

Review

# Marine Algae Polysaccharides as Basis for Wound Dressings, Drug Delivery, and Tissue Engineering: A Review

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**Abstract:** The present review considers the physicochemical and biological properties of polysaccharides (PS) from brown, red, and green algae (alginates, fucoidans, carrageenans, and ulvans) used in the latest technologies of regenerative medicine (tissue engineering, modulation of the drug delivery system, and the design of wound dressing materials). Information on various types of modern biodegradable and biocompatible PS-based wound dressings (membranes, foams, hydrogels, nanofibers, and sponges) is provided; the results of experimental and clinical trials of some dressing materials in the treatment of wounds of various origins are analyzed. Special attention is paid to the ability of PS to form hydrogels, as hydrogel dressings meet the basic requirements set out for a perfect wound dressing. The current trends in the development of new-generation PS-based materials for designing drug delivery systems and various tissue-engineering scaffolds, which makes it possible to create human-specific tissues and develop target-oriented and personalized regenerative medicine products, are also discussed.

**Keywords:** algae polysaccharides; alginates; fucoidans; carrageenans; ulvans; hydrogel; wound dressings; wound healing; drug delivery; tissue engineering

## 1. Introduction

In recent years, algae polysaccharides (PS) have attracted increasing attention due to their unique structure resembling the human extracellular matrix, a wide spectrum of biological activities, high biocompatibility, biodegradability, low toxicity, renewability, significant moisture-retaining and swelling ability, and colloidal properties. Algae PS have found a wide range of applications in technologies of regenerative medicine, including the design of wound dressing materials. A vast range of wound dressings with a high application potential has been developed on a basis of PS.

Novel and unique new-generation PS-based materials for modulating drug delivery systems (DDS), implantable medical devices, as well as organ and tissue transplants, are created using the latest advances in modern polymer-production technologies. The new strategy takes into account the required physicochemical and biological properties of PS and synthetic polymers that provide opportunities for tissue-engineering technologies to be applied in reconstructive and transplant surgery.

Tissue engineering is aimed at creating viable biological structures with the desirable spatial arrangement using three-dimensional (3D) bioprinting based on biocompatible materials (combinations of various biopolymers and synthetic polymers), which can also include living cells.

Three-dimensional bioprinting is a rapidly developing trend of modern biomedicine which is used for building viable biological structures with desirable spatial arrangement. The final product of 3D bioprinting is implanted in the body, where it is completely dissolved and replaced by host

tissues within a few months. This technology allows the progressive development of such fields of medicine as reconstructive and transplant surgery, implantable medical devices, and controlled drug delivery [1–4].

The best studied and promising compounds to be used in these technologies are sulfated PS from various algae species (alginates and fucoidans from brown algae, carrageenans from red algae, and ulvans from green algae).

## 2. Wound Healing and Current Trends in the Design of Wound Dressings

A wound is a damage of tissues and/or organs accompanied by the destruction of the integrity of the integumentary system (skin and mucous membrane). There is no any standard classification of wounds. Various approaches to wound classification (by etiology, localization, type of damage, depth, degree of complexity, degree of infection, etc.) characterize wounds in order to provide their adequate treatment. The following factors are of greatest importance in the evaluation of wounds: the nature and etiology of the injury, the time of its occurrence, whether the injury is acute or chronic, and the depth of damage to the skin and underlying tissues. Understanding the basic mechanisms of wound healing, as well as knowledge of the type and function of the available dressing materials, allows a systemic approach to the choice of dressings to be integrated into the individual patient's treatment plan. Wound repair, or healing, is a complex cascade of several overlapping phases that results in the restoration of the anatomical structure and function of the damaged skin. This biological process is highly coordinated, including various forms of cell rejuvenation such as collagenation, epithelialization, and tissue remodeling [5–7].

Most authors distinguish four phases of wound healing: hemostasis (coagulation of exudates and blood clotting, which occur immediately after the injury is inflicted), inflammation (release of proteases, reactive oxygen species (ROS), cytokines, and growth factors, on days 1–5 post-injury), proliferation (granulation, tissue formation, and angiogenesis, on days 6–14), and remodeling (contraction, re-epithelialization, and formation of the scar tissue, from day 15 to 6 months). Some of the authors combine inflammation and hemostasis into the initial phase, since the inflammation phase occurs simultaneously with the hemostasis phase [6,8,9].

The objectives of the treatment during phases 1–2 is hemostasis, the rejection of necrotic tissue, the evacuation of wound fluid, improvement of the tissue nutrition, and infection control. For this purpose, wound dressing materials with hemostatic, protective, and sorption properties are used to provide the sufficient outflow of the wound exudate. To modulate the inflammatory response, wound dressings with relevant drugs (anti-inflammatory agents, antibiotics, antiseptics, anesthetics, proteolytic enzymes, etc.) are used. The main objective of treatment in the proliferation phase is the protection of granulations, the stimulation of reparative processes with a growth factor, and the prevention of infection. At the granulation stage, atraumatic, moisturizing wound dressings with antibiotics can be used. In the remodeling phase, treatment should be aimed at stimulating reparative processes and epithelialization, as well as at preventing the formation of hypertrophic, keloid, and atrophic scars. For this purpose, atraumatic, moisturizing wound dressings, ointments and gels with insignificant osmotic activity are used. To stimulate the epithelium growth, wound dressings with regenerating properties are used. To facilitate tissue regeneration at the sites of local wounds, wound dressings providing the delivery of growth factors and biologically active substances (BAS) are used. At all stages of treatment, it is also important to observe the key requirements for wound dressings: optimal gas exchange, moist environment in the wound, biological compatibility, as well as the prevention of allergic reactions, irritation, and burning pain [10].

There are a wide range of wound dressing (healing) materials. Proper wound dressing and the patient's treatment plan should be selected with many factors taking into account, including the general health condition of patient, the complexity of wound and its etiology, and the wound healing phase [10–13]. With the exception of primary closed surgical wounds, a single type of wound dressing is rarely used to treat chronic or non-healing open acute wounds. Complex (with damage of internal organs, major vessels, large nerve trunks, or bones) and combined wounds (with simultaneous damage of various organs of several anatomical regions such as thoracoabdominal

wounds) require complex treatment. In this regard, modern wound dressing materials applied should be multifunctional.

An analysis of numerous studies made it possible to summarize the basic requirements set out for modern wound dressing materials: they should have a minimum adhesion to the wound surface; the adsorption effect to remove excess wound exudate and the associated toxic compounds; the hemostatic action if necessary; they should be involved in gas exchange and provide high moisture on the wound surface; elasticity and vapor permeability with simultaneous impermeability to microorganisms; thermal insulation; opportunity to be applied without additional fixation; biocompatibility; they should undergo sterilization and easily decompose after usage; they should be strong, efficient, but sufficiently inexpensive [4,10–13].

Current trends in the design of wound dressings are aimed at using bio- and synthetic polymers in the form of hydrogels, thin films (membranes), nanofibers, wafer, foams, and sponges. Among the structural types of wound dressings, hydrogel coatings deserve special attention.

Hydrogels are considered promising biomaterials for biomedical use. They have found a wide range of applications in various fields of medicine, from wound dressings for hemostasis to drug delivery, tissue engineering, and biosensors. Hydrogel dressings are believed to possess the properties of a perfect wound dressing material. Hydrogels are 3D structures (scaffolds) made of hydrophilic polymer chains with the respective structure and properties. The presence of 3D polymer scaffold imparts the hydrogels' mechanical properties of solid bodies (lack of fluidity, the ability to keep shape, strength, and such properties such as plasticity and elasticity). Hydrogels resemble the extracellular skin matrix, including collagen and elastin fibers, glucose aminoglycans and proteoglycans, non-collagen structural proteins, and mineral components and, therefore, are capable of performing various functions characteristic of the extracellular matrix. Being usually transparent, hydrogels allow monitoring the wound condition without removing the dressing. The use of hydrogel dressings helps to maintain a moist environment on a clean, healthy, granulating wound and to facilitate autolytic debridement in wounds with necrotic tissues such as slough or eschar. Hydrogels can be applied to pressure ulcers, skin tears, surgical wounds, and burns. These dressings are suitable for wounds with minimum to moderate exudate [10,14–18].

For the past 15 years, numerous studies have focused on the development of materials for local drug delivery using multifunctional compounds that not only facilitate stabilization and the controlled drug delivery to targets, but also provide biocompatibility. As drug delivery systems (DDS, e.g., antibacterial or anti-inflammatory drugs, proteolytic enzymes, growth factors, and BAS), hydrogels attract much attention mainly due to their highly porous structure which allows a drug to be loaded into the gel matrix and then gradually released [14,18,19].

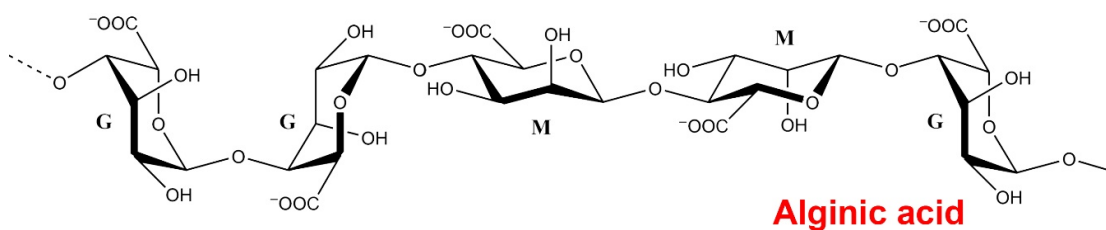
Hydrogel-based DDS include nano- or micro-sized particles, nanofibres, microspheres, and microneedles. Nano- and micro-sized particles have a number of advantages such as availability for delivery in various routes of administration, adaptation of particle size and surface characteristics, and the opportunity of the controlled and prolonged release of a drug at the desired targets. The development of carriers in the form of micro-sized particles has provided new opportunities for the development of DDS with improved pharmacokinetic and pharmacodynamic properties [15,16,19–21]. Nanofibers, due to their high surface-to-volume ratio, are considered suitable substrates when a highly porous structure is desired. Unlike conventional rigid porous structures, nanofibers are dynamic systems in which the size and shape of pores can vary to form a flexible or rigidly crosslinked structure. As a rule, nanofibers are used for the encapsulation and controlled release of drugs, as well as in tissue-engineering technologies such as, in particular, 3D bioprinting [2,4,14,19,22].

Thus, current trends in the development of new-generation materials to design wound dressings, DDS, and implantable structures are represented by new strategies, including the use of new polymer materials that combine the desired physicochemical and biological properties. Such an approach can provide biocompatible and biodegradable natural biopolymers derived from marine organisms as promising materials. The most noteworthy of them are algae PS (alginates, fucoidans from brown algae, carrageenans from red algae, and ulvans from green algae).

### 3. Marine Algae Polysaccharides as Basis for Wound Dressings, Drug Delivery, and Tissue Engineering

#### 3.1. Alginates

Alginates are mixed Na and / or K, Ca and Mg water-soluble salts of alginic acid. The latter is one of the most widespread natural PS derived mainly from brown algae of the genera *Laminaria*, *Ascophyllum*, and *Fucus*. Alginates belong to the family of linear copolymers and consist of residues of  $\beta$ -d-mannuronic and  $\alpha$ -L-guluronic acids [6,23–26] (Figure 1).



**Figure 1.** Structure of the  $\alpha$ -L-guluronic and the  $\beta$ -D-mannuronic alginate residues. Alginates are a linear acidic polysaccharides (PS) with the central backbone composed of a sequence of  $\alpha$ -L-guluronic acid (blocks G),  $\beta$ -D-mannuronic acid (blocks M), and the regions of alternating sequences of M and G residues.

The expected successful use of alginates as a potential material in modern biotechnologies, including the design of wound dressings, is due to their unique properties, such as high biological activity, biocompatibility, biodegradability, non-toxicity, lack of immunogenicity, high absorption capacity, the ability to form hydrogels, and their low production cost. Alginate-based dressings can absorb fluids up to 20 times their weight and can be applied to both infected and non-infected wounds [27–31].

The most important factor in wound management is the ability of alginates to form hydrogels in aqueous solutions after the addition of bivalent metal salts. Guluronic acid forms harder gels, whereas mannuronic acid can form softer gels [26,27]. The gel-forming properties of alginates make them one of the most readily used biopolymers with a wide range of applications, including wound dressings, DDS, and tissue engineering [23,32].

The range of the biological activities of the hydrogel polymer matrix can be extended by using compositions based on blends of alginate with other biopolymers, both natural (e.g. chitosan, hyaluronic acid, collagen, fibrin, gelatin and cellulose) and synthetic. Thus, Murakami et al. [27] prepared hydrogel blends of chitin / chitosan, fucoidan and alginate, Saara et al. [33] sodium alginate/gelatin-based hydrogels, Singh et al. [34] polyvinylpyrrolidone/alginate hydrogel containing nanosilver, Xing et al. [35] alginate-chitosan hydrogel, and Straccia et al. [36] alginate hydrogels coated with chitosan for wound dressing application.

It should be noted that most commercial wound dressings are produced using alginates (Algicell™, Integra LifeSciences Corp; Biatain™, Coloplast; Comfeel Plus™, Coloplast; Fibracol, Systagenix; Kaltostat®, ConvaTec; Maxorb® ES, Medline Industries Inc.; Nu-derm™, KCI, Acclivity Company; Sorbagon®, Hartmann Inc.; Suprasorb®, L&R Inc.; etc.) (Table 1). The main indications for all alginate-based wound dressings are providing a moist wound environment and facilitating autolysis for partial- and full-thickness wounds with large amounts of drainage, infected or non-infected wounds.

**Table 1.** Some commercially available biocompatible and biodegradable wound dressings based on marine algae polysaccharides.

Commercially Available Alginate-Based Wound Dressings	Composition	Applications	Links
Algicell™ Algicell® (Integra LifeSciences Corp.)	Sodium alginate, 1.4% silver dressings	To heavily exudative partial or full-thickness wounds. Diabetic foot ulcer, leg ulcers, pressure ulcers, donor sites, and traumatic and surgical wounds.	[37]
Algindex Ag® Gel (DeRoyal)  Algindex Ag® Foam (DeRoyal)	A combination of ionic silver, alginate and maltodextrin dressings	Venous ulcers, pressure ulcers (stages 1–4), dermal lesions (or secreting skin injuries), second-degree burns or donor sites. Provides immediate and sustained antimicrobial activity.	[38]
Algimaf (Palma Co., Ltd., Russia)	Porous sheets of lyophilized gel based on sodium alginate, calcium gluconate, mafenide acetate and phenosanoic acid	Superficial burns of the II–III degree, long healing ulcers and wounds in the I phase of wound healing, trophic ulcers during the formation of foci of necrosis.	[39]
Algipor (Palma Co., Ltd., Russia)	Porous sheets of lyophilized gel based on sodium alginate, calcium gluconate, mafenide acetate and phenosanoic acid	Superficial burns of the II–IIIA degree, sluggish wounds, trophic ulcers, bedsores, long healing wounds, deep caries and pulpitis.	
AlgiSite M™ (Smith and Nephew, Inc.)	Fast-gelling calcium alginate dressing	Leg ulcers, pressure ulcers, diabetic foot ulcers, surgical wounds.	[40,41]
Algivon® (Advancis Medical UK)	Calcium alginate dressing impregnated with 100% Manuka honey dressings	Necrotic wounds, wounds with odors, dorsal and plantar superficial ulcers.	[42]
Amerx® (Amerx Health Care Corp.)	Calcium alginate dressings	Heavy exudating chronic and acute wounds.	[43]
Biatain™ Biatain® (Coloplast Corp.)	Fast-gelling alginate and sodium carboxymethyl cellulose dressings	Wounds with severe exudation, including lower limb ulcers, pressure sores, diabetic ulcers and second-degree burns. Biatain alginate dressing in the form of a tape is used to treat deep wounds.	[44,45]
Biokol (Co., Ltd. Biokol, Russia)	Hydrocolloid monolayer composite film consists of 2 polymers: natural (a mixture of carrageenan, sodium or calcium alginate and methyl cellulose) and a synthetic fluorine-containing polymer (copolymer of vinylidenfluoride with hexafluoropropylene)	Residual wounds after extensive burns, skin graft protection, protection of donor sites for burns and plastic surgeries, protection of excised wound surfaces, trophic ulcers.	[46]
CalciCare™ (Hollister Incorporated)	Calcium alginate dressings (high guluronic acid calcium/sodium alginate), strengthening nylon web	To heavily exudating wounds, infected wounds, venous leg ulcers.	[47]

Comfeel Plus™ Comfeel Sea-Sorb (Coloplast)	Sodium carboxymethylcellulose and calcium alginate dressings	Ulcers such as venous leg ulcers, pressure ulcers, burns, donor sites, postoperative wounds and necrotic wounds.	[48,49]
CovaWound™ (Covalon Technologies, Ltd.)	Alginate dressings (calcium salt of alginic acid riched by mannuronic acid)	Heavily exuding wounds like partial-thickness burns, donor sites, leg, pressure, arterial, diabetic and venous stasis ulcers, cavity wounds, post-surgical incisions, trauma wounds, and most other granulating wounds.	[41,50]
DermaGinate™ (DermaRite Industries, LLC) (Dynarex)	Calcium alginate dressings	Acute or chronic partial- to full-thickness wounds with moderate to heavy exudate such as: pressure ulcers, diabetic ulcers, post-operative wounds, trauma wounds, leg ulcers, grafts and donor site. Can absorb up to 17 times its own weight.	[51]
ExcelGinate™ (MPM Medical, Inc.)	Calcium alginate dressings	Partial- to full-thickness wounds with moderate to heavy drainage.	[52]
Fibracol™Plus (Systagenix)	Calcium alginate (10%) and collagen (90%) dressings	Diabetic ulcers, pressure ulcers, venous ulcers, full-thickness and partial-thickness wounds, second-degree burns, abrasions, ulcers caused by mixed vascular etiologies, donor sites and other bleeding surface wounds, traumatic wound healing by secondary intention, dehisced surgical incisions.	[53]
Guardix-SG® (Hanmi Pharm. Co. Ltd.)	Sodium alginate and poloxamer dressings	To prevent post-operative adhesions in thyroid and spine surgeries.	[54,55]
Hyalogran® (Haemo Pharma)	An ester of hyaluronic acid and sodium alginate, microgranulate material	Ulcers, diabetic wounds, pressure sores, ischemic, necrotic wounds.	[56]
Kaltostat™ Kaltostat® (ConvaTec)	Sodium alginate dressings	Pressure ulcers, venous ulcers, diabetic ulcers, donor sites, and traumatic wounds exuding cavity wounds such as pressure injuries, venous stasis ulcers, arterial ulcers, diabetic ulcers, lacerations, post-surgical wounds and other external wounds inflicted by trauma	[27,57]
Kendall™ (Cardinal Health)	Calcium alginate dressings with added benefit of zinc	Arterial, diabetic, pressure and venous insufficiency ulcers, donor sites, abrasions, lacerations and skin tears, partial-thickness (second-degree) burns, deep and tunneling wounds.	[58]
Luofucon® Extra Silver (Huizhou Foryou Medical Devices Co., Ltd.)	<u>Antibacterial silver alginate dressings</u>	Heavily exuding wound, venous/arterial leg ulcer, diabetic ulcer, pressure ulcer, donor sites, abrasions, lacerations and post-surgical wound.	[59]

Maxorb® ES (Medline Industries, Inc.)	Reinforced CMC/calcium alginate ribbon dressings	Pressure injuries, partial- and full-thickness wounds, diabetic ulcers, leg ulcers of various etiologies, surgical wounds, donor sites and first- and second-degree burns.	[41,60]
Maxorb® Extra (Medline Industries, Inc.)	Calcium alginate and sodium carboxymethyl-cellulose fibers		
Maxorb® II (Medline Industries, Inc.)	An ultra-absorptive alginate dressing		
Melgisorb® Plus (Mölnlycke Health Care US, LLC)	Calcium alginate dressings	Heavily exuding partial- to full-thickness wounds, pressure, venous, arterial and diabetic ulcers, donor sites, post-operative wounds, dermal lesions and traumatic wounds.	[41,61]
Nu-derm™ (KCI-An Acelity Company)	High guluronic acid alginate and carboxymethylcellulose (CMC) fiber	Heavily exuding chronic wounds, pressure ulcers, leg ulcers, venous stasis ulcers, diabetic ulcers and arterial ulcers, and to control minor bleeding in superficial acute wounds (such as abrasions, lacerations, donor sites and postoperative wounds).	[41,62]
Restore® (Hollister Incorporated)	Calcium alginate dressings	Arterial, venous, diabetic and pressure (stage 1–4) ulcers; post-surgical incisions; donor sites; dermal lesions, trauma injuries, incisions or other trauma wounds; superficial (first-degree) and partial-thickness (second-degree) burns. Can also be used under compression bandages, and may also assist in supporting the control of minor bleeding in superficial wounds.	[63]
SeaSorb® (Coloplast)	Calcium alginate dressings	High exuding wounds, ulcers such as diabetic and leg pressure ulcers.	[55,64]
Sorbalgon® Sorbalgon T (Hartmann USA, Inc.)	Sodium and calcium alginate dressings	Arterial ulcers, diabetic foot ulcers, heavily draining wounds, pressure ulcers/injuries, surgical site infections, bariatric patients, superficial burns (I degree), deep partial-thickness (deep II degree) burns, full-thickness (III and IV degree), chronic wounds. Invasive for plugging into the wound (deep cavities and pockets).	[49,65]
Sorbsan™ (Unomedical)	Calcium alginate dressings	Arterial, venous, and diabetic leg ulcers, pressure ulcers, post-operative wounds, donor and graft sites and traumatic wounds.	[49,66]
Suprasorb® L&R USA, Inc. (Lohmann & Rauscher)	Calcium alginate dressings	Highly exuding acute and chronic wounds including pressure ulcers, venous ulcers, skin donor sites and post-operative wounds.	[67]
3M™ Tegaderm™ (3M Corporate)	High gelling alginate dressings	Maintain a moist wound healing environment, provides a viral and bacterial barrier.	[68,69]

Tegagen™ (3M Corporate)	Sodium alginate dressings	Diabetic and infected wounds.	[70]
Tegagel™ (3M Corporate)	Alginate dressings	Skin graft donor sites, diabetic leg ulcers, pressure ulcers, post-operative wounds.	[49]
Tromboguard® (Tricomed en)	Sodium alginate, calcium alginate, chitosan, polyurethane and silver cations dressings	Postoperative wounds, traumatic wounds, gun shots, skin graft donor sites, bleeding from accidents.	[71]

Note: data from review [6] were used as the basis and supplemented by us.

Alginate-based wound dressing materials are practically applied in the form of amorphous gels, membranes or films, foams, nanofibers, and sponges [30].

Alginate-based films, when combined with other polymers, enhance the wound-healing process by providing permeability to water vapor, carbon dioxide, and oxygen, as well as by protecting the wound from bacterial infections, e.g., when applied along with various antimicrobial agents [72–75]. However, as noted by some authors, alginate-based films were not effective for wounds with excessive exudates [5,76].

Alginate-based foams are solid porous matrices that undergo sterilization, and when introduced into wounds, do not cause patient discomfort. Foams, characterized by increased hydration time, can be removed from wound without serious tissue damage. They can absorb exudate, protect wounds from maceration, improve gas exchange, and can create a moist wound environment. However, their use requires frequent dressing change; foams do not suit dry wounds and wounds with little exudate [5]. Thus, alginate-based foams loaded with antibacterial agents have been developed for treating infected wounds [77,78].

Sodium alginate-based nanofibers, which emulate the extracellular matrix, enhance the proliferation of epithelial cells and the formation of new tissue. They facilitate hemostasis in damaged tissues, improve exudate absorption, contribute to drug delivery through the skin, cell respiration, and the penetration of large amounts of gas, thereby preventing bacterial infections [79–82].

Wafer dressings are produced by the freeze-drying of blends of alginate with other polymer solutions. The resulting solid porous structure is similar to foam dressings and can be applied to exuding wound surfaces. For example, a wafer made of sodium alginate, xanthan gum, and methylcellulose, which quickly absorbs exudate, thus causing a transition from a glassy state to viscous gel [83], or alginate and gelatin-based bio-polymeric wafers containing silver sulfadiazine for wound healing [84] have been recently developed.

Moreover, a combination of alginate and sericin with platelet lysate in the form of freeze-dried sponge is proposed as a design of bioactive wound dressing to treat skin lesions. The highest level of growth factor release occurred within 48 h, which is an optimum time for the healing process to be started in vivo. In a mouse skin lesion model, biomembranes with platelet lysate facilitated the healing process by inducing an accelerated and more pronounced burst of inflammation and the formation of the granulation tissue and new collagen deposition that led to a faster skin regeneration [85].

Other alginate-based composites for wound dressings have been obtained in the form of gels, ointments, and creams. Thus, Ahmed et al. [86] proposed a topical composition of chitosan and sodium alginate loaded with Fucidin or aloe vera with vitamin C.

Alginate-based hydrogels are the most promising materials as carriers for drug delivery, improving wound healing and tissue regeneration. Hydrogel developed in such form acts as a controlled-release platform containing antibiotics, anti-inflammatory agents, hyaluronic acid, etc. [32,87,88]. For instance, a porous 3D matrix composed of calcium phosphate cement in combination with alginate is used as a novel scaffold for drug-delivery applications [89].

Xing et al. [88] reported about a covalent alginate / chitosan polysaccharide-based hydrogel in the form of microspheres for BSA encapsulation (bovine serum albumin) and for soft tissue engineering covalently polysaccharide-based alginate/chitosan hydrogel embedded with alginate microspheres for BSA (bull serum albumin) encapsulation and soft tissue engineering. As a gastrointestinal DDS, microcapsules resistant to the acidic environment of the stomach have been designed. The mucoadhesive



microcapsules are obtained by the ionotropic gelation of sodium alginate with chitosan in the presence of calcium chloride, containing amoxicillin trihydrate. The resulting microcapsules show a high drug capture efficiency (84%) and are aimed at the effective treatment of *Helicobacter pylori* infection [90].

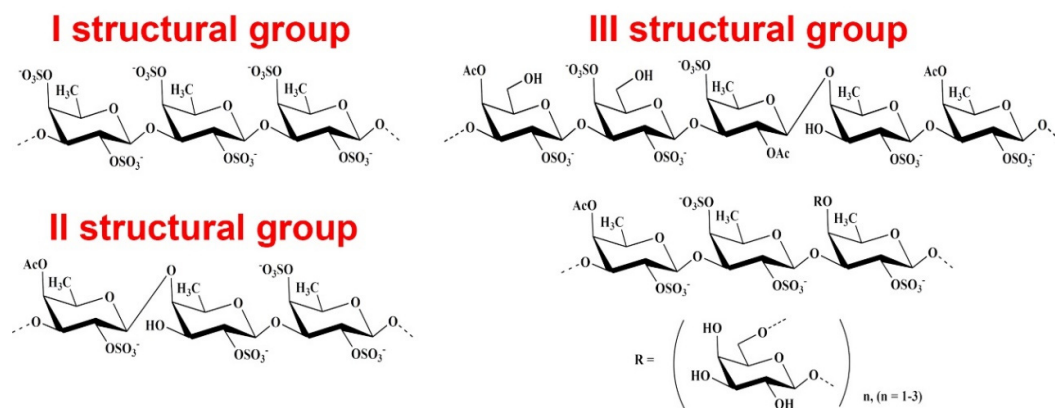
Moreover, alginate-based microcapsules as gastroretentive DDS with a slow release of metronidazole have been developed for targeting *H. pylori* [91]. Boateng et al. [84] designed freeze-dried composite alginate- and gelatin-based bio-polymeric wafers containing silver sulfadiazine for wound healing, and Gowda et al. [92] — wafers for chronic wound healing. Pawar et al. [93] proposed including streptomycin and diclofenac in a polyox, carrageenan, and sodium alginate wafer dressing for effective chronic wound healing.

Yu et al. [94] prepared wound dressings consisting of alginate hydrogel and simvastatin-incorporated mesoporous hydroxyapatite microspheres for cutaneous wound healing. Mohandas et al. [95] designed alginate hydrogel/nano zinc oxide composite bandages for infected wounds. Exosomes (EXO) isolated from the supernatant of cultured adipose-derived stem cells (ADSC) were loaded in the alginate-based hydrogel, which was used as a bioactive scaffold to fix EXO at the wound site in an animal model. This bioactive wound dressing was biodegradable and biocompatible which significantly improved wound healing, collagen synthesis, and angiopoiesis in the wound area [20].

Alginates are widely used in tissue-engineering technologies such as, in particular, 3D bioprinting. Biocompatible alginate-based scaffolds are highly efficient in tissue engineering and regenerative medicine, as evidenced by numerous reports in recent years [3,25,89,96–99]. Alginate-based gel and bio-composites with other polymers that have recently been obtained can be used for a wide range of bone–tissue-engineering purposes, e.g., for the regeneration of bone and cartilage, as well as in stem-cell transplantation as an injectable biomaterial for new bone tissue regeneration [89,96,100]. Alginate/chitosan hybrid structures contribute to enhanced mechanical strength and structural stability, as well as accelerate vascularization and facilitate osteogenesis after embedding in bone [100].

### 3.2. *Fucoidans*

Fucoidans are heterogeneous sulfated PS naturally found as constituents of cell wall in the brown algae of the genus *Fucus*. These are mixture of structurally diverse fucose-rich, sulfated PS built of a backbone of monosaccharide residues (mainly L-fucopyranoses, often galactose and other monosaccharides) having various substitutions. A detailed structural analysis of fucoidans is currently challenging and therefore, the structural diversity of these polysaccharides is far from being fully understood [101–105] (Figure 2).



**Figure 2.** Structural fragments of fucoidans. Most of the known fucoidans belong to three structural types: the first type contains (1→3)-linked L-fucopyranose residues in the main chain; the second type is alternating (1→3)- and (1→4)-linked residues of L-fucopyranose; the third type of fucoidans (galactofucans) contains fucose and galactose residues, and sometimes these monosaccharides are

represented in the structures of fucoidans in comparable amounts. In addition to fucose, fucoidans often contain small amounts of other monosaccharides.

The variety of the biological effects of fucoidans, associated with the features of their structure resembling that of mammalian glycosaminoglycans, the high biocompatibility, and the lack of toxicity are of great practical interest for the development of new-generation polymer materials. The most important activities of fucoidans are antioxidant, antiviral/antibacterial, immunomodulatory, angiogenic, and anticoagulant [103,105–114].

Numerous studies consider the effects of fucoidans as a key regulator of wound healing. For example, the effect of low-molecular-weight (5 kDa) fucoidan (LMF) from *Undaria pinnatifida* on wound healing has been studied using a full-thickness dermal excision rat model [108]. In groups of animals with wounds treated with a LMF solution, a dose-dependent reduction in the wound area was observed. A histological examination of the wounds showed an acceleration of the angiogenesis processes and collagen remodeling. In addition, a treatment of wounds with LMF led to a decrease in lipid peroxidation and increased antioxidant activity. The ability of fucoidans to interact, through mechanisms similar to heparin binding, with various growth factors (e.g., fibroblast growth factor (bFGF), transforming growth factor- $\beta$  (TGF- $\beta$ )) and stimulate fibroblast proliferation was reported by some authors [115,116]. Song et al. [117] also showed that fucoidan significantly stimulates the proliferation of human fibroblasts, thus, contributing to the reconstruction of skin epidermis and the restoration of keratinocytes.

The osteogenic effects of sulfated PS, including the stimulation of activity and the mineralization of osteoblasts, the inhibition of osteoclast resorption [118–120], as well as the inhibition and the differentiation of osteoclasts and reducing osteoporosis, were described in ovariectomized rats [121,122].

The antimicrobial and anticoagulant potential of fucoidans is efficiently used in the treatment of soft tissue wounds. For example, fucoidan was formulated into transdermal DDS designed for the treatment of inflammatory skin diseases (targeting inflammatory skin conditions) [108] or as an anticoagulant after topical application, what is a very important aspect of wound healing [7].

The unique biological properties of fucoidans make them a useful component of hydrogels, while the lack of fucoidan gelation can be overcome by combining fucoidan with various polymers that give it a positive charge such as, e.g., chitosan and its derivatives, protamine, polyethyleneimine, poly(alkylamine hydrochloride), poly(isobutyl cyanoacrylate), poly(lactide-co-glycolide), poly-L-ornithin, hexadecylamine, poly(alkyl cyanoacrylate), etc. [123,124].

Numerous studies provide information on the designs of hydrogels and biofilms containing fucoidan as a wound-healing agent and indicate their high effectiveness [27,125–128]. Thus, Sezer et al. [125] proposed a fucoidan–chitosan hydrogel and determined the optimum ratio of the components. The structure and effectiveness of the hydrogel improved with the increasing concentration of fucoidan. An assessment of the in vivo effectiveness of the burn-healing activity of the obtained hydrogel showed high rates of epithelialization and cell proliferation [125].

Feki et al. [129] evaluated the wound-healing potential of composite hydrogel films with fucoidan and poly (vinyl alcohol) (PVA). A fucoidan / PVA combination at a ratio of 70:30 significantly enhanced the burn wound-healing effect within 8 days of treatment, as evidenced by the data of histological examination (a higher collagen content compared with the control group and a complete re-epithelialization of wound with total epidermal renewal) [129]. Murakami et al. [27] prepared hydrogel blends of chitin/chitosan, fucoidan, and alginate as healing-impaired wound dressings. Such hydrogels were characterized by a better and long-lasting exudate absorption compared to a commercial preparation (Kaltostat®, ConvaTec, containing calcium alginate fiber). An in vivo trial of hydrogel showed the ability of fucoidan to interact with growth factors (FGF-1 and FGF-2) and with cytokines that regulate epidermal reconstruction and angiogenesis processes. Hydrogels had an increased exudate absorption capacity without maceration for 18 h [27].

The wide range of biological activities and physicochemical properties of fucoidan contribute to the development of drug carriers such as nano-sized particles, micro-sized particle liposomes, or semi-solid forms. The use of fucoidan not only protects the loaded active agent, but also increases the

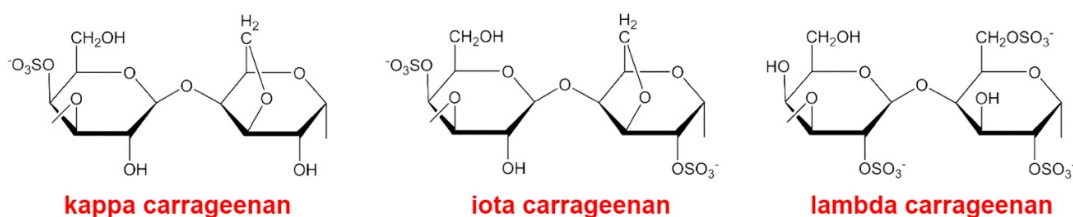
effectiveness of the treatment. With its lower anticoagulant activity than that of heparin and with the ability to interact with growth factors, fucoidan was used to develop a drug carrier for tissue regeneration. Thus, Nakamura et al. [130] developed a chitosan/fucoidan micro complex hydrogel for injection, which prevented the fibroblast growth factor 2 (FGF-2) from inactivation and enhanced its activity [130]. In vitro and in vivo experiments demonstrated that micro complex hydrogel efficiently and gradually releases FGF-2. Within 1 week after the subcutaneous injection of the hydrogel in mice, significant neovascularization was observed near the injection site. The hydrogel was biodegradable and disappeared after 4 weeks [130].

Current trends in the development of polymer technologies are based on the use of various combinations of fucoidin with chitosan, gelatin, alginate, or hydroxyapatite, etc. in the design of 3D scaffold structures [107,131].

Solid polymeric chitosan–alginate biocomposite scaffolds containing fucoidan (Chi–Alg–fucoidan) are characterized as promising biomaterials for bone tissue regeneration or as bone graft substitutes. In vitro experiments showed greater cell proliferation and increased the secretion of alkaline phosphatase using the Chi–Alg–fucoidan biocomposite compared to those of a scaffold without fucoidan (Chi–Alg). In contrast to the Chi–Alg scaffold, the mineralization and adsorption of protein were two times as high in the case of the Chi–Alg–fucoidan biocomposite which indicates its applicability for bone tissue regeneration [98,131]. Fucoidan-based micro- and macroporous 3D scaffolds loaded with the vascular endothelial growth factor (VEGF) were also designed to ensure angiogenic activity in ischemic tissues and to facilitate neovascularization. Such scaffolds provided a larger area and density of new vessels compared to fucoidan-free scaffolds. The addition of fucoidan with a molecular weight of 39 kDa substantially decreased the rate of VEGF release, compared to the control, irrespective of the hydrogel pore size and contributed to a significant increase in the number of endothelial progenitor cells and the rate of their proliferation. The authors also report the synergism of the effects of fucoidan and VEGF [107].

### 3.3. Carrageenans

Carrageenans are sulfated linear PS derived from the red algae Rhodophyceae, also known as sulfated polygalactan, whose chemical structure is based on a repeating disaccharide unit consisting of D-galactose residues connected via alternating  $\beta$ -1 $\rightarrow$ 4- and -1 $\rightarrow$ 3-glycosidic bonds. These PS are classified by location and the amount of sulfate groups in the monosaccharide residues and the presence of 3,6-angirogalactose in 4-O-substituted residues and are divided into carrageenans kappa ( $\kappa$ ), iota ( $\iota$ ) and lambda ( $\lambda$ ) [132–135] (Figure 3).



**Figure 3.** Structural fragments of carrageenans. Carrageenans are sulfated linear PS, whose chemical structure is based on a repeating disaccharide unit consisting of D-galactose residues connected via alternating  $\beta$ -1 $\rightarrow$ 4- and -1 $\rightarrow$ 3-glycosidic bonds. Thus, sulfated PS of red algae of the class Rhodophyceae consist of repeating dimers of  $\alpha$ -1,4-D-galactose which are connected via alternating  $\alpha$ -1 $\rightarrow$ 3- and  $\beta$ -1 $\rightarrow$ 4-glycosidic bonds and substituted by one ( $\kappa$ -carrageenan), two ( $\iota$ -carrageenan), or three ( $\lambda$ -carrageenan) sulfate ester groups in each repeating unit.

The variability of the primary structure of carrageenans determines the diversity of their macromolecular organization and the wide spectrum of biological activities (immunomodulatory,

antitumor, antiviral, antioxidant, anticoagulant, etc.), which make them readily applicable in regenerative medicine technologies [135–137].

The physicochemical properties of carrageenans allow them to undergo both thermal and ion gelation and be combined with other materials to form hydrogel systems. The gel properties depend on the position and amount of sulfate esters:  $\iota$ -carrageenan forms soft gels in the presence of divalent calcium ions;  $\kappa$ -carrageenan forms hard and brittle gels in the presence of potassium ions [134,135,138,139].

For example, the designs of hydrogel blends of carrageenan with gelatin or chitosan [140,141], hydrogel based on carrageenan and poloxamer 407 [142], hydrogel nanocomposites based on carrageenan and sodium carboxymethyl cellulose [143] have been proposed for drug delivery. Carrageenan with poly(oxyalkyleneamine) [144], and methacrylic anhydride [145] is used to form multilayered 3D structures.

There are reports on the development of carrageenan-based hydrogels for wound-healing dressing materials (in the form of membranes, films, or wafer), DDS (with the controlled release of antibacterial and antitumor agents, proteins, genes, cells), and tissue engineering (3D scaffolds) [17,134,146–151]. Thus, single- and multilayered film dressing based on  $\kappa$ -carrageenan and  $\kappa$ -carrageenan/chitosan, which has been proposed recently, shows a more pronounced adhesive potential compared to pectin and heparin dressing [152]. Boateng et al. [148] report about polyethylene oxide (Polyox®, Dow Chemical) and  $\kappa$ -carrageenan-based solvent cast films used for drug delivery to wounds. The films were loaded with antimicrobial (streptomycin) and anti-inflammatory (diclofenac) agents for enhanced healing effects in chronic wounds. These films were studied by texture analysis (for mechanical and mucoadhesive properties), scanning electron microscopy, differential scanning calorimetry, X-ray diffraction, infrared spectroscopy; studies of their drug-release and antibacterial properties were also conducted. The films showed a smooth, homogeneous surface morphology, excellent transparency, high elasticity, and acceptable mechanical properties. The drug-loaded films had a high ability to absorb wound fluid, as well as pronounced mucoadhesive capabilities which allow the effective adherence to and the protection of a wound. In addition, these films showed a controlled release of both streptomycin and diclofenac within 72 h and a high inhibitory activity against pathogenic microorganisms (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*) [148]. Makino et al. [146] developed a  $\lambda$ -carrageenan-based hydrogel loaded with dibucaine hydrochloride. The hydrogel showed the pulsatile drug release with a time interval of 50 min [146]. Li et al. [142] report the development of a novel hydrogel system based on a combination of poloxamer 407 and carrageenan for the intranasal delivery of ketorolac tromethamine. A pharmacokinetic study of intranasal hydrogel on rats demonstrated an enhanced absolute bioavailability ( $68.8 \pm 23.3\%$ ) and a prolonged mean residence time of the drug ( $8.8 \pm 3.5$  h) compared to the control ( $24.8 \pm 13.8\%$  vs.  $3.9 \pm 0.6$  h, respectively). An assessment of nasal ciliotoxicity showed that the hydrogel is safe for intranasal use [142].

The research by Popa et al. [147] was aimed to develop and characterize novel carrageenan- and alginate-based hydrogel as a delivery system maintaining the viability of encapsulated cells. According to the obtained results, various compositions, both in the form of beads and fibers, show significant potential as carrier materials for cell delivery to be applied in tissue-engineering/regenerative medicine [147]. Rode et al. [153] also report the development of a carrageenan-based hydrogel as a scaffold for the delivery of skin-derived multipotent stromal cells. Gutiérrez-Zamorano et al. [154] studied the effect of a carrageenan-encapsulated probiotic strain, *Lactobacillus fermentum* UCO-979C, against the pathogenic *H. pylori* SS1 under simulated gastric conditions (fasting or standard diet, pH 3.0 under microaerophilic condition and agitation). Muhamad et al. [155] proposed  $\kappa$ -carrageenan/sodium carboxymethyl cellulose beads as a carrier of  $\beta$ -carotene, using genipin as a natural stitching reagent, and tested the effects on  $\beta$ -carotene release. According to the results, the crosslinked beads had a lower swelling ability in all pH conditions, and the swelling ratio decreased with increasing genipin concentration (95.24% at pH 1.2; 100% at pH 7.4 in 0.5 mM genipin solution; 76.2% at pH 1.2; 85.71% at pH 7.4 in 1.5 mM genipin solution). It was also found that the beads released  $\beta$ -carotene slower and in lesser amounts after being crosslinked [155].

Grenha et al. [156] blended new nano-sized particles of carrageenan and chitosan (natural marine-derived biopolymers) to study their efficiency as carriers for the release of therapeutic macromolecules. The formulated nano-carriers (with sizes ranging from 350 to 650 nm) showed the exceptional capability of the controlled release of a model protein, ovalbumin, for up to 3 weeks with an increased loading capacity of 4–17%. Moreover, the nanoparticles exhibited high biocompatibility with no cytotoxicity in bioassays based on a cell culture of L929 fibroblasts [156].

One of the recent studies reports on the design and functional characteristics of two bioactive polymers,  $\kappa$ -carrageenan and sodium alginate, as medicated wafer dressings for chronic wounds [151]. The wafers were loaded with microbial biosurfactants at concentrations of 0.1% and 0.2% rhamnolipids and 0.1% and 5% sophorolipids. The new dressings possessed perfect functional physicochemical properties that make them suitable to be potentially used for chronic wound treatment [151].

Carrageenan-based hydrogels have great promise in tissue engineering. Since the sulfated backbone of carrageenans is constituted of long chains of alternating  $\alpha$ -1 $\rightarrow$ 3 D-galactose, and  $\beta$ -1 $\rightarrow$ 4 $\rightarrow$ 3, 6-anhydro-galactose with ester sulfates, which resemble the structure of mammalian glycosaminoglycans, carrageenan-based hydrogels are of interest for the purpose of cartilage regeneration [134,157]. A series of studies have demonstrated the chondrogenicity, nontoxicity, and mechanical properties of  $\kappa$ -carrageenan-based hydrogels similar to those of native cartilage. Human adipose stem cells encapsulated in such hydrogels remained viable for 21 days, providing adequate support for cartilage regeneration [158,159].

Liang et al. [160] designed composite hydrogels with a hierarchically porous architecture based on positively charged chitosan and negatively charged carrageenan. The hydrogels exhibited excellent mechanical properties, as well as pH- and salt-responsiveness. They contributed to the high adhesion and proliferative activity of the chondrocyte culture in vitro, thus, exhibiting a high potential for application in cartilage regeneration. This work provides a facile and fast fabrication pathway for the construction of ampholytic hydrogel from polycation and polyanion in an electroneutrality system [160].

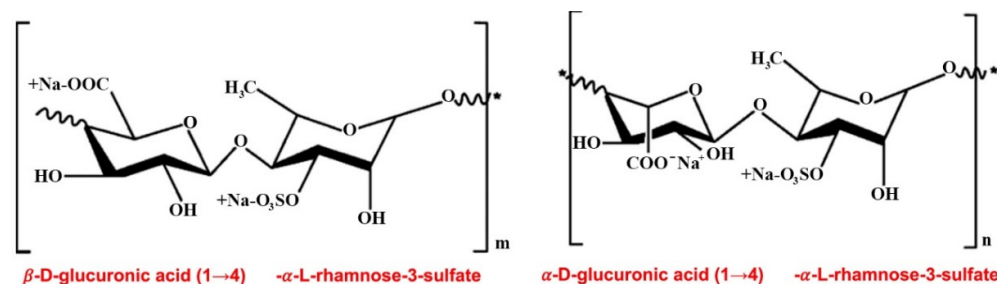
The potential of using carrageenan-based hydrogels for bone regeneration is considered in a number of studies. For example, Goonoo et al. [161] report about novel bone engineering using  $\kappa$ -carrageenan- and polyhydroxybutyrate-based fibers. Blends with carrageenan, unlike pure polyester fibers, enhanced the potential for biomineralization and osteogenic differentiation of a SaOS-2 cell culture (Human Bone osteosarcoma cell line). Li et al. [141] developed an iota-carrageenan/chitosan/gelatin scaffold that emulates the extracellular matrix. Such scaffolds showed excellent support for the attachment and proliferation of adipose-derived mesenchymal stem cells (MSCs) in vitro, enhanced their capability of differentiation, as well as contributed to neo-vascularization during osteogenesis. According to the authors, these scaffolds are a perfect material for bone tissue engineering [141].

Kim et al. [162] simulated alginate hydrogels with carrageenan under different printing parameters and presented them in printability maps for extrusion-based bioprinting. Three-dimensional deposition patterns of both alginate and alginate/carrageenan hydrogels were assessed and compared with each other by the continuous monitoring of shape fidelity in 3D structures. The cell viability of the 3D alginate/carrageenan composite scaffolds, printed using optimized printing parameters, was evaluated using live/dead staining and confocal fluorescence imaging. The enhanced viability of cell cultures in 3D composite hydrogels and the improved rheological behaviors were established by real-time assessment. The results of the study show the high potential of carrageenan to be used as a prospective bioink with remarkable mechanical properties suitable for the precise fabrication of 3D hydrogel scaffolds based on bioprinting techniques [162].

Johari et al. [163] evaluated carrageenan from *Kappaphycus alvarezii* as an alternative infused material (filler) in a poly(3-hydroxybutyrate-co-3-hydroxyvalerate) porous 3D scaffold. The optimum concentration of carrageenan for long-term (>2 weeks) cell functioning was established. The authors concluded that carrageenan, as a composite material, shows a great potential for tissue engineering [163].

### 3.4. Ulvans

Ulvans are water-soluble sulfated heteropolysaccharides derived from the cell walls of the green algae of the genus *Ulva*, that have sulfate, rhamnose, xylose, iduronic and glucuronic acids as the main constituents [164–172] (Figure 4).



**Figure 4.** Structures of the main repeating disaccharides constituting ulvans. The backbone of the chemical structure of ulvans is composed of glucuronic acid and repeating disaccharide units (xylose and rhamnose):  $\alpha$ - and  $\beta$ -(1→4)-linked sugar residues (such as  $\alpha$ -1,4- and  $\alpha$ -1,2,4-linked L-rhamnose),  $\beta$ -1,4- and terminally linked d-glucuronic acid, and  $\beta$ -1,4-linked d-xylose.

The uniqueness of the ulvan structure is explained by the specific configuration and the presence of rare sugars: iduronic acid and sulfated rhamnose. Thus, ulvans represent a new source of biopolymers with a wide spectrum of physicochemical properties and biological activities [164,165,167–172].

The specific configuration and biological properties of ulvans, like those of fucoidans, determined by the chemical affinity of its repeating unit with glycosaminoglycans such as hyaluronan and chondroitin sulfate, are of particular interest for applications in pharmaceutical production. These include antioxidant, immunomodulatory, antimicrobial and anticoagulant properties necessary for designing wound dressings, DDS, and in tissue engineering. An important feature of ulvans is their ability to form thermoreversible gels in the presence of  $B^+$  and  $Ca^{+2}$  ions at a pH between 7.5 and 8.0 [169,170,173–178].

Tziveleka et al. [171] have systematized ulvan-based structures, including hydrogels, membranes, particles, nanofibres, and 3D porous structures, whose application can vary from wound dressings to DDS or tissue engineering. For the development of hybrid materials, ulvans are used independently or by complexation, crosslinking, or chemical modification [176,179–182]. In particular, Alves et al. [181] have developed ulvan membranes as novel biomaterials for drug delivery applications or as wound dressings, which are water-insoluble and stable in physiological conditions, by deploying chemical crosslinking with an epoxide (1,4-butanediol diglycidyl ether) via the formation of ether bonds on ulvan's hydroxyl groups. Yoshimura et al. [183] report about the preparation of biodegradable hydrogels by the crosslinking of ulvan with divinylsulfone (DVS) under alkaline conditions. Gelation was observed consistently when the ulvan obtained at 80 °C was crosslinked with DVS. Both the biodegradation rate and water absorbency of hydrogels were found to depend on the feed amount of DVS, with the highest water absorbency being observed for the sample with the DVS feed ratio of 20% (w/w) [183].

The unique properties of ulvan membranes contribute much to their potential use both as wound dressings and as DDS. The presence of ulvan, with its high biological activity, in such matrices brings substantial benefit. Thus, Alves et al. [181] loaded ulvan membranes with dexamethasone as a therapeutic model drug. The initial steady release of the drug (nearly 49% within the first 8 h) was followed by a slower and sustained release for up to 14 days [181]. Ulvan was also used as a base in hydrophilic matrix tablets containing the chronobiotic hormone melatonin. The observed in vitro melatonin release profile of most of the ulvan-based formulations was relatively higher than that of the commercial drug Circadin® (Rad Neurim Pharmaceuticals Eec Ltd.) [184].

Toskas et al. [180] produced ulvan-based nanofibers with an average diameter of 84 nm by blending with poly (vinyl alcohol) in the presence of boric acid and  $\text{Ca}^{+2}$  ions. The nanofiber ability of an ulvan-rich extract was achieved for the first time via electrospinning. Due to the presence of ulvans, nanofibers had a homogeneous structure with a high degree of orientation [180]. Kikionis et al. [185] developed ulvan-based nanofibers by blending ulvan in different proportions with other polymers such as polycaprolactone and polyethylene oxide.

Numerous works consider an aspect of ulvans application to be tissue engineering [164,171,176,186–189]. Alves et al. [186,187] have developed a stable 3D porous scaffold capable of the controlled absorption of fluid and having improved mechanical properties for tissue engineering and in particular, for bone engineering. Barros et al. [188] formulated bone cements by the carboxymethylation of chitosan and ulvan from *Ulva lactuca*. The authors reported that the inclusion of carboxymethylated ulvan in bone cements improved its mechanical properties [188]. Dash et al. [189] assessed the activity of osteogenic cells in scaffolds based on polyelectrolyte complexes of chitosan and ulvan, further functionalized by deploying alkaline phosphatase (ALP) as a mineralization inducer. Successful mineralization was achieved using deposited minerals, observed as globular structures, which promoted cell attachment, proliferation, and extracellular matrix formation. According to the authors, such scaffolds make it possible to develop resorbable materials for tissue engineering [189].

#### 4. Conclusions

As evidenced by the publications considered in the present review, the PS of brown, red, and green algae (alginates, fucoidans, carrageenans, and ulvans) are very promising biomaterials to be used in regenerative medicine and tissue-engineering technologies. This is explained by their unique structure, physical and chemical properties, and high therapeutic activity that are advantageous for macro-organisms in general and important for applying in modern technologies. Of particular importance is their biological tunability, biocompatibility and biodegradability, renewability and non-toxicity. An important feature of these biopolymers is the ability to form hydrogels in aqueous solutions alone or in blends with other compounds. Hydrogel-based scaffolds are very promising materials for a wide range of medical applications, including wound dressing, drug delivery systems, and tissue engineering.

Algae PS show a high wound healing efficiency due to the key biological properties such as antioxidant, immunomodulatory, antiviral/antibacterial, anti-inflammatory, and anticoagulant properties. They allowed many wound dressings of various forms and types to be developed on the basis of PS, taking into account an integrated approach to the treatment of wounds and wide application in clinical practice. Wound healing is a multi-phase process involving various factors and cellular mediators. The use of conventional (standard) wound dressing materials, even those containing a drug, often cannot provide successful wound healing, and deep and chronic wounds cannot be adequately treated with their use. Moreover, the damage of bone tissues requires the fixation or use of bone fillers. The use of biocompatible and biodegradable natural biopolymers derived from marine organisms, as promising materials for the development of innovative wound dressings, can be a comprehensive approach that takes into account the type and characteristics of a wound, the phase of wound healing, etc., thus, providing effective and complete healing within a shorter period of time.

Current trends are focused on the development of new-generation materials not only for wound dressings, but also for the advanced delivery of drugs, growth factors, biologically active substances, proteins, genes, cells, and implantable materials that are combined with tissue-engineering technologies. PS-based biomaterials are also used in the development of tissue-engineering structures. The wide range of biological activities of algae PS, their biocompatibility and biodegradability, gelling ability, hydrophilicity, and natural rigidity make them perfect candidates to be used as biomaterials for the 3D bioprinting of tissues and organs. The advantage of PS for 3D bioprinting and other applications in tissue engineering is the resemblance of their structure with the human extracellular matrix and their inherent biological activity. Various structures in the form of

hydrogels, 3D-porous scaffolds, and nanofibers, whose applications may vary from drug delivery to tissue-engineering purposes, have been developed on the basis of PS.

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