaction	Alginate carboxylate groups ($-\text{COO}^-$); fucoidan sulfate groups ($-\text{OSO}_3^-$)	Predominantly repulsive electrostatic forces modulated by ionic strength, counterions, and water-mediated bridging interactions. Low ionic strength promotes cooperative interpolymer complexation.	Formation of interpolymer networks and improved structural organization.	FTIR band shifts are suggestive only; alternative interpretations are possible. Basis: fucoidan–alginate solutions and films	[46]
Ca^{2+} -mediated ionic crosslinking	Ca^{2+} ions, guluronate residues of alginate	Ca^{2+} binds guluronate sequences via the “egg-box” model (established for alginate); fucoidan sulfate groups may be partially screened or may compete for Ca^{2+} (proposed, concentration-dependent).	Increased mechanical strength, controlled swelling, tunable mesh size and permeability.	Molecular dynamics (alginate only); mechanical testing of fucoidan–alginate gels [47]	[48,49]

Table 2. Cont.

Interaction Mechanism	Functional Groups/Components	Mechanistic Description	Structural/Functional Effects	Analytical Evidence	References
Hydrogen bonding interactions	Fucoidan hydroxyl groups (C2, C3, C4), alginate hydroxyl and carboxyl groups	Intermolecular hydrogen bonds between polymer chains are proposed to stabilize the composite network.	Improved viscoelastic behavior, water retention, and hydrogel stability.	FTIR broadening near 3400 cm^{-1} (suggestive only); simulations of alginate–water systems	[50,51]
pH-dependent ionization	Alginate $\text{COOH}/\text{-COO}^-$; fucoidan -OSO_3^-	pH changes alter the degree of ionization and electrostatic interactions within the network.	Controls swelling, structural stability, porosity, and diffusion behavior.	pH-dependent swelling and rheology (mainly alginate-based systems)	[11,52]
Donnan equilibrium effect	Fixed charges (-COO^- , -OSO_3^-) and counterions (Na^+ , Ca^{2+})	Uneven ion distribution generates osmotic pressure that drives water uptake and swelling within the hydrogel matrix.	Regulates hydration, swelling ratio, mesh size, and mechanical characteristics.	Flory–Rehner swelling analysis (established for polyelectrolyte and alginate gels; not reported for fucoidan–alginate)	[53,54]
Network density and mesh size	Polymer chains and ionic cross-links	Controlled by polymer ratio, ion concentration, and pH conditions.	Determines diffusion, permeability, mechanical modulus and encapsulation efficiency. Mesh sizes of polysaccharide gels are typically in the nanometer range (indicative, not established for the composite).	SAXS/SANS (data for fucoidan–alginate gels are scarce)	[11,52]

The charge density balance between alginate and fucoidan is a crucial factor in their interaction, controlling the structural organization of the fucoidan–alginate composite, in addition to contributions from pH-dependent ionization, ion-mediated cross-linking and osmotic effects. Alginate is composed of β -D-mannuronate and α -L-guluronate residues and is a polyanionic polysaccharide containing carboxyl groups with a pKa of approximately 3.4–4.4. On the other hand, fucoidan contains abundant secondary hydroxyl groups and sulfate esters ($\text{pKa} < 1.5$), thereby possessing a higher charge density. The ionization state at physiological pH is governed by the differential ionization behavior of the two polysaccharides, since at pH 7.4 fucoidan is fully deprotonated (SO_3^-) while alginate is predominantly deprotonated (COO^-) [46]. However, at extremely low pH values (< 3.4), protonation of the alginate carboxyl groups disrupts the electrostatic environment of the polymer, which weakens electrostatic repulsion and potentially leads to network contraction. Hydrogen bonding involving hydroxyl, carboxylate, and sulfate groups located along the polysaccharide chains, and intermolecular entanglement between the polysaccharide chains, is proposed to further stabilize the interaction between fucoidan and alginate. These non-covalent interactions may improve gel stability and mechanical strength by enhancing the cohesiveness of the polymer matrix [46]. Furthermore, changes in the ionic environment and polymer mixing ratio can substantially influence the degree of molecular association, thereby modulating the permeability and network density of the composite system.

5.2. Sulfate–Carboxylate Electrostatic Effects

It is important to state explicitly that alginate (carboxylate, $\text{pKa} \sim 3.4\text{--}4.4$) and fucoidan (sulfate ester, $\text{pKa} < 1.5$) are both anionic polyelectrolytes under essentially all biologically and industrially relevant pH conditions (pH above ~ 2); their like-charged carboxylate and sulfate groups therefore do not attract each other directly and are, on purely coulombic grounds, mutually repulsive. Any net favorable interaction between the two polymers must therefore be mediated by mechanisms other than direct sulfate–carboxylate electrostatic

attraction, such as multivalent cation (Ca^{2+}) bridging between chains, charge screening by co-extracted or added cationic species, short-range ion-pairing effects with counterions, or hydrogen bonding, as detailed below. While the preceding section focuses on the overall charge density and its pH dependence, this section examines the detailed electrostatic balance between sulfate and carboxylate groups. Ionic strength and the presence of counterions affect the complex equilibrium of electrostatic interactions between carboxylate groups on alginate and sulfate groups on fucoidan. Such interactions are predominantly repulsive; however, short-range interactions, such as ion pairing or water-mediated bridging between these charged groups, can generate weak attractive interactions. Interpolymer association between fucoidan and sodium alginate has been reported in both solutions and in films and it appears to be more favorable at low ionic strength [55]. It has also been proposed that some sulfate groups of fucoidan are partially shielded by positively charged protein moieties co-extracted with the polysaccharides, particularly in crude extracts [47]. Such shielding is expected to reduce repulsion (an inference from studies on alginate and other polyelectrolytes [56]) and may favor more stable hybrid networks; however, direct evidence for purified fucoidan–alginate gels is limited.

To expand on the structural aspects, the spatial arrangement of these charged groups along the polymer backbone dictates how closely the chains can pack together. In addition, variables such as molecular weight distribution and polymer concentration also heavily influence the strength of intermolecular associations. Higher concentrations force the chains into closer proximity, which ultimately governs the mechanical properties, network density, and structural stability of the alginate and fucoidan composite system.

5.3. Ca^{2+} Binding

Calcium ions (Ca^{2+}) serve two main functions in this composite system: they mediate alginate gel cross-linking and modulate the interaction with fucoidan. Alginate preferentially binds to Ca^{2+} via its guluronate-rich sequences. This specific binding conforms to the well-known egg-box model, in which calcium ions are accommodated in the cavities between paired polymer chains to stabilize the structure of the entire gel matrix.

In addition to cross-linking alginate, the strongly anionic sulfate groups in fucoidan can be partially screened by divalent Ca^{2+} binding. Such screening could reduce the repulsion between fucoidan and the negatively charged carboxylate groups of alginates and may favor the formation of hybrid networks; however, this is a plausible mechanism inferred from related systems rather than a demonstrated one. In alginate systems, Ca^{2+} has been shown to undergo ion exchange with Na^+ ions. This ion exchange induces significant changes to the hydration shell around the molecules and contributes to the stabilization of composite materials under neutral or slightly acidic conditions [48].

The Ca^{2+} -mediated modulation described above is considered to contribute to the mechanical strength and structural stability of fucoidan–alginate hydrogels, and the network density and mesh size can in principle be tuned by adjusting the ion concentration; the mechanical properties of fucoidan–alginate hydrogels have been investigated experimentally [49]. Controlling cross-linking and polymer association in this way is important for practical applications, because it determines permeability, swelling, and the release of bioactive molecules. Ca^{2+} can also affect the viscoelastic characteristics and water retention capacity of alginate hydrogels.

It should be emphasized that fucoidan does not uniformly “reinforce” alginate cross-linking; its effect is concentration- and condition-dependent and can be either reinforcing or disruptive. At low fucoidan–alginate ratios and moderate Ca^{2+} concentrations, the sulfate groups of fucoidan compete only weakly with the guluronate blocks of alginate for Ca^{2+} , and the dominant effect is the secondary hydrogen-bonding/ionic-shielding stabilization

described above, which can increase network homogeneity and mechanical strength. At higher fucoidan loadings or higher degree of fucoidan sulfation; however, fucoidan can compete more directly for available Ca^{2+} , sequestering divalent cations away from the alginate egg-box junctions; this competitive binding can reduce the effective alginate cross-linking density, increase network heterogeneity and mesh size, and enhance swelling and permeability, at the cost of mechanical stiffness. Ionic strength and the order of component addition (e.g., pre-mixing fucoidan and alginate before Ca^{2+} addition, compared with adding fucoidan to a pre-formed alginate gel) further determine which regime dominates. Consequently, whether a given fucoidan–alginate formulation behaves as a reinforced, weakened, or simply more porous network relative to alginate alone should be established empirically for each specific composition and cross-linking protocol, rather than assumed a priori from the general principle that fucoidan “enhances” the alginate network. Consistent with this, an experimental study of fucoidan in Ca^{2+} -alginate gels reported a slightly lower Young’s modulus but a markedly greater extensibility (about 90% strain before fracture) and a 3–4-fold higher compressive force with strain stiffening, whereas Ca^{2+} binding and stability in saline were similar, and low-molecular-weight fucoidan was leached out first [49]. Fucoidan therefore cannot be assumed to reinforce the alginate network.

5.4. Hydrogen Bonding

Hydrogen bonding is proposed to be one of the major mechanisms by which alginate and fucoidan interact. The hydroxyl groups ($-\text{OH}$) in fucoidan at the C2, C3, and C4 positions are capable of hydrogen bonding with the oxygen atoms of the carboxyl ($-\text{COOH}$)/carboxylate ($-\text{COO}^-$) and hydroxyl ($-\text{OH}$) groups of alginate [47]. In FTIR spectra, broadening of the band around 3400 cm^{-1} is commonly interpreted as evidence of hydrogen bonding, but this alone is not definitive proof of a specific interaction, because changes in hydration, polymer concentration, and the ionic environment can produce similar spectral changes. Molecular simulations of related polysaccharide systems suggest that such hydrogen bonds can persist over extended simulation times, which could help maintain water-holding capacity; however, this has not been demonstrated for fucoidan–alginate gels. Hydrogen bonding may contribute to mechanical strength, viscoelasticity, and hydration capability, as proposed for related fucoidan hydrogels [50]. Together with ionic cross-linking, hydrogen bonding may contribute to a compact network with tunable porosity and water retention. Stabilization at the molecular level is particularly important for drug delivery, tissue engineering, and wound-healing applications, where controlled diffusion and structural robustness are essential [57].

5.5. pH Dependent Ionization Behavior

The interaction between alginate and fucoidan is highly pH-dependent. At pH values below 3.4, the carboxylate groups in alginate are largely protonated to form carboxylic acid groups (COOH), which can lead to charge neutralization and reduced matrix stability. Conversely, at neutral to alkaline pH, the carboxylate groups of alginates are predominantly ionized, so electrostatic repulsion and swelling are greatest, and the network may swell extensively or dissolve if metal-ion-mediated cross-linking is insufficient. The ionization state is expected to be a critical factor governing changes in the structural and functional properties of the composite system under different environmental conditions. These changes affect mechanical strength, porosity, and water-retention properties, as well as hydrogen bonding, polymer chain entanglement, and electrostatic interactions [11]. On this basis, swelling behavior, diffusion rates, and ion accessibility within the network can be modulated by pH control. This tunability is particularly valuable for tissue engineering

scaffolds, pH-responsive drug delivery systems, and biomaterials that require adaptability to specific environmental conditions [52].

5.6. Donnan Equilibrium

Donnan equilibrium describes the uneven distribution of mobile ions throughout the network [53]. As a large number of fixed charges ($-\text{COO}^-$ and $-\text{OSO}_3^-$) on the polymers attract counterions (Na^+ , Ca^{2+}) into the gel, an internal osmotic pressure is generated, which promotes water inflow and regulates network hydration. The swelling behavior of fucoidan–alginate systems is governed by the osmotic pressure differential that arises from the trapped counterions within the polyelectrolyte matrix. This is well established for polyelectrolyte gels and for alginate gels, where swelling can be analyzed using Flory-Rehner theory [54]; its quantitative application to fucoidan–alginate gels has not, to our knowledge, been reported. The internal osmotic pressure not only regulates the degree of swelling and hydration, but also directly influences the density, mesh size and mechanical strength of the composite hydrogel. The amount of water uptake, stiffness, and the transport of solutes can be adjusted precisely by controlling the concentration and type of the counterions (e.g., by adding monovalent and divalent salts), which suggests that Donnan effects should be considered in the design of fucoidan–alginate hydrogels [11].

5.7. Network Density and Mesh Size

Network density and mesh size are other important physicochemical properties of fucoidan–alginate systems. These parameters may be tailored by varying the concentration of ions, the polymer ratio, and pH. Mesh sizes of ionically cross-linked polysaccharide hydrogels are generally in the nanometer range (typically a few to several tens of nanometers as determined by small-angle scattering), but direct SAXS or SANS measurements on fucoidan–alginate gels are scarce, so this range should be regarded as indicative and inferred from related systems rather than established for the composite. In general, decreasing the mesh size, for example by increasing the Ca^{2+} concentration, increases the modulus and reduces permeability; the effect of the fucoidan-to-alginate ratio on mesh size has not been established [11]. This tunability is desirable in applications such as tissue engineering and drug delivery. In addition to mechanical strength and permeability, network density and mesh size also influence the diffusion of solutes, swelling kinetics, and the encapsulation efficiency of bioactive molecules. For tissue engineering scaffolds, these parameters can be carefully tailored to control drug release, cell infiltration and nutrient transport. The interplay between ionic cross-linking, the alginate-to-fucoidan ratio, and environmental conditions is therefore a promising route for optimizing these composite hydrogels [55].

5.8. Cross-Linking Degree, Yield, and Its Relationship to Degradation

In addition to the individual electrostatic, Ca^{2+} -mediated, hydrogen-bonding and Donnan-equilibrium contributions described above, the overall extent of cross-linking (also termed reticulation) is itself a key design parameter for fucoidan–alginate networks. Cross-linking may be physical, arising from ionic bridging (e.g., the Ca^{2+} egg-box junctions between guluronate blocks) and secondary hydrogen bonding/electrostatic complexation with fucoidan sulfate groups, or covalent, introduced deliberately using bifunctional agents (e.g., genipin or glutaraldehyde where amine groups are available, or oxidized alginate (alginate dialdehyde)) to increase long-term mechanical and hydrolytic stability. The choice between physical and covalent (or dual/hybrid) cross-linking dictates the balance between reversibility, injectability and mechanical robustness required for a given application [58,59].

Quantifying the extent of cross-linking is essential for comparing formulations and for correlating network structure with function. Commonly used approaches include: equilibrium swelling-ratio measurements, in which a lower swelling ratio (and correspondingly

smaller mesh size) indicates a higher cross-linking density; rheological or compression testing, from which the shear or Young's modulus is related to cross-link density via rubber-elasticity theory; titration or colorimetric assays of residual (unreacted) functional groups (e.g., free carboxyl or sulfate groups) before and after cross-linking, which give the fraction of groups consumed in cross-link formation (the "cross-linking" or "effective cross-linker ratio"); and spectroscopic methods (^1H NMR, FTIR) that quantify the degree of modification. When combined with enzymatic or chemical degradation of the network followed by SEC-MS analysis of the resulting fragments, these methods allow the degree of cross-linking to be calculated directly [58,60].

Cross-linking density and degradation are intrinsically linked. Because ionic (Ca^{2+} -mediated) cross-links in alginate are non-covalent, they are labile to calcium-chelating species (e.g., citrate, phosphate, EDTA) and to exchange with monovalent ions in physiological fluids. Consequently, a decrease in cross-linking density over time therefore manifests as progressive swelling, loss of mechanical integrity and, ultimately, erosion of the network. More densely cross-linked hydrogels degrade more slowly and lose mass more gradually than their loosely cross-linked counterparts [58,59]. Covalent or dual (ionic + covalent) cross-linking strategies can be used to slow this chelation-driven de-cross-linking, thereby tuning the degradation rate independently of ionic strength. This approach is particularly relevant for applications such as sustained drug delivery and load-bearing scaffolds that require predictable, controllable degradation kinetics.

6. Advanced Design Strategies for Fucoidan–Alginate Systems

Before discussing specific design strategies, it is important to explicitly distinguish nanogels from macroscopic hydrogels, since the two terms are sometimes used loosely in the fucoidan–alginate literature despite substantial practical differences. Hydrogels are macroscopic, bulk three-dimensional networks (typically ranging from millimeters to centimeters in size) formed by casting, molding, injection or 3D printing; they are generally prepared and used directly (e.g., as a scaffold, dressing, or implant) and often require no dedicated downstream purification step, although washing or dialysis may be needed to remove unreacted reagents. Furthermore, they can be characterized by bulk rheology, swelling, and compression testing, and they are typically sterilized and handled as a single macroscopic object. Nanogels, in contrast, are nanoscale (generally below $\sim 1\ \mu\text{m}$, often 50–400 nm), hydrated, cross-linked polymer networks that can swell; the cross-links may be chemical or physical (for example ionic or polyelectrolyte-complex junctions). Not every nanoparticle is a nanogel: compact or solid polymer particles, polymer-coated cores and nanosized polyelectrolyte complexes are classified as nanoparticles unless a swellable cross-linked network has been demonstrated, for example by swelling behavior, a change in hydrodynamic size with pH or ionic strength, or measurements of cross-linking. Nanogels are usually prepared by ionic gelation, polyelectrolyte complexation, or emulsion and inverse-emulsion cross-linking, whereas nanoprecipitation and similar methods generally yield nanoparticles whose network character must be verified. Nanogels and nanoparticles require colloidal-stability characterization (dynamic light scattering, zeta potential and TEM/SEM), and are typically administered as a suspension (e.g., parenterally, orally or topically) rather than implanted as a solid object. Their small size dictates different drug-loading, release and biological-fate behavior (e.g., cellular uptake, systemic circulation and renal clearance become relevant, unlike in bulk hydrogels). These differences also extend to sterilization (terminal sterilization of a bulk hydrogel versus aseptic processing or filtration of a nanogel suspension) and to the translational pathway. In this review, the term "nanogel" is used only where the cited source describes a cross-linked, hydrated network; otherwise "nanoparticle" or "nanosystem" is used. Table 3 summarizes the

fucoidan–alginate systems discussed in this review and separates experimentally reported composites (Panel A) from proposed, review-based and comparator systems (Panel B). Only Panel A represents demonstrated fucoidan–alginate composites, and Table 3 is not a dataset for quantitative comparison because many entries do not report the fucoidan source, molecular weight, sulfate content, alginate M/G ratio or polymer ratio.

Table 3. Fucoidan–alginate hydrogel and nanogel systems and their evidence base. Panel A: systems in which fucoidan and alginate were combined and characterized in the cited primary study. Panel B: proposed systems, systems described only in reviews, and a comparator without alginate; Panel B is included for comparison and is not evidence of fucoidan–alginate composite performance.

System Type	Fucoidan Source	Alginate Source/M: G	F:A Ratio	Cross-Linker	Gelation Method	Size/Dimensions	Key Reported Parameters	Application (Evidence Stage)	References
Panel A—Experimentally reported Fucoidan–Alginate composites									
Hydrogel (macro)	Not specified	Not specified	Varied fucoidan content; see [49]	Ca ²⁺ (CaCl ₂ /CaCO ₃)	Ionic (egg-box) gelation, bulk casting	mm–cm scale, bulk gel	Fucoidan-containing Ca ²⁺ -alginate gels: slightly lower Young's modulus but about 90% strain before fracture, 3–4-fold higher compressive force and strain stiffening; similar Ca ²⁺ binding and stability in saline; low-molecular-weight fucoidan leached first	Biomaterial characterization/cell encapsulation (in vitro)	[49]
Hydrogel/scaffold (macro, composite)	<i>Sargassum ilicifolium</i>	Sodium alginate	Fucoidan-loaded (ratio not summarized here)	Ca ²⁺ (alginate)	Ca ²⁺ -cross-linked alginate-nano-hydroxyapatite-nano-graphene oxide scaffold	Macroscopic scaffold	Slower degradation; sustained fucoidan release over 120 h in PBS; ~1.5-fold greater C3H10T1/2 cell proliferation than the scaffold without fucoidan	Bone tissue engineering (in vitro)	[61]
Panel B—Proposed, review-based or comparator systems (not demonstrated fucoidan–alginate composites)									
Hydrogel (macro, bioprinted; proposed)	Not specified	Alginate-based inks	Not specified	Ca ²⁺ (post-print bath)	Extrusion 3D bioprinting + ionic cross-linking	Printed scaffold, mm–cm	Alginate-based inks printable after Ca ²⁺ cross-linking; fucoidan addition is proposed, not demonstrated in the cited sources	Tissue engineering (proposed; no fucoidan–alginate printing study cited)	[62,63]
Nanoparticle (alginate; nanogel character not demonstrated)	Not always specified	Alginate (internal gelation/nanoprecipitation)	Alginate core + fucoidan cargo	Ca ²⁺ /ionic gelation	Internal gelation or nanoprecipitation	100–400 nm	pH-responsive, sustained release	Oral/parenteral delivery (as summarized in a review; primary data not reviewed here)	[64]
Nanoparticle (surface-coated)	Brown seaweed	Alginate core, fucoidan surface coat	Fucoidan shell on alginate core	Electrostatic surface coating	Surface coating of pre-formed core	Sub-micron (exact size study-dependent)	Antithrombotic/anti-inflammatory/P-selectin targeting; enhanced macrophage/endothelial uptake vs. uncoated	Targeted delivery (proposed; as summarized in reviews)	[64,65]
Nanoparticle (polyelectrolyte complex; comparator, no alginate)	Brown seaweed	n/a (cationic copolymer partner, not alginate)	Fucoidan-cationic polymer	Electrostatic complexation	Polyelectrolyte complexation	Nanoscale (study-dependent)	Encapsulated methotrexate; enhanced efficacy and skin penetration	Topical anti-inflammatory delivery (as summarized in a review)	[65]

6.1. Design Principles of Fucoidan–Alginate Composite Hydrogels

Alginate can readily form hydrogels via ionic cross-linking with divalent cations, such as calcium [66]. Calcium ions bind cooperatively to the guluronic acid (G-block) regions of alginate, resulting in the formation of a 3D egg-box structure that creates physical cross-links between polymer chains and governs gelation. This principle underpins the solution spinning of alginate fibers and hydrogels in biomedical applications [64]. Alginate and fucoidan copolymer hydrogels provide a means to exploit the structural and bioactive properties of both polymer types. In such systems, alginate is generally considered the primary gelling matrix, whereas fucoidan is proposed to contribute bioactivity and to modulate drug release. These composite gels typically exhibit pseudoplastic (shear-thinning) behavior, with viscosity decreasing as the shear rate increases. Shear-thinning behavior is generally favorable for topical application because it facilitates spreading. The properties

of alginate, particularly molecular weight and the ratio between mannuronic acid and guluronic acid (M/G ratio), influence the mechanical strength and processability of the resulting hydrogels [14]. Alginate fibers from different algal sources differ in strength and flexibility, which affects their suitability for dressings and scaffolds [67]). Direct three-way comparisons of alginate alone, fucoidan alone and the composite are available for only a few properties (Table 4). On the available evidence, fucoidan's contribution is better described as complementary (alginate provides gelation, fucoidan provides bioactivity) than as a demonstrated synergistic effect.

Table 4. Comparative evidence for alginate, fucoidan, and their composite hydrogels.

Property	Alginate Alone	Fucoidan Alone	Fucoidan–Alginate Composite	Status of Direct Evidence
Ca ²⁺ gelation and mechanics	Forms egg-box gels; strength depends on M/G ratio and molecular weight [14]	Behaves mainly as a viscous solution rather than a strong gel	Fucoidan-containing Ca ²⁺ -alginate gels: slightly lower Young's modulus but markedly greater extensibility than alginate gels, with similar Ca ²⁺ binding [49]	One system [49]; no evidence of synergy; effect may depend on fucoidan content
Degradation/stability	Ionic cross-links are labile toward chelators and ion exchange	Not applicable (soluble polymer)	Fucoidan-loaded alginate–nano-hydroxyapatite–nano-graphene oxide scaffold degraded more slowly than the scaffold without fucoidan [63]	Single scaffold study [63]; may be formulation-specific
Release	Porous network can release cargo (general)	Acts as cargo or coating rather than matrix	Fucoidan released in a sustained manner over 120 h in PBS [63]	Single study [63]
Biological activity	Described as osteoconductive but bio-inert for osteoinduction [68]	Osteogenic differentiation of stem cells reported in vitro [63]	About 1.5-fold greater cell proliferation than scaffold without fucoidan, in vitro [63]	Complementary or additive at most; a fucoidan-alone arm is not described in the abstract available to us, so synergy is not tested

6.2. Responsive Gel Systems

6.2.1. pH-Responsive Hydrogels

The most advanced formulations are “smart” hydrogels, which are materials designed to change their properties in response to specific environmental triggers [69]. Such triggers can include changes in pH, temperature, or enzyme levels. The fucoidan–alginate composite is intrinsically pH-responsive, owing to alginate being a polyanionic polymer rich in carboxylic acid groups. At a low pH (e.g., in the stomach), these groups are protonated, causing the gel to shrink and retain its contents. Conversely, at higher pH (e.g., in the intestine), these groups deprotonate and become negatively charged, inducing electrostatic repulsion and making the gel network swell and release its contents [70]. Beyond the intrinsic carboxyl/sulfate groups of alginate and fucoidan, pH-responsiveness can be further tuned by grafting or blending in synthetic pH-sensitive monomers, including anionic (weak-acid) monomers such as acrylic acid and methacrylic acid, which ionize and swell at high pH, and cationic (weak-base) monomers such as N-vinylimidazole, 4-vinylpyridine, 2-(diethylamino)ethyl methacrylate (DEAEMA) and 2-(dimethylamino)ethyl methacrylate (DMAEMA), which protonate and swell at low pH; copolymerizing or interpenetrating these monomers with the fucoidan–alginate network allows the pH window and sharpness of the swelling transition to be tailored to a specific target site [69].

This property is attractive for oral drug delivery. After loading a drug or nutraceutical into the fucoidan–alginate beads, the beads shield their cargo from the harsh gastric acid and swell upon reaching the intestine, where the pH shift triggers release for subsequent absorption. Additionally, fucoidan, itself a sulfated polyanion, participates in these electrostatic interactions and can fine-tune the swelling behavior and release profile. Such “smart” behavior allows for targeted delivery to specific gastrointestinal regions, which may increase drug efficacy and reduce systemic side effects [71].

6.2.2. Temperature-Responsive Hydrogels

In addition to pH responsiveness, thermoresponsive behavior can be incorporated into fucoidan–alginate systems by grafting or blending in polymers that display a lower critical solution temperature (LCST), the temperature above which the polymer transitions from a hydrated, hydrophilic coil to a collapsed, hydrophobic globule. The most widely used LCST polymer is poly(N-isopropylacrylamide) (PNIPAM), which has an LCST of approximately 32 °C. Because this is close to physiological temperature, making it attractive for in situ gelling, injectable formulations [72]. Alginate-g-PNIPAM and related graft copolymers combine the ionic (Ca^{2+}) gelation of alginate with the thermal collapse of PNIPAM side chains, yielding dual pH/temperature-responsive or shear-thinning, thermally gelling hydrogels whose sol–gel transition and rheological properties of these systems can be tuned by adjusting the PNIPAM content and grafting density [73]. Incorporating a similar thermoresponsive component into fucoidan–alginate composites represent a promising, largely unexplored strategy for producing injectable systems that gel spontaneously at body temperature while retaining the bioactivity conferred by fucoidan.

6.2.3. 3D Bioprinting with Fucoidan–Alginate Bio-Inks

3D bioprinting represents a paradigm shift in tissue engineering based on additive manufacturing principles. It enables the use of a computer 3D model (derived from patient CT scans) to construct accurate, multiscale, multilayered structures in situ that mimic the native architecture of human tissue. At the heart of this technology is the bio-ink, a printable substance that may include living cells. One of the most common polymers for bio-ink formation is alginate, because its solutions are viscous (and hence printable) and can be cross-linked by immersion in a calcium chloride solution, thus maintaining the printed shape [61]. However, while alginate provides excellent structural support, it lacks biological cues that prompt cells to grow, proliferate, or differentiate into new tissue [1]. Incorporating fucoidan in an alginate bio-ink could add bioactivity; fucoidan has been reported to influence cell attachment, growth and differentiation in other settings. For instance, fucoidan has been reported to be pro-angiogenic; that is, it induces the formation of new blood vessels which is crucial for sustaining large printed tissue constructs. Alginate-based bio-inks have been used to print scaffolds for cartilage tissue engineering [62]; adding fucoidan is a logical extension, but the sources cited here do not report printed fucoidan–alginate constructs, so this remains a proposal.

6.2.4. Injectable Hydrogels

Another significant advance is the development of injectable hydrogels for minimally invasive therapy. The ideal scenario is to have the liquid material loaded into a syringe that immediately gels upon injection into the body. This enables the repair of damaged tissues, such as knee cartilage, or the localized deposition of drugs without the need for open surgery. Fucoidan–alginate composites are proposed for this purpose because shear-thinning (pseudoplastic) behavior is expected. Specifically, while in the syringe, the gel remains thick and solid-like; however, when pressure is applied (during injection), its viscosity decreases, enabling it to flow easily through a small-gauge needle. Upon pressure

release, viscosity recovers at the injection site [74]. This process enables in situ gelation through the assembly of cross-linked materials. For instance, a fucoidan–alginate solution can be co-injected with a Ca^{2+} solution, allowing it to form a gel in situ at the target site. The potential advantage of such a system is that the hydrogel is not merely a passive scaffold [64]; rather, fucoidan could act as a therapeutically active depot. Injectable alginate gels have been applied to stem cell delivery, where the gel can protect cells during injection; correspondingly, a role for fucoidan in promoting cell survival and differentiation has been proposed [75].

6.3. Nanogel and Nanoparticle Design Strategies

The anionic nature of fucoidan, attributable to its sulfate ester groups, enables ionic complexation with cationic polymers or molecules—an approach often employed in the development of nanogels and nanoparticles for sustained drug delivery. Through polyelectrolyte complexation, fucoidan can form stable nanocarriers with positively charged biopolymers. Such systems have been investigated for the encapsulation of anti-inflammatory and other drugs [65]. Fucoidan can also serve as the shell or core for these nanosystems [71]. Surface bioactivity (e.g., antithrombotic, anti-inflammatory, or anticancer properties) and biocompatibility can be imparted to nanoparticles by incorporating fucoidan into their shells. The properties of fucoidan, such as molecular weight, solubility, sulfation degree, and pH responsiveness, may be used to tailor the functionality, drug loading efficiency, and release kinetics of these nanosystems [65,71].

Although the best-documented fucoidan-based nanosystems in the literature are based on fucoidan–chitosan polyelectrolyte complexes, fucoidan–alginate nanosystems have been described much less frequently. Two strategies for constructing fucoidan–alginate nanosystems have been reported. In the first, alginate nanoparticles (nanogels where a cross-linked, hydrated network is shown), formed by internal gelation or nanoprecipitation, are used as the structural matrix, and fucoidan is added as a bioactive cargo. In the second, alginate nanoparticle cores are coated with fucoidan; because fucoidan and alginate are both anionic, this coating cannot rely on direct electrostatic attraction and instead requires a cationic linker or Ca^{2+} bridging. Both strategies are summarized in [64]. We did not identify primary studies that fully characterize fucoidan–alginate nanoparticles (size, zeta potential, loading, release, and biological response), so values for these properties cannot be compared with those of the hydrogels. Systematic investigation of the effects of fucoidan molecular weight, sulfation degree, and alginate M/G ratio on nanoparticle size, zeta potential, drug loading and release kinetics will be essential for establishing rational design rules for this class of all-marine nanosystems.

7. Advanced Applications in Tissue Engineering and Regenerative Medicine

Before the individual applications are discussed, the strength of the underlying evidence should be stated plainly (Table 5). To our knowledge, the only cited primary study that clearly combines alginate and fucoidan in a single scaffold [63], and it reports in vitro data only. The other cited works are reviews, studies of fucoidan or alginate alone, or studies of either polymer combined with other materials. Statements below about fucoidan–alginate composites are therefore largely extrapolations from the separate polymers, and are worded accordingly. The limitations discussed above (anticoagulant activity of highly sulfated fucoidan, source variability, sterilization effects, degradation products, immunogenicity, long-term biocompatibility, dose standardization, and the regulatory classification of combination biomaterials) apply to every application below, and the clinical translation of fucoidan–alginate composites should be regarded as being at an early preclinical stage.

Table 5. Level of evidence supported by the main sources. Classification is based on the cited sources' titles and abstracts; it indicates what each source supports, not the efficacy of the materials.

Application	Material (As Stated in the Source)	Study Type	Presence of Both Alginate and Fucoidan	Evidence Level Supported	References
Bone	Ca ²⁺ -cross-linked alginate–nano-hydroxyapatite–nano-graphene oxide scaffold loaded with fucoidan	Primary study	Yes	In vitro (proliferation, degradation, release, apatite formation)	[63]
Bone	Alginate composite hydrogels	Review	Not composite-specific	Secondary source	[76]
Cartilage	Marine polysaccharides in tissue engineering; cytokines in cartilage engineering and osteoarthritis	Book chapter; review	No	Secondary sources; no fucoidan–alginate cartilage data	[77,78]
Nerve	Peripheral nerve regeneration; nerve guide conduits for optic nerve regeneration	Reviews	No	Secondary sources; no fucoidan–alginate conduit data	[79,80]
Wound healing	Fucoidan-gelatin dressing	Primary study	No (gelatin, not alginate)	Primary data on a related system; not assessed further here	[81]
Wound healing	Alginate-based dressings	Systematic review	No fucoidan	Secondary source	[82]
Wound healing/immunomodulation	Alginate of varying M/G ratio; Sr ²⁺ -cross-linked hydrogel (alginate, carboxymethyl chitosan, naringin)	Primary studies	No fucoidan	Primary data on alginate-based systems	[83,84]
Anti-inflammatory	Injectable self-healing fucoidan hydrogel; fucoidan fraction and fraction-based hydrogel	Primary studies in vitro and in vivo, per its title	Alginate not indicated in the titles	Fucoidan-based hydrogels; composition to be checked in the sources	[85,86]
Drug/growth-factor delivery	Fucoidan in pharmaceutical formulations; fucoidan-based nanomaterials; hybrid wound scaffolds	Reviews	Not composite-specific	Secondary sources	[64,87,88]
Anticancer	Fucoidans from four brown algae, alone and with paclitaxel, in HeLa G-63 cells	Primary study	No alginate	In vitro	[28]

7.1. Bone Tissue Engineering

Reconstructing large bone defects caused by trauma and disease remains a major clinical challenge [89]. A successful bone scaffold should not only serve as a temporary structure for the ingrowth of new bone (i.e., osteoconduction), but also provide signals that instruct stem cells to differentiate into bone-forming cells (osteoblasts)—a process known as osteoinduction (Figure 4). When used alone, alginate is an excellent osteoconductive scaffold; however, it is bioinert and does not induce new bone formation [76]. Fucoidan has been proposed to supply such a bioactive signal [90]. Fucoidan has been reported to promote the osteogenic differentiation of mesenchymal stem cells in vitro; a role in modulating inflammation at a defect site is plausible from its general anti-inflammatory activity but has not been shown for the scaffolds cited here. The only cited study that combines alginate and fucoidan in a bone scaffold used a Ca²⁺-cross-linked alginate–nano-hydroxyapatite–nano-graphene oxide matrix loaded with fucoidan from *Sargassum ilicifolium*; in vitro, the fucoidan-loaded scaffold showed slower degradation, sustained fucoidan release over 120 h in PBS, and about 1.5-fold greater proliferation of C3H10T1/2 cells than the scaffold without fucoidan [63]. Alginate composite hydrogels for bone repair [76], and porous sponge scaffolds of related polysaccharide-hydroxyapatite composites have been described [91]. Evidence stage: in vitro only for fucoidan–alginate scaffolds; the sources cited here report no in vivo or clinical data for such scaffolds, so improved bone regeneration relative to alginate alone has not been demonstrated.

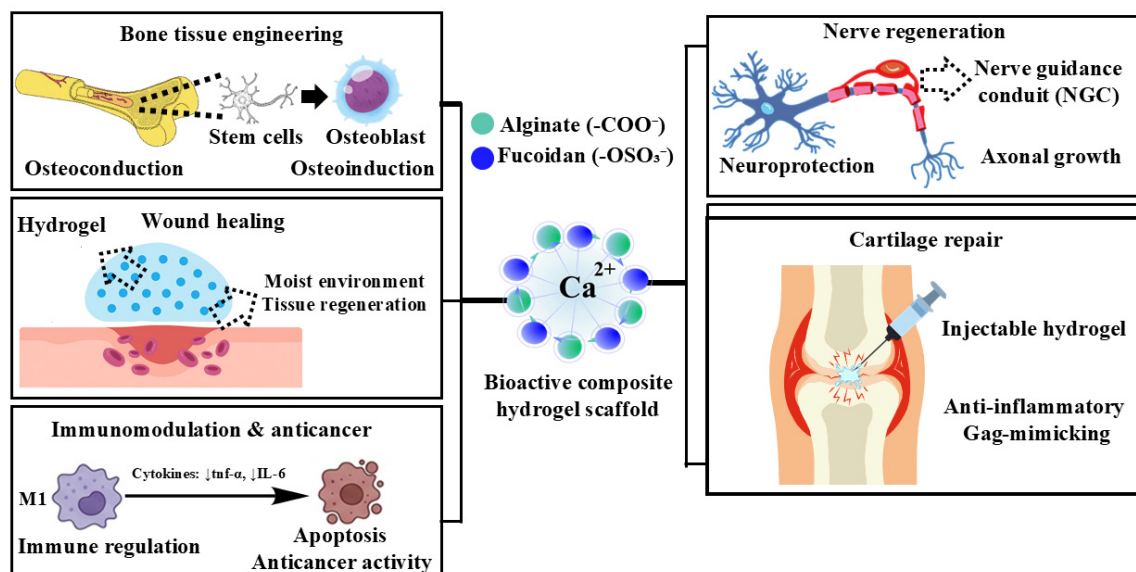


Figure 4. Biomedical applications of fucoidan–alginate composite hydrogels. Calcium cross-linked fucoidan–alginate hydrogels are promising for bone tissue engineering, wound healing, immunomodulation, nerve regeneration, and cartilage repair, owing to their biocompatibility, bioactivity, and regenerative properties. The figure is a schematic overview of applications that have been proposed or investigated. The level of evidence for fucoidan–alginate composites differ between applications and is mostly in vitro or preclinical.

7.2. Articular Cartilage Repair

Articular cartilage, the thin tissue that covers the ends of bones in joints, is particularly challenging to repair due to its lack of a blood supply (it is avascular) [92]. Cartilage damage, frequently caused by sports injuries or osteoarthritis, is largely irreversible and represents a major source of pain. Injectable hydrogels are widely proposed as a minimally invasive approach for this purpose. A fucoidan–alginate composite could, in principle, be injected as a liquid into the cartilage defect and gel in situ to conform to the lesion [77]. Two roles for fucoidan in such a system are plausible. First, fucoidan has been reported to have anti-inflammatory activity [75]. In an osteoarthritic joint, chronic inflammation is the primary driver of cartilage degradation. It has been proposed that an injected gel would remain in the joint and provide sustained local delivery that attenuates inflammation, but this has not been shown for fucoidan–alginate gels in the sources cited here. Second, fucoidan is a sulfated polysaccharide, whereas glycosaminoglycans (GAGs) are major components of the native cartilage matrix [93]. Fucoidan might mimic some roles of these GAGs, for example water attraction; however, this is merely a hypothesis. The roles of pro- and anti-inflammatory cytokines in cartilage tissue engineering and osteoarthritis treatment are discussed [78], which does not report data on fucoidan–alginate composites.

7.3. Peripheral Nerve Regeneration

Peripheral nerve repair is a potential, yet challenging, application [79]. When a nerve in an arm or leg is severed, it must be sutured precisely back together to enable regrowth. For relatively large gaps, surgeons frequently employ a nerve guidance conduit (NGC), a hollow tube connecting the two ends of the severed nerve. However, while the tube provides a physical track, successful axonal regeneration often fails to occur if the internal microenvironment is not supportive. In a fucoidan–alginate conduit, alginate would be expected to provide a soft structural “track” for the nerve to grow across, while fucoidan has been reported in the broader literature to protect nerve cells from oxidative stress and to promote neurite extension (the small “fingers” that nerve cells extend). If

confirmed, promoting neurite outgrowth within a conduit could improve the likelihood of regeneration [80].

7.4. Wound Healing

Owing to its ability to form gels, retain moisture, and biodegrade, thereby promoting a moist healing environment and tissue regeneration, alginate is commonly employed in wound dressings and tissue scaffolds [82]. Encapsulating fucoidan into alginate matrices has been proposed to promote healing by inducing cell migration, regulating inflammation and accelerating granulation tissue formation. As indirect support, a fucoidan-gelatin dressing (without alginate) accelerated wound healing with antibacterial and anti-inflammatory activity [81]. Such systems may provide a biologically active microenvironment for cell proliferation and extracellular matrix remodeling. Fucoidan has been reported to enhance angiogenic responses by binding to growth factors, whereas alginate forms a hydrated 3D matrix that supports nutrient transport and cell infiltration. A combination of the two polymers has been proposed to improve dressing stability and promote granulation tissue formation, collagen synthesis and re-epithelialization; whether, this is synergistic or merely additive has not been tested directly. Fucoidan–alginate hydrogels may therefore be of interest for chronic wounds and skin regeneration, but this remains to be shown experimentally. Evidence stage: for fucoidan–alginate dressings specifically [15,94] the primary evidence cited concerns fucoidan-gelatin or alginate-based materials. No clinical trial of fucoidan–alginate dressings is cited, whereas alginate-based dressings alone have been reviewed systematically [82].

7.5. Drug and Growth Factor Delivery

The porous structure of alginate hydrogel networks permits the easy incorporation and controlled release of bioactive agents (e.g., small-molecule drugs, proteins and growth factors, essential oils, and probiotic or living cells). Incorporating fucoidan into alginate-based formulations imparts not only sustained release properties but also additional bioactivity, which is proposed to improve cellular uptake and controlled release. Hybrid hydrogels and nanogels of marine polysaccharides have been described for the transdermal delivery of essential oils (EOs), growth factors and small-molecule drugs [94]. Fucoidan-based hydrogels and nanoparticles have been investigated as delivery systems for a variety of therapeutic agents. For instance, fucoidan-based nanoparticles for delivering anticancer drugs such as doxorubicin have been reported to show sustained drug release and improved tumor-site delivery in preclinical studies [87]. Hybrid wound scaffolds for the localized delivery of growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [88]. Composite systems have also been proposed as carriers for stem cells, proteins and anti-inflammatory agents. These reports indicate potential for targeted therapy, regenerative medicine and controlled drug delivery. Evidence stage: The delivery statements above rest on review articles [15,88,94] rather than on the primary studies of fucoidan–alginate carriers; the underlying data are *in vitro* or preclinical, and no clinical-stage or approved fucoidan–alginate delivery product is cited here.

7.6. Anti-Inflammatory and Anticancer Activity

Fucoidan has been reported to have anti-inflammatory and anticancer activities, including inhibition of pro-inflammatory cytokines and angiogenesis and induction of apoptosis in cancer cells [28,75]. Incorporation into an alginate delivery system has been proposed to localize these activities and to reduce systemic exposure, but enhanced efficacy of the composite relative to free fucoidan has not been shown in the sources cited here. Alginate is expected to provide the structural integrity needed for sustained fucoidan release; an injectable, self-healing fucoidan hydrogel with anti-inflammatory activity has been

described [86]. It has been suggested that fucoidan–alginate composites could serve as multifunctional platforms that both deliver drugs and have inherent biological activity. Fucoidan’s sulfated structure enables interactions with growth factors, cytokines, and cell surface receptors, further contributing to its role in modulating cellular signaling pathways during inflammation and tumor progression. These interactions prolong the residence time of bioactive molecules at the target tissue within hydrogel and nanogel formulations, which could enhance local activity. Furthermore, the porosity and cross-linking density of alginate matrices can be tuned to achieve the desired release rate; fucoidan–alginate composites may therefore be of interest for localized cancer therapy, post-surgical tumor treatment, and chronic inflammatory diseases, which require prolonged release and minimal off-target effects. Evidence stage: hypothesis-level to preclinical. The anticancer statements rest on studies of fucoidan itself (e.g., in vitro cytotoxicity and paclitaxel combination in HeLa cells [28]) and on reviews; no study of a fucoidan–alginate carrier for cancer therapy is cited here, and no clinical evidence is cited.

7.7. Immunomodulatory Potential

The immunomodulatory properties of fucoidan, a sulfated polysaccharide mainly found in brown algae, have been reported to include both the polarization of macrophages toward the anti-inflammatory M2 phenotype and the inhibition of pro-inflammatory cytokines such as TNF- α and IL-6 [95,96]. Fucoidan can also modulate dendritic cell maturation. Whether these capabilities are preserved after incorporation into a hydrogel depends on the accessibility of sulfate groups and on release, and has not been established for fucoidan–alginate composites in the sources cited here. Studies have shown that fucoidan can inhibit N-acetylgalactosaminidase, an enzyme produced by tumor- and virus-infected cells that contributes to immune suppression by deactivating macrophage-activating factor. This inhibition helps normalize the immune response [93]. Alginate-based hydrogels have been described as having improved immune compatibility and an antioxidant effect [97]; this concerns alginate and does not show an effect of fucoidan. Specific fucoidan fractions, such as JHCF4 from *Sargassum fusiforme*, inhibited nitric oxide (NO) production in LPS-induced RAW 264.7 macrophages, with an IC₅₀ of 23.35 μ g/mL, and attenuated the secretion of prostaglandin E₂, TNF- α and IL-6 [85]. Moreover, the mannuronic-to-guluronic acid ratio in alginate can impact its anti-inflammatory properties by modulating macrophage polarization. Alginates with higher M/G ratios have been shown to influence macrophage migration and differentiation [92]. A multifunctional hydrogel comprising sodium alginate, carboxymethyl chitosan, naringin, and Sr²⁺ demonstrated M2 macrophage polarization, which contributes to its antibacterial, antioxidant, and anti-inflammatory functions in wound healing. Evidence stage: the immunomodulatory data cited are in vitro data for isolated fucoidan fractions and data for alginate-only or alginate-other-polymer hydrogels [83,85] also reports in vivo data for a fucoidan-based hydrogel. Immunomodulation by a fucoidan–alginate composite is not demonstrated in the sources cited here.

8. Safety, Regulatory, and Scalability of Marine Polysaccharides

8.1. Regulatory and Safety Considerations

To ensure the safety and regulatory compliance of marine polysaccharides, such as fucoidan and alginate, in pharmaceutical and biomedical applications, their comprehensive characterization is essential [87]. Their structural complexity and biological functionality require in-depth analysis to support safety, efficacy, and quality uniformity [98]. All these parameters are important and are significantly affected by extraction and processing methods, which in turn influence the feasibility of large-scale production and environmental performance [18].

In addition to the regulatory characterization, the safety of fucoidan–alginate composite hydrogels and nanogels is crucial for their biomedical and pharmaceutical applications. Both polysaccharides are considered biocompatible and biodegradable, but the complete safety profile will depend on polymer purity, molecular weight, degree of sulfation and formulation composition. Unwanted biological responses can arise from residue of seaweed biomass, such as proteins, heavy metals, endotoxins, and high iodine concentrations, if these impurities are not properly removed during processing. Furthermore, the anticoagulant activity of highly sulfated fucoidan fractions may affect blood coagulation pathways and thus needs to be carefully evaluated in biological studies. Therefore, comprehensive cytotoxicity, hemocompatibility, immunogenicity, and long-term biocompatibility assessments are essential to ensure the safe clinical translation of fucoidan–alginate composite systems [33]. These evaluations confirm the consistency and safety of the material, reinforcing its therapeutic benefits and overall safety profile. For regulatory compliance and product stability and batch-to-batch uniformity during scale-up, standardization of the analytical procedures and rigorous quality control are necessary [99]. Beyond the general categories noted above, fucoidan–alginate composite-specific safety evaluation should explicitly address: the anticoagulant activity of fucoidan, which depends on both molecular weight and sulfation degree and can be either a desirable bioactivity or an important safety liability depending on the clinical context (e.g., it may be contraindicated in perioperative or bleeding-risk settings); residual extraction reagents (e.g., acids, organic solvents, or DES components) that may remain in the final material; algal-source variability (species, harvest season, geographical origin), which affects batch-to-batch composition and therefore safety margins; degradation products generated as the composite erodes *in vivo*, which should themselves be evaluated for toxicity; and the effects of the sterilization method (e.g., autoclaving, gamma irradiation, ethylene oxide) on molecular weight, sulfation pattern and bioactivity, since several common sterilization methods are known to depolymerize sulfated polysaccharides. Further translational gaps include the lack of human data for fucoidan–alginate composites, limited long-term biocompatibility and degradation-product data, dose standardization for a bioactive polymer whose activity depends on molecular weight and sulfation, and the regulatory classification of such materials (for example, as a medical device, a combination product or a drug-delivery system), which depends on the jurisdiction and intended use and must be clarified on a case-by-case basis.

Food applications (e.g., encapsulation matrices, edible films, functional ingredients) primarily require compliance with food-additive purity limits (e.g., heavy metals, microbial load), acceptable sensory properties, and cost-effective, non-sterile manufacturing, with degradation needing only to be compatible with shelf-life and digestion. Biomedical applications (e.g., implantable scaffolds, injectable hydrogels, parenteral nanoparticles), by contrast, require pharmaceutical-grade purity. This includes the removal of endotoxins, residual proteins and heavy metals to much lower thresholds, as well as aseptic or terminal sterilization that does not degrade the polysaccharide or its bioactivity, well-defined and reproducible mechanical performance and degradation kinetics matched to the tissue-healing timeline, and compliance with medical-device or drug-product regulatory pathways) rather than food-safety pathways. Consequently, a fucoidan–alginate formulation validated for food use cannot be assumed to be safe or functionally adequate for biomedical use, and vice versa; the specific translational pathway and associated requirements should be specified explicitly whenever a formulation strategy is proposed in this review.

8.2. Scalability and Environmental Sustainability

Efficient, sustainable and economically viable extraction methods are critical to the commercial success of marine polysaccharides. Traditional extraction methods, such as

acid, solvent, or hydrothermal treatment, consume large amounts of energy and generate chemical wastes; they are therefore generally considered less suitable for sustainable large-scale production [25]. Emerging green alternatives—including microwave-assisted extraction, ultrasound-assisted extraction, enzyme-assisted extraction, pressurized liquid extraction, and subcritical water extraction—offer potential solutions [100]. These methods are reported to reduce solvent consumption, energy requirements or extraction time and, in some studies, to improve yield, though their effects on purity and molecular integrity vary. Supercritical CO₂ extraction is also of interest because CO₂ is nontoxic [32]; however, its suitability for polar polysaccharides such as fucoidan and alginate has not been established. Regulatory compliance and scalability will probably depend on analytical validation combined with extraction strategies whose environmental performance is actually quantified [101]. Standardizing these processes can support product safety and reproducibility, but does not in itself guarantee safety or environmental responsibility [102]. In practical terms, ultrasound- and enzyme-assisted extraction are generally regarded as closer to scale-up, since the equipment and enzymes are commercially available, whereas microwave-assisted, subcritical water and supercritical CO₂ extraction are less mature and need higher capital investment; however, we did not identify techno-economic or life-cycle data comparing these methods for fucoidan or alginate, so this ranking is a qualitative judgment. Deep eutectic solvent-based extraction is of interest because DES components can be of low toxicity and potentially recyclable, but solvent recovery and reuse, residual solvent in the product and economic viability at scale have not been established [22]. Consequently, environmental sustainability (reduced solvent/energy use, biodegradable reagents) and economic and technical scalability do not always improve in parallel, and this trade-off, rather than a uniform “green equals scalable” assumption, should guide technology selection for a given production scale.

Ultimately, large-scale production of fucoidan–alginate hydrogels remain a challenge, despite encouraging laboratory-scale results. Algal species, harvesting season, geographical origin, molecular weight distribution, sulfation pattern, and alginate M/G ratio can all have a significant impact on the performance and reproducibility of hydrogels. In addition, gelation parameters, cross-linking density, viscosity, mechanical properties, and drug release characteristics must be carefully controlled during industrial manufacturing to achieve batch-to-batch uniformity. Other challenges include sterility, storage stability, transport, good manufacturing practice (GMP), preservation of bioactivity, and cost-effectiveness. Addressing these challenges is a prerequisite for the commercialization and clinical application of fucoidan–alginate-based biomaterials, and the field is still some distance from clinical use.

8.3. Future Directions

Future research should focus on several key areas to facilitate the industrial translation of fucoidan–alginate hydrogels. First, standardized extraction, purification, and characterization protocols should be established to minimize variations arising from algal species, harvesting seasons, and geographical origins, thereby improving reproducibility and batch-to-batch consistency [70]. Second, comprehensive polysaccharide fingerprint databases integrating molecular weight distribution, monosaccharide composition, sulfation patterns, M/G ratios, and spectroscopic data should be developed to support quality control, raw material selection, and product standardization [103]. Third, high-throughput bioactivity evaluation platforms should be established to efficiently screen polysaccharides with desirable biological functions and predict their therapeutic potential [104]. Fourth, systematic studies that compare alginate alone, fucoidan alone and the composite under identical conditions are needed to establish whether effects are additive, synergistic or antagonistic.

Finally, data-driven modeling could address specific unresolved problems identified in this review. These include predicting how fucoidan sulfate content and molecular weight, as well as alginate M/G ratio jointly affect modulus, swelling, and mesh size at a given Ca^{2+} concentration, pH, and ionic strength; optimizing extraction parameters, such as ultrasonic power and time, to retain the molecular weight and sulfate content needed for gelation; and linking molecular fingerprints to release kinetics and cell responses. Model inputs would include molecular weight, sulfation degree and position, M/G ratio, polymer ratio, Ca^{2+} concentration, pH, and ionic strength; outputs would include G' , G'' , swelling ratio, mesh size, release-rate constants, and cell-response metrics. AI-assisted approaches have been applied to polysaccharide hydrogel design more broadly [105], but their use for fucoidan–alginate composites is limited by a lack of systematic, comparable datasets, which therefore must come first.

9. Conclusions

Fucoidan–alginate composite nanogels and hydrogels represent an interesting class of marine-derived biomaterials that combine the gelling versatility of alginate with bioactivity reported for fucoidan. While biocompatibility and sustainability are expected, they have been demonstrated only to a limited extent for these composites. This review highlights the complementary roles of the sulfated, fucose-rich fucoidan and the ionically cross-linkable guluronic acid blocks of alginate in forming 3D networks with potentially tunable release, water retention and mechanical strength. Genuine synergy has rarely been tested, and the available direct comparisons indicate that the effect of fucoidan on the alginate network depends on concentration and Ca^{2+} conditions. These platforms have been widely investigated for biomedical and functional food applications, including wound healing, tissue regeneration, drug/growth factor delivery, the encapsulation of bioactive compounds, and active food packaging; however, most reported systems remain at the laboratory or preclinical stage rather than in clinical or commercial use. Greener extraction technologies (such as ultrasound-assisted, microwave-assisted and enzyme-assisted extraction) may lower the environmental impact of obtaining these polymers, but this has not yet been supported by life-cycle or techno-economic data. The field remains at an early stage: most evidence is *in vitro* or preclinical, human data are lacking, and further challenges include the structural variability of fucoidan, incomplete knowledge of intermolecular interactions, safety questions such as anticoagulant activity, and difficulties in scalability and regulatory standardization. The approaches to characterization, cross-linking quantification and stimuli-responsive design discussed here may be transferable to other sulfated or carboxylated polysaccharide composites, although the dominant interactions differ between systems. Progress will depend on resolving the mechanistic, safety, scalability and regulatory questions identified in this review. This will require integrated analytical tools and structure–function design, and on direct comparative studies that separate the effects of fucoidan, alginate and their combination, supported by *in vivo* and clinical testing.

Author Contributions: K.: Writing—original draft, Methodology, Investigation, Conceptualization. T.-Z.M.: Methodology, Writing—review and editing. Q.-Y.X.: Methodology, Writing—review and editing. K.-L.C.: Writing—review and editing. S.Y.: Writing—review and editing. U.A.: Writing—review and editing. M.A.R.: Writing—review and editing. S.-Y.Z.: Writing—review and editing, Supervision. R.L.: Writing—review and editing, Supervision, Project administration, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Guangdong Basic and Applied Basic Research Foundation (2026A1515011668, 2025A1515011519), the Shenzhen Science and Technology Program (KCXFZ20240903094014019), the Key Research Projects of Guangdong Provincial Universities (2025ZDZX2029), the Special Funds for Universities in Guangdong Province in the Key Areas of

Biomedicine and Health (2023ZDZX2025), the Cross-Innovation Open Project of Food Flavor and Health, Beijing Technology and Business University (FFHCI-2026068) and the Program for Scientific Research Start-up Funds of Guangdong Ocean University (R20078).

Institutional Review Board Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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

Abbreviations

The following abbreviations are used in this manuscript:

M/G	Mannuronic acid/Guluronic acid ratio
UAE	Ultrasound-Assisted Extraction
MAE	Microwave-Assisted Extraction
EAE	Enzyme-Assisted Extraction
RSM	Response Surface Methodology
HPAEC	High-Performance Anion-Exchange Chromatography
HPAEC-PAD	High-Performance Anion-Exchange Chromatography–Pulsed Amperometric Detection
HPLC	High-Performance Liquid Chromatography
PMP	1-Phenyl-3-Methyl-5-Pyrazolone
PMP-HPLC	Precolumn PMP derivatization–High-Performance Liquid Chromatography
NMR	Nuclear Magnetic Resonance
¹ H-NMR	Proton Nuclear Magnetic Resonance
HMBC	Heteronuclear Multiple Bond Correlation
GC-MS	Gas Chromatography–Mass Spectrometry
SEC	Size-Exclusion Chromatography
RI	Refractive Index
G′	Storage Modulus
G″	Loss Modulus
3D	Three-Dimensional
bFGF	Basic Fibroblast Growth Factor
IL-6	Interleukin-6
NO	Nitric Oxide
GMP	Good Manufacturing Practices
AI	Artificial Intelligence
FTIR	Fourier-transform infrared spectroscopy
GPC	Gel permeation chromatography
LCST	Lower critical solution temperature
PNIPAM	Poly(N-isopropylacrylamide)
DES	Deep eutectic solvent
DEAEMA	2-(Diethylamino)ethyl methacrylate
DMAEMA	2-(Dimethylamino)ethyl methacrylate
LCA	Life cycle assessment
SAXS	Small-angle X-ray scattering
SANS	Small-angle neutron scattering
MALS	Multi-angle light scattering
ESI-MS	Electrospray ionization tandem mass spectrometry
EDTA	Ethylenediaminetetraacetic acid
VEGF	Vascular endothelial growth factor
TNF-α	Tumor necrosis factor alpha

LPS	Lipopolysaccharide
PBS	Phosphate-buffered saline
GAGs	Glycosaminoglycans
NGC	Nerve guidance conduit
IC ₅₀	Half-maximal inhibitory concentration
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ISO	International Organization for Standardization
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
SEC-MALLS	Size-exclusion chromatography coupled with multi-angle laser light scattering

References

- Samalens, F.; Thomas, M.; Claverie, M.; Castejon, N.; Zhang, Y.; Pigot, T.; Blanc, S.; Fernandes, S.C.M. Progresses and future prospects in biodegradation of marine biopolymers and emerging biopolymer-based materials for sustainable marine ecosystems. *Green Chem.* **2022**, *24*, 1762–1779. [\[CrossRef\]](#)
- Xie, C.; Lee, Z.J.; Ye, S.; Barrow, C.J.; Dunshea, F.R.; Suleria, H.A.R. A Review on Seaweeds and Seaweed-Derived Polysaccharides: Nutrition, Chemistry, Bioactivities, and Applications. *Food Rev. Int.* **2024**, *40*, 1312–1347. [\[CrossRef\]](#)
- Liu, T.; Ren, Q.; Wang, S.; Gao, J.; Shen, C.; Zhang, S.; Wang, Y.; Guan, F. Chemical modification of polysaccharides: A review of synthetic approaches, biological activity and the structure–activity relationship. *Molecules* **2023**, *28*, 6073. [\[CrossRef\]](#) [\[PubMed\]](#)
- Yang, J.; Wang, S. Polysaccharide-based multifunctional hydrogel bio-adhesives for wound healing: A review. *Gels* **2023**, *9*, 138. [\[CrossRef\]](#) [\[PubMed\]](#)
- Chen, Y.; Zhang, N.; Chen, X. Structurally modified polysaccharides: Physicochemical properties, biological activities, structure–activity relationship, and applications. *J. Agric. Food Chem.* **2024**, *72*, 3259–3276. [\[CrossRef\]](#) [\[PubMed\]](#)
- Otero, P.; Carpena, M.; Garcia-Oliveira, P.; Echave, J.; Soria-Lopez, A.; Garcia-Perez, P.; Fraga-Corral, M.; Cao, H.; Nie, S.; Xiao, J.; et al. Seaweed polysaccharides: Emerging extraction technologies, chemical modifications and bioactive properties. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 1901–1929. [\[CrossRef\]](#) [\[PubMed\]](#)
- Sousa, V.; Monteiro, L.P.G.; Rocha, D.H.A.; Rodrigues, J.M.M.; Borges, J.; Mano, J.F. Marine-origin polysaccharides and their chemically modified derivatives as sources of advanced biofunctional materials for biomedical applications. *Biomacromolecules* **2025**, *26*, 4735. [\[CrossRef\]](#) [\[PubMed\]](#)
- Lin, J.; Jiao, G.; Kermanshahi-Pour, A. Algal polysaccharides-based hydrogels: Extraction, synthesis, characterization, and applications. *Mar. Drugs* **2022**, *20*, 306. [\[CrossRef\]](#) [\[PubMed\]](#)
- Zhao, T.; Yang, M.; Ma, L.; Liu, X.; Ding, Q.; Chai, G.; Lu, Y.; Wei, H.; Zhang, S.; Ding, C. Structural modification and biological activity of polysaccharides. *Molecules* **2023**, *28*, 5416. [\[CrossRef\]](#) [\[PubMed\]](#)
- Davydova, V.N.; Sorokina, I.V.; Volod'ko, A.V.; Sokolova, E.V.; Borisova, M.S.; Yermak, I.M. The comparative immunotropic activity of carrageenan, chitosan and their complexes. *Mar. Drugs* **2020**, *18*, 458. [\[CrossRef\]](#) [\[PubMed\]](#)
- Hao, Y.; Zheng, W.; Sun, Z.; Zhang, D.; Sui, K.; Shen, P.; Li, P.; Zhou, Q. Marine polysaccharide-based composite hydrogels containing fucoidan: Preparation, physicochemical characterization, and biocompatible evaluation. *Int. J. Biol. Macromol.* **2021**, *183*, 1978–1986. [\[CrossRef\]](#) [\[PubMed\]](#)
- Fanina, S.; Casillo, A.; Corsaro, M.M. Mediterranean seaweed polysaccharides: Insight into chemical structures, applications, and structure/application correlations. *Mar. Drugs* **2025**, *24*, 11. [\[CrossRef\]](#) [\[PubMed\]](#)
- Siddiqua Prova, O.; Afrin, S.; Tabish, T.A.; Rizwan, M. Fucoidan based hydrogel biomaterials for tissue engineering. *Biomater. Sci.* **2025**, *13*, 6572–6597. [\[CrossRef\]](#) [\[PubMed\]](#)
- Abka-Khajouei, R.; Tounsi, L.; Shahabi, N.; Patel, A.K.; Abdelkafi, S.; Michaud, P. Structures, properties and applications of alginates. *Mar. Drugs* **2022**, *20*, 364. [\[CrossRef\]](#) [\[PubMed\]](#)
- Cui, Z.; Jiang, F.; Li, L.; Chi, Z.; Liu, C. Advances in biomedical applications of hydrogels from seaweed-derived sulfated polysaccharides: Carrageenan, fucoidan, and ulvan. *J. Ocean Univ. China* **2024**, *23*, 1329–1346. [\[CrossRef\]](#)
- Zayed, A.; El-Aasr, M.; Ibrahim, A.-R.S.; Ulber, R. Fucoidan characterization: Determination of purity and physicochemical and chemical properties. *Mar. Drugs* **2020**, *18*, 571. [\[CrossRef\]](#) [\[PubMed\]](#)
- Zhou, Q.-L.; Wang, Z.; Chen, W.-T.; Liu, X.-F.; Cheong, K.-L.; Zou, Y.-X.; Zhong, S.-Y.; Li, R. The structural characteristics, biological activities and mechanisms of bioactive brown seaweed polysaccharides: A review. *J. Funct. Foods* **2024**, *119*, 106303. [\[CrossRef\]](#)

18. James, K.; Ramirez, J.; Barner, L.; Moghaddam, L. Technology comparison for sequential extraction of fucoidan and sodium alginate from *Ascophyllum nodosum* using a glycerol and choline chloride solvent. *Clean. Eng. Technol.* **2024**, *18*, 100707. [[CrossRef](#)]
19. Chadwick, M.; Carvalho, L.G.; Vanegas, C.; Dimartino, S. A comparative review of alternative fucoidan extraction techniques from seaweed. *Mar. Drugs* **2025**, *23*, 27. [[CrossRef](#)] [[PubMed](#)]
20. Holtkamp, A.D.; Kelly, S.; Ulber, R.; Lang, S. Fucoidans and fucoidanases—Focus on techniques for molecular structure elucidation and modification of marine polysaccharides. *Appl. Microbiol. Biotechnol.* **2009**, *82*, 1–11. [[CrossRef](#)] [[PubMed](#)]
21. Pongjanyakul, T. Alginate–magnesium aluminum silicate films: Importance of alginate block structures. *Int. J. Pharm.* **2009**, *365*, 100–108. [[CrossRef](#)] [[PubMed](#)]
22. Hiemstra, I.S.; Meinema, J.T.; Eppink, M.M.; Wijffels, R.H.; Kazbar, A. Choline chloride-based solvents as alternative media for alginate extraction from brown seaweed. *LWT* **2024**, *214*, 117174. [[CrossRef](#)]
23. Rahman, M.M.; Shahid, A.; Hossain, T.; Sheikh, S.; Rahman, S.; Uddin, N.; Rahim, A.; Khan, R.A.; Hossain, I. Sources, extractions, and applications of alginate: A review. *Discov. Appl. Sci.* **2024**, *6*, 443. [[CrossRef](#)]
24. Saji, S.; Hebden, A.; Goswami, P.; Du, C. A brief review on the development of alginate extraction process and its sustainability. *Sustainability* **2022**, *14*, 5181. [[CrossRef](#)]
25. Flores-Contreras, E.A.; Araújo, R.G.; Rodríguez-Aguayo, A.A.; Guzmán-Román, M.; García-Venegas, J.C.; Nájera-Martínez, E.F.; Sosa-Hernández, J.E.; Iqbal, H.M.N.; Melchor-Martínez, E.M.; Parra-Saldivar, R. Polysaccharides from the *Sargassum* and brown algae genus: Extraction, purification, and their potential therapeutic applications. *Plants* **2023**, *12*, 2445. [[CrossRef](#)] [[PubMed](#)]
26. Lim, S.J.; Aida, W.M.W. Extraction of Sulfated Polysaccharides (fucoidan) from Brown Seaweed. In *Seaweed Polysaccharides*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 27–46.
27. Alshareef, S.A. *Alginate from Brown Seaweeds: Extraction, Characterisation, Modification and the Studies on Its Applications for Hydrogels*; Bangor University: Bangor, UK, 2019.
28. Obluchinskaya, E.D.; Pozharitskaya, O.N.; Lapina, I.M.; Kulminskaya, A.A.; Zhurishkina, E.V.; Shikov, A.N. Comparative evaluation of dynamic maceration and ultrasonic assisted extraction of fucoidan from four arctic brown algae on its antioxidant and anticancer properties. *Mar. Drugs* **2025**, *23*, 230. [[CrossRef](#)] [[PubMed](#)]
29. Ummat, V.; Zhao, M.; Sivagnanam, S.P.; Karuppusamy, S.; Lyons, H.; Fitzpatrick, S.; Noore, S.; Rai, D.K.; Gómez-Mascaraque, L.G.; O'donnell, C.; et al. Ultrasound-assisted extraction of alginate from *Fucus vesiculosus* seaweed by-product post-fucoidan extraction. *Mar. Drugs* **2024**, *22*, 516. [[CrossRef](#)] [[PubMed](#)]
30. Felicia, W.X.L.; Rovina, K.; Zuldin, W.H.; Suriati, L.; Huda, N.; Nurdiani, R. Sustainable valorization of alginate, a review of green extraction, structure–function relationships, and next-generation food applications. *Food Bioprocess Technol.* **2026**, *19*, 97. [[CrossRef](#)]
31. Kabir, M.F.; Ju, L.-K. On optimization of enzymatic processes: Temperature effects on activity and long-term deactivation kinetics. *Process Biochem.* **2023**, *130*, 734–746. [[CrossRef](#)]
32. Gomez, L.; Tiwari, B.; Garcia-Vaquero, M. Emerging Extraction Techniques: Microwave-assisted Extraction. In *Sustainable Seaweed Technologies*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 207–224.
33. Lesco, K.C.; Williams, S.K.R.; Laurens, L.M. Marine algae polysaccharides: An overview of characterization techniques for structural and molecular elucidation. *Mar. Drugs* **2025**, *23*, 105. [[CrossRef](#)] [[PubMed](#)]
34. Birgersson, P.S.; Hannasvik, A.M.; Aachmann, F.L. Sequential chemical and enzymatic extraction of fucoidans from brown algae yields distinct fucoidan types. *Algal Res.* **2025**, *93*, 104450. [[CrossRef](#)]
35. Türker, G.; Ak, İ. Structural Features and Antioxidant Activity of Polysaccharides from *Colpomenia sinuosa* (Phaeophyceae). *Turk. J. Fish. Aquat. Sci.* **2026**, *26*, TRJFAS28657. [[CrossRef](#)]
36. Chen, X.; Wang, Y.; Ye, Y.; Yu, H.; Wu, B. The Pre-and Post-Column Derivatization on Monosaccharide Composition Analysis, a Review. *Chem. Biodivers.* **2024**, *21*, e202400749. [[CrossRef](#)] [[PubMed](#)]
37. Flórez-Fernández, N.; Vaamonde-García, C.; Torres, M.D.; Buján, M.; Muñíos, A.; Muñíos, A.; Lamas-Vázquez, M.J.; Meijide-Failde, R.; Blanco, F.J.; Domínguez, H. Relevance of the extraction stage on the anti-inflammatory action of fucoidans. *Pharmaceutics* **2023**, *15*, 808. [[CrossRef](#)] [[PubMed](#)]
38. Amin, M.N.G.; Rosenau, T.; Böhmendorfer, S. The structure of fucoidan by linkage analysis tailored for fucose in four algae species: *Fucus serratus*, *Fucus evanescens*, *Fucus vesiculosus* and *Laminaria hyperborea*. *Carbohydr. Polym. Technol. Appl.* **2024**, *7*, 100455. [[CrossRef](#)]
39. Dodero, A.; Vicini, S.; Alloisio, M.; Castellano, M. Rheological properties of sodium alginate solutions in the presence of added salt: An application of Kulicke equation. *Rheol. Acta* **2020**, *59*, 365–374. [[CrossRef](#)]
40. Masuelli, M.A.; Illanes, C.O. Review of the characterization of sodium alginate by intrinsic viscosity measurements: Comparative analysis between conventional and single point methods. *Int. J. Biomater. Sci. Eng.* **2014**, *1*, 1–11.
41. Martins, A.; Alves, C.; Silva, J.; Pinteus, S.; Gaspar, H.; Pedrosa, R. Sulfated polysaccharides from macroalgae—A simple roadmap for chemical characterization. *Polymers* **2023**, *15*, 399. [[CrossRef](#)] [[PubMed](#)]

42. Horinaka, J.-I.; Kimura, A.; Takigawa, T. Rheological properties of concentrated solutions of fucoidan in water and in an ionic liquid. *Polymer* **2020**, *211*, 123090. [\[CrossRef\]](#)
43. Norouzi, A.; Mehrgan, M.; Roomiani, L.; Islami, H.R.; Raissy, M. Ultrasound-assisted extraction of polysaccharides from brown alga (*Sargassum angustifolium*): Structural characterization, antioxidant, and antitumor activities. *J. Food Meas. Charact.* **2023**, *17*, 6330–6340. [\[CrossRef\]](#)
44. Choi, I.; Lee, Y.; Lyu, J.S.; Lee, J.-S.; Han, J. Characterization of ionically crosslinked alginate films: Effect of different anion-based metal cations on the improvement of water-resistant properties. *Food Hydrocoll.* **2022**, *131*, 107785. [\[CrossRef\]](#)
45. Hentati, F.; Pierre, G.; Ursu, A.V.; Vial, C.; Delattre, C.; Abdelkafi, S.; Michaud, P. Rheological investigations of water-soluble polysaccharides from the Tunisian brown seaweed *Cystoseira compressa*. *Food Hydrocoll.* **2020**, *103*, 105631. [\[CrossRef\]](#)
46. Brovko, O.; Palamarchuk, I.; Gorshkova, N.; Bogolitsyn, K. Physicochemical properties and compatibility of sodium alginate and fucoidan solutions. *Int. J. Biol. Macromol.* **2023**, *243*, 125309. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Zhang, J.; Tang, J.; Shi, S.; He, J.; Liu, W.; Li, Y.; Zeng, X.; Pang, J.; Wu, C. Preparation and characterization of pH-sensitive calcium alginate hydrogel beads as delivery carriers for the controlled release of fucoxanthin. *Food Hydrocoll.* **2025**, *163*, 111106. [\[CrossRef\]](#)
48. Li, Z.J.; Srebnik, S.; Rojas, O.J. Revisiting cation complexation and hydrogen bonding of single-chain polyguluronate alginate. *Biomacromolecules* **2021**, *22*, 4027–4036. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Kjesbu, J.S.; Wæhre, T.K.; Strand, W.I.; Nordgård, C.T.; Strand, B.L.; Aachmann, F.L. Physical-mechanical properties of fucoidan-alginate composite hydrogels. *Carbohydr. Polym.* **2026**, *378*, 125007. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Wang, N.; Tian, J.; Wang, L.; Song, S.; Ai, C.; Janaswamy, S.; Wen, C. Fucoidan hydrogels induced by κ -carrageenan: Rheological, thermal and structural characterization. *Int. J. Biol. Macromol.* **2021**, *191*, 514–520. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Anugrah, D.S.B.; Darmalim, L.V.; Polanen, M.R.I.; Putro, P.A.; Sasongko, N.A.; Siahaan, P.; Ramadhan, Z.R. Quantum chemical calculation for intermolecular interactions of alginate dimer-water molecules. *Gels* **2022**, *8*, 703. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Gomaa, M.; Fawzy, M.A.; Hifney, A.F.; Abdel-Gawad, K.M. Use of the brown seaweed *Sargassum latifolium* in the design of alginate-fucoidan based films with natural antioxidant properties and kinetic modeling of moisture sorption and polyphenolic release. *Food Hydrocoll.* **2018**, *82*, 64–72. [\[CrossRef\]](#)
53. Thu, B.; Bruheim, P.; Espevik, T.; Smidsrød, O.; Soon-Shiong, P.; Skjåk-Bræk, G. Alginate polycation microcapsules: II. Some functional properties. *Biomaterials* **1996**, *17*, 1069–1079. [\[PubMed\]](#)
54. Moe, S.T.; Skjaak-Braek, G.; Elgsaeter, A.; Smidsroed, O. Swelling of covalently crosslinked alginate gels: Influence of ionic solutes and nonpolar solvents. *Macromolecules* **1993**, *26*, 3589–3597. [\[CrossRef\]](#)
55. Brovko, O.; Palamarchuk, I.; Gorshkova, N.; Chukhchin, D. Investigation of interpolymer complexes of fucoidan with sodium alginate in solutions and films. *J. Appl. Phycol.* **2025**, *37*, 539–551. [\[CrossRef\]](#)
56. Li, X.; Wang, Y.; Sun, C.; Zhao, Y.; Lu, W.; Fang, Y. Collapse-reexpansion conformational transition of alginate under non-specific ion conditions. *Food Hydrocoll.* **2025**, *160*, 110744. [\[CrossRef\]](#)
57. Jalalibidgoli, F.; Irankhahi, P.; Hajihassani, H.; Ghotbi-Ravandi, A.A. Innovative applications of marine macroalgae polysaccharides in tissue engineering and drug delivery: A review study. *Health Sci. Rep.* **2025**, *8*, e71365. [\[CrossRef\]](#) [\[PubMed\]](#)
58. Jang, J.; Seol, Y.-J.; Kim, H.J.; Kundu, J.; Kim, S.W.; Cho, D.-W. Effects of alginate hydrogel cross-linking density on mechanical and biological behaviors for tissue engineering. *J. Mech. Behav. Biomed. Mater.* **2014**, *37*, 69–77. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Birdi, G.; Bridson, R.H.; Smith, A.M.; Bohari, S.P.M.; Grover, L.M. Modification of alginate degradation properties using orthosilicic acid. *J. Mech. Behav. Biomed. Mater.* **2012**, *6*, 181–187. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Kenne, L.; Gohil, S.; Nilsson, E.M.; Karlsson, A.; Ericsson, D.; Kenne, A.H.; Nord, L.I. Modification and cross-linking parameters in hyaluronic acid hydrogels—Definitions and analytical methods. *Carbohydr. Polym.* **2013**, *91*, 410–418. [\[CrossRef\]](#) [\[PubMed\]](#)
61. Devi, G.V.; Nagendra, A.H.; Shenoy, P.S.; Chatterjee, K.; Venkatesan, J. Fucoidan-incorporated composite scaffold stimulates osteogenic differentiation of mesenchymal stem cells for bone tissue engineering. *Mar. Drugs* **2022**, *20*, 589. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Nguyen, D.Q.; Phan, N.T.H.; Ha, L.B. Developing printable and non-toxic gelatin-alginate ink for 3D printing using calcium chloride pre-crosslinking. *Adv. Biomed. Eng.* **2024**, *13*, 293–300. [\[CrossRef\]](#)
63. Jahani, A.; Nourbakhsh, M.S.; Ebrahimzadeh, M.H.; Mohammadi, M.; Yari, D.; Moradi, A. Biomolecules-loading of 3D-printed alginate-based scaffolds for cartilage tissue engineering applications: A review on current status and future prospective. *Arch. Bone Jt. Surg.* **2024**, *12*, 92. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Haggag, Y.A.; Elrahman, A.A.A.; Ulber, R.; Zayed, A. Fucoidan in pharmaceutical formulations: A comprehensive review for smart drug delivery systems. *Mar. Drugs* **2023**, *21*, 112. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Dubashynskaya, N.V.; Gasilova, E.R.; Skorik, Y.A. Nano-sized fucoidan interpolyelectrolyte complexes: Recent advances in design and prospects for biomedical applications. *Int. J. Mol. Sci.* **2023**, *24*, 2615. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Malektaj, H.; Drozdov, A.D.; Christiansen, J.D. Mechanical properties of alginate hydrogels cross-linked with multivalent cations. *Polymers* **2023**, *15*, 3012. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Qosim, N.; Dai, Y.; Williams, G.R.; Edirisinghe, M. Structure, properties, forming, and applications of alginate fibers: A review. *Int. Mater. Rev.* **2024**, *69*, 309–333. [\[CrossRef\]](#)

68. Saikia, N. Inorganic-based nanoparticles and biomaterials as biocompatible scaffolds for regenerative medicine and tissue engineering: Current advances and trends of development. *Inorganics* **2024**, *12*, 292. [\[CrossRef\]](#)
69. Kocak, G.; Tuncer, C.; Bütün, V. pH-Responsive polymers. *Polym. Chem.* **2016**, *8*, 144–176. [\[CrossRef\]](#)
70. El-Sheekh, M.M.; Alkafaas, S.S.; Bases, E.; Zhu, F.; Yan, X.; Yousuf, W.E.; El Shafay, S.M.; El-Shenody, R.A.; Abu-Resha, A.M.; Etman, A.E.; et al. Fucoidan and alginate from brown seaweeds: Extraction, structural diversity, biocompatibility, biodegradability, and biomedical applications. *Front. Plant Sci.* **2026**, *17*, 1845395. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Zhang, X.; Wei, Z.; Xue, C. Physicochemical properties of fucoidan and its applications as building blocks of nutraceutical delivery systems. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 8935–8953. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Ansari, M.J.; Rajendran, R.R.; Mohanto, S.; Agarwal, U.; Panda, K.; Dhotre, K.; Manne, R.; Deepak, A.; Zafar, A.; Yasir, M.; et al. Poly (N-isopropylacrylamide)-based hydrogels for biomedical applications: A review of the state-of-the-art. *Gels* **2022**, *8*, 454. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Safakas, K.; Saravanou, S.-F.; Iatridi, Z.; Tsitsilianis, C. Alginate-g-PNIPAM-based thermo/shear-responsive injectable hydrogels: Tailoring the rheological properties by adjusting the LCST of the grafting chains. *Int. J. Mol. Sci.* **2021**, *22*, 3824. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Almawash, S.; Osman, S.K.; Mustafa, G.; El Hamd, M.A. Current and future prospective of injectable hydrogels—Design challenges and limitations. *Pharmaceuticals* **2022**, *15*, 371. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Anisha, G.S.; Padmakumari, S.; Patel, A.K.; Pandey, A.; Singhanian, R.R. Fucoidan from marine macroalgae: Biological actions and applications in regenerative medicine, drug delivery systems and food industry. *Bioengineering* **2022**, *9*, 472. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Chen, X.; Wu, T.; Bu, Y.; Yan, H.; Lin, Q. Fabrication and biomedical application of alginate composite hydrogels in bone tissue engineering: A review. *Int. J. Mol. Sci.* **2024**, *25*, 7810. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Narasimhan, A.M.; Ravikumar, A.; Nambiar, S.; Punnoose, A.M.; Jayaraman, M.; Raghavendran, H.R.B. Marine Seaweed Polysaccharides in Tissue Engineering. In *Functional Ingredients from Algae for Foods and Nutraceuticals*; Elsevier: Amsterdam, The Netherlands, 2023; pp. 519–551.
78. Liu, S.; Deng, Z.; Chen, K.; Jian, S.; Zhou, F.; Yang, Y.; Fu, Z.; Xie, H.; Xiong, J.; Zhu, W. Cartilage tissue engineering: From proinflammatory and anti-inflammatory cytokines to osteoarthritis treatments. *Mol. Med. Rep.* **2022**, *25*, 99. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Supra, R.; Agrawal, D.K. Peripheral nerve regeneration: Opportunities and challenges. *J. Spine Res. Surg.* **2023**, *5*, 10. [\[CrossRef\]](#) [\[PubMed\]](#)
80. Obeng, E.; Shen, B.; Wang, W.; Xie, Z.; Zhang, W.; Li, Z.; Yao, Q.; Wu, W. Engineered bio-functional material-based nerve guide conduits for optic nerve regeneration: A view from the cellular perspective, challenges and the future outlook. *Regen. Biomater.* **2025**, *12*, rbac133. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Lu, Y.; Zhu, X.; Hu, C.; Li, P.; Zhao, M.; Lu, J.; Xia, G. A fucoidan-gelatin wound dressing accelerates wound healing by enhancing antibacterial and anti-inflammatory activities. *Int. J. Biol. Macromol.* **2022**, *223*, 36–48. [\[CrossRef\]](#) [\[PubMed\]](#)
82. da Silva, C.M.; da Silva, C.M.; Reis, R.L.; Jahno, V.D. The efficient role of sodium alginate-based biodegradable dressings for skin wound healing application: A systematic review. *J. Biomater. Sci. Polym. Ed.* **2024**, *35*, 397–414. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Wu, S.; Wu, J.; Yu, H.; Zhang, J.; Huang, J.; Zhou, L.; Deng, L.; Li, H. Varying ratios of M/G in alginate to modulate macrophages polarization and its application for wound healing in diabetic. *Int. J. Biol. Macromol.* **2024**, *270*, 132387. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Meng, Q.; Wei, Q.; Zhang, W.; Wu, Q.; Jiang, Y.; Hu, Z.; Zhang, Y.; Wang, Q. Immunomodulatory Sr²⁺-crosslinked hydrogel with antibacterial, antioxidant, and anti-inflammatory activities for accelerated skin wound healing. *Mater. Des.* **2026**, *262*, 115497. [\[CrossRef\]](#)
85. Zhuang, S.-J.; Xu, H.-K.; Hu, X.; Wu, T.-C.; Li, J.-N.; Lee, H.-G.; Yu, P.; Dai, Y.-L.; Jeon, Y.-J. In vitro and in vivo anti-inflammatory properties of an active fucoidan fraction from *Sargassum fusiforme* and a fraction-based hydrogel. *Int. J. Biol. Macromol.* **2024**, *265*, 130866. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Afrin, S.; Prova, O.S.; Qureshi, A.T.; Ishaq, M.W.; Callmann, C.E.; Rizwan, M. Injectable and self-healing fucoidan hydrogel: A natural anti-inflammatory biomaterial. *Biomaterials* **2025**, *326*, 123649. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Iqbal, M.W.; Riaz, T.; Mahmood, S.; Bilal, M.; Manzoor, M.F.; Qamar, S.A.; Qi, X. Fucoidan-based nanomaterial and its multifunctional role for pharmaceutical and biomedical applications. *Crit. Rev. Food Sci. Nutr.* **2024**, *64*, 354–380. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Patel, R.; Shah, S.; Prajapati, B. Functional Hybrid Wound Scaffolds for Controlled Drug Delivery and Smart Wound Management: A Decade of Progress. *AAPS PharmSciTech* **2026**, *27*, 228. [\[CrossRef\]](#) [\[PubMed\]](#)
89. Papakostidis, C.; Giannoudis, P.V. Reconstruction of infected long bone defects: Issues and Challenges. *Injury* **2023**, *54*, 807–810. [\[CrossRef\]](#) [\[PubMed\]](#)
90. Ferdushi, R.; Park, S.; Seo, Y.J.; Key, J. Fucoidan-based Nanomedicine for Hearing Loss: Emerging Roles as Carrier and Therapeutic Agent. *Pharm. Res.* **2025**, *42*, 1481–1496. [\[CrossRef\]](#) [\[PubMed\]](#)

91. Gutiérrez-Sánchez, M.; Flores-Rocha, S.; Pozos-Guillén, A.; Flores, H.; Escobar-Barrios, V.; Palestino-Escobedo, A.G.; Escobar-García, D.M. Design, characterization, and biocompatibility of chitosan-nano-hydroxyapatite/tricalcium phosphate sponges. *Tissue Cell* **2025**, *94*, 102804. [[CrossRef](#)] [[PubMed](#)]
92. Brittberg, M. New frontiers for cartilage repair, joint preservation and prevention. *J. Cartil. Jt. Preserv.* **2022**, *2*, 100060. [[CrossRef](#)]
93. Zima, J.; Nováková, E.; Špaglová, M.; Šupolíková, M. Normalization of Immune Response via Chondroitin Sulfate and Fucoidan Targeting N-Acetylgalactosaminidase. *Sci. Pharm.* **2025**, *93*, 47. [[CrossRef](#)]
94. Kuznetsova, T.A.; Andryukov, B.G.; Besednova, N.N.; Zaporozhets, T.S.; Kalinin, A.V. Marine algae polysaccharides as basis for wound dressings, drug delivery, and tissue engineering: A review. *J. Mar. Sci. Eng.* **2020**, *8*, 481. [[CrossRef](#)]
95. Li, R.; Zhou, Q.-L.; Chen, S.-T.; Tai, M.-R.; Cai, H.-Y.; Ding, R.; Liu, X.-F.; Chen, J.-P.; Luo, L.-X.; Zhong, S.-Y. Chemical characterization and immunomodulatory activity of fucoidan from *Sargassum hemiphyllum*. *Mar. Drugs* **2022**, *21*, 18. [[CrossRef](#)] [[PubMed](#)]
96. Li, R.; Zhou, Q.-L.; Yang, R.-Y.; Chen, S.-T.; Ding, R.; Liu, X.-F.; Luo, L.-X.; Xia, Q.-Y.; Zhong, S.-Y.; Qi, Y.; et al. Determining the potent immunostimulation potential arising from the heteropolysaccharide structure of a novel fucoidan, derived from *Sargassum Zhangii*. *Food Chem. X* **2023**, *18*, 100712. [[CrossRef](#)] [[PubMed](#)]
97. Ji, B.; Zhang, L.; Xiao, L.; Guo, Z.; Liu, Z. Antibacterial Agent-Loaded Hydrogels for Implant-Associated Osteomyelitis: A Review. *Macromol. Biosci.* **2026**, *26*, e00528. [[CrossRef](#)] [[PubMed](#)]
98. Citkowska, A.; Szekalska, M.; Winnicka, K. Possibilities of fucoidan utilization in the development of pharmaceutical dosage forms. *Mar. Drugs* **2019**, *17*, 458. [[CrossRef](#)] [[PubMed](#)]
99. Tanna, B.; Mishra, A. Nutraceutical potential of seaweed polysaccharides: Structure, bioactivity, safety, and toxicity. *Compr. Rev. Food Sci. Food Saf.* **2019**, *18*, 817–831. [[CrossRef](#)] [[PubMed](#)]
100. Bogdan, C.; Molnar, M.; Dima, E.I.; Olteanu, A.A.; Safta, D.A.; Moldovan, M.-L. Marine macroalgae in topical formulations: Bioactive compounds, variability, analytical challenges and skin benefits. *Pharmaceutics* **2025**, *17*, 1143. [[CrossRef](#)] [[PubMed](#)]
101. Bouizgma, K.; Rabbah, N.; Abbas, Z.; Abourriche, A. Unlocking sustainable extraction of natural antioxidants: Green solvents, smart technologies, scalability and future directions. *Sep. Sci. Technol.* **2025**, *60*, 657–683. [[CrossRef](#)]
102. Moreira, J.B.; Santos, T.D.; Cruz, C.G.; da Silveira, J.T.; de Carvalho, L.F.; de Moraes, M.G.; Costa, J.A.V. Algal polysaccharides-based nanomaterials: General aspects and potential applications in food and biomedical fields. *Polysaccharides* **2023**, *4*, 371–389. [[CrossRef](#)]
103. Cai, S.-Y.; Chen, H.; Shi, L.; Yang, T.; Huang, X.; Chen, W.; Zhang, Y. Establishment of the ion chromatography fingerprint of fucoidan from *Sargassum horneri*. *Food Res. Dev.* **2025**, *46*, 180–186.
104. Liu, Y.; Che, S.; Xu, J.; Guo, Y. Unlocking the potential of functional food polysaccharides: The zebrafish model as a revolutionary high-throughput screening platform. *Carbohydr. Polym.* **2026**, *378*, 124917. [[CrossRef](#)] [[PubMed](#)]
105. Li, F.; Gan, L.; Yang, X.; Tan, Z.; Shi, H.; Lai, C.; Zhang, D. Progress of AI assisted synthesis of polysaccharides-based hydrogel and their applications in biomedical field. *Int. J. Biol. Macromol.* **2025**, *287*, 138643. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.