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Alginates from Brown Seaweeds as a Promising Natural Source: A Review of Its Properties and Health Benefits

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ABSTRACT

Alginates, hydrophilic anionic polysaccharides with notable bioactivity and biocompatibility, have drawn significant attention, particularly due to their extensive use in the pharmaceutical industry and associated health benefits. Brown seaweeds serve as the primary source of alginates. However, extraction methods, especially traditional ones, face efficiency challenges, impacting the yield. Green extraction methods promise an eco-friendly alternative, but their industrial-scale implementation is still unproven. Importantly, these extraction methods could yield alginates of different molecular weights and consequent varied biological effects. Alginates possess antibacterial, antioxidant, anti-diabetic, and immunomodulatory properties, forming the cornerstone of their health benefits and pharmaceutical applications. The hydrogel formation characteristic of alginates is crucial for pharmaceutical applications, including drug delivery, wound dressing, and tissue regeneration. Despite the existence of numerous articles exploring the extraction methods, properties, and applications of alginates, a gap exists in the literature that connects these aspects with health benefits. This review aims to bridge this gap by providing a comprehensive discussion of the extraction methods, properties, health benefits, and pharmaceutical applications of alginates.

KEYWORDS

Alginates; brown seaweeds; health benefits; pharmaceutical applications; extraction methods

Introduction

Alginates also referred to as algin or alginic acid, are hydrophilic or anionic polysaccharides. Alginates' wide use in the pharmaceutical industry and potential health benefits, sparked considerable research interest in alginates.

A primary source of alginates is brown seaweed (Phaeophyceae), which includes various species such as *Laminaria hyperborea*, *Laminaria Digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, *Macrocystis pyrifera*[1]. It is found in the cell walls of brown seaweed which provides a flexible mechanical structure to protect seaweed from damage due to strong water movements.[1] Notably, *Durvillaea potatorum*, *Macrocystis pyrifera*, and *Ecklonia radiata* are known to have high yields of alginates, with up to 55%, 46.8% and 44% of dry weight, respectively.[2,3] These species vary in their morphology, composition, and distribution, which ultimately affects the yield and quality of the extracted alginates. It is also notable that the time and area of the collection can impact the alginate yield for the same species. Based on Kumar's[4] research for *Sargassum wightii*, the main axis of the plant that was collected in March has the highest alginates content, which is about 33%.

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Current research suggests that different extraction methods yield alginates with varying molecular weights, which can result in distinct biological effects, such as the antioxidant effect. These extraction methods can be categorized into conventional and green extractions.[5] The latter method involves the use of ultrasound, microwave, mechanical force, or the addition of enzymes to enhance efficacy and confer specific properties on the alginates, as discussed in this review. Unfortunately, these green extraction methods are not yet widely implemented on a large scale.

Alginates exhibit antibacterial, antioxidant,[6] antidiabetics,[7] antiobesity[8] and immunomodulatory properties, making them beneficial for human health and pharmaceutical applications. For instance, oral administration of alginates can inhibit bacterial growth in digestive system. The ability of alginates to induce satiety and their resistance to digestion in the stomach suggests potential applications in weight management.[9] Moreover, the anti-diabetic properties of alginates may be leveraged for blood sugar regulation.

The ability of alginates to form hydrogels underlies their broad utility. In the presence of divalent compounds such as Ca^{2+}, which are due to interionic interactions with G residues, alginates rapidly crosslink. This is one of the most common methods for obtaining a hydrogel, while still incorporating covalent crosslinking, thermal gelation, and cell cross-linking. For decades, these cross-linking mechanisms have been the method of encapsulating biomolecules and cells. Because of the biocompatibility of ionic gelation mechanisms, coupled with their lower costs and toxicity, alginates are frequently selected for medical applications, such as drug delivery, wound dressing and tissue engineering.[10]

This review provides a comprehensive overview of alginates. Focusing on their extraction, properties, health benefits and applications in pharmaceuticals bridged the gap in the literature by addressing the dearth of comprehensive studies in these areas. It explores the structure and general properties of alginates, as well as the hydrogel formation of alginates, including ionic cross-linking, covalent cross-linking, thermal gelation, and cell cross-linking. Additionally, this review examines the antibacterial, antioxidant and immunomodulatory properties of alginates. Furthermore, it discusses the health benefits of alginates concerning gastrointestinal health, weight management and satiety effects, and impact on diabetes. The review also delves into the pharmaceutical applications of alginates in drug delivery, wound dressing and tissue engineering.

Extraction method

Alginates can be extracted using a variety of methods including conventional chemical extraction (Figure 1) and extraction method with other techniques assisted, including but not limited to microwave, ultrasound, enzyme and extrusion. Except for the conventional method, the other four extraction methods can be referred to as green extraction methods.[5] These methods incorporate assisted techniques based on the conventional method and are used to enhance the efficiency of alginate production while saving energy and reducing waste.

The conventional chemical extraction process follows similar steps across different methods. Fresh seaweed is washed, dried, and ground into powder. The seaweed biomass is then soaked in an organic solvent (ethanol is the most used) to remove unwanted compounds such as lipids and polyphenols. Subsequently, an acid or alkali is added to break the cell wall, followed by sodium carbonate extraction to obtain water-soluble alginates. Alginates can be precipitated from the solution using one of three pathways: the sodium alginate pathway, the calcium alginate pathway, or the alginic acid pathway, with the sodium alginate pathway being the most commonly used.[5]

For ultrasound-assisted extraction, incorporating ultrasound with optimized parameters significantly reduces the extraction time from 2 hours to 30 minutes, while doubling the yield. According to nuclear magnetic resonance (NMR) analysis, 30 minutes of ultrasound does not affect the structure of polysaccharides.[11] The mechanism of ultrasound-assisted extraction involves using ultrasound to destruct the plant tissues and break the cell wall and cell membrane by acoustic cavitation. This facilitates the penetration of the solvent into the plant tissue matrix, thus accelerating the dissolution of materials like cytoplasm and cell-sap into the extraction solvent.[12]

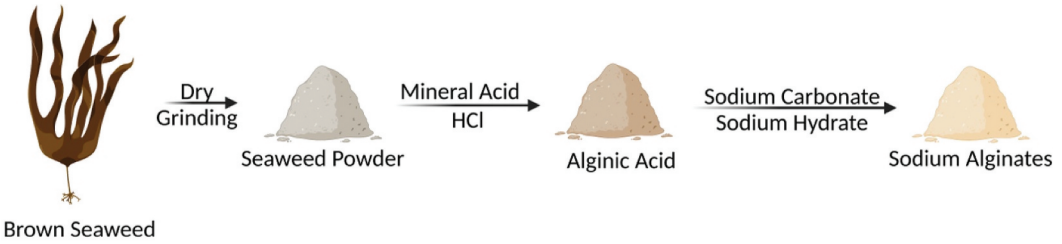

Figure 1. The conventional extraction of Alginates.

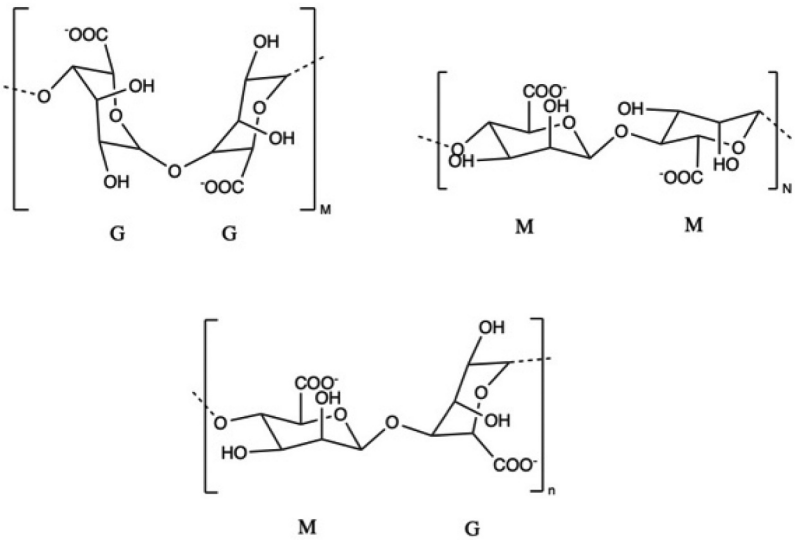

Figure 2. Structure of G blocks, M blocks and aligned G and M blocks.[10] redrawn by ChemBioDraw 20.0.

For microwave-assisted extraction, the mechanism is that microwaves generate heat power through ionic conduction and dipole rotations, crucial in removing the algae matrix and aiding the dissolution of sodium alginate into the solvent.[13] Torabi et al.[14] showed that the effect of microwave on extraction yield (EY) is quadratic. While the conclusion from the research is the range of 300W to 400W is generally considered optimal, with powers above 500W potentially causing yield loss. The explanation is increasing microwave power within an appropriate range can improve extraction efficiency while reducing the extraction period, but high-level microwave power may lead to thermal degradation to reduce effectiveness.

Enzyme-assisted extraction involves adding enzymes to the extraction process to catalyse the reaction, increasing efficiency and reducing waste. In alginate extraction, the use of enzymes results in alginate polymers with higher purity with the lowest concentration of proteins and polyphenols.[15] After treatment with alcalase, with the high molecular-weight alginates lost, lower molecular-weight alginates are produced as a consequence. Notably, alcalase treated alginates can induce RAW264.7 cells to release inflammatory cytokines while exhibiting high antioxidant ability.[16]

Extrusion-assisted extraction uses a twin screw extruder to aid in the extraction process, offering advantages such as reduced time, decreased solvent and reactant usage, minimal waste generation, safe and applicability in various industries.[17] In Sugiono et al.'s study[18] of extrusion-assisted extraction, the result showed that there is a quadratic relationship between parameters and residence time distribution of algae's stay in the screw channel. Furthermore, increasing the solution ratio, feed rate and pH were found to increase the residence time distribution.

Although this method offers a higher yield with a large molecular weight and holds great promise for alginates extraction, its application to alginates extracted from brown seaweeds remains underexplored.

Table 1 summarizes some methods for alginates extraction. Notably, there are two data for enzyme extraction that have significant differences, one is about 90% and another is only 9%. As mentioned before, the difference might be from different species and with different extraction conditions. According to the results[15] which has a 9% alginates yield (*Fucus vesiculosus*), it used four enzymes that have four different and lower yields: Alcalase (9.60 ± 1.03%), Viscozyme (9.19 ± 0.75%), Neutrase (8.76 ± 0.22%), and Celluclast (8.75 ± 0.17%). In contrast, the other one with a 90% yield used *Ascophyllum nodosum*,[19] the lowest yield is from using microwave-assisted method with even 56 ± 1%.

Property

Structure and general properties

Alginates is a linear polysaccharide consisting of repeating units of 1,4-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues.[34] Three types of alginates may be formed, including homopolymer sections for consecutive G and M blocks, homopolymer segments for consecutive M blocks or heteropolymer sections in randomly aligned G and M residues (Figure 2).[35] Depending on the specific seaweeds for which alginates are extracted, the M and G block contents and length of each block including an alternating block are different.[36] Alginates commonly exist in the forms of sodium alginates, calcium alginates and alginic acid.

The M/G ratio would influence alginates' quality and properties. According to the research of alginates of *Sargassum filipendula* from Brazil,[37] the M/G ratio lower than 1, it may form resistant gels which can be used for food and cosmetic applications.[33] There are conclusions that in alginates, mannuronic acid residues are the active cytokine inducers.[38] Based on this study, they found that alginates with low G block have about 10 times more than high G ones in inducing cytokine production.

The MW of sodium alginates is different, for example, for commercial use, the sodium alginates range from 32,000 to 400,000 g/mol,[10] which has long M and G chains with polydispersity index from 1.5 to 3 (Mw/Mn). At the same time, increasing the molecular weight of alginates increases the gelling rate and physical properties of the gel (tensile strength, elasticity, viscosity).[39] However, the combination of cells and high viscosity solution that need high shear forces to mix would cause damage to cell membranes, and delay the recovery, which leads to a high cell death rate.[40]

Alginates can dissolve in water while insoluble in fats, oils, and organic solvents. The solubility depends on M/G ratio, pH, MW, and crosslink with other compounds. Alginates that have high GG blocks would have higher water solubility than high MM blocks.[41] Based on the previous study, higher amounts of M blocks lead to stronger and less soluble films while crosslinked with $CaCl_2$ would present lower solubility.[42]

Hydrogel formation

In the biomedicine area, alginates are widely used in drug delivery, wound dressing, and tissue engineering as the form of hydrogels which are high cross-link three-dimension networks containing hydrophilic polymers.[43] Hydrogels have the advantage of biocompatibility, biodegradability, proper mechanical strength and so on.[44] Hydrogels are formed by hydrophilic polymers through physical and chemical cross-linking. Their physical and chemical properties depend on the type of cross-link, the concentration of the cross-linking agent, chemical compounds and the molecular weight of polymers.[45] Alginates have four common hydro-gelling methods[10] and will be explained as follow.

Table 1. Common extraction for alginates.

Species	Size	Soaking	Acid/Alkali	Extraction	Precipitation	Drying	Yield	Type	Ref
Ascophyllum nodosum	Powder	80% (v/v) Ethanol	0.01 M HCl	3% (w/v) Na_2CO_3	95% (v/v) ethanol	Freeze-dried 48 h	72 ± 4% **	Conventional	[19]
Alaria esculenta, Saccharina latissima and Ascophyllum nodosum	<0.5 mm		0.2 M HCl (1:25 w/v)	0.1 M $NaHCO_3$ 2 h and NaOH pH = 8	Isopropanol	65°C overnight		Conventional	[20]
Durvillaea potatorum	250–1400 µm	100% Ethanol	HCl pH = 1	0.2 M Na2CO3	50% Ethanol	Freeze-dried	55.2 ± 0.51%	Conventional	[21]
Ecklonia radiata	250–1400 µm	100% Ethanol	HCl pH = 1	0.2 M Na_2CO_3	50% Ethanol	Freeze-dried	29.3 ± 0.05–44.0 ± 0.15%	Conventional	[21]
Laminaria digitata	8, 16, 30 mm	4% w/w Na_2CO_3	0.5 M H_2SO_4 one night	4% Na_2CO_3	H2SO4		38.37–38.82%	Conventional	[22]
Laminaria hyperborea	Powder	0.2% Aqueous solution of formalin, Et, Me, Ac, EW, ME, or AW*	0.2 M HCl (ratio 1:10 w/v)	2% Na_2CO_3	96% Aqueous Ethanol	dried at 45°C for 72 h	4.2–12.8% ***	Conventional	[23]
Macrocystis pyrifera	250–1400 µm	100% Ethanol	HCl pH = 1	0.2 M Na_2CO_3	50% Ethanol	Freeze-dried	38.9 ± 0.45%	Conventional	[21]
Sargassum muticum		0.2% Formaldehyde for 24 h (ratio 1:10 w/v)	0.2 M HCl (1:10 w/v)	3% Na_2CO_3	93% Aqueous Ethanol	dried at 65°C until constant weight	13.57 ± 0.13%	Conventional	[24]
Sargassum natans	505 ± 5 µm	2% Formaldehyde	0.5 M H_2SO_4	Na_2CO_3 & bleach sodium hypochlorite	0.5 M H2SO4 pH = 2; alcohol; 5% Na2CO3	Freeze-dried 48 h	21%	Conventional	[25]
Sargassum vulgare		2% Formaldehyde 24 h	0.2 M HCl 24 h	2% Na_2CO_3	Ethanol	Under ambient atmosphere	16.90%	Conventional	[26]
Seirococcus axillaris	250–1400 µm	100% Ethanol	HCl pH = 1	0.2 M Na_2CO_3	50% Ethanol	Freeze-dried	41.3 ± 0.66%	Conventional	[2]
Ascophyllum nodosum	Powder	80% (v/v) ethanol	0.1 M sodium acetate buffer pH = 4.5 & heated to 50°C in a water bath	3% (w/v) Na_2CO_3	95% (v/v) ethanol	Freeze-dried 48 h	**90 ± 5% ** **	Enzyme-assisted	[19]
Fucus vesiculosus	Pre-treated biomass	10% (w/v) Calcium chloride	1 M HCl pH = 2	1 M HCl pH = 2	96% (v/v) ethanol	Freeze-dried 48 h	**9.60%**	Enzyme-assisted	[15]
Sargassum cristaefolium	60 mesh	Distilled water	0.03 M HCl pH = 3	Na_2CO_3 pH = 8 ~ 12	96% Ethanol	Vacuum-dried at 45°C for 24 h	34.96 ± 0.09%	Extrusion-assisted	[18]
Ascophyllum nodosum	Powder	80% (v/v) Ethanol	0.01 M HCl	3% (w/v) Na_2CO_3	95% (v/v) Ethanol	Freeze-dried 48 h	56 ± 1% **	Microwave-assisted	[19]
Ascophyllum nodosum	1–2 mm	80% (v/v) Ethanol	0.1 M HCl	0.1 M Na_2CO_3	Ethanol	dried at 40°C	18.24%	Microwave-assisted	[27]

(*Continued*)

Table 1. (Continued).

Species	Size	Soaking	Acid/Alkali	Extraction	Precipitation	Drying	Yield	Type	Ref
Nizimuddinia zanardini	Powder	99% Ethanol	HCl pH = 1	0.2 M Na_2CO_3	Absolute Ethanol	vacuum-dried at 45°C	31.39%	Microwave-assisted	[14]
Saccorhiza polyschides	<2 mm	Deionized water pH = 4 (HCl)	0.1 M HCl	10% (w/v) Na_2CO_3	50% Ethanol	Freeze-dried	20.8–26.4%	Microwave-assisted	[28]
Sargassum sp.	Dried seaweed	0.4% Formalin	1% HCl; 10% HCl pH = 2,3	Na_2CO_3	Ethanol	Dried in the sun for 12 hours until the moisture content of 12%	0.5–37.13%	Microwave-assisted	[29]
Ascophyllum nodosum	Powder	80% (v/v) Ethanol	0.01 M HCl	3% (w/v) Na_2CO_3	95% (v/v) ethanol	Freeze-dried 48 h	70 ± 4% **	Ultrasound-assisted	[19]
Sargassum angustifolium	0.250 to 2 mm	Water-chloroform-methanol mixture (1: 2: 4 v/v/v)	0.1 M HCl, 3 h, 60°C	2% Na_2CO_3	Absolute Ethanol	Lyophilize	17%	Ultrasound-assisted	[30]
Ascophyllum nodosum		1% (w/w) CaCl2	5% (w/w) HCl	3% (w/w) Na_2CO_3	50% ethanol	aired for 24 h and finally dried at 50°C for 2.5 h	18.3 ± 0.4–23.7 ± 0.5%	Ultrasound-assisted	[31]
Sargassum angustifolium		2 wt% formaldehyde and 90 vol% Ethanol	0.1 M HCl	2.5% (w/v) Na_2CO_3	Absolute Ethanol	Dried at 40°C for 24 h	7.8–45%	Ultrasound-assisted	[32]
Sargassum binderi and Turbinaria ornata	Powder	80% Ethanol	1N HCl	0.5% Na_2CO_3 & 5% $CaCl_2$	Ethanol	Freeze-dried	27%	Ultrasound-assisted	[11]
Sargassum muticum		Water	lemon juice pH = 3	Na_2CO_3		vacuum oven at −0.8 bar at 40°C for 48 h	13.60%	Ultrasound-assisted	[33]

*Pure Ethanol (Et), pure mEthanol (Me), pure acetone (Ac), 50 wt% Aqueous phase mixture of Ethanol (EW), 50 wt% Aqueous phase mixture of methanol (ME), and 50 wt% Aqueous phase mixture of acetone (AW) from the original paper.

**the yield = sodium alginate weight/the pre-extracted *Ascophyllum nodosum*.

v/v: volume ratio; w/w=wt% : weight ratio; w/v: weight/volume ratio; v/w: volume/weight ratio.

Ionic cross-linking

Sol-gel transformation of alginates can occur under the aqueous sodium alginates solution with cross-link cations. For example, by adding $CaCO_3$ in the acidic environment, Ca^{2+} would be dissociated and initiates gelation of the alginates.[46] The Ca^{2+} would replace the sodium ion at the binding site, which leads to a cross-link "egg-box" model (Fig. 3). This process can be called cooperative in that the first ion has difficulty in binding while the second is easier to bind.[47] The bivalent cation is a proper cross-link agent, including Cd^{2+}, Co^{2+}, Cu^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+} and Zn^{2+} while Ca^{2+} is the most widely used one.[48] Because the G block allows bivalent cations to have a higher degree of coordination to let bivalent cations bind better into G blocks.[10] However, a recent study showed that Ag^{+} can be used as a cross-linking agent and the beads made by this process are a candidate for drug carrier.[49]

As we mentioned above, after cross-linking with bivalent cations, alginates would have sol-gel transformation. Depending on the alginates solution concentration, forming methods and M/G ratio, it can be formed to different thicknesses. Previous studies showed that high G blocks would increase the interaction between chains and increase the film thickness.[51] The concentration of $CaCl_2$ solution would influence the surface morphology of films.[52] Changing the concentration of a solution, cross-linking conditions, and adding other compounds can change the mechanical strength and flexibility of alginate films.

Covalent cross-linking

Ionic crosslinked alginate saline gels exhibit a notable drawback in terms of their stability in physiological conditions. Water-based media leads to the release of divalent cations. Over time, hydrogels dissolve in an uncontrolled manner.[53] As a result, alternative covalent cross-linking strategies have been devised. These novel approaches can generate gels with enhanced stability, uniformity, and controllable mechanical properties.[54] In numerous covalent cross-linking reactions, the Schiff-base reaction demonstrates a non-cytotoxic cross-linking process under non-toxic chemical cross-linking agents, while the entire self-healing process occurs spontaneously without the need for stimulation from outside.[55] The microspheres consisted of oxidized alginates and carboxyethyl chitosan by Schiff-base reaction exhibited faster gelation, reduced swelling ratio, and a slower degradation process *in vitro*.[55] In another study, the 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride (EDC)/N-hydroxy-succinimide (NHS)-catalyzed amidation reaction was employed to couple sodium alginates (SA) and aminopropyl vinyl ether (APVE), facilitating the incorporation of vinyl ether side chains into the SA backbone. The synthesized SA-VE exhibited the spontaneous formation of a hydrogen-bonded hydrogel, SA-VE/H2O, within 10 seconds upon the addition of deionized (DI) water.[56]

Notably, photo cross-linking is one of the methods of using covalent cross-linking. It is adding eosin Y that is dissolved by 1-vinyl-pyrrolidinone and tritanol amine into alginates solution, then using exposure 514 nm laser for 30 seconds, the hydrogel is formed.[57] Although this method has great advantages, there still has a problem caused by unreacted photo-initiators and their side products

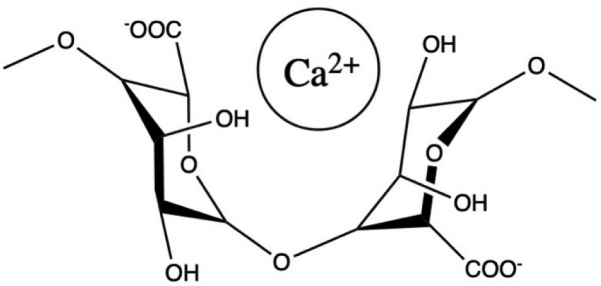

Figure 3. The egg box structure of Alginates.[50] redrawn by ChemBioDraw 20.0.

which cannot be removed and stay inside the hydrogel to limit the application, especially, pharmaceutical formulations.[58] However, a study developed a new hydrogel made of photoactive cinnamoyl-modified alginate. This hydrogel can self-photo-induced cross-linking with the existence of UV light for enough exposure time without a photo-initiator. And this new-type hydrogel is a potential candidate as an encapsulator for paracetamol.[59]

Thermal gelation

Thermos-sensitive hydrogels have been widely developed due to the release of bioactive compounds that are controlled and sensitive to changes in temperature, which give the thermos-sensitive hydrogels advantages in the drug delivery area. In the body, temperature-induced transfers of sol-gels are safer and more suitable for injectable applications because they do not require any denaturing cross-linking agents.[60] However, alginates are not thermal sensitive. But Zhao et a.[61] made thermo-sensitive semi-IPN hydrogels containing sodium alginates showing that the hydrogels swelling ratio would increase with the concentration of sodium alginates but decreased with the increase in temperature. Lencina et a.[62] also obtain thermos-responsive hydrogels consisting of alginate-*g*-poly (N-isopropylacrylamide) copolymers and this hydrogel is developed by low doses of gamma radiation.

Cell cross-linking

Cell cross-linking is to use a cell as a cross-linking agent. Lee et a.[63] added arginine, glycine, and aspartic acid to alginates by the water-soluble solution to form a long storage modulus. The result showed that cells are the cross-linking agent and improve the formation of a hydrogel. The mechanism is the interaction between cell receptors and adhesion ligands that can be used in forming reversible gel systems. However, the cell cross-linking method for alginates is still in the shadow.

In all, alginates films are applied in a variety of areas, e.g., food packaging, pharmaceutical and medical industries, agricultural sector, and cosmetic industry due to their film-forming properties. They are capable of being applied as coatings, encapsulating matrices, wound care products and several other applications.

Antibacterial

Antibacterial ability means that compounds or drugs have the efficiency to inhibit the growth of bacteria or kill the bacteria, and it is also a measurement of how a compound or drug confronts the bacterial infection. Sodium alginates solution does not have the antibacterial ability, to endow antibacterial activity it must be done functionalization. Previous studies have shown that some nanoparticles of metal,[64] such as silver, copper, and gold, have antibacterial ability. Therefore, we can combine the alginates with these metallic nanoparticles to give sodium alginates antibacterial ability. For example, crosslink with $CaCl_2$ and immerging in the Cu (II). Strong biocidal action against *E. coli* has been shown while Cu (II) releasement has a negative relationship with the number of sodium alginates and $CaCl_2$.[65] Adding silver composite nanospheres into an oxidized sodium alginates sponge would endow this combination with the antibacterial ability for *P. aeruginosa*, *E. coli* and *Staphylococcus aureus*.[66] Immersing sodium alginates when it has crosslinked with $CaCl_2$ into S-nitroso-*N*-acetyl-penicillamine (SNAP) to obtain alginates microspheres that can release NO.[67] The release of NO is under control while the release period can reach 93 hours. The antibacterial efficiency of *S. aureus* and *E. coli* bacteria can be even 100%.

Antioxidant

The ability of hydroxyl radical-scavenging and bleaching of β-carotene be analysed for the alginates derived from *Cystoseira barbata*.[68] The hydroxyl radical-scavenging ability is dose-dependent, as well as the bleaching of β-carotene, increasing the concentration of sodium alginates, the ability of hydroxyl radical-scavenging and bleaching of β-carotene would be high.

ABTS and superoxide radical ($O2^{-}$) scavenging assays showed that lower-weight alginates from heat treatment would have better antioxidant ability than non-treatment ones. This could be the result of the production of additional functional groups.[6] At the same time, alginates from *Cystoseira barbata*, *Sargassum angustifolium*,[16] and *Turbinaria conoides*[69] have been analysed for the stable form of the DPPH, which can be produced in a dependent way that due to they play the role of proton blockers.

Immunomodulation

A previous study by Niloofar et a.,[16] used 10 to 50 µg/mL alginates solution to analyse the immunomodulation of alginates with RAW264.7 macrophage cells. Alginates, treated by alcalase, at 50 µg/mL showed the greatest increase in RAW264.7 cell proliferation. This not only determines that alginates do not have toxicity for macrophage cells but also signals macrophage cells to proliferate. Additionally, another study[70] suggests that molecular size and M/G ratio are important structural parameters influencing the TNF-α-inducing activity by using RAW264.7 cells. However, only alginate oligomers showed immunomodulation ability. The mechanism may be that alginate oligomers are involved in the formation of multiple cytokines, and this is different for different species. The molecular weight of alginates has also been suggested to have a decisive effect on the magnitude of cell induction that results from smaller molecules, and more active immunomodulation ability.[71]

Health benefits of alginates

As mentioned before, alginates have anti-ability which confers alginates benefits of health. Antibacterial ability made alginates to inhibit bacterial growth in vivo is possible, such as the digest system. The potential ability of antidiabetic let the alginates apply in diabetes management. Application in weight management is because of its ability of water-soluble, undigested by the stomach, and satiety. Figure 4 showed the health benefits of alginates in gastrointestinal health, weight management and satiety effects, and potential implications in diabetes management.[72,73]

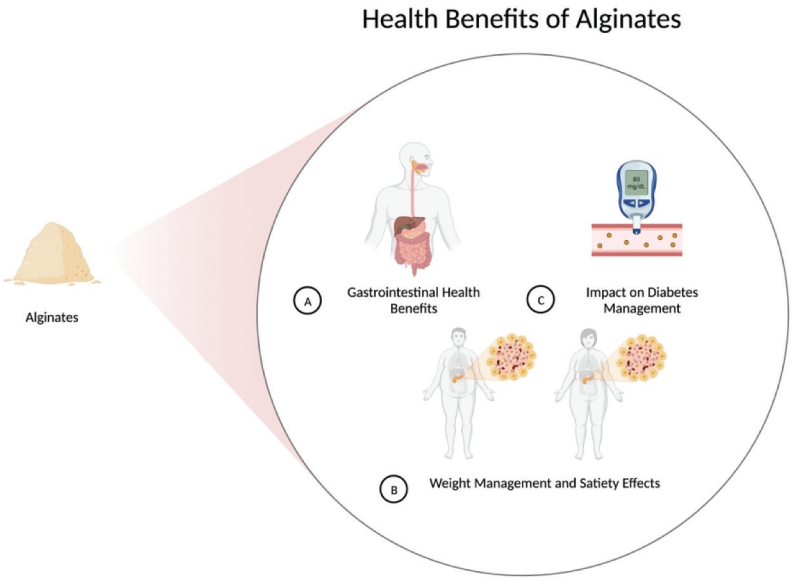

Figure 4. Health benefits of alginates.

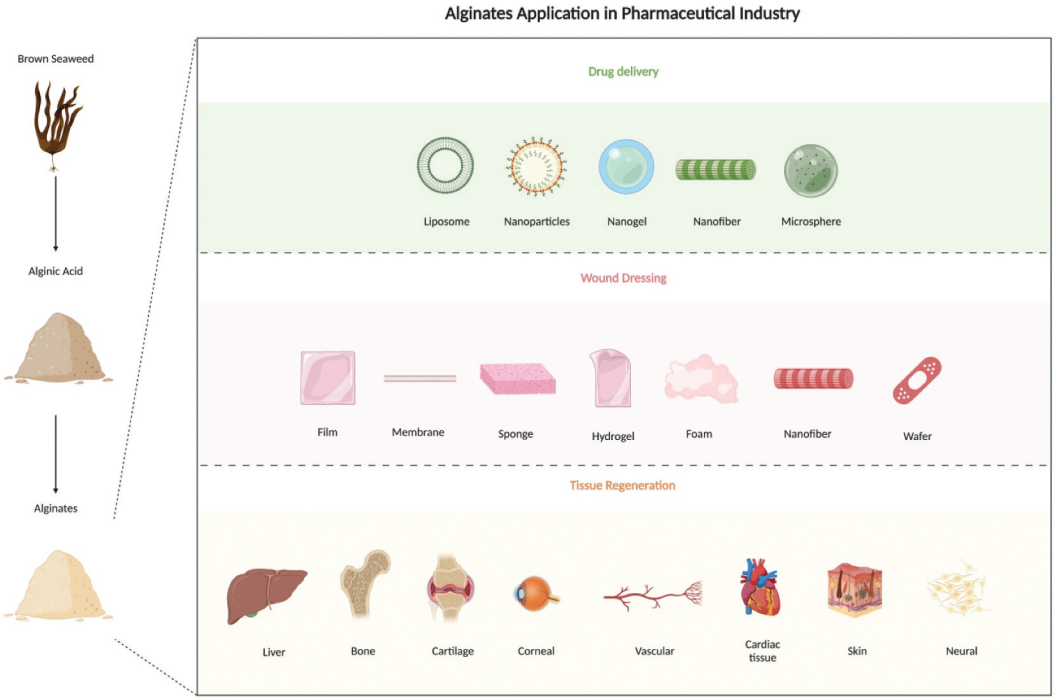

Figure 5. Pharmaceutical application of Alginates.

Gastrointestinal health benefits

Alginate has the ability to inhibit bacterial growth in the digestive system. In a study of eight healthy male diets with additional 10 g alginate once a day lasting for two weeks, results showed that during this period, bifidobacteria concentration increased significantly while the levels of Enterobacteriaceae and the frequency of occurrence of lecithinase-negative clostridia decreased. No levels or incidences of other normal microorganisms change had been detected as well.[74] Alginates with high M content also can bind to iron, helping to treat diseases related to excessive unabsorbed luminal iron in the colon. A human study[75] determines that having 3 g alginate was tolerated with minor side effects. There was no significant impact on haematological parameters or intestinal microbiome, the results in human intestinal microbial ecosystem simulation are the same. But the challenge is alginates may be degraded by bacteria or enzymes in the gastro-intestine. Alginates, along with their oligosaccharides (AOS), both confer gastrointestinal health benefits. A recent study revealed that AOS decrease damage to small intestine cell membranes and microvilli caused by busulfan which is used in anticancer while AOS promote blood metabolome to assist small intestinal recovery.[76] Using microbiota from mice dosed with AOS can mitigate small intestinal mucositis[77] and also support AOS have gastrointestinal health benefits.

Weight management and satiety effects

Overweight and obesity have grown to epidemic proportions. Based on the 2017 global burden of diseases shows that over 4 million people die each year because of being overweight or obese.[78] Therefore, there is no time delay. Alginates can be utilised for antiobesity activity for a variety of reasons, including the fact that they are water-soluble, cannot be digested by the stomach, cause satiety, and improve gastrointestinal motility.[9] These factors may fall under the category of dietary treatments. Wang et a.[8] found that sodium alginates had the ability to reduce weight gain, adiposity

index, and glucose homoeostasis brought on by the high-fat diet based on the mice model. Additionally, it can successfully treat hyperlipidemia and hyperglycemia while lowering the risk of cardiovascular disease. Notably, sodium alginates can restore the colonic genome's shape and functionality to support immune system modulation. To find out if calcium-gelled, alginates-pectin drinking can lower satiety and food intake, Christine et a.[79] had research of 29 female adults who were overweight or obese. The results show that this drinking works, but additional research is required to explore the likely mechanism. According to a study by El Khoury et a.,[80] putting gel sodium alginates in chocolate milk can considerably lower pre-meal glycemia, insulinemia, and hunger in healthy male adults without having a detrimental impact on caloric intake. Adding alginates into bread may have the potential in the treatment of obesity[81] due to its inhibition effect of pancreatic lipase. The results explore that alginates would not be digested and recoverable in the gut model, while the molecular of alginates would not be affected by the cooking, digestion and extraction. Even at 150°C, alginates still have inhibition properties. Above all showed that alginates have potential applications in weight management and satiety effects for humans based on dietary interventions.

Impact on diabetes management

One mechanism of antidiabetic compounds involves delaying carbohydrate absorption through α-glucosidase inhibitors, which lower postprandial blood glucose concentration by inhibiting carbohydrate absorption in the upper small intestine.[82] According to the conclusion from Idota et a.[7] research with a rat model, *in vitro, the* study showed that calcium alginates have markedly inhibited α-glucosidase activity while the in vivo study established that 5% calcium alginate with a weight of 270-mesh-pass (Sieve size is about 53 μm) was the most resultful to suppress the postprandial increase of blood glucose. Kato et a.[83] had done a randomized clinical trial to determine that adding calcium alginates to Udon noodles would suppress the highest amount of blood glucose concentration postprandially and glucose absorption, while blood calcium concentration increased without other parameter values changed.

Unfortunately, the antidiabetic ability of polysaccharides from brown seaweeds are mostly focusing on fucoidans, which showed significant antidiabetic ability.[84] But alginates are always used to deliver medications for managing diabetes. The calcium alginates microspheres used to obtain Metformin, medicine for treatment for type 2 diabetes, for oral treatment of type 2 diabetes can extend the drug's release in the stomach and offer continuous release at intestinal fluid, according to the conclusion from Maestrelli, Mura[85] study with mice model. At the same time, Metformin's blood glucose-lowering effects have greatly improved.

Pharmaceutical application

As early as 1970, Food and Drugs Administration (FDA) had approved the use of alginates in food, pharma, and medicine.[86] The most famous application of alginates in pharmaceuticals is drug delivery. Due to the hydrogel formation of alginates, it can form various forms to encapsulate the drug and release the drug in vivo under specific conditions. Wound dressing is also another wide use of alginates and there have already many products in the market. Because of the alginates' scaffold's structure, tissue engineering especially tissue regeneration is an area where alginates are involved. Figure 5. illustrates the various pharmaceutical applications of alginates, highlighting their roles in drug delivery, wound dressings, and tissue regeneration.

Drug delivery

Alginates are a natural biopolymer that derive from brown seaweed and gain wider use in drug delivery. Alginate's properties allow it to encapsulate and deliver drugs to targeted areas effectively. The drug delivery system (DDS) based on alginates has several advantages, including biocompatibility

and biodegradability. Gel forming ability of alginates allow alginates to do sol-gel transformation under the aqueous sodium alginates solution with cross-link cations, which enable the formation of numerous drug delivery platforms, including but not limited to hydrogels, liposomes, microspheres, beads, nanofibers, nanoparticles etc.[87,88] Table 2 is a mini summary of alginates' application in drug delivery.

The drug release timing can be managed via an alginate-based drug delivery system (DDS), limiting drug degradation and providing targeted delivery. It may be more beneficial if the bond between the drug and the alginates can be exploited to control the drug release kinetics.[10] Drug release can be controlled by adjusting the external environment, including pH, UV, temperature, and the addition of microbubbles.[89–91] Because of this, it is possible to carefully monitor medication release kinetics in order to increase treatment effectiveness and decrease side effects.[92] A DDS based on alginates, gelatine, and Fe3O4 magnetic nanoparticles with a pH-dependent release system was devised and created by Rana et al.[93] The prospect of treating cancer with this DDS is fascinating. Another example is Sheng et al. created a dual-drug delivery system (DDDS) for the treatment of colorectal cancer. Methotrexate and aspirin are loaded into an alginates and sodium carboxymethyl cellulose hydrogel using Ca^{2+} as a crosslinking agent. Aspirin and methotrexate can be shielded from absorption by the body using this hydrogel. This hydrogel exhibits excellent biocompatibility and can prevent methotrexate and aspirin from being absorbed by the stomach.[94]

Furthermore, alginates' biocompatibility and biodegradability ensure that DDS based on alginates can be metabolized and degraded in vivo, minimizing potential negative effects. DDS based on the alginates also can protect the drug against the harsh physical environment and enhance the stability to promote the drug delivery to specific tissues or cells.[94]

In conclusion, given their notable properties, alginates have significant potential as a valuable material for DDS. Its biocompatibility, biodegradability and other important properties make this system become an attractive choice for controlled-release applications. Ongoing research and development aim to connect alginates with other low or high-molecular-weight polymers to optimize alginates' performance to apply in various therapy and pave the way for innovative and effective drug delivery strategies.[95]

Wound dressings

Alginates have been widely used in wound dressing ascribed to their biocompatibility, film-forming, and hydrogel. The platform is based on alginates for wound dressing in the forms of hydrogel, films, foams, nanofibers, membranes, sponges, wafers, etc. Table 3 is a mini summary of these platforms. The mechanism of alginates in wound dressing is with the existence of binary cations such as calcium ions, alginates can form the gels,[10] which maintain the moist physical environment to avoid bacterial infection by absorbing the fluid of wound.[124] This leads to promoting re-epithelialization and granulation tissue formation.[10]

As a mature, products based on alginates in wound dressing have already in the market, showed in Table 4.

Tissue engineering

Alginates have drawn attention in the tissue engineering area which aims to create functional tissues and cells by the combination of cell and biomaterials.[159] Alginate has been proven to be a valuable biomaterial in scaffolds and matrices based on unique properties, used in various tissue engineering applications, including bone, cartilage, skin, and vascular tissue regeneration,[160] which shows a mini summary in Table 5.

Alginates exhibit significant biocompatibility, making them non-toxic to cells and avoiding any detrimental effects. However, under specific condition,[161] alginates demonstrate an appropriate host response. When designing and developing tissue engineering materials using alginates, it becomes

Table 2. Mini summary of alginates applications in drug delivery.

					Outcome			
Platforms	Compositions	Drug loading	Preparation methods	Targeting	Characterisation*	Encapsulation efficiency	Control release	Ref
Liposomes	Alginates, plant proteins	Rosmarinic acid	Ionic gelation	Gastro and intestine	Size 106.7 ± 0.9; PDI 0.21 ± 0.01; zeta potential – 21.17 ± 0.46 mv	TPC: 94.66 ± 0.38%; DPPH: 93.26 ± 1.20%; ABTS: 93.17 ± 0.58%; rosmarinic acid: 97.64 ± 0.25%	release of rosmarinic acid during 120 min in SGF, followed by the continued release in SIF for up to 30 min.	[96]
Liposomes	Cysteine modified alginate	Insulin (arginine-insulin complex)	Thin film hydration method	Intestine	Size <200 nm; zeta potential –22.8 mv	75.90%	After releasing for 6 h, insulin from AINS-Lip and AINS-Lip-Gel was 60% and 35.8%, respectively	[97]
Liposomes	Genipin(GP), whey protein isolate (WPI), sodium alginate (SA)	Flax seed oil (in-3 fatty acids)	-	Gastro and intestine	Sa-wpi-nanoliposome: size 459.6 ± 2.0 nm; pdi 0.28 ± 0.02; zeta potential – 17.8 ± 0.23 mv	Alpha-linolenic acid: 85.2 ± 1.3%; linolenic acid: 84.9 ± 0.21%	The limit of detection (LOD) and limit of quantitation (LOQ) of n3 were 565.3 and 1713.0 (ng/µl), respectively. The limit of detection (LOD) and limit of quantitation (LOQ) of n6 were 325.5 and 986.3 (ng/µl), respectively.	[98]
Liposomes	Sa-coated collagen peptide	Collagen peptides (cp)	Extrusion method	Gastro and intestine	0.3% sa coating: size 249.9 nm; the absolute value of zeta potential 40.1 mv;	70.99%	0.3% sodium alginate: 29.23% and 40.32% of collagen peptides were released at 6 h and 12 h	[99]
Liposomes	Alginate coated chitosan	Naringenin	Ultrasonic emulsification, ionic gelation	Intestinal lumen	Alginate and chitosan 1:3 size 216.44 ± 06 nm;, pdi 0.39 ± 0.14; zeta potential – 36.01 ± 2.7 mv	91.00%	pH 7.4 more than 90% naringenin was released following a slow sustained fashion	[100]
Liposomes	Alginate	Doxorubicin	Thin film hydration method	oral mucosa	Average size 136 ± 44 nm	-	decrease in oral cancer cells viability to an average of 38% and 15% after 24 and 48 h,	[101]

(*Continued*)

Table 2. (Continued).

Platforms	Compositions	Drug loading	Preparation methods	Targeting	Outcome			Ref
					Characterisation*	Encapsulation efficiency	Control release	
Nanofibers	Alginate	Lavender oil	Solution electrospinning	-	size 93 ± 22 nm;	Well incorporated	active for more than 2 days, and able to release the antibacterial and anti-inflammatory agent	[102]
Nanofibers	SA	Lutein	Solution electrospinning	-	Size 240–340 nm; angle values 33.5 ± 0.22°Cross-linked for 1 h	91.9% ± 2.58%	crosslink for 1 h, average release rate of 12.5%/h and complete lutein was released in 10 h	[103]
Nanofibers	2 wt% sa and 10 wt% polyvinyl alcohol (PVA)	Gatifloxacin (GH)	Solution electrospinning	Skin	Maximum degree of swelling 209 ± 4.1%	95%	90% of the GH was released from the electrospun fibres within 6 h of incubation, the release was sustained for 24 h	[104]
Nanofibers	PVA/SA/graphene oxide (GO)/zno 7 wt% PVA、2 wt% SA、0.5 wt% GO	Glutaraldehyde	Solution electrospinning	-	Size average 199 ± 22 nm; 48 crosslink contact angle 72.84°	-	effective inhibition of S. aureus strains	[105]
Beads	Magnetic cofe2o4 nanostructures (MCFO) and alginate	Chlorpheniramine maleate (CPAM)	Ionic cross-linking gelation	-	Size 9.72 ± 0.15 nm;	About 70% (ph 7.4)	in vitro release profiles were altered by varying the pH and compositions of beads while it was directly proportional to the polymer concentration and CPAM content	[106]
Beads	Agar and alginate	Indomethacin	-	-	Size about 1000 μm	82.50–94.01%	63% – 91% for 12 h (pH 7.4)	[107]
Microspheres	The alginic acid sodium salt	Ketoprofen and benzoic acid	Emulsion – gelation	Gastro and intestine	Size 116 ± 6 μm;	13.42 ± 0.78% for ketoprofen; 23.33 ± 2.01% for benzoic acid	0.075 min – 1 ketoprofen and 0.160 min – 1 benzoic acid	[108]
Microspheres	RGD-alginate (RGD-Alg) and nanosilicate laponite (LAP).	Human dental pulp stem cells (HDPSCS) and vascular endothelial growth factor (VEGF)	Electrostatic microdroplet method	Root canal	Size 350 ~ 450 μm; storage modulus: 0.5% laponite 1800 pa; 1 laponite 10,000 pa	200 ng/ml VEGF-165	14 days, 0.5% Lap released 24 ng/mL VEGF, 1% Lap released ~16 ng/mL	[109]

(*Continued*)

Table 2. (Continued).

Platforms	Compositions	Drug loading	Preparation methods	Targeting	Outcome			Ref
					Characterisation*	Encapsulation efficiency	Control release	
Microspheres	SA	Curcumin	Emulsion-gelation	-	5% alginate concentration: size 72.2 μm	5% alginate concentration: 53.36 ± 1.80%	day 28 release reached 98.32%	[110]
Microspheres	SA	Retinoic acid	One-pot method	Eye	Size 95.7 ± 9.6 μm	1.76 ± 0.05 μg/mg	constant release	[111]
Microspheres	HA-SH-Ag/Alginate-Ca microspheres (hyaluronic acid: HA, anti-inflammatory thiolated-HA: HA-SH)	Sliver ion	Gas-shearing device	Gut	Size 264.64 ± 13.98 μm	-	100 mg per minute	[112]
Microspheres	SA	Soy isoflavone	Emulsification followed by calcium cross-linking	Skin	Size 18.12 ± 5.6–24.07 ± 2.8 μm, direct positive relationship with SA concentration, negative relationship with the cross-linker.	75.12 ± 8.1–97.6 ± 4.5%, direct positive relationship with SA and cross-linker concentrations	82.5% pH = 7.4	[113]
Nanogels	Alginate aldehyde – gelatin	Curcumin	Inverse miniemulsion technique	Breast	acidic pH; size 431 ± 3 nm; zeta potential of − 36 ± 5 mv	72 ± 2%	70% in 48 h	[114]
Nanogels	Alginate-cisplatin	cisplatin	-	Atherosclerosis	sizes of 99.3 nm; PDI 0.177; zeta potential of −28.8 mv	Loading efficiency 13.78 ± 0.32%	pH = 5, released within 48 h	[115]
Nanogels	Alginate-coated chitosan (ACC) and chitosan-coated alginate (CCA)	Mupirocin	Ionic gelation	-	ACC: size 16.5 ± 0.95 nm, PDI 0.57, zeta potential −35.13 ± 15.2 mv CCA: size 17.84 ± 2.3 nm, PDI 0.05, zeta potential 20.74 ± 3.51 mv	0.1% mupirocin ACC: 35.62 ± 0.5% CCA: 35 ± 0.41%	0.15% mupirocin-loaded at 72 h, CCA reaches 96% ACC reaches 70% drug release	[116]
Nanogels	Quercetin-alginate	Quercetin	Emulsion polymerization method	Lung	Size 61.87 nm; zeta potential −30 mv	97.7 ± 1.2%	the antioxidant ability could increase by 10% compared to the free quercetin; good cytocompatibility	[117]

(*Continued*)

Table 2. (Continued).

Platforms	Compositions	Drug loading	Preparation methods	Targeting	Outcome			Ref
					Characterisation*	Encapsulation efficiency	Control release	
Nanogels	SA	Albiflorin	Reverse microemulsion method	Nose	Low does; zeta potential – 19.8 ± 0.9 mv	content of albiflorin 2.43%	100% in the first 12 hours in the PBS (pH = 6.4)	[118]
Nanoparticles	Alginate	Miltefosine	External gelation method	-	Similar as size 346.5 ± 30.6 nm; PDI 0.40 ± 0.07; zeta potential – 36.2 ± 6.8 mv	81.70% ±6.64	24 h, 7.55%	[119]
Nanoparticles	Alginate	Grape pomace extract	Ionic gelation	Gastro and intestine	Size 270 to 1051 nm; zeta potential – 15 and −32 mv	38.8 to 64.7%	-	[120]
Nanoparticles	Alginate	Capsaicin	Phase inversion temperature method and ultrasonic homogenization		Size 19.4 ± 1.8 nm; PDI 0.21 ± 0.01; zeta potential – 24.9 ± 0.7 mv	98.7% ± 0.6%	100% capsaicin would release in 5 days	[121]
Nanoparticles	Chitosan and SA	Doxycycline	Coacervation method	Spleen and blood	Size about 0.4 μm; zeta potential about 60 mv	80.20 ± 0.89%	72.11 ± 0.77% for 24 h	[122]
Nanoparticles	Alginate polyelectrolyte	Lysozyme	Coacervation	-	Size 118.5 ± 0.0–158.8 ± 3.4 nm; PDI 0.145 ± 0.001–0.262 ± 0.001; zeta potential – 40.0 ± 1.0–43.9 ± 0.2	65–89%	rapid initial burst (<13%), sustained lysozyme release (<50%) over 72 h	[123]

*Size means loading drug one, some using different parameters to prepare alginates and the result is a range. Same as PDI and Zeta potential.
PDI: polydispersity index.

Table 3. The mini summary of alginates in wound dressing.

Platforms	Composition	Drug loading	Properties	Potential Application	Ref
Films/Membranes	Alginates (Alg)	Vicenin-2 (VCN-2)	The film is smooth, translucent, and good with flexibility. Enhanced cell proliferation and migration, also regulated the production of pro-inflammatory cytokines	Wound healing in hyperglycemic condition	[125]
Films/Membranes	Sodium alginates (SA)/povidone iodine	-	Reduce the inflammatory response, higher wound closure	Wound closure	[126]
Films/Membranes	SA/chitosan/collagen	Berberine	Antibacterial activity, hemostasis, accelerating wound healing, biocompatibility	Wound treatment	[127]
Films/Membranes	SA	Papain	Promoting the debridement	Wound dressing	[128]
Films/Membranes	SA/chitosan	Polymyxin sulphate and lidocaine chloride	Antibacterial activity, hemostasis, accelerating wound healing, non-cytotoxicity	Wound healing	[129]
Foams/Sponge	Alg	Silver and asiaticoside (AS)	Active compounds release, non-cytotoxicity, the foam is soft and flexible	Wound healing	[130]
Foams/Sponge	SA/graphene oxide/chitosan oligosaccharide	-	Antibacterial, hemostatic and promoting healing	Wound dressing	[131]
Foams/Sponge	Chitosan/Alg/hyaluronic acid	-	Activate the extrinsic and intrinsic pathways of blood coagulation, with no obvious cytotoxicity, or hemocompatibility. Promote the wound healing	Wound dressing	[132]
Foams/Sponge	Alg/gum acacia	Ampicillin and norfloxacin	Clotting capability and antibacterial activity	Infected and bleeding wound	[133]
Foams/Sponge	Alg/carboxymethyl chitosan/	Kangfuxin	Antibacterial behaviour, cytocompatibility, and rapid hemostasis	Full-thickness wound healing	[134]
Hydrogel	Calcium alginate (CA)	Ciprofloxacin	Against Gram-positive and Gram-negative bacteria	Potential healing for foot ulcers	[135]
Hydrogel	Alg/Eudragit	Edaravone	The dose-dependent, low dose of edaravone nanocomposite hydrogel is conducive to wound repair while a high dose of edaravone is destructive to wound healing.	Impaired wound healing in diabetes	[136]
Hydrogel	Alg	Cannabidiol	Antioxidant and anti-inflammatory, accelerated wound healing	Wound healing	[137]
Hydrogel	Alg/chitosan oligosaccharide/ZnO	-	Antibacterial activity and biocompatibility. The mechanical performance was enhanced.	Wound healing	[138]
Hydrogel	SA	Platelet-rich plasma	Release of epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF), high wound closure effectiveness	Wound healing	[139]
Nanofibres	SA/polyvinyl alcohol (PVA)	Honey	Against Gram-positive and Gram-negative bacteria, non-cytotoxicity and biocompatibility	Wound dressing	[140]
Nanofibres	CA/2,2,6,6-tetramethylpiperidine-1-oxyl oxidized bacterial cellulose (TOBC)	-	Promote cell adhesion and proliferation, antibacterial activity	biomimetic antimicrobial hydrogel dressings	[141]
Nanofibres	SA/polyvinyl alcohol (PVA)/	Dexpanthenol	Biocompatibility and cell adhesion	Wound healing and specific tissues regeneration	[142]

(*Continued*)

Table 3. (Continued).

Platforms	Composition	Drug loading	Properties	Potential Application	Ref
Nanofibres	Chitosan/Alg	Gentamicin (Gn)	High concentration Gn showed a stronger antibacterial activity, 1–3% Gn improved cell attachment and proliferation, 3% Gn enhanced skin regeneration	Skin regeneration	[143]
Nanofibres	Alg/poly (vinyl alcohol)/gelatin	Ciprofloxacin	Antimicrobial activity	Wound healing	[144]
Wafers	Polyox/SA	Diclofenac (DLF) and Streptomycin (STP)	Antibacterial activity, reducing chronic inflammation	Wound dressing	[145]
Wafers	CA	Ciprofloxacin	Against Gram-positive and Gram-negative bacteria	Wound dressing for diabetic foot ulcers	[146]
Wafers	CA/aloe vera gel	Nanosilver	Antibacterial activity	Wound dressing	[147]
Wafers	Chitosan/SA	Berberine	Reduced oral mucositis severity and the expression of inflammatory factors	Oral Mucositis	[148]
Wafers	SA/gelatin	Silver sulfadiazine	Reduce bacterial load within infected wounds	Wound dressing	[149]

Table 4. Mini summary of commercial alginate product in wound dressing.

Product brand	Composition	Application	Ref
Biatain®	85% alginate and 15% carboxymethylcellulose	Pressure injuries, venous leg ulcers, arterial ulcers, diabetic foot ulcers, donor sites or traumatic wounds.	[54]
Cutimed®	calcium sodium alginate (80% calcium and 20% sodium)	Useful for moderate to heavily exuding wounds, shallow wounds, lesions with rough edges, or deeper sites that are hard to dress	[150]
DermaGinate®	CA/sliver	Postoperative wounds, trauma wounds, pressure ulcers, leg ulcers, diabetic ulcers, grafts, donor sites	[151]
AMERX®	100% CA	Pressure ulcers, arterial ulcers, venous ulcers, diabetic ulcers, donor sites, post-operative wounds, dermal lesions, cuts and abrasions.	[152]
Restore®	calcium sodium alginate	Arterial, venous, diabetic, and pressure (stage 1–4) injuries; post-surgical incisions; donor sites; dermal lesions, trauma injuries, incisions, or other trauma wounds; superficial (first-degree) and partial-thickness (second-degree) burns.	[153]
MedVance®	CA	Leg ulcers, diabetic foot ulcers, pressure ulcers, cavity wounds and surgical and traumatic wounds healing by secondary intention.	[154]
Maxorb®	CA and sodium carboxymethylcellulose fibres	Diabetic, leg and pressure (stage 2–4) ulcers; surgical wounds; donor sites; lacerations and abrasions; superficial (first-degree) and partial-thickness (second-degree) burns	[155]
KALTOSTAT®	Alginate Calcium Sodium	Moderately to highly exuding chronic and acute wounds, and for wounds with minor bleeding	[156]
Suprasorb®	CA fibre, Cellulose fibre	Arterial ulcers, venous ulcers, diabetic ulcers, decubitus ulcers, surgical wounds, skin grafts and donor sites	[157]
Sorbalgon®	CA/sliver	Postoperative wounds, traumatic wounds, leg ulcers, pressure injuries, diabetic ulcers, cavity wounds, grafts, and donor sites.	[158]

essential to incorporate peptides or proteins that facilitate cell adhesion.[162] A case of this is the addition of fluorenyl methoxycarbonyl-diphenylalanine (FmocFF) peptide to alginates, resulting in the formation of a rigid hydrogel suitable for bone regeneration. Furthermore, this hydrogel enhances the adhesion, proliferation, and osteogenic differentiation of MC3T3-E1 preosteoblast cells.[163] Moreover, when combined with 30% nanohydroxyapatite, alginates have shown enhanced cellular proliferation and activation in vivo. In ex vivo studies, this combination has demonstrated improved collagenous deposition and trabecular bone formation. However, it is worth noting that ratios of 50% and 70% have been found to induce detrimental biological responses, necessitating optimization of the ratio.[164] Additionally, alginates also combinate with other materials, such as natural biopolymers, to enhance their properties to widen their application in tissue engineering. For example, the combination of chitosan and alginate is developed for the treatment of articular cartilage.[162]

Alginates as the most common bio-inks in 3D bioprinting, applications in vascular tissues, bone and cartilage have been made a figure. For example, there is a hydrogel consisting of methacrylated carrageenan and sodium alginates[165] showed liquid crystal properties, cell culture confirmed that it promotes cell growth. Through a 3D extrusion system, this hydrogel has a penetrating formation. All these properties let the hydrogel has the ability to apply in vascular tissue engineering.

Limitation and future perspective

Despite the significant potential demonstrated by alginates in various applications, it is crucial to recognize the existing research limitations and uncover areas that have not been fully explored yet and the ability to integrate alginate extraction with the production of other value-added products.[5]

While alginates are utilized in drug delivery for cancer therapy, it remains unclear whether they possess anticancer bioactivity. Most of the research in this field is primarily focused on investigating other brown seaweed polysaccharides fucoidan.[177] At the same time, current studies for alginates bioactivity are far less attention than it deserves. Alginates have antiobesity and antidiabetic properties, although there are several research based on animal models or human trials, the products in the market are still less than the products for pharmaceutical use.

Table 5. Mini summary of alginates in tissue engineering.

Tissue types	Composition	Drug loading	Properties	Applications	Ref
Bone	Sodium alginates (SA)/ hydroxyapatite nanorods	Ciprofloxacin	Biocompatibility, antibacterial activity	Bone filler antibiotic devices	[166]
Bone	Poly (lactic-co-glycolic acid) biopolymer/alginates (Alg) hydrogel/magnesium oxide nanoparticles	Mg2+	Enhance osteoblastic activity in vitro and stimulate in-situ bone regeneration in vivo in terms of total bone volume, bone mineral density (BMD), and trabecular thickness after the operation.	in-situ bone regeneration clinically	[167]
Bone	Gelatin/Alg	Cerium oxide	Enhanced osteogenic differentiation with the free radical scavenging property.	Bone regenerative therapies	[168]
Cartilage	chitosan/Alg/hydroxyapatite hybrid	-	Improved scaffolds' elastic modulus and thermal stability behaviour. Improvement in swelling, hydrophilicity properties, and cell viability, chondrocyte cell attachment and viability increased.	Cartilage regeneration	[169]
Cartilage	Poly ε-caprolactone/alginate sulfate/extracellular matrix	-	Better viscosity, cell viability, and proliferation	Nasal cartilage regeneration	[170]
Cartilage	Alginate hydrogel	Growth factor TGF-β1 or BMP-4	Effective tissue restoration	Repair and regeneration of articular hyaline cartilage	[171]
Liver	Alg/calcium	Glycyrrhizin (GL)	Biocompatibility maintains the viability, proliferation and liver function, and improved the mRNA expression of cytochrome P450	New culture system for the bioartificial liver device	[172]
Liver	fibrin/alginate dialdehyde/ gelatin	-	Cells on this hydrogel have metabolically active and perform natural hepatic cell function well	3D scaffold system for liver engineering	[173]
Liver	Galactosylated chitosan/Alg	Collagen	This microcapsule can create an efficient hepatic microenvironment	The 3D platform for modular hepatic tissue engineering	[174]
Vascular tissue	Alg/gelatine	-	Allowing cardiomyocyte contractility and endothelial cell structural self-organisation	Cardiac patches for myocardial regeneration	[175]
Vascular tissue	Sulfated alginate/cationic polyurethane	-	Higher endothelial cells attachment, higher anticoagulation ability and significantly less platelet adhesion	Biodegradable and biocompatible for vascular engineering	[176]
Vascular tissue	Methacrylated carrageenan/SA	-	Liquid crystal properties and promote cell growth.	Tubular tissue regeneration	[165]

Hydrogel formation and cell cross-linking are the basis of alginates as the potential application for delivery of cells into the body for therapeutic purposes which need to explore and pay more attention to it.[63] Enhance the control over gelation kinetics, for example, explore the temperature-responsive polymers,[178] photo-responsive hydrogels,[179] and stimuli-responsive hydrogels,[180] based on the alginates, which may help to produce hydrogels that are more precise and specific. Adding bioactive factors into hydrogels,[181] such as peptides, hormones and even cells gives the hydrogels specific properties to satisfy treatment requirements. Same to alginates used in tissue engineering, cannot currently simultaneously satisfy all the required strategy parameters (mechanical strength, degradation, and bioactivities) for tissue engineering.[162] Therefore, exploring the methods that can improve and optimize hydrogels based on alginates to have required strategy parameters simultaneously is urgent. Additionally, multiscale hierarchical architecture is a future development direction for alginates, a study has already shown that bioinspired calcium silicate nanowires and alginate composite hydrogels have the potential in tissue regeneration from bone to tendon.[182]

Conclusion

Alginates, a class of polysaccharides, leverage their biochemical properties to play pivotal roles in the pharmaceutical and food industries, bringing considerable benefits to human health. In recent years, alginates derived from brown seaweeds have garnered significant attention due to their bioactivity and biocompatibility. To enhance yield and extraction efficiency while conserving energy and reducing waste, green extraction methods have been proposed. Despite their promise, these methods have yet to gain widespread use. Owing to their antioxidant, antibacterial, and anti-diabetic properties, alginates confer various health benefits, including aiding in gastrointestinal, weight, and diabetes management. Products capitalizing on these benefits have already reached the market. The formation of hydrogels by alginates underpins their pharmaceutical applications, with their use in the creation of liposomes, nanoparticles, and beads for drug delivery widely explored. Moreover, they have been studied in the context of tissue regeneration for bone, cartilage, skin, and vascular systems. By combining with bioactive compounds, alginates have found increased application in the wound dressing area. Despite their wide-ranging use, the potential applications of alginates remain vast and largely unexplored. Future research on alginates should focus on optimizing extraction methods, investigating alginate bioactivity, integrating bioactive compounds to meet specific requirements, and developing products with a multiscale hierarchical architecture.

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Disclosure statement

The author(s) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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