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"Marine Biopolymer Alginate: An Evolution In Endodontics"

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Abstract:
Biopolymers are natural polymers derived from renewable sources such as plants, algae, and microbes. Alginate is a natural marine biopolymer that has been widely used in biomedical applications, but research on its use as an endodontic material is still sparse in the literature. Marine biopolymers are easily available and meet other biopolymers' characteristics for material fabrication. Marine Biopolymers exhibits good biocompatibility, biodegradable nature, good structural strength, and induce cell proliferation and differentiation. Its good resorbable nature and solubility in water with good gel strength favour physical and mechanical properties support for dental applications. Also, Marine biopolymers exhibit antimicrobial, antioxidant, and anti-inflammatory activities. Based on the available literature, alginate has emerged as a cell carrier and scaffold in regenerative endodontics, a microcapsule delivery system for intracanal medicaments, a chelating agent reinforcing material and a root canal sealer. Further well-designed experiments and clinical trials are needed to warrant the promising advent of this hydrogel-based biomaterial. This review article aims to summarize the emerging roles of alginate and to outline its prospective implications as a core biomaterial in endodontics.
Keywords: *Alginate, Marine biopolymers, Regenerative endodontics, Intracanal medicaments.*

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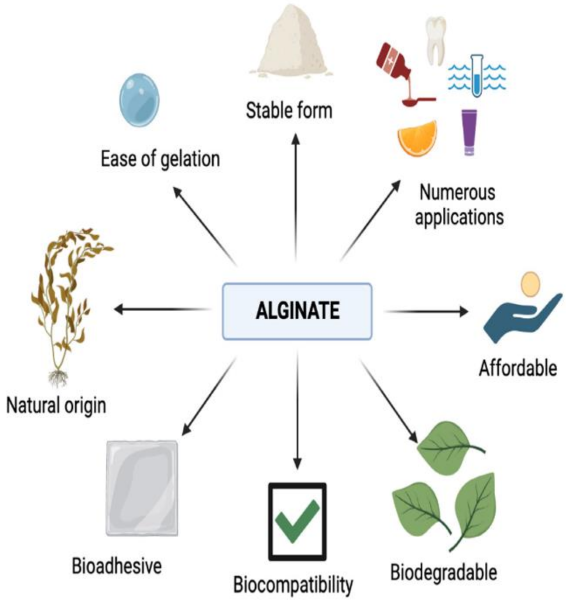
I. Introduction

Renewable biomaterials are one sustainable strategy to reduce waste production and environmental degradation.[1] In recent decades, the bioeconomy and biotechnology have continuously advanced to creative and inventive uses of products made from biopolymers.[2] A biomaterial is any natural or synthetic material that makes up all or part of a living structure or biomedical device that performs, enhances, or substitutes a natural function.[3] Polymers are generally classified as natural and synthetically derived. Natural polymers have superior interactions with cells due to their bioactive characteristics, which enables them to improve the function of the cells in biological systems.[4] Proteins, polysaccharides, polynucleotides (silk, gelatin, elastin, chitin, chitosan, alginate) are the three main categories of natural polymers.[5]

Dental biomaterials are natural tissues and biocompatible synthetic materials that can restore decayed, injured, or fractured tooth tissue. Biopolymers are categorized into reversible (agar, carrageenan) and irreversible (alginate) in nature, especially used in dental applications. Apart from dental applications, these polymers are used in food and drug delivery applications.[6] In restorative dentistry, biomaterial research has evolved towards regenerative (resorbable) or bioinert (biostable) materials to enhance material adherence, promote faster healing, and enable rapid tissue regeneration.[7]

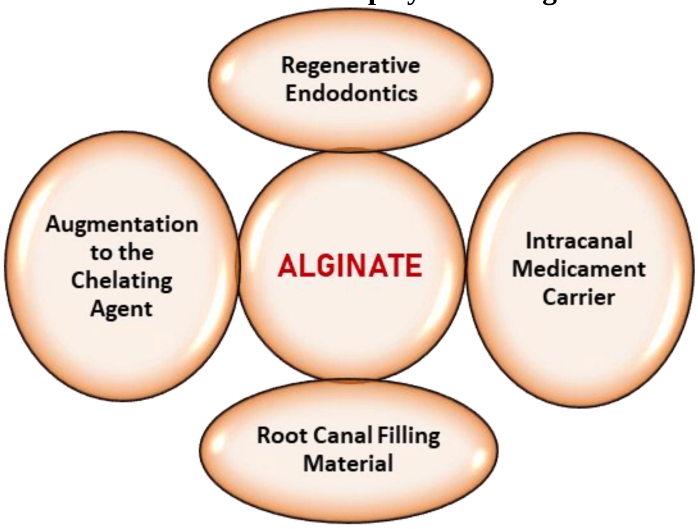
Alginate, also known as alginic acid salt, is a common biopolymeric hydrocolloid derived predominantly from seaweeds.[8] Alginate is a compound made up of blocks of (1-4)-linked -D-mannuronic acid (M) and -L-guluronic acid (G) monomers with three distinct polymer segments. It can form hydrogel by participating in intermolecular cross-linking with divalent cations such as calcium ion ($Ca2+$).[9] Furthermore, due to its biocompatibility, low cost, acceptable odor and taste, ease of handling, low toxicity, and moderate gelation qualities, alginate has aroused the interest of numerous researchers.[7] Because of its structural analogy to the extracellular matrix of living tissues, alginate hydrogel has a wide range of uses in wound healing, cell transplantation, and tissue engineering or regeneration.[8] Another advantage of alginate is its propensity to hydrate and form gel, which enables certain medications or active substances to be supplied for longer periods of time at the place of interest, thereby acting as controlled-release drug delivery systems.[7]

In dentistry, hydrocolloid alginate is often used as a dental impression material to create gypsum casts for a variety of therapeutic reasons, such as provisional crowns and bridges, orthodontic study models, mouth guards, bleaching trays, and removable dental prosthesis.[10,11] Endodontics is a dental specialty that focuses on diagnosing and treating inflamed and diseased dental pulp tissues. Unquestionably, dental caries or tooth decay continues to be a major contributor to the requirement for endodontic therapy.[7] Along with the decreasing rate of tooth loss, this underscores the importance of constantly evolving biomaterials utilized in endodontic applications, such as pulp treatments, irrigating solution, intracanal medicaments, obturation, and pulpal regeneration.[12] Furthermore, researchers have been enticed to introduce alginate into the field of endodontics because of its distinctive features. For example, alginate has been proposed as a regenerative scaffold because of its semi-permeable feature, which allows cells to bind, proliferate, and differentiate.[7] Alginate's sol-gel transition capabilities as an endodontic biomaterial allows it to be created as prefabricated or injectable scaffolds that fit the intricate structure of the root canal system.[13]



Even though alginate is now commonly utilized as a dental material, research on its specific use as an endodontic material remains scarce in the literature. Thus, the goal of this pioneer review was to identify and summarize the current roles of alginate biopolymer in endodontics, as well as to sketch out potential future research on the use of alginate as the core endodontic biomaterial.

II. Applications of Marine Derived Biopolymers – Alginate in Endodontics



Role of alginate in Regenerative Endodontics

Root canal treatment is presently the conventional therapy for irreversible pulpitis, however challenges like bacterial microleakage, low fracture resistance, and potential loss of vitality make the prognosis for root canal treatment uncertain.[7] Thus, dental pulp stem cell regeneration has transformed the ability to regenerate damaged tooth dentine and pulp tissue. Furthermore, a novel approach has been identified by employing hydrogels to transfer progenitor stem cells from the apical papilla directly into the root canal.[14] It has also been proposed that the use of alginate has become a popular trend, facilitating the advancement of stem cell-based endodontic regeneration research and clinical applications.

Bhoj M et al.[13] created an alginate-based microenvironment that resembles gutta-percha and reflects the internal cellular and molecular parameters required for pulp tissue regeneration. RGD (Arginine-glycine-aspartate) alginate was employed to encapsulate human umbilical vascular endothelial cells and dental pulp stem cells with preserved growth factors. The study observed an increased proliferation of dental pulp stem cells and human umbilical vein endothelial cells, indicating an excellent regenerative impact. Similarly, Devillard R et al.[14] developed a biological scaffold consisting of alginate and collagen to function as a biological gutta-percha for regenerative endodontic treatment. On this alginate-collagen scaffold, human apical papilla stem cells may scatter, survive, multiply, and develop into osteoblast-like cells with calcified osseous extracellular matrix, creating an ideal root canal healing environment.

To encapsulate stem cells from the apical papilla, Athirasala A et al.[15] produced a hybrid 3D bio-ink hydrogel containing 3% w/v alginate, resulting in an increased trend of cell survival over time. This conclusion concurs with that of Yu H et al.[16], who discovered that 3D-printed alginate-gelatine scaffolds promote cell growth and adhesion while also holding more calcium and phosphorus ions, which are beneficial to cell proliferation.

Furthermore, Zhang R et al.[17] created a novel injectable hydrogel microsphere that can encapsulate human dental pulp stem cells and vascular endothelial growth factor by combining an arginine-glycine-aspartate-alginate (RGD-alginate) solution with various concentrations of laponite. Pure alginate was shown to have the lowest degree of degradation, with cell survival rates in RGD-alginate microspheres atop 90%.

Cell differentiation and tissue regeneration have long been associated with the stiffness of stem cell scaffold materials. Extracellular matrix scaffolds with high stiffness allow stem cells to develop into odontoblasts and build mineralized tissue, whereas scaffolds with low rigidity allow soft pulp-like tissue to regenerate more easily.[18] The current evidence suggests that alginate has a regulated stiffness that promotes cell survival and differentiation in endodontic engineering applications. Increased silicone content can improve the mechanical properties and degradation profile of alginate-based hydrogels by facilitating higher Si-OH bonding.[19] Nonetheless, hydrogel marine biopolymers have several benefits for stem cell growth, including large surface areas, fast material transfer, three-dimensional spaces, and extracellular matrix-like structures.[7]

Lai WY et al.[19] synthesized cell blocks composed of stem cells from human dental pulp loaded with alginate/fish gelatine hydrogels at the core and human umbilical vascular endothelial cells loaded with silicone ion-infused fish gelatine methacrylate at the periphery. The results revealed that the ability to release Si ions improved mimicking of the environment, increased expressions and secretions of angiogenesis-related indicators, and raised expression of odontogenic-related markers, making it suitable for endodontic regeneration.

Role of Alginate as Intracanal Medicament Carrier

Because of the highly complex architecture of root canal systems and the ability of root dentine buffering, prolonged administration of antimicrobial drugs to the infected region remains constrained. Nanocellulose-alginate microcapsules are small enough to penetrate dentin tubules and have been observed to sustain good stability over time, making them ideal for carrying root canal irrigating solutions.[20,21]

Chlorhexidine (CHX) is a well-known chemical that is commonly employed as a root canal irrigating agent or intracanal medicament during endodontic therapy to disinfect and clean the root canal system. Evelyna A et al.[20] synthesized nanocellulose-alginate nanocomposites to encapsulate CHX and discovered that these nanocomposites significantly boosted the CHX release rate in the infected root canal environment. Nurdin D et al.[21] conducted a similar study, synthesising silica microcapsules to contain 2% CHX and then coating them with chitosan and sodium alginate. The study found that the microcapsules and CHX created a link that aided in the release of CHX, with the maximum value observed at pH 5.5.

However, previous research only tested with 2% CHX; so, subsequent research should focus on the performance of alginate-based microcapsules as a carrier of additional intracanal medicaments, such as calcium hydroxide, antibiotics, and bioactive and natural antibacterial ingredients.

Role of Alginate as Root Canal Filling Material

One of the most important aspects of good endodontic therapy is to seal the root canal system using bioinert gutta-percha and sealant. Huang G et al. [22] found that injecting 1% sodium alginate to the liquid component of a novel bioactive glass-based root canal sealer resulted with favourable flowability, thickness, setting time, solubility, and a uniform morphology, all of which are indicative of clinical endodontic use. It also displayed satisfactory sealing ability, low cytotoxicity, and high biocompatibility.

Role of Alginate as Augmentation to the Chelating Agent

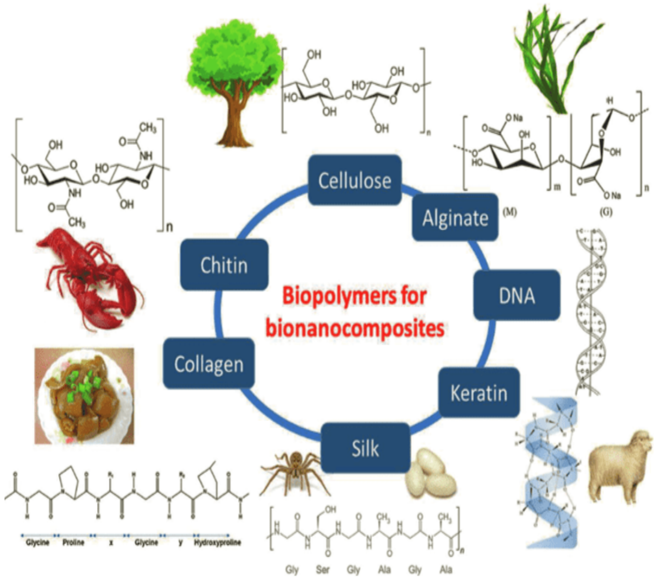
Chelating agents are employed in endodontic treatment to soften root canal dentinal structures to eliminate the smear layer. Girard S et al. [23] devised a new experimental root canal chelating agent that contained 2% alginate, 3% aerosol, 10% Tween 80, and 18% Heme binding protein (HEBP) and analysed it against commercially available chelating agents. The experimental chelating agent with alginate reinforcement had no effect on free residual chlorine in the hypochlorite solution but shown better chelating characteristics, including a significant reduction in smear layers in the coronal and middle root portions.

III. Other Applications of Seaweed Derived Biopolymers - Alginate in Dentistry

Biopolymers composites

A composite may consist of a nanoparticle, various polymers, synthetic polymers, suitable polymers, cross-linking agents, plasticizers, and antibacterial or antioxidant agents. A biopolymer composite is a combination or mixture of sustaining elements that form a final material for diverse or particular applications.[24] The majority of polymers used in dental applications include polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), glycidyl methacrylate, methyl methacrylate, and others.[6]

Various composite materials have been manufactured during the last decade utilizing nanoparticles, but seaweed nanocomposites are emerging in an array of biological, medical, and dental applications. Different bionanocomposites have been developed through the integration of marine biopolymers with ZnO, SiO2, hydroxyapatite, TiO2, and CuO nanoparticles, alginate-carrageenan combinations with green synthesized nanoparticles, fucoidan-based nanoparticles fused with another natural biopolymer, and so forth.[25,26] These bio nanocomposites are biocompatible and exhibit antibacterial, antioxidant, anticoagulant, and anti-inflammatory effects.[6]



Thin Films Derived from Biopolymers

Biopolymeric films have been employed in various specialties of dentistry, including preventive, restorative, and regenerative treatments.[27] Biologically produced polymers, such as polylactic acid, are utilized in dental pulp and dentin regeneration applications. Polymeric films are used extensively in dentistry for a variety of purposes, including biofilm and dental caries prevention, tooth erosion prevention, drug administration, restorative dentistry, prosthetic dentistry, implantology, periodontics, corrosion reduction, and friction reduction.[28,29] Furthermore, surface modification approaches for nanoparticles will facilitate the fabrication of nano capsules with bio adhesion capabilities. Currently, the majority of polymeric films are synthetic or semi-synthetic in nature, however seaweed polymers have limited applications in dentistry and require extensive research to replace synthetic polymers.[6]

Fabrication of Membranes/Graft Materials

Hydrogel membranes are commonly utilized in tissue engineering, NiTi implants, and orthodontics. However, some of them lack adequate mechanical strength and compatibility. As a result, biomembranes composed of naturally generated polymers are very useful in terms of biocompatibility and have the ability to regenerate natural tissue.[30] Because the membranes are employed in periodontal applications, the biopolymer should have properties such as lubrication and antiwear, anti-biofouling, cellular adhesion promotion, drug delivery, and biosensing.[6]

Drug Delivery Applications

Biopolymers derived from seaweed, such as carrageenan and alginates, are commonly employed as drug delivery gels. The development of stimuli-responsive blends of biopolymers is a dynamic topic of research, due to the effect of the medium's nature, heat, presence of ions, and electro positivity or electronegativity of ions.[31,32] Thermal responsive (agarose and cellulose), pH-responsive (alginate and carrageenan), and physiochemically responsive biopolymers (fucoidan and ulvan) derived from seaweeds can be used as smart materials in dental and other biomedical applications because they can be tuned to make them economically affordable as well.[6]

Dental Impression

Alginates are often used material for dental impressions. Alginates are sulfated polysaccharides that originate from brown seaweeds such as kelp.[7] First and foremost, the set time is critical in making an impression, as it defines the correct dental impressions of patients in a short amount of time. Impression materials are made up of polymers, cross-linker agents, pH modifiers, sequestrants, fillers, and other color changers.[33,34] Other natural seaweed polymers that may be useful in the fabrication of impression materials include marine derived biopolymer alginate, carrageenan, ulvan, fucoidan, and agarose.[6]

Bioink Development for 3D Printing

3D printing is a booming subject in medicine, particularly in dentistry and oral surgery. Bioink development implementing natural biopolymers shows promising advantages in this industry.[6] Bioink is naturally derived and non-toxic to human cells. Seaweed biopolymers, particularly alginate and carrageenan, are already known bioinks.[35,36] Because of their varied chemical characteristics and ease of combining with other materials, seaweed biopolymers are a preferable source for bioink development. Seaweed-based biopolymers have excellent rheological qualities and are developing as a new avenue in 3D printing technology in the dental arena.[37,38] Polymers/biopolymers are currently used to create anatomical 3D models, guides, and scaffolds/membranes for bone defects in oral and maxillofacial surgery, 3D printed dentures and prosthesis in prosthodontics, 3D printed dental models and clear aligners in orthodontics, computed tomography-based endodontic guides for root canal treatments, and 3D printed scaffolds in periodontics.[39]

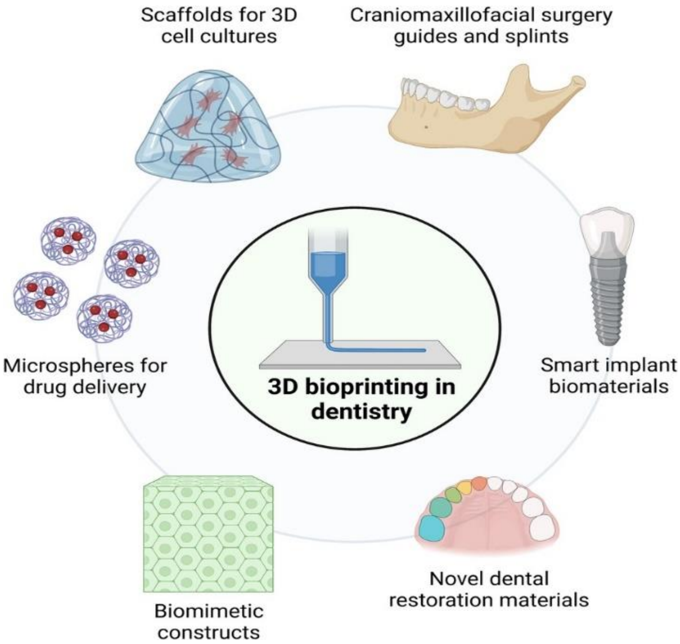


Table 1: Seaweed biopolymers in dental applications[6]

Seaweeds	Biopolymers	Dental applications
Red seaweeds	Agar, Carrageenan	Hydrogels, Oral drug delivery, Scaffolds, Biomembrane, Anti-microbial activity medium, Nanoparticles coatings, Bionanocomposites, Bone tissue engineering, Nanofibers, 3D printing (bioink)
Brown seaweeds	Alginic acid and alginate, Sodium alginate, Fucoidan	Impression plaster, Wound healing/dressing for oral cavity/drug delivery, Hydrogels, Scaffolds, Biomembrane, GTR, GBR, Adhesives/ resins, 3D printing bioink, Nanoparticles coatings, Bone tissue engineering, Nanocomposites, Nanofibers
Green seaweeds	Ulvan, Cellulose	Hydrogels, Scaffolds, Biomembrane, Nanocomposites, Nanofibers

V. Conclusion

Seaweed-derived biopolymers are commonly employed in a range of sectors. However, their use in dentistry is considerably less. Alginates have been employed for making dental impressions for a long time. Other biopolymers identified in seaweeds are still being researched in the dental sector. The current research completely identifies, summarizes, and analyzes the uses of alginate as a potentially beneficial biomaterial in a variety of endodontic applications. Despite the minimal data available in the literature, alginate has emerged as a new biomaterial that can be utilized as a cell carrier and scaffold in regenerative endodontics, a microcapsule delivery system for intracanal medicaments, a chelating agent reinforcing material, and a root canal sealer. Inevitably, one of the primary goals for the coming decade is the development of alginate-based endodontic materials that can be used clinically with favorable outcomes. Thus, additional well-designed experimental research and clinical trials are required to achieve this goal by determining the efficacy of marine-derived alginate-based biomaterials, which have significant implications in the field of dental sciences, notably endodontics.

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