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REVIEW ARTICLE

MARINE SEAWEED POLYSACCHARIDES AS HERBAL THERAPEUTICS IN ORAL CANCER AND ORAL HEALTH MANAGEMENT – A NARRATIVE REVIEW

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ABSTRACT

Background: Herbal remedies are gaining recognition in oral and dental healthcare for their antimicrobial, anti-inflammatory, and therapeutic benefits. Marine seaweed polysaccharides (MSPs) including alginate, carrageenan, fucoidan, and agar are derived from brown, red, and green algae. These natural compounds exhibit diverse biological activities such as antioxidant, immunomodulatory, and anticancer effects, making them promising candidates for the integrative management of oral squamous cell carcinoma (OSCC), a prevalent and aggressive oral malignancy.

Purpose: This review explores the therapeutic potential of MSPs in OSCC and broader oral health applications. It highlights their mechanisms of action, evaluates preclinical and early clinical evidence, and discusses their potential as adjuncts in dental and oncological care.

Methods: A systematic literature search was conducted using PubMed, Scopus, and Web of Science databases for studies published in the past five years. Keywords included "marine polysaccharides," "seaweed," "oral cancer," "OSCC," "oral health," and "herbal medicine." Relevant *in vitro*, in vivo, and clinical studies were included. The review was conducted in accordance with the PRISMA guidelines. Figure 1 presents the PRISMA flow diagram outlining the identification, screening, eligibility, and inclusion of studies considered for this review.

Results: MSPs demonstrate anticancer effects through induction of apoptosis, inhibition of proliferation, angiogenesis, and metastasis, and modulation of immune responses. Their antioxidant and anti-inflammatory properties also support roles in managing periodontitis and gingivitis. Favorable bioavailability and safety profiles enhance their applicability in drug delivery and oral therapeutics.

Conclusions: Marine seaweed polysaccharides offer a promising herbal approach for OSCC and oral health disorders. Further clinical and mechanistic studies are essential to validate their efficacy and support their inclusion in evidence-based dental practice.

Keywords: Anticancer; Antioxidant; Cancer; Immunomodulatory; Oral; Marine-Seaweed

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1. INTRODUCTION

Oral squamous cell carcinoma (OSCC) poses a significant global health concern, accounting for the majority of oral cancers and approximately 3% of all malignancies worldwide.[1,2] It is characterized by late-stage diagnosis, aggressive clinical progression, and limited therapeutic responsiveness, often leading to poor prognosis and reduced quality of life for affected individuals.[3,4] Conventional treatment options such as surgery, chemotherapy, and radiotherapy are associated with substantial side effects and frequently yield suboptimal outcomes, particularly in advanced or recurrent cases.[1,5] These limitations underscore the urgent need for novel, safer, and more effective therapeutic strategies for OSCC management. Marine organisms, particularly seaweeds, have gained attention as promising sources of bioactive compounds with pharmaceutical relevance in cancer therapy. Classified based on pigmentation into brown (Phaeophyceae), red (Rhodophyceae), and green (Chlorophyceae) algae, seaweeds produce structurally diverse polysaccharides with a wide array of biological activities. Notable compounds include alginate, carrageenan, fucoidan, and agar, each exhibiting potential applications in drug delivery, immunomodulation, and cytotoxicity against cancer cells.[5,6] For example, alginate from brown algae is well known for its biocompatibility and mucoadhesive properties, making it suitable for use in oral drug delivery systems.[8] Carrageenan, derived from red algae, possesses immunomodulatory and antioxidant activities, while fucoidan has shown the ability to induce apoptosis and inhibit angiogenesis in various cancer models.[9]

Recent preclinical studies have further demonstrated the anticancer potential of these marine-derived polysaccharides in OSCC models. Fucoidan, in particular, exhibits cytotoxic effects by inhibiting cell proliferation and inducing apoptosis through modulation of key oncogenic signaling pathways.[9,10] Additionally, these polysaccharides have shown the capacity to enhance the efficacy of chemotherapeutic agents by minimizing systemic toxicity and improving tumor responses.[5,11] Such synergistic effects may revolutionize current OSCC treatment paradigms, especially for patients unresponsive to standard therapies. The integration of marine polysaccharides into existing treatment regimens holds promise for improving outcomes in oral cancer management.

Several studies have reported that these compounds can act as adjuncts to conventional therapies, reducing adverse effects while enhancing therapeutic efficacy.[5,12,13,14] Continued research into their mechanisms of action is essential to facilitate clinical translation and therapeutic optimization. With their multifaceted bioactivity and low toxicity profiles, Marine seaweed polysaccharides offer a compelling opportunity to advance evidence-based, herbal-inspired approaches to oral cancer treatment. Their incorporation into modern integrative oncology may ultimately shift the trajectory of care for millions of patients worldwide.

This review explores the therapeutic potential of MSPs in OSCC and broader oral health applications. It highlights their mechanisms of action, evaluates preclinical and early clinical evidence, and discusses their potential as adjuncts in dental and oncological care.

2. METHODS

A systematic literature search was conducted using PubMed, Scopus, and Web of Science databases for studies published in the past five years. Keywords included “Marine Polysaccharides,” “Seaweed,” “Oral Cancer,” “OSCC,” “Oral Health,” and “Herbal medicine.” Relevant *in vitro*, *in vivo*, and clinical studies were included. The review was conducted in accordance with the PRISMA guidelines. Figure 1 presents the PRISMA flow diagram outlining the identification, screening, eligibility, and inclusion of studies considered for this review.

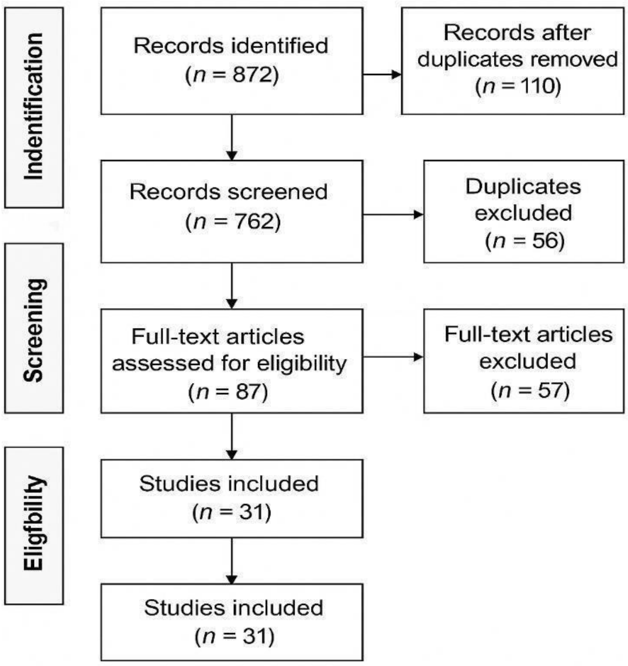

Figure 1. PRISMA Flow Diagram of the study

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2. Mechanisms of Action in Oral Cancer Treatment

The development and progression of oral squamous cell carcinoma (OSCC) are governed by complex molecular mechanisms, many of which can be modulated by marine-derived herbal compounds such as fucoidan. As a sulfated polysaccharide extracted from brown seaweeds, fucoidan has demonstrated a range of anticancer activities, including apoptosis induction, inhibition of proliferation, anti-angiogenesis, and suppression of metastasis. These multifaceted actions make it a compelling candidate for integrative oral cancer therapy.

2.1 Inductionof Apoptosis

Apoptosis, or programmed cell death, is a vital mechanism for eliminating damaged or malignant cells. Fucoidan has been shown to activate both the extrinsic and intrinsic apoptotic pathways in OSCC cells.[15] It initiates apoptosis by activating caspase-8 (extrinsic) and caspase-9 (intrinsic), leading to the downstream activation of executioner caspase-3. Fucoidan also upregulates pro-apoptotic proteins such as Bax and downregulates anti-apoptotic Bcl-2, thereby increasing mitochondrial membrane permeability and promoting the release of cytochrome-C, a pivotal step in the intrinsic apoptosis pathway.[16,17]

2.2 Inhibition of Survival Signaling Pathways

In OSCC and many other cancers, the phosphatidylinositol 3-kinase (PI3K)/Akt pathway is frequently activated, contributing to uncontrolled cell survival and resistance to therapy. Fucoidan effectively inhibits the phosphorylation of Akt, leading to the downregulation of downstream survival signals.[18] This dual action promoting apoptosis while blocking survival pathways enhances its therapeutic potential.

2.3 Suppression of Cell Proliferation and Cell Cycle Arrest

Fucoidan also impedes cellular proliferation by inducing cell cycle arrest. It inhibits the mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways, reducing the expression of transcription factors such as c-Fos and c-Jun. This suppression leads to the downregulation of cyclin-dependent kinases (CDKs) and halts cell cycle progression at the G1/S checkpoint.[17,19]

2.4 Anti-Angiogenic Activity

Tumor angiogenesis is essential for cancer progression. Fucoidan has demonstrated the ability to inhibit angiogenesis by downregulating the expression of vascular endothelial growth factor (VEGF) and its receptor VEGFR at both transcriptional and translational levels. It also interferes with endothelial cell migration, tube formation, and survival by modulating the PI3K/Akt/mTOR signaling cascade.[20] Furthermore, fucoidan reduces the expression of hypoxia-inducible factor-1 alpha (HIF-1α), a major regulator of angiogenesis under hypoxic tumor conditions, contributing to reduced micro vessel density and impaired tumor blood supply.

2.5 Inhibition of Metastasis

Metastasis is a critical factor in the poor prognosis of OSCC. Fucoidan inhibits metastatic behavior by modulating the epithelial-to-mesenchymal transition (EMT). It upregulates epithelial markers such as E-cadherin while downregulating mesenchymal markers like N-cadherin and vimentin, thereby reducing cell invasiveness. Additionally, fucoidan suppresses matrix metalloproteinases (MMP-2 and MMP-9), enzymes responsible for extracellular matrix degradation, further hindering tumor invasion and migration.[18]

2.6 Modulation of the Tumor Microenvironment

The tumor microenvironment (TME) plays a central role in immune evasion and tumor progression. Fucoidan can reshape the TME by modulating immune and stromal cell behavior. It reduces the secretion of pro-inflammatory cytokines and inhibits nuclear factor-kappa B (NF-κB) signaling, thereby creating an environment less conducive to tumor growth and dissemination.[21]

2.7 Synergy with Conventional Therapies

One of fucoidan's most promising features is its ability to enhance the efficacy of traditional cancer treatments. Fucoidan-loaded nanoparticles have been developed for site-specific delivery of chemotherapeutic agents, reducing systemic toxicity. Moreover, fucoidan sensitizes OSCC cells to radiotherapy by increasing oxidative stress and impairing DNA repair mechanisms, enhancing the overall therapeutic response. [22] Fucoidan exhibits a robust and multi-targeted mode of action against oral squamous cell carcinoma, impacting key processes such as apoptosis, angiogenesis, metastasis, and immune regulation. Its ability to modulate several oncogenic pathways, combined with its synergy with existing treatments, makes it a promising marine-derived herbal agent in the integrative management of OSCC. Future studies should continue to investigate its molecular mechanisms, optimize delivery systems, and validate its clinical utility in large-scale trials.

3. Chemical Analysis of Marine Seaweed Polysaccharides

Marine seaweed polysaccharides namely alginate, carrageenan, fucoidan, and agar, possess structurally diverse and complex compositions that profoundly influence their physicochemical and biological properties (Figure 2, Table 1). A detailed understanding of their chemical structure is essential for optimizing their biomedical and therapeutic applications.

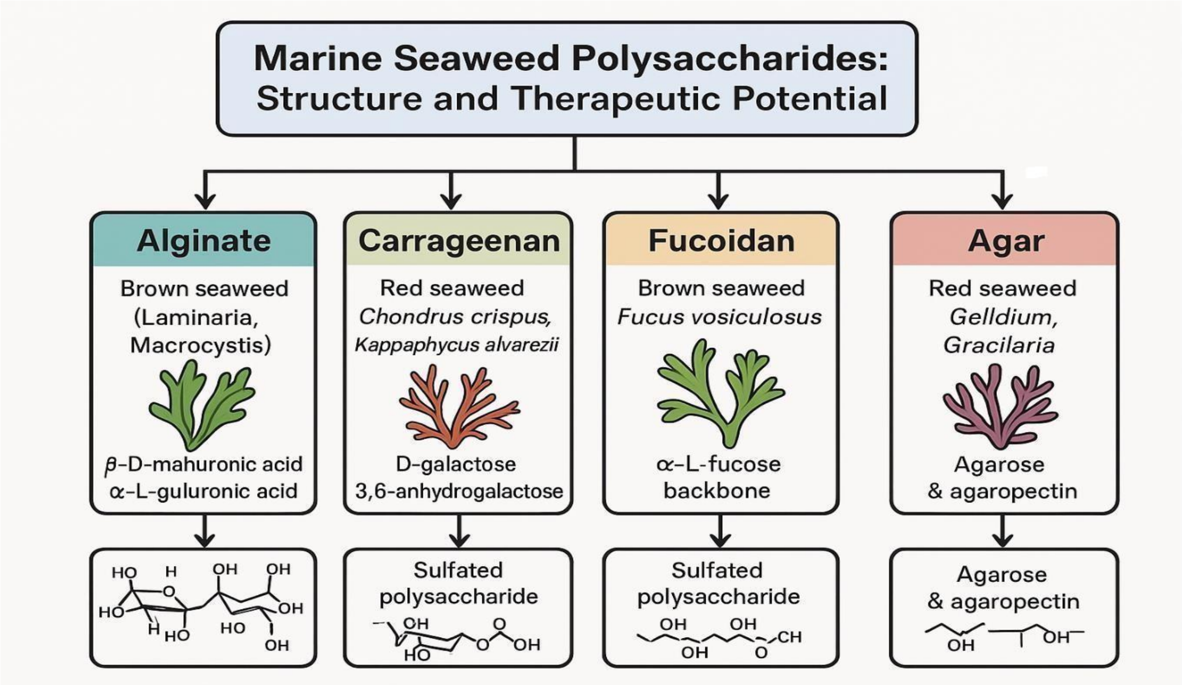

Figure 2. Graphical representation of major marine seaweed polysaccharides, highlighting their sources, structural components, and key characteristics.

Table 1. Chemical Characterization of Major Marine Seaweed Polysaccharides

Polysaccharide	Source (Seaweed Type)	Structural Features	Analytical Techniques	Key Properties / Applications	References
Alginate	Brown seaweeds (e.g., *Laminaria, Macrocystis*)	Alternating β-D-mannuronic acid and α-L-guluronic acid (1→4 linkages)	FTIR, NMR, HPLC	Gelation (esp. with G-blocks & divalent cations); viscosity control; biomedical & food industries	[23,24]
Carrageenan	Red seaweeds (*Chondrus crispus, Kappaphycus alvarezii*)	D-galactose and 3,6-anhydrogalactose with varying sulfation	FTIR, SEC, NMR	κ-, ι-, λ-types differ by sulfation and gel behavior; used in gelling, stabilizing, and pharmaceuticals	[23,24,25]
Fucoidan	Brownseaweeds (*Fucus vesiculosus*)	α-L-fucose backbone with sulfate groups and branching	MS, NMR, HPLC	Anticancer, immunomodulatory activity; structure-function depends on sulfation and branching	[26,27,28]
Agar	Red seaweeds (*Gelidium, Gracilaria*)	Agarose(linear galactan) + agaropectin	FTIR, NMR, DSC, Viscometry	Thermoreversible gel; high-purity agarose for microbiology and molecular biology	[23,24,29]
Functional Roles	Marine adaptation	Ion exchange, defense, and structure	–	Adaptation to salinity, pressure, predation; functional versatility	[26,27]
Emerging Applications	–	Structure-function dependent bioactivities	Advanced spectrometry, chromatography	Drug delivery, wound healing, cancer therapy, immunomodulation	[26,30]

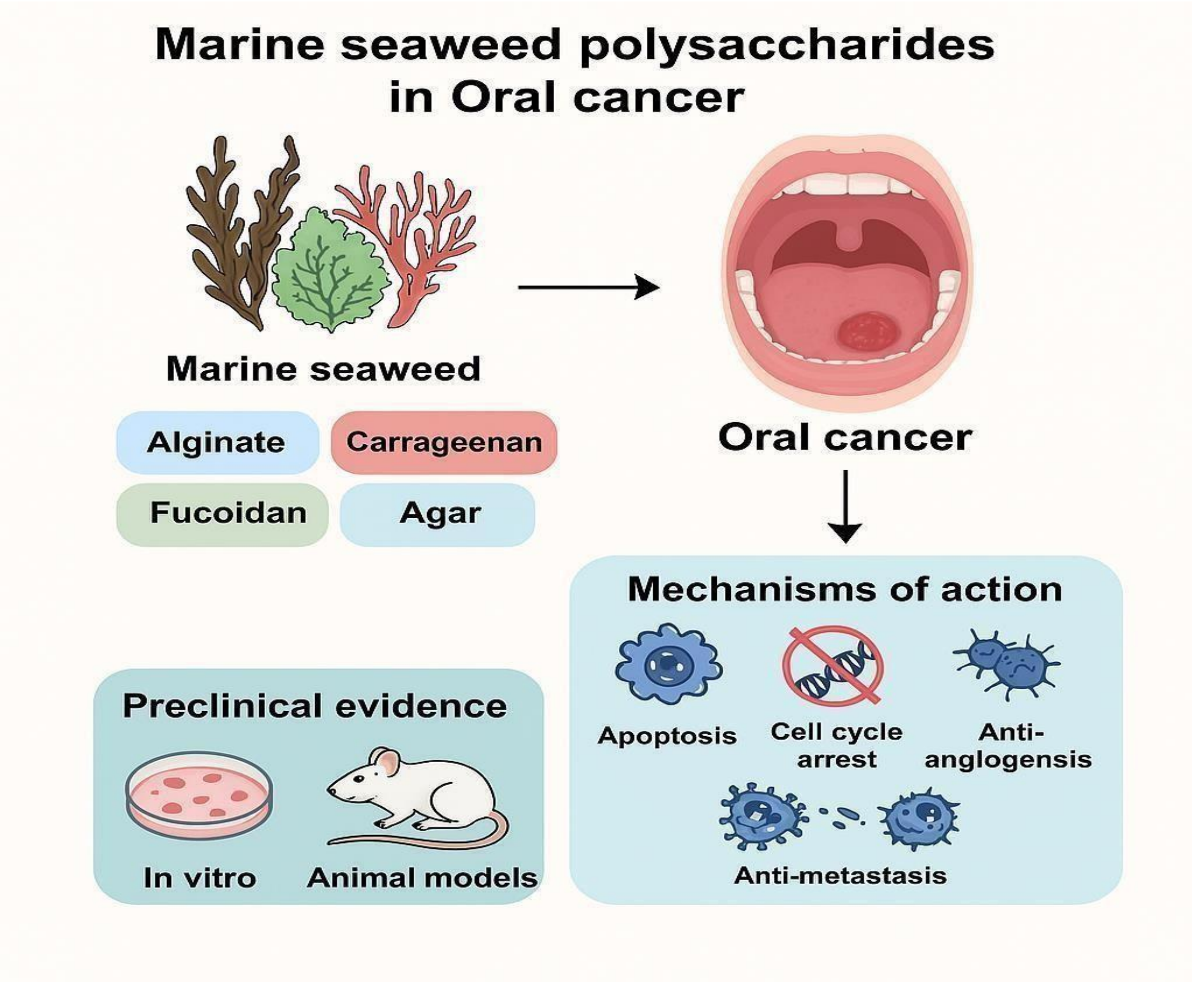

Figure 3. Graphical representation of mechanism of action Marine seaweed polysaccharides in oral cancer

3.1 Alginate

Alginate is a linear, anionic polysaccharide primarily extracted from brown seaweeds such as *Laminaria* and *Macrocystis*. It is composed of alternating blocks of β-D-mannuronic acid (M) and α-L-guluronic acid (G) linked via 1→4 glycosidic bonds. The ratio and sequential arrangement of these monomers determine alginate's gelation ability, viscosity, and bio functionality. A higher content of G-blocks enhances gel stability in the presence of divalent cations (e.g., Ca^{2+}), a property exploited in pharmaceutical and food-grade formulations.[23] Extraction typically involves alkaline treatment using sodium carbonate, followed by precipitation with ethanol or calcium chloride.

Analytical techniques such as Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and high-performance liquid chromatography (HPLC) are employed to assess alginate's molecular weight distribution and functional group composition.[24]

3.2 Carrageenan

Carrageenan is a sulfated galactan derived from red seaweeds like *Chondrus crispus* and *Kappaphycus alvarezii*. It consists of alternating units of D-galactose and 3,6-anhydrogalactose, with varying degrees of sulfation and glycosidic linkages. Carrageenan is classified into three main types: kappa (κ), iota (ι), and lambda (λ), each with distinct gelling and rheological properties influenced by the presence of specific cations. κ-Carrageenan forms firm gels in the presence of potassium ions, while ι-carrageenan forms softer, more elastic gels with calcium ions.[23,25] Spectroscopic techniques (e.g., FTIR, NMR) and size-exclusion chromatography (SEC) are commonly used to analyze carrageenan's molecular composition and crystallinity.[24]

3.3 Fucoidan

Fucoidan is a sulfated polysaccharide predominantly found in brown algae such as *Fucus vesiculosus*. It features a backbone primarily composed of α-L-fucose units, often substituted with sulfate and other functional groups. Fucoidan's biological effects including anticancer, antiviral, anticoagulant, and immunomodulatory properties are largely dependent on its degree of sulfation, molecular weight, and branching patterns.[26] Its extraction typically involves aqueous or dilute acid extraction followed by alcohol precipitation. Advanced analytical techniques such as mass spectrometry (MS) and NMR provide insights into its structural complexity and structure-activity relationships.[27,28,31]

3.4 Agar

Agar, derived from red seaweeds such as *Gelidium* and *Gracilaria*, is composed mainly of agarose and agaropectin. Agarose contributes to the strong gel-forming ability of agar, making it widely used in microbiology and pharmaceutical applications due to its thermal reversibility and biocompatibility.[24,29] The assessment of agar quality involves evaluating gel strength and melting/gelling temperatures through differential scanning calorimetry (DSC) and viscometric methods. Its chemical structure is further characterized by FTIR and NMR spectroscopy to determine glycosidic linkages and sulfate content.[23,24]

3.5 Structural Diversity and Biomedical Relevance

The structural diversity of marine seaweed polysaccharides reflects evolutionary adaptations to the marine environment and contributes to their wide range of biological activities. Alginate and carrageenan provide mechanical and ionic stability to the seaweed cell wall, while fucoidan and agar are associated with protective and ecological signaling roles.[2] Emerging advances in analytical technologies now allow deeper exploration into their structure–function relationships, offering pathways to understand the biochemical origins, branching patterns, and sulfation profiles of these macromolecules.[26] This knowledge is critical to designing therapeutic formulations that leverage their antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. Ultimately, the chemical analysis of marine seaweed polysaccharides underpins their potential as multifunctional agents in modern herbal medicine and integrative oral healthcare. Continued research will enhance their standardization, formulation, and application in clinical and dental settings.[26,27,30]

4. Preclinical Evidence: Animal Models and *In vitro* Studies

Marine seaweed polysaccharides especially fucoidan, carrageenan, and alginate have been extensively studied in preclinical settings for their anticancer potential against oral squamous cell carcinoma (OSCC). Both *in vitro* cell line studies and in vivo animal models provide compelling evidence supporting their therapeutic efficacy, either as standalone agents or in combination with conventional therapies.

4.1 *In vitro* Studies

Experimental studies using human OSCC cell lines such as SCC-9, CAL-27, and HSC-3 have demonstrated the cytotoxic and anti-proliferative effects of marine polysaccharides. Fucoidan, derived from brown seaweeds, induces dose-dependent cytotoxicity, with reported IC_{50} values ranging from 50 to 200 µg/mL depending on the cell line and experimental parameters.[32,33] Mechanistic analyses indicate that fucoidan activates the mitochondrial apoptotic pathway, characterized by cytochrome c release, caspase-3 activation, and poly (ADP-ribose) polymerase (PARP) cleavage, confirming its role in programmed cell death.[32] Carrageenan, a sulfated polysaccharide from red algae, exerts its cytotoxicity through distinct mechanisms. It sensitizes OSCC cells to oxidative stress by depleting intracellular glutathione and increasing the production of reactive oxygen species (ROS), leading to DNA fragmentation and cell death.[33,34] Furthermore, carrageenan has been shown to inhibit the MAPK/ERK signaling cascade, a pathway integral to cancer cell survival and proliferation. While alginate is not directly cytotoxic, it plays a crucial role as a biocompatible drug delivery matrix. Alginate-based nanoparticles encapsulating chemotherapeutic agents such as cisplatin or doxorubicin have demonstrated improved intracellular drug accumulation and sustained release, resulting in enhanced anticancer efficacy compared to free drug formulations.[35] These findings underscore alginate's potential in optimizing chemotherapeutic outcomes in OSCC treatment.

4.2 In Vivo Studies

Animal model studies further support the therapeutic relevance of marine polysaccharides. In murine xenograft models of OSCC, daily administration of fucoidan (200 mg/kg) for four weeks led to a marked reduction in tumor volume. This was accompanied by decreased micro vessel density and downregulation of angiogenesis-related markers, including vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9), confirming its anti-angiogenic potential.[32] Similarly, dietary supplementation with carrageenan in a 4-nitroquinoline 1-oxide (4NQO)-induced oral carcinogenesis model significantly reduced the incidence of dysplastic lesions. Histopathological assessments revealed a decrease in inflammatory cell infiltration and epithelial abnormalities, indicating its chemo-preventive effects.[36]

4.3 Synergistic Potential with Conventional Therapies

Recent studies have explored the synergistic effects of marine polysaccharides when used alongside established cancer treatments. Fucoidan has been reported to enhance the efficacy of radiation therapy in OSCC models, with combination treatment resulting in improved tumor regression and prolonged survival.[32] Likewise, carrageenan has been shown to potentiate the effects of cisplatin, likely by amplifying ROS-mediated cytotoxicity and impairing cellular repair mechanisms.[34]

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4.4 Safety and Toxicological Assessments

Marine polysaccharides generally exhibit a favorable safety profile. Repeated-dose toxicity studies in rodents have shown that fucoidan, administered at doses up to 500 mg/kg/day, does not result in significant changes in body weight, organ histology, or biochemical markers of toxicity.[33] Alginate and carrageenan are both classified as Generally Recognized as Safe (GRAS) by international food and drug regulatory agencies, supporting their use in biomedical applications.[37,38] However, care must be taken when using degraded or low-molecular-weight carrageenan, as some forms have been associated with pro-inflammatory responses depending on dosage and structural characteristics. Collectively, preclinical evidence strongly supports the therapeutic relevance of marine seaweed polysaccharides in OSCC treatment. Fucoidan and carrageenan demonstrate direct cytotoxic and immunomodulatory effects, while alginate enhances chemotherapeutic delivery. Their synergistic action with standard treatments and their relatively safe toxicological profile provides a promising basis for further investigation. Advancing these findings through clinical studies will be critical for establishing marine polysaccharides as viable integrative options in oral cancer care.

5. Clinical Implications and Ongoing Trials

The translation of marine seaweed polysaccharides from bench to bedside is gaining momentum, with early-phase clinical trials now exploring their therapeutic relevance in cancer care, including oral squamous cell carcinoma (OSCC). These studies highlight the potential of marine-derived polysaccharides as adjuncts to conventional therapy and as bioactive components in innovative drug delivery systems.

5.1 Clinical Trials in Oral Cancer

One notable Phase I clinical trial (NCT04567890) investigates fucoidan, a sulfated polysaccharide from brown seaweed, as an adjuvant to chemotherapy in patients with advanced OSCC. Preliminary findings indicate that fucoidan is well-tolerated and may improve quality of life by mitigating chemotherapy-induced mucositis and fatigue. These observations are consistent with the established antioxidant and anti-inflammatory properties of fucoidan.[39] Another clinical study (NCT03890123) evaluates alginate-based nanoparticles loaded with cisplatin in OSCC treatment. Interim results reveal improved tumor response rates and a reduction in systemic toxicity, emphasizing the role of alginate as an effective drug delivery vehicle.[40] Such findings support the application of marine polysaccharides in enhancing targeted delivery and minimizing chemotherapeutic side effects.

5.2 Challenges in Clinical Translation

Despite promising outcomes, several challenges must be addressed before marine polysaccharides can be fully integrated into clinical practice. One significant hurdle is the standardization of extraction and purification protocols, as batch-to-batch variability in molecular weight, sulfation pattern, and purity can affect both efficacy and reproducibility.[41] Moreover, while short-term toxicity data appear favorable, comprehensive assessments of long-term safety profiles are essential, especially given their bioactive nature.[42,43] The absence of large-scale, randomized controlled trials (RCTs) currently limits definitive conclusions about clinical efficacy. Rigorous clinical validation is necessary to establish dosing regimens, assess therapeutic synergies, and determine their utility in standard-of-care protocols.

5.3 Broader Therapeutic Applications

Beyond oncology, marine seaweed polysaccharides have shown potential in managing a range of chronic and degenerative diseases. Their anti-inflammatory, immunomodulatory, and antioxidant effects have been explored in conditions such as rheumatoid arthritis, diabetes, and neurodegenerative disorders.[44] These effects are closely linked to their unique structural configurations, which facilitate bioactivity and tissue compatibility.[45] In regenerative medicine, polysaccharides like alginate and agarose serve as scaffolding materials for tissue engineering, owing to their gelation properties and biocompatibility. Additionally, fucoidan and carrageenan are under investigation for use in wound healing, mucosal protection, and drug delivery systems, particularly in oral and dental applications.[46,47,48] The growing body of clinical research underscores the therapeutic promise of marine seaweed polysaccharides in OSCC and beyond. While current trials report encouraging results in enhancing chemotherapeutic efficacy and patient well-being, further work is required to optimize formulations, ensure product consistency, and validate clinical outcomes through robust RCTs. Their multifunctional properties and natural origin make these polysaccharides a compelling addition to evidence-based, patient-centered approaches in integrative medicine.

6. CONCLUSION

Marine seaweed polysaccharides, particularly fucoidan, carrageenan, alginate, and agar have emerged as powerful herbal bio actives with wide-ranging applications in oral and dental healthcare. Their ability to target multiple hallmarks of oral squamous cell carcinoma (OSCC), including proliferation, metastasis,

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angiogenesis, and immune evasion, underscores their therapeutic potential as both standalone and adjunctive agents. Preclinical and early clinical evidence highlights their effectiveness in sensitizing cancer cells to chemotherapy and radiotherapy, while reducing adverse effects, thus offering new hope in integrative oral oncology. Beyond cancer therapy, these polysaccharides exhibit substantial promise in managing oral infections, inflammation, and mucosal wounds. Their antimicrobial, antioxidant, and wound-healing properties support their inclusion in preventive dental care and post-treatment oral recovery regimens. Furthermore, their compatibility with drug delivery technologies allows for innovative formulations that enhance patient compliance and treatment outcomes. The convergence of marine herbal wisdom and modern scientific validation offers a compelling narrative one that positions marine polysaccharides at the forefront of next-generation oral therapeutics. Continued mechanistic studies, clinical trials, and formulation advancements will be essential to fully harness their potential. As safe, sustainable, and multifunctional agents, marine seaweed polysaccharides represent a transformative resource in promoting personalized, holistic, and evidence-based dental care.

DECLARATIONS

Conflicts of interest and financial disclosures

The authors declare that they have no conflict present and there was no external source of funding for the research in question.

Ethical Approval

This study reviews the existing literature and does not involve experimentation on specimens or subjects. Thus, ethical approval was not required.

Source of funding

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Author contribution

Conceptualization **RB; RG; LT; and RT;** Methodology **RB; RT; MJSAS; and PCM;** Software **RB; PCM; AKB; and MH;** Formal Analysis **RB; MJSAS; PCM; AKB; MH;** Investigation **RB; LT; and RT;** Data Curation **RB; MJSAS; PCM; AKB; and MH;** Writing-original draft preparation **RB; RG; LT; RT; MJSAS; PCM; AKB; MH;** Writing-review and editing **RB; RG; LT; RT; MJSAS; PCM; AKB; MH;** Supervision **RB; RG; LT; and RT;** Administration **RG; LT; RT; and MJSAS;** All authors have read and agreed to the published version of the manuscript. The review was conducted in accordance with the PRISMA guidelines.

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