



# ALGAE-DERIVED BIOACTIVE COMPOUNDS IN DENTISTRY: CHEMICAL AND BIOCHEMICAL INSIGHTS — A COMPREHENSIVE REVIEW

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**Abstract:** Marine algae represent a valuable and still underexplored source of bioactive compounds with significant potential in dentistry. Rich in polysaccharides, polyphenols, pigments, and minerals, these organisms exhibit multiple biological activities, including antibacterial, anti-inflammatory, antioxidant, antiviral, and anticancer effects relevant to oral health. Algal-derived compounds such as fucoidan, carrageenan, alginate, and ulvan have demonstrated the ability to inhibit oral pathogens, modulate inflammatory responses, and support tissue regeneration. In addition, marine algae-derived biomaterials show promising applications in several dental fields, including periodontal and bone regeneration, dental impression materials, enamel remineralization, and oral hygiene products. This review aims to highlight the biological properties of marine algae and their potential dental applications, emphasizing their role as natural and biocompatible alternatives or complementary approaches to conventional methods and materials used in modern dental practice.

**Keywords:** marine algae, seaweeds, bioactive compounds, oral health

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## Introduction

Algae comprise a highly diverse assemblage of photosynthetic organisms that inhabit marine, freshwater, and terrestrial ecosystems and contribute significantly to global primary production and oxygen generation.<sup>1,2,3</sup> They range in complexity from unicellular microalgae to large multicellular macroalgae (seaweeds), displaying remarkable morphological, physiological, and biochemical complexity.<sup>4,5</sup> In recent decades, algae have attracted considerable attention as a rich source of structurally diverse bioactive compounds, including polysaccharides, polyphenols, pigments, fatty acids, and peptides, many of which exhibit antimicrobial, antioxidant, anti-inflammatory, and regenerative activities.<sup>6,7</sup> These properties have stimulated growing interest in the potential application of algal metabolites in biomedical sciences, including the development of novel materials and therapeutic agents for dentistry and oral health.<sup>6</sup>

Despite the widespread use of the term “algae,” it does not correspond to a single phylogenetic lineage but rather encompasses a heterogeneous group of organisms that share the ability to perform oxygenic photosynthesis and typically inhabit aquatic environments.<sup>2</sup> Historically, algae were classified primarily based on morphological features, pigmentation, and life-cycle characteristics.<sup>8,9</sup> However, advances in molecular phylogenetics and ultrastructural analysis have demonstrated that algal groups evolved independently across several major evolutionary lineages, rendering the traditional concept of algae polyphyletic.<sup>1,2</sup> This evolutionary diversity has contributed to persistent difficulties in algal taxonomy and classification.<sup>10,11</sup> Therefore, from a biological perspective,

the term "algae" encompasses a broad and taxonomically intricate assemblage of organisms, reflecting a highly the novelty of the study.

Modern systematic approaches increasingly rely on molecular and phylogenomic data to establish evolutionary relationships among organisms.<sup>12</sup> One of the most comprehensive modern classification frameworks is that proposed by Ruggiero et al., which recognizes two superkingdoms (Prokaryota and Eukaryota) and seven kingdoms: Archaea, Bacteria, Protozoa, Chromista, Fungi, Plantae, and Animalia.<sup>10</sup> Within this system of classification, organisms traditionally referred to as algae are distributed among multiple kingdoms, reflecting their diverse evolutionary origins. For example, green algae (Chlorophyta) and red algae (Rhodophyta) are placed within the kingdom Plantae, whereas brown algae (Phaeophyceae) and diatoms belong to the kingdom Chromista.<sup>1,10</sup> Additionally, cyanobacteria—historically called "blue-green algae" and famous for the well-known *Spirulina* (*Arthrospira*)—are now recognized as prokaryotic organisms and classified within the kingdom Bacteria.<sup>10</sup>

Consequently, the taxonomy of algae remains complex and dynamic, continuously evolving as new molecular and genomic data refine our understanding of evolutionary relationships among photosynthetic organisms.<sup>1,11</sup>

Recognizing this taxonomic complexity is essential for interpreting algal biodiversity and for exploring the biochemical diversity of algal metabolites, particularly in interdisciplinary research fields such as the investigation of algae-derived bioactive compounds with potential applications in dentistry.<sup>13</sup>

The novelty of this review consists in providing a chemistry-driven perspective that links the structural and biochemical characteristics of algae-

derived compounds with their molecular mechanisms of action and their specific applications in dentistry, offering an integrated framework relevant for the development of novel dental biomaterials and therapeutics.

## 1. BIOLOGICAL PROPERTIES AND MECHANISMS OF SEAWEEDS

Microalgae exhibit considerable potential for applications in dental medicine because of their antiviral, anti-inflammatory, antibacterial, antifungal, and anticancer activities within the oral cavity.<sup>14</sup> The incorporation of algal-derived components, such as 1 % iota-carrageenan, blue-green algae (*Aphanizomenon flos-aquae*), and *Laminaria japonica*, into toothpaste formulations has been shown to confer effective antimicrobial activity.<sup>15</sup> Furthermore, algal extracts have demonstrated promise for the development of additional oral hygiene products, including mouthwashes and chewing gums.<sup>16</sup>

Algal polysaccharides are also capable of forming shape-memory gels, making them suitable for impression materials used in dentistry.<sup>17</sup> Kiziltan et al. reported the potential application of seaweeds extracts in combination with collagen matrices for oral regenerative therapy, highlighting their applicability for transmucosal delivery. Collectively, microalgae represent an essential source of biologically active compounds for innovation in the prevention, treatment, and tissue regeneration strategies in dentistry.<sup>18</sup>

Marine ecosystems constitute a largely underexplored source of bioactive compounds characterized by unique structural features. (**Figure 1**) For instance, seaweeds, which have been utilized over a long history in

traditional medicine, contain both primary and secondary metabolites with notable biological activities, including antimicrobial, anti-inflammatory, anticancer, and antioxidant effects.<sup>19</sup>

According to findings reported in the scientific literature, brown algae (*Phaeophyceae*) are demonstrating superior outcomes biofilm-forming microorganisms in comparison with green algae, thereby underscoring their considerable therapeutic potential.<sup>19</sup>

### **1.1. Antibacterial activity**

Extracts obtained from brown seaweeds have demonstrated significant antibacterial properties. For example, Zamimi et al. highlighted the antimicrobial effect of *Laminaria japonica* ethanolic extract against oral bacteria, reporting low minimum inhibitory concentration (MIC) values ranging from 62.5 to 250 µg/mL and minimum bactericidal concentration (MBC) values ranging from 250 to 500 µg/mL. These findings suggest a strong, dose-dependent effect, accompanied by observable alterations in the bacterial cell surface. Moreover, the same authors reported that *Padina tetrastromatica* and *P. boergesenii* exhibited relevant inhibitory activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as evidenced by clear zones of inhibition. Overall, the low MIC and MBC values further confirm the substantial antibacterial potential of marine algal extracts.<sup>20</sup>

On the other hand, several authors, including Sangavi et al., have revealed that *Padina boergesenii* (MEPB), the extract of a brown alga, rich in phenolic compounds and fatty acids, exhibits significant anticariogenic effect against *Streptococcus mutans*, the primary etiological agent of dental caries. The reported findings indicate that MEPB effectively inhibits biofilm formation and reduces bacterial virulence factors without

compromising cellular viability. GC–MS/MS analysis established that the main active compounds responsible for these antibiofilm effects include hexadecanoic acid (palmitic acid), octadecanoic acid (stearic acid), oleic acid, phytol, and various phenolic derivatives. Owing to its non-toxic and anti-infective properties, MEPB emerges as a promising marine-derived resource for dental applications, with considerable potential for incorporation into oral hygiene products, particularly toothpastes, for the prevention and control of dental caries.<sup>21</sup>

In addition, Hamouda et al. evaluated *Ulva lactuca*-based nanocomposites for dental applications by producing nanocellulose and *Ulva/Ag/cellulose* nanocomposites and assessing their antibacterial activity against *Streptococcus mutans* and *Lactobacillus acidophilus*, two key bacteria implicated in the progress of dental caries. The study demonstrated that the *Ulva/Ag/cellulose* nanocomposites exhibited superior antibacterial activity compared to nanocellulose alone, and their combination with fluoride significantly enhanced the antimicrobial effect. Consequently, *Ulva/Ag/cellulose* nanocomposites represent a natural, safe, and cost-effective alternative with potential application in toothpastes and dental restorative materials for the prevention and control of dental caries.<sup>22</sup>

Fucoidan, a sulfated polysaccharide extracted from seaweeds, exhibits significant antimicrobial and antibiofilm activity against cariogenic bacteria, like *Streptococcus mutans*, *S. sobrinus*, *S. sanguinis*, *S. ratti*, *S. criceti*, *S. gordonii*, and *S. anginosus*, as well as against periodontopathogenic species such as *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*. Based on experimental studies, Hudiyati et al. highlighted that fucoidan derived from *Fucus vesiculosus* was the only

tested compound that exerted antimicrobial effect against dental plaque bacteria, such as *Enterococcus faecalis*, *S. mutans*, *S. oralis*, *S. sobrinus*, and *S. sanguinis*. Importantly, at higher concentrations, fucoidan inhibited biofilm development and cellular growth of *S. sobrinus* and *S. mutans*, preventing their adhesion to dental and porcelain surfaces. Additionally, fucoidan has been shown to possess antifungal activity against *Candida albicans*, further supporting its potential as a natural therapeutic agent for dental caries and oral infections prophylaxis.<sup>23</sup>

In a recent study of natural antibiofilm agents, Jun et al. evaluated fucoidan F85, a sulfated polysaccharide derived from marine algae, for its effect against dental plaque bacteria. The results demonstrated that fucoidan F85 significantly suppressed biofilm formation and planktonic cell growth of *Streptococcus mutans* and *S. sobrinus* at concentrations exceeding 250 µg/mL. In the case of *Enterococcus faecalis*, the inhibitory effect reached approximately 91.3 % after 24 hours, although this effect was no longer evident after 48 hours. Furthermore, the antibiofilm activity was found to be concentration-dependent. Chemical analysis revealed that fucoidan F85 consisted almost entirely of fucose units and contained approximately 14 % sulfate, while thermal treatment was shown to alter its antimicrobial activity. Based on these findings, fucoidan F85 may be recognized as an important candidate for the development of natural antibiofilm agents aimed at the prevention and control of dental caries.<sup>24</sup>

According to the scientific literature, the growth of bacterial plaque and biofilm formation on removable acrylic orthodontic appliances may increase the risk of enamel demineralization and periodontal disease. In this context, Pourhajibagher et al. evaluated the antimicrobial effects, antivirulence potential, and mechanical characteristics of photoactivated

orthodontic acrylic resin enriched with various concentrations of *Ulva lactuca* (a marine green macroalga) against *Streptococcus mutans*. The minimum inhibitory concentration (MIC) of *U. lactuca* against *S. mutans* was first determined. Acrylic resin specimens were then fabricated incorporating 0.2 %, 0.5 %, 1 %, 2.5 %, 5 %, and 10 % *U. lactuca* and were compared with standard acrylic resin in terms of flexural strength, antimicrobial effects, antibiofilm activity, and virulence gene expression assessed by quantitative real-time PCR. The findings demonstrated that *U. lactuca* at concentrations ranging from 1 % to 10 % significantly diminished the growth of *S. mutans*. It was therefore concluded that the incorporation of photoactivated *U. lactuca* at a concentration of 1 % (w/w) into orthodontic acrylic resin confers antibacterial and antibiofilm properties against *S. mutans* without adversely affecting its flexural strength.<sup>25</sup>

In a study performed by Lan et al., composite dental rings based on alginate and poly- $\epsilon$ -caprolactone (PCL) were developed for the controlled release of metronidazole, with the aim of preventing bacterial colonization on dental implants. The rings were fabricated using a solvent-casting method and three types of systems were compared: alginate, PCL, and PCL/alginate composites, with different drug-loading ratios (5:1, 10:1, and 50:1). The results showed that the outer PCL layer, being more rigid and less porous, acted as a barrier that reduced the initial burst release of metronidazole while providing mechanical stability to the system. *In vitro* studies demonstrated rapid drug release from the alginate rings, whereas the composite rings exhibited a moderate initial release followed by a long-term controlled release extending up to 303 days. The release kinetics followed the Ritger–Peppas model, showing a predominantly diffusion-controlled mechanism. By adjusting the polymer ratios, the minimum inhibitory

concentration needed for antimicrobial defence was achieved, highlighting the potential of these composite rings for applications in dental implantology.<sup>26</sup>

## 1.2. Antioxidant activity

Marine algae constitute a rich and diverse source of natural antioxidants, containing numerous bioactive compounds with strong antioxidant potential relevant to oral health applications. In particular, brown seaweeds such as kelp, wakame, and *Laminaria* are notable for their content of fucoxanthin and fucoidan. Fucoxanthin, a carotenoid shown in high concentrations in brown seaweeds, exhibits strong antioxidant activity by scavenging free radicals and reducing oxidative stress, thereby protecting cells from damage. Its antioxidant effects are associated with the stimulation of endogenous antioxidant enzymes. Additionally, fucoxanthin demonstrates anti-inflammatory and anticancer activities and has shown tissue-protective effects in various disease models by mitigating oxidative stress and inflammatory responses.<sup>25, 27</sup>

Recent studies have highlighted the potential of marine algae as natural sources of antioxidants. Thus, Sudirman et al. demonstrated that *Sargassum sp.*, a brown alga belonging to the class Phaeophyceae and rich in bioactive compounds including polyphenols, exhibits significant antioxidant activity. Following the extraction of polyphenols from different *Sargassum* species, such as *S. crassifolium* and *S. oligocystum*, it was shown that these compounds are capable of inhibiting DPPH free radicals, with inhibition percentages of the extract ranging from 15.53 % to 43.65 %, where the extract was dissolved in ethanol to get a concentration of 1.25 mg/mL. The highest antioxidant effect was obtained when distilled water was used as the

extraction solvent, due to its higher recovery of phenolic acids, flavonoids, and tannins. Furthermore, the efficacy of these bioactive compounds was found to depend on factors such as the extraction method, the grinding of the raw material, and the type of solvent used. Overall, the results indicated that *Sargassum sp.* extracts represent a valuable source of natural antioxidants, with potential applications in pharmaceuticals and functional products for protection against oxidative stress.<sup>28</sup>

In the context of the growing interest in natural solutions in dentistry, *Zonaria variegata* (syn. *Lobophora variegata*), a brown marine alga widespread in tropical and subtropical regions, emerges as a valuable source of bioactive secondary metabolites with high therapeutic potential. The study by Manisha suggested that *Z. variegata* extract exhibits antimicrobial and antibiofilm properties relevant for the control of dental biofilm, a major factor in the development of caries. Another important aspect is the high antioxidant activity of the extract, which is essential for reducing oxidative stress correlated with oral diseases like caries and periodontitis, as well as its anti-inflammatory effects, confirmed by the BSA (Bovine Serum Albumin) denaturation assay. These results evidence the potential of *Z. variegata* as an effective, safe, and natural alternative to synthetic compounds used in dental care products and treatments.<sup>29</sup>

Antioxidant activity represents one of the most frequently reported biological function of bioactive compounds derived from seaweeds, and it is attributed to a wide variety of substances, like polysaccharides, polyphenols, pigments, terpenoids, fatty acids, proteins, and vitamins. Studies reported in the scientific literature indicate that these antioxidant activities, present in green, red, and brown seaweeds, underscore the significant potential of

marine algae as natural sources of antioxidants with promising biomedical and pharmaceutical applications (Table 1).<sup>30</sup>

**Table 1.** Selected bioactive compounds identified in brown, red, and green marine algae (adapted from Cadar et al.<sup>30</sup>)

Biochemical Compounds	Brown Algae Species	Red Algae Species	Green Algae Species
Fatty acids	–	<i>Palmaria palmata</i>	–
	–	<i>Grateloupia turuturu</i>	–
Carotenoids	–	<i>Hypnea musciformis</i>	–
Flavonoids	<i>Gongolaria barbata</i>	<i>Gigartina acicularis</i>	–
Fucoxanthin	<i>Undaria pinnatifida</i>	–	–
	<i>Dictyota cervicornis</i> (formerly <i>D. indica</i> )	–	–
	<i>Cladostephus spongiosus</i>	–	–
Pigments	<i>Ceramium virgatum</i>	–	<i>Ulva lactuca</i>
	–	–	<i>Codium adhaerens</i>
		<i>Pyropia yezoensis</i>	–
	<i>Fucus virsoides</i>	–	–
	–	<i>Gracilaria corticate</i>	–
Chlorophyll pigments	–	–	<i>Caulerpa racemosa</i>
Polyphenols	<i>Sargassum tenerrimum</i>	–	–
	<i>Dictyota dichotoma</i> and <i>Padina pavonica</i>	–	–
Polysaccharides	<i>Sargassum fulvellum</i> and <i>S. wightii</i>	–	–
	<i>Nizamuddinina zanardinii</i>	–	–

	<i>Sargassum fusiforme</i>	–	–
	<i>Undaria pinnatifida</i>	–	–
	<i>Padina boryana</i>	–	–
	<i>Ecklonia maxima</i>	–	–
Proteins and protein compounds	<i>Gracilariopsis lemaneiformis</i>	–	–
	–	<i>Pyropia yezoensis</i>	–
Terpenoids	–	<i>Laurencia tristicha</i>	–
Ulvan	–	–	<i>Ulva lactuca</i>

### 1.3. Anti-inflammatory activity

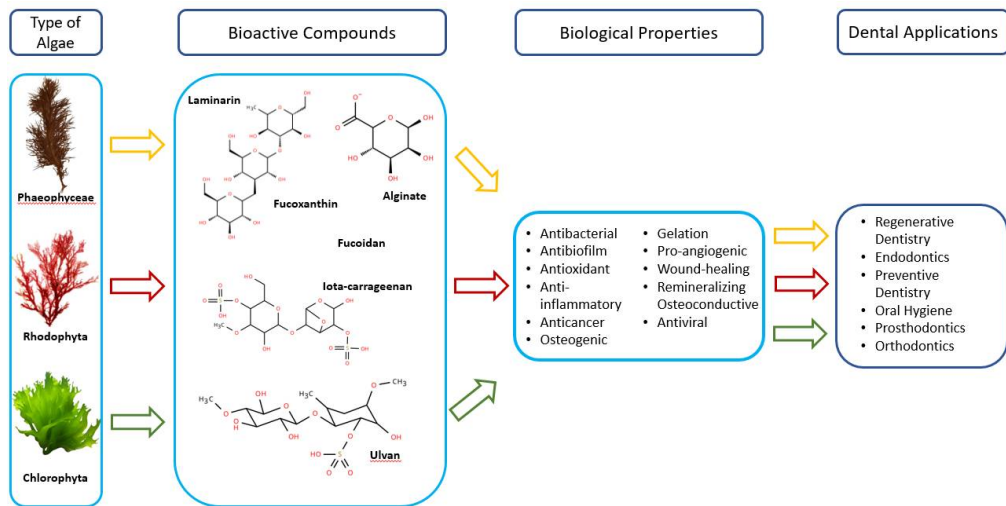
In the context of exploring natural therapies for oral inflammatory diseases, marine algae have attracted increasing interest as potential natural therapeutic agents for oral inflammatory diseases.<sup>31</sup> Based on the findings of Lee et al., the effects of *Caulerpa okamuræ* extract on the inflammatory response caused by *Porphyromonas gingivalis* in RAW 264.7 macrophages were evaluated. Stimulation with *P. gingivalis* led to increased nitric oxide (NO) production, upregulation of proinflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), and elevated expression of inducible nitric oxide synthase (iNOS). Treatment with *C. okamuræ* extract significantly reduced these responses in a dose-dependent manner without inducing cytotoxicity. The underlying mechanism involved suppression of IKK and I $\kappa$ B $\alpha$  phosphorylation, inhibition of NF- $\kappa$ B activation, and blockade of its nuclear translocation. These findings demonstrate that *C. okamuræ* extract exerts potent anti-inflammatory effects and may serve as a promising basis for developing therapeutic agents to prevent and manage periodontal diseases.<sup>32</sup>

The marine environment represents a significant source of bioactive compounds with anti-inflammatory effects, derived from diverse marine organisms. Santhiravel et al. demonstrated that *Actinomycetes*,

*Cyanobacteria*, and marine algae produce substances such as fucoidan and carrageenan, which inhibit inflammatory mediators by modulating specific cellular pathways. Additionally, other marine-derived compounds, including omega-3 fatty acids and metabolites extracted from marine invertebrates, exhibit potent anti-inflammatory activity, highlighting the therapeutic potential of marine resources.<sup>33</sup>

Also, marine-derived polysaccharides from algae have attracted considerable attention due to their potent anti-inflammatory and immunomodulatory properties in oral health. Fucoidan, a sulfated polysaccharide derived from brown algae has been demonstrated to inhibit proinflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , which play central roles in periodontal disease progression, chronic inflammation, tissue destruction, and alveolar bone loss.<sup>16</sup> Moreover, fucoidan modulates the activity of immune cells, such as macrophages, natural killer (NK) cells, dendritic cells, and lymphocytes, demonstrating both *in vitro* and *in vivo* efficacy and indicating its broad therapeutic potential.<sup>34</sup>

Similarly, ulvan, a polysaccharide from the extracellular matrix of green algae, exhibits anti-inflammatory activity. *In vitro* studies show its potential to reduce gingival inflammation and slow periodontitis progression. Carrageenans from red seaweeds also modulate gingival inflammatory responses by reducing the synthesis and release of inflammatory mediators, exerting protective effects against oral inflammation. Collectively, these marine algal polysaccharides represent promising natural bioactive agents for the prevention and management of periodontal inflammation, offering safe and effective alternatives or adjuncts to conventional synthetic anti-inflammatory therapies.<sup>16</sup>



**Figure 1.** A schematic illustration showing marine algae and their applications in dental medicine.

#### 1.4. Mechanisms of anticancer - Action against oral cancer

Brown marine algae are richer in polysaccharides compared to yellow or green algae, which confers them significant therapeutic properties, including anticancer potential. The primary polysaccharides include laminarin, alginate, and fucoiodan, and some species also contain porphyrin derivatives or alginic acid, which can be utilized as drug delivery systems. Thus, fucoiodan, a long-chain sulfated polysaccharide, is abundant in species such as *Undaria pinnatifida*, *Laminaria japonica*, and *Fucus vesiculosus*, and is composed predominantly of sulfated L-fucose, with minor amounts of glucose, mannose, xylose, and rhamnose.<sup>35</sup>

Fucoiodan exerts antitumor effects against oral cancer by modulating MAPK kinases, increasing ERK1/2 activity while decreasing p38 MAPK and AKT signaling, thereby inducing selective apoptosis in oral cancer cells. It also induces oxidative stress, affects DNA damage and antioxidant signaling, and inhibits the proliferation of oral cancer cells without

significantly affecting non-malignant cells, making it a safe and promising anticancer agent.<sup>36</sup>

### **1.5. Antiviral activity**

Herpes simplex virus type 1 (HSV-1), following primary infection, establishes latency in sensory neuronal ganglia. Viral reactivation is dependent on host susceptibility and can be triggered by factors such as exposure to extreme temperatures (heat or cold), local trauma, febrile episodes, and psychophysiological stress, clinically manifesting as oral herpes.<sup>35,14</sup>

Carrageenan, a polysaccharide extracted from red algae, exhibits antiviral activity against HPV. While it shows potential for the prevention and treatment of oral HPV infection, its safety for human use requires evaluation. Alli et al. investigated the effects of carrageenan on human salivary gland cells and reconstructed oral mucosal tissue using *in vitro* assays. The results demonstrated that carrageenan is non-toxic to oral tissues, even at concentrations up to 20,000-fold higher than the IC50 against HPV, using the RHOE tissue model, which is standardized for testing dental materials. These findings highlight the safety of carrageenan for oral cells and tissues and suggest that its formulation as a mouthwash could be a promising method for preventing or reducing oral HPV infection. However, despite these favorable *in vitro* results, future clinical studies should be conducted cautiously, using exploratory protocols aimed at generating initial human safety data.<sup>37</sup>

## **2. DENTAL APPLICATIONS OF SEaweEDS**

### **2.1. Brown algae (Phaeophyceae)**

#### *2.1.1. Dental pulp protection*

Direct pulp capping (DPC) is designed to preserve the vitality of the dental pulp following exposure caused by carriers or trauma, with the aim of delaying or avoiding endodontic therapy. The efficacy of this technique

depends on the material applied directly to the pulp exposure, which must ensure a tight seal, stimulate the formation of reparative dentin, and remain stable in the oral environment.<sup>38</sup>

Mineral trioxide aggregate (MTA) and calcium hydroxide are frequently used materials for the treatment of vital pulp exposures resulting from dental caries or trauma. To overcome some limitations of MTA, such as tooth discoloration, difficult handling, long setting time, and high cost, Hudiyati et al. investigated the incorporation of fucoidan. They compared a Portland cement–zirconia oxide formulation (89 % / 20 %) with variants containing 5 % and 10 % fucoidan, observing that fucoidan addition significantly reduced the setting time, enhanced cell migration, increased sulfur levels, and elevated alkaline phosphatase activity, although the 5 % concentration reduced compressive strength. These findings indicate that fucoidan is a promising regenerative additive for standard pulp-capping materials.<sup>23</sup>

### 2.1.2. *Root canal irrigant*

During root canal instrumentation, whether performed with manual or rotary instruments, a smear layer (SL) is formed, consisting of dentin debris, cellular remnants, and microbial components. This layer can remain on the canal walls and occlude the dentinal tubules, reducing the efficacy of obturation and, consequently, the long-term success of endodontic treatment. Therefore, complete removal of the SL is essential, and the implementation of an appropriate and effective irrigation protocol is a critical factor for achieving successful endodontic therapy and preventing post-treatment complications.<sup>39</sup>

Smear layer removal could potentially be achieved using natural derivatives such as brown algae (*Sargassum sp.*), which contain biologically

active compounds such as alkaloids, steroids, triterpenes, flavonoids, tannins, and saponins. Trilaksana et al. reported a notable difference between 15 % brown algae (*Sargassum sp.*) extract and 17 % EDTA in the middle third of the root canal. Furthermore, the 15 % *Sargassum sp.* extract was more effective in removing the smear layer from the canal wall in comparison to 2.5 % NaOCl.<sup>40</sup>

### *2.1.3. Regeneration in periodontal conditions*

Periodontal disease is a common chronic inflammatory condition characterized by the progressive destruction of the tooth-supporting structures, which may lead to loss of periodontal attachment, tooth loss, and impaired masticatory function. The primary objective of periodontal therapy is not only to slow or halt disease progression but also to regenerate the affected periodontal tissues. In this context, the biological agents, substances capable of modulating cellular behaviour and promoting new tissue formation have gained increasing interest due to their potential to improve treatment outcomes.<sup>41</sup>

A randomized clinical study carried out by Eshwar et al. evaluated the application of an injectable hydrogel composed of chitosan and fucoidan for the treatment of intraosseous defects associated with periodontal disease. Clinical assessments at three and six months revealed a remarkable reduction in probing depth and an increase in clinical attachment levels in the hydrogel-treated group compared to the group treated with concentrated growth factor (CGF). After nine months, defect fill was greater in the hydrogel group. Beyond hydrogel applications, fucoidan has been incorporated with other compounds to enhance bone regeneration. Incorporated into tricalcium phosphate and chitosan scaffolds, fucoidan improved osteocalcin release and promoted osteogenic differentiation of

human mesenchymal stromal cells. Moreover, fucoidan when combined with polydopamine enhanced the osteogenic potential of periodontal ligament stem cells, as evidenced by increased alkaline phosphatase activity and upregulation of osteogenic markers, including osterix, runt-related transcription factor 2 (Runx2), osteopontin, osteocalcin, and type I collagen.<sup>42</sup>

#### *2.1.4. Alveolar bone regeneration in dentoalveolar surgery*

Bone resorption following tooth extraction is a natural phase of the healing process. However, it may result in significant volumetric loss and dimensional changes of the alveolar ridge. Immediate placement of a grafting material into the post-extraction socket helps maintain alveolar bone volume, reducing subsequent bone loss and attenuating early tissue remodelling. This strategy is particularly important for prosthetic planning and dental implant placement, as preservation of the alveolar structure facilitates accurate implant positioning, ensures prosthetic stability, and contributes to optimal long-term functional and aesthetic outcomes.<sup>43</sup>

Traditional bone graft materials, for example, allografts, xenografts, and alloplasts, primarily provide mechanical support. However, there has been increasing attention paid toward synthetic tissue-engineered scaffolds for bone regeneration. According to current literature, natural or plant-based materials, including marine-derived biomaterials such as chitosan, alginate, and fucoidan, have demonstrated therapeutic regenerative capacity. Combining these materials can create promising scaffolds for alveolar bone reconstruction.<sup>44</sup>

Data from the research performed by Venkatesan et al., demonstrated that the development of a chitosan–alginate–fucoidan (Chi–Alg–Fucoidan) scaffold with high porosity, exhibits substantial water and protein absorption, promotes mineralization, and supports cell migration and

proliferation. Modifying the component ratios, particularly by increasing the alginate content, enhanced the antibacterial properties, absorption capacity, and its function as a cell carrier. All materials used are naturally derived and readily available, making the scaffold effective with minimal side effects. Consequently, the Chi–Alg–Fucoidan scaffold shows significant potential as a bone substitute material because of its porous structure and capability to support cellular regeneration.<sup>45</sup>

Alginate, a polysaccharide primarily extracted from marine algae, represents a biomaterial showing potential for bone tissue engineering because of its biocompatibility, biodegradability, lack of immunogenicity, capability to encapsulate cells and bioactive molecules, and ion-chelating properties. Its versatility allows the fabrication of diverse structures, including hydrogels, microspheres, foams, fibers, and sponges, adaptable to various regenerative applications. As a scaffold, alginate is commonly employed as a delivery system for osteoinductive factors including bone morphogenetic proteins (BMPs) and for mesenchymal stem cells, thereby facilitating tissue repair and regeneration in bone defects.<sup>46</sup>

Fucoidan, a sulfated polysaccharide found in notable amounts in brown seaweeds, especially in species of the genus *Sargassum*, plays a key role in promoting bone mineralization. It exerts its effects by enhancing alkaline phosphatase activity and upregulating the expression of type I collagen, osteocalcin, and bone morphogenetic protein-2 (BMP-2), which are essential for the formation and deposition of the mineralized matrix. Numerous recent studies have confirmed that fucoidan used in recovery processes stimulates the expression of alkaline phosphatase, type I collagen, the transcription factor RUNX2, osteopontin, and osteocalcin.<sup>47</sup> For example, Kim et al. highlighted that fucoidan promotes osteogenic

differentiation of human amniotic fluid-derived stem cells, supporting its capacity as a promising biomaterial for bone tissue regeneration.<sup>48</sup>

### 2.1.5. Dental impression materials (alginates)

The irreversible hydrocolloid, known as alginate, is the most frequently used impression material in dentistry because of its ease of handling, accuracy in recording details, good patient tolerance, and affordability. The main active ingredients are sodium alginate, potassium alginate, and triethanolamine alginate, which can be obtained from brown seaweeds such as *Sargassum sp.*, *Turbinaria sp.*, *Hormophysa sp.*, and *Padina sp.* Hamrun et al. conducted a study on the effect of potassium alginate derived from *Sargassum polycystum* as a dental impression material, highlighting that it could represent a viable alternative to classical commercial products. The study found that the most accurate impressions were obtained at a concentration of 15 %, while the most stable impressions were achieved at a concentration of 16 %, lasting up to 15 minutes. However, further research is needed regarding the properties of this material.<sup>49</sup>

The study reported that the extraction of sodium alginate from *Sargassum sp.* can yield either a material of high purity but low viscosity, or a material of reduced purity but increased viscosity, which limits its use as a hydrocolloid impression material. To obtain a suitable sodium alginate, it is necessary to produce a high-purity product with increased viscosity to ensure appropriate consistency and setting time. Meanwhile, Devina et al. also demonstrated that the purity of sodium alginate obtained from *Sargassum sp.* is comparable to that of standard alginate. Nevertheless, the

high viscosity required for dental impression applications were not achieved, making it currently unsuitable for this purpose.<sup>50</sup>

#### 2.1.6. Mouthwash

According to research conducted by Dutot et al., extracts of *Silybum marianum* and *Fucus vesiculosus*, combined with seawater, were evaluated in human subjects for the first time in a mouthwash formulation derived from marine sources, due to their complementary properties: antibacterial and antibiofilm effects for *Silybum marianum*, and anti-inflammatory effects for *Fucus vesiculosus*.<sup>51</sup> Statistical analysis demonstrated that using this mouthwash for one week significantly reduced gingival inflammation and dental plaque accumulation, while exhibiting an excellent safety and tolerability profile. Furthermore, oral microbiota analysis showed an improvement in microbial composition, with an increase in health-associated taxa and a decrease in species implicated in disease, such as *Porphyromonas endodontalis*, suggesting that this formulation may contribute to restoring oral microbial balance. Overall, the findings indicate that natural oral care products derived from marine algae and coastal plants acts as a promising option or adjunct to conventional chemical mouthwashes for managing gingivitis and maintaining oral health.<sup>51</sup>

## 2.2. Red algae (Rhodophyta)

### 2.2.1. Periodontal regeneration

Periodontal diseases, especially periodontitis, are characterized by the progressive destruction of the gingiva, periodontal ligament, and alveolar bone, which can ultimately lead in the end to tooth loss if left untreated. Biomolecules derived from red seaweeds, especially fucoidan and carrageenan, have shown promise as candidates for periodontal regeneration

because of their anti-inflammatory, pro-angiogenic, and wound-healing stimulating characteristics. According to the literature, Xie et al. demonstrated that fucoidan, a sulfated polysaccharide obtained from *A. spicifera* and *Grateloupia filicina* species, exhibits significant potential in periodontal tissue repair by modulating inflammatory signalling pathways and stimulating angiogenesis, thereby facilitating the regeneration of the periodontal ligament and alveolar bone. Another important aspect is fucoidan's ability to enhance fibroblast and osteoblast migration and differentiation, contributing to the healing of damaged periodontal structure. Additionally, its capacity to stimulate collagen synthesis and extracellular matrix deposition provides a dual benefit by promoting both soft tissue healing and bone regeneration, its therapeutic value in periodontal applications.<sup>52</sup>

The regenerative potential of fucoidan is also supported by its capacity to stimulate vascularization and fibroblast recruitment, both of which are essential for the functional restoration of tissues.<sup>53</sup> Experimental *in vivo* studies conducted by Bajpai et al. reported that hydrogels containing fucoidan enhance the closure of periodontal defects, accelerate gingival wound healing, and contribute to the restoration of the structural integrity of the periodontium. Additionally, carrageenan, extracted from *K. alvarezii* and *E. denticulatum* species, also plays a significant role in periodontal regeneration by accelerating gingival tissue repair and facilitating the reestablishment of periodontal attachment. Recently published experimental evidence has indicated that carrageenan-based structures are effective in reducing local inflammation and stimulating epithelial regeneration, rendering them suitable for use in guided tissue regeneration membranes.<sup>54</sup>

Johnson et al. developed antimicrobial hydrogels based on cellulose nanofibers (CNF) and  $\kappa$ -carrageenan nanoparticles (CO) for the treatment of periodontitis, integrated with surfactin and Herbedotcin, for the treatment of periodontitis. The hydrogels demonstrated high thermal stability, controlled release properties, and significant water absorption capability. *In vitro* test results revealed strong antimicrobial activity against *Streptococcus mutans*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Pseudomonas aeruginosa*, reducing biofilm formation and bacterial metabolic activity alongside increased malondialdehyde (MDA) levels. In addition, the hydrogels decreased the generation of reactive oxygen species (ROS), and the production of transcription factors and cytokines in human gingival fibroblast (HGF) cells under inflammatory conditions. As a result, the developed hydrogels exhibited significant antibacterial and anti-inflammatory properties, suggesting their potential as effective therapeutic agents for periodontitis.<sup>55</sup>

### 2.2.2. Bone regeneration

Bone regeneration is essential for the effectiveness of dental implants and bone grafts, and scaffolds derived from red marine algae, particularly carrageenan-based scaffolds, have demonstrated considerable potential owing to their biocompatibility, structural strength, and similarity to the natural extracellular matrix.<sup>56,57</sup> These scaffolds provide both mechanical stability and support the biological processes of osteogenesis and osseointegration, promoting osteoblast adhesion, proliferation, and differentiation. Their effectiveness can be further enhanced by combining them with bioactive compounds such as hydroxyapatite, which mimics the mineralized bone matrix.<sup>56</sup> Additionally, other red marine algae, including

*G. corticata*, *G. amansii*, *L. papillosa*, *A. spicifera*, and *P. tenera*, provide polysaccharides and metabolites with osteoinductive, antioxidant, and antimicrobial properties, contributing to bone mineralization, stimulation of growth factors, and improved scaffold biocompatibility.<sup>57</sup> The biodegradability of these structures allows for their gradual resorption and replacement with natural bone tissue, removing the need for surgical removal and decreasing the risk of chronic inflammation. Therefore, red marine algae-based scaffolds represent promising multifunctional biomaterials for bone grafting and implant integration, offering an effective and natural alternative to conventional synthetic materials.<sup>56,57,58</sup>

AlgiPore™ is a bone substitute material based on natural hydroxyapatite derived from marine algae, and has been used clinically for over three decades due to its osteoconductive and biocompatible properties. Recent studies have demonstrated that AlgiPore™ can serve as a carrier for growth factors and mesenchymal stem cells, thereby enhancing its regenerative potential. For example, Zhao et al. reported its effectiveness in promoting bone healing, although human studies remain limited. More recent investigations have combined AlgiPore™ with  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) to optimize resorption times while maintaining the volumetric support necessary for osteogenesis. Long-term evidence, including a 14-year follow-up, has demonstrated high implant success rates (approximately 95 %) in atrophic maxillae undergoing sinus grafting with AlgiPore™, reinforcing its status as a biocompatible, biodegradable material with strong bone integration capacity. In clinical practice, AlgiPore™ is predominantly used for post-extraction socket preservation, preventing alveolar ridge volume loss and facilitating subsequent implant placement.<sup>59</sup>

### 2.2.3. Dental impression polysaccharide based-materials

Red marine algae, rich in polysaccharides, are increasingly recognized as important resources for the development of innovative dental materials due to their biocompatibility, natural origin, and ability to support tissue regeneration. Polysaccharides from red algae, such as alginate, agar-agar, and carrageenan, each offer beneficial uses in dental applications. Alginate, extracted from *Gracilaria edulis* and *G. dura* species is frequently used in impression materials due to its high manipulability, short setting time, and capacity to produce high-quality dental impressions with minimal discomfort of patient. Agar-agar, derived from *G. acerosa* and *G. pusillum*, is used in impression materials for its thermoreversible gelation properties, accuracy in reproduction, and cost-effectiveness, being capable of competing with synthetic polymers in precision applications like dental prosthetics.<sup>60</sup>

### 2.2.4. Dental mineralization

The clinical study carried out by Carrilho et al. evaluated the biotechnological potential of the macroalga *Lithothamnion calcareum* in modulating dental enamel demineralization. A distinctive characteristic of *L. calcareum* is the presence of calcium and magnesium carbonate deposits within its cell walls. The selection of this species for the control and support of enamel mineralization was based on its high calcium content and its established use as a nutraceutical supplement for the prevention of bone loss and the promotion of bone regeneration. Based on the premise that enamel remineralization can be stimulated through exposure to calcium-saturated sources, it was hypothesized that calcium-rich marine extracts could either prevent the release of calcium and phosphate ions from enamel or promote

their reprecipitation on the tooth surface. The results demonstrated that *L. calcareum* extract exerted a modulatory effect on enamel demineralization comparable to, or even greater than sodium fluoride. In light of these findings, the data suggest that *L. calcareum* represents a potentially effective alternative for the prevention and treatment of oral conditions correlated with enamel demineralization, including dental caries and dental erosion.<sup>61</sup>

Chakravarthy et al. undertook a comparative in vitro study to examine the remineralization potential of dental enamel using two red seaweeds species, *Lithothamnion calcareum* and *Lithothamnion superpositum*. These species are of particular interest because their cell walls contain calcium and magnesium carbonate deposits, providing a natural source of calcium necessary for remineralization. The study also aimed to determine whether these red algae could surpass the remineralization efficacy of the commercial product CPP-ACPF. The results were promising, indicating that both red marine algae species are capable of stimulating dental enamel remineralization.<sup>62</sup>

The marine algae species *A. fragilissima* is distinguished by its high calcium carbonate content, present in the form of magnesium-substituted calcite and aragonite. Research conducted by Hemamalini et al. investigated several marine algae species and reported that *A. fragilissima* contains approximately 11,720.4 ppm of calcium (~1.172 % g/g) in the dried sample. It was demonstrated that the calcified thallus of this species is predominantly composed of high-magnesium calcite, indicating significant calcium carbonate accumulation within its skeletal structure. This magnesium-rich composition not just provides mechanical strength and structural stability to the thallus but also offers considerable

remineralization potential. Calcium and carbonate ions released from the algal powder may contribute to the restoration of dental enamel, particularly in demineralized areas surrounding orthodontic brackets. Furthermore, marine algal powders have been shown to improve enamel microhardness and reduce lesion depth, highlighting their potential as bioactive ingredients in orthodontic adhesives, dental varnishes and remineralizing toothpastes.<sup>63</sup>

### **2.3. Green algae (Chlorophyta) active compounds used in Mouthwash designed products**

Mohandoss et al. developed a mouthwash based on biogenic silver nanoparticles (AgNPs) synthesized using ulvan, a polysaccharide obtained from the green alga *Ulva lactuca*. The TEM results revealed spherical particles with sizes ranging from 8 to 33 nm. In addition, the synthesized nanoparticles demonstrated significant antioxidant properties. The study further evaluated the antimicrobial activity of the mouthwash against relevant oral pathogens, including *Lactobacillus*, *Streptococcus mutans*, and *Staphylococcus aureus*. The results indicated high antimicrobial efficacy, with no observed cytotoxicity. Experimental data suggested that the ulvan- and silver nanoparticle-based mouthwash may represent a promising antimicrobial agent for the prevention and treatment of common oral conditions like dental caries and periodontitis. Nevertheless, more studies are required to validate its long-term clinical safety and efficacy.<sup>64</sup>

This potential for application was further confirmed by a study done by Cho et al., which investigated the potential of a mouthwash based on *Enteromorpha linza* extract aimed for reducing the bacterial plaque and gingival inflammation, compared with a positive control represented by Listerine®. After four weeks of use, the *E. linza* mouthwash resulted in significant reductions in plaque index, gingival bleeding, and gingivitis

severity, along with inhibition of the periodontopathogenic bacteria *Porphyromonas gingivalis* and *Prevotella intermedia*. The observed clinical and antimicrobial efficacy was comparable to that of the conventional mouthwash, supporting the potential of marine algae extracts as a favourable natural alternative for the prevention and management of gingival diseases.<sup>65</sup>

### **Concluding remarks and perspectives**

Marine algae represent a versatile and sustainable source of natural bioactive compounds with significant potential in modern dentistry. Their diverse metabolites, including polysaccharides, polyphenols, pigments, and minerals, provide antibacterial, anti-inflammatory, antioxidant, antiviral, and tissue-regenerative properties, supporting a wide range of dental applications.

Algae-derived materials, such as fucoidan, alginate, carrageenan, and ulvan, have demonstrated significant potential in dentistry, including periodontal and bone regeneration (e.g., fucoidan-based hydrogels and scaffolds), dental pulp protection (fucoidan-modified capping materials), enamel remineralization (calcium-rich red algae extracts such as *Lithothamnion calcareum*), impression materials (alginate-based hydrocolloids), and oral hygiene products (ulvan- or carrageenan-based mouthwashes), offering biocompatible and natural alternatives to conventional therapies.

While preclinical studies are encouraging, further clinical research is required to fully validate their efficacy, determine optimal formulations, and ensure long-term safety. Continued exploration of marine algae may lead to innovative, effective, and environmentally friendly strategies that enhance oral health and expand the tools available in preventive, restorative, and regenerative dentistry.

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