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Therapeutic potential of fucoidan in dentistry: A review

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ABSTRACT

Fucoidan, produced by the cell walls of brown seaweed, possesses biological effects, covering anticancer, antiviral, anti-inflammatory, antioxidant, and a potential for promoting angiogenesis and osteogenesis. This study aimed to compile diverse scientific results on fucoidan's therapeutic prospect in dentistry and the mechanism of action in the therapy of oral diseases. A literature search was carried out using keywords with Boolean operators, including fucoidan (AND) oral (OR) dental (OR) dentistry, to identify related publications from PubMed, ScienceDirect, and Google Scholar databases. The results showed that fucoidan had various therapeutic potentials in the field of dentistry, including anticancer, anti-inflammatory, radioprotection, protection of dental pulp tissue, and bone regeneration. These characteristics were related to the sulfate composition and molecular weight. Fucoidan has various therapeutic potentials crucial for oral health. Hence, it might be used for material development and drug production in dentistry.

Implication for health policy/practice/research/medical education:
The analysis presents a detailed insight into fucoidan, which has a variety of bioactivities related to oral health. Furthermore, this review categorizes the potential of fucoidan based on the latest published studies, providing a valuable basis for further development of fucoidan-based therapies for oral inflammation, oral cancer, drug delivery, and tissue regeneration in dentistry, as well as for the improvement of dental material properties.

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Introduction

Fucoidan is a type of polysaccharide generated by the brown seaweed's cell walls and various tissues of sea invertebrates, including sea cucumbers and sea urchins (1). The popularity has risen among some Asian populations in South Korea, China, and Japan. This material is a soluble heteropolysaccharide primarily made up of sulfate groups and L-fucose, as illustrated in Figure 1. L-fucose-4-sulfate serves as the primary monosaccharide constituent (2). More than 90% of the total sugar content is attributed to the presence of L-fucose (3). Fucoidan might additionally encompass various monosaccharides, covering galactose, uronic acid, glucose, xylose, rhamnose, mannose, or arabinose (4).

Fucoidan is comprised of units of L-fucose, also known as L-fucopyranose. The residue sulfation may take place at positions C-4, C-2, and rarely C-3. The construction and sulfation arrangement in the primary sugar chain is associated with the type of species (5).

Fucoidan structure varies according to species, growing environment, and harvest season (6,7). Additionally, the extraction process significantly affects the physicochemical characteristics and arrangement (8). The diverse biological activities of fucoidan are linked to its ionic structure, and the molecules carry a negative charge owing to sulfate residues. The presence of this negative charge facilitates the formation of complexes with molecules carrying a positive charge. Fucoidan is a biocompatible and biodegradable compound that has been recognized by the Food and Drug Administration (FDA) in the "generally recognized as safe" (GRAS) category (9).

The biological activities are very diverse, including

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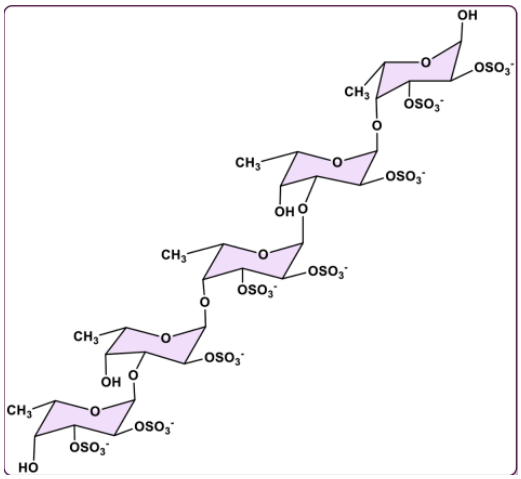

Figure 1. Fucoidan structure of *Fucus vesiculosus* (4).

anticancer (10-12), antioxidant (13-15), anticoagulant (16,17), antithrombotic (18), immunomodulatory (19,20), antiviral (21-23), and anti-inflammatory properties (24-26). Fucoidan is also known to alleviate metabolic syndrome (27-29), It also has angiogenic (30,31) and osteogenic (32-34) potential.

The applications of fucoidan-containing nanosystems as imaging agents, small medication delivery, protein delivery, anti-coagulant, gene delivery, and regenerative therapy have been previously reviewed (1). Ramos-de-la-Peña et al evaluated the structural as well as bioactive activities of fucoidan in the therapy of lung cancer, cartilage regeneration, respiratory diseases, antithrombotic therapy, and the prevention of diabetes-related complications (4). Oliveira et al evaluated the anti-tumor potential in lung cancer, colorectal cancer, breast cancer, and melanoma (35). Additionally, Pradhan et al explored the antiviral potential to treat SARS-CoV-2 (36). These reviews concentrated on the use of fucoidan for human diseases, but none of them focused on oral health. This review aimed to present the therapeutic effects of fucoidan, such as anti-inflammatory, anti-microbe, tissue regeneration, and drug delivery for therapy in dentistry. By presenting scientific data on therapeutic potentials of fucoidan, this study is expected to provide insight and serve as a reference in the development of fucoidan-based bioactive agents for drugs and dental materials.

Methods

The therapeutic potentials of fucoidan information were collected from electronic databases, including PubMed, ScienceDirect, and Google Scholar. The keywords used were fucoidan (AND) oral (OR) dental (OR) dentistry, and only articles published in the last 10 years (2013-2023) were used. Several studies on the application of fucoidan in biomedical science were also included to provide a broad view of the subject. Therefore, a total of 45 research articles were selected, with the criteria of being written in the English language and not being review articles, case reports, and unpublished data, such as theses and conference papers. The article selection method is shown in a flowchart in Figure 2.

Antimicrobial and antibiofilm

The oral biofilm represents a complex microbial population in humans, comprising more than 700 species, which are presumed to contribute to the formation of dental plaque biofilm (37). Gram-positive carbohydrate fermentation bacteria dominate dental biofilms, which cause tooth decay leading to pulpitis and periapical periodontitis. The largest number of bacteria in the supra and subgingiva biofilm are gram-negative anaerobic proteolytic types, which induce gingival inflammation, periodontal ligament, and alveolar bone destruction, as well as eventually tooth loss (38). In oral health care, the primary focus is on reducing pathogenic bacteria and utilizing natural products to treat disorders caused by oral bacteria, thereby helping to prevent drug resistance (39).

Fucoidan has been shown to have antimicrobial effects against cariogenic bacteria, including *Streptococcus mutans, S. sobrinus, S. sanguinis, S. ratti, S. criceti, S. gordonii,* and *S. anginosus*. It also has antibacterial effects against periodontopathogenic bacteria such as *Actinobacillus actinomycetes, Prevotella intermedia, Fusobacterium nucleatum,* and *Porphyromonas gingivalis* (40).

A study examined the antibacterial and anti-biofilm mechanisms of sulfated polysaccharides generated by eight distinct species of algae. Only fucoidan from *Fucus vesiculosus* had an antimicrobial effect against dental plaque bacteria, including *Enterococcus faecalis*, *Streptococcus mutans*, *S. oralis, S. sobrinus,* and *S. sanguinis*. Fucoidan, in concentrations exceeding 250 mg mL^{-1}, impeded the development of biofilms and the growth of cells in *S. sobrinus* and *S. mutans* (41). This compound prevented the attachment of *S. mutans* to the surface of bovine teeth and porcelain, while also showing antifungal activity against *Candida albicans* (42).

Dental pulp protection

Dental pulp is connective tissue surrounded with dentin and functions in supporting tooth energy by providing important factors through the apical foramen. It has initiatory, formative, protective, nutritional, and reparative functions (43). Vital tooth pulp can be exposed to the external environment due to caries, mechanical sources, and trauma, with untreated cases potentially leading to pulpitis and pulp necrosis (44).

Direct pulp capping is a procedure for treating exposed vital pulp, wherein specific materials are placed over the exposed area to encourage the formation of reparative dentin. Mineral trioxide aggregate (MTA) and calcium hydroxide are two substances utilized in this therapy (44). Compared to calcium hydroxide, MTA therapy produces better results by decreasing inflammation, hyperemia,

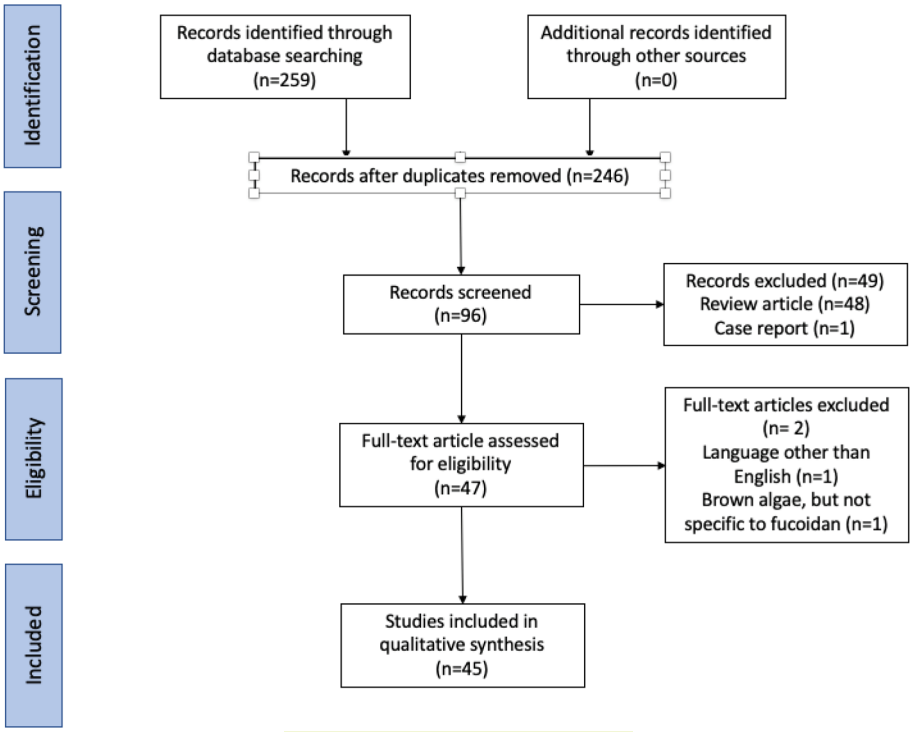

Figure 2. Flowchart of study selection.

and necrosis, as well as resisting bacterial leakage and protecting the pulp, allowing healing and maintaining pulp vitality. However, the drawbacks include teeth discoloration, difficult manipulation, a long setting time, and relatively high cost (45).

Several options have been explored to address the limitations, including the incorporation of fucoidan. A material cap consisting of portland cement (89%) and zirconium oxide (20%) was compared to basic components comprising 5% and 10% fucoidan. According to the findings, regardless of concentration, fucoidan notably decreased the setting times, both initial and final, although there was a reduction in compression strength at a 5% concentration. Sulfur levels, cell migration, and alkaline phosphatase activity all increased. Therefore, fucoidan may be considered a useful regenerative addition to standard pulp-capping materials (46).

Bone regeneration

Periodontal disease, a persistent inflammatory condition that impacts the tissues supporting the teeth, stands as a contributor to bone deterioration within the oral cavity. Biomaterials that are biocompatible, biodegradable, anti-inflammation, and adhesive are used in the regenerative therapy of bone defects in periodontal disease.

A randomized clinical trial assessed the use of injectable hydrogel containing chitosan and fucoidan in the treatment of intra-bony defects associated with periodontal conditions. At three- and six-month evaluations, this study found that the therapy significantly reduced probing depth values and increased clinical attachment levels than the group treated with concentrated growth factor (CGF). After nine months, defect filling in the hydrogel group was also more elevated than in CGF cluster (47).

Fucoidan has also been combined with other compounds for bone regeneration. The incorporation to the tricalcium phosphate-chitosan scaffold enhanced the release of osteocalcin. This study found that fucoidan promoted osteogenic differentiation in human mesenchymal stromal cells (32). Furthermore, fucoidan in combination with polydopamine improved the osteogenic potential of periodontal ligament stem cells. This was shown by improved alkaline phosphatase activity and expression of osterix, runt-related transcription factor 2, osteopontin, osteocalcin, and collagen type I (48).

Oral inflammatory diseases therapy

Oral inflammatory disease is the most general lesion found in the oral cavity and greatly affects life quality. Topical medications are frequently used to treat these oral lesions but the delivery of drugs to the oral mucosa is low because of salivary flow, mastication, swallowing, and speech function (49).

Chitosan/fucoidan hydrogel was developed as a delivery system for triamcinolone acetonide, a topical steroid commonly used to treat oral inflammatory conditions. Fucoidan enhanced swelling behavior, mechanical strength, and adhesive qualities in chitosan hydrogel. The addition of triamcinolone acetonide to the hydrogel improved elastic characteristics, suppressed the inflammatory response, and promoted collagen fiber production. This composite hydrogel also showed optimal

antibacterial, cytocompatibility, and histocompatibility properties (50).

Fucoidan, also known for its prebiotic properties, may assist probiotics in ulcer therapy. The mixture with alginate in hydrogel form and probiotics for use as oral patches showed superior ulcer healing potential than commercial oral patches, by promoting cell migration, stimulating epithelium formation, aiding collagen fiber deposition, and facilitating neovascularization (51).

Oral cancer therapy

Oral cancer is the sixth most prevalent cancer worldwide, and its increasing incidence in recent years has become a notable global health issue (52). GLOBOCAN 2018 estimated the occurrence of 354 864 lip and oral cavity cancer cases worldwide, with approximately 177 384 casualties per year (53). Tobacco smoking and alcohol consumption pose risks, as does the practice of betel chewing in specific regions (54). Apart from surgical approaches, radiotherapy and chemotherapy currently serve as the primary treatments for oral cancer. However, these methods come with side effects, for instance, diarrhea and nausea (54). Hence, many new anticancer compounds are currently being explored.

A functional drink including fucoidan, as well as other natural substances namely vegetable juice, mulberry, and wheat grass effectively prevented the potential of oral cancer in a dose and time-dependent manner. Oral cancer was inhibited by inducing apoptosis, arresting the G2/M cell rotation, and lowering migration-related epithelial-mesenchymal transition markers (55).

Fucoidan has been established to impact macrophage recruitment and inhibit oral squamous carcinoma cell invasion (56). A multilayered nanofiber patch incorporating fucoidan has been shown to damage oral squamous carcinoma cells and regenerate the oral epithelium (57). It also elevated the levels of mitochondrial superoxide and reactive oxygen species while reducing cellular glutathione levels in cancer cells. Oxidative stress in cancer cells is related to a reduction in antioxidant signaling genes (58).

Salivary gland radioprotection

The most prevalent primary malignancy of the endocrine system is thyroid cancer, and its incidence is increasing globally. In 2017, the condition was estimated to impact 56 870 Americans, with approximately 75% of cases arising in women (59).

The standard treatment involves thyroidectomy, continued by the elimination of any remaining tissue on the thyroid through heightened doses of radioactive iodine (^{131}I). However, aside from the thyroid gland, iodine (^{131}I) accumulates in salivary gland cells and interferes with the function. Patients also frequently complain about xerostomia and chronic salivary dysfunction. Saliva has an essential role in oral homeostasis, and deficiency elevates the oral morbidity jeopardy. The aim of therapy is to maintain or recover sustained salivary discharge, greatly improving the life quality of individuals with thyroid cancer (60).

The administration of radioiodine is critical in the therapy of thyroid cancer because it removes cancer tissue and prevents its recurrence. However, the effects are extended to other organs like the salivary glands, digestive tract, and breasts, leading to unfavorable reactions. The most prevalent side effects include salivary gland damage, which causes discomfort and swelling. Radioiodine also results in xerostomia, taste alterations, mouth pain, and swallowing difficulties (61).

Several studies attempted to use antioxidants in preventing radioiodine-induced salivary gland dysfunction. Fucoidan is one chemical with anti-inflammatory, antioxidant, and immunomodulatory characteristics (62). The effect on salivary gland dysfunction following radioiodine administration was studied, and the group treated with fucoidan had a higher saliva flow rate than the radioiodine group. Salivary gland histology showed areas of mucin-rich parenchyma and decreased periductal fibrosis. Fucoidan therapy also resulted in increased myoepithelial and salivary epithelial cells as well as decreased apoptotic cells (63).

Oral mucositis therapy

Mucositis refers to an injury to the mucosal lining of the upper and lower digestive tracts, often an adverse effect of cancer therapy with chemotherapy and radiation. Oral mucositis poses a challenge for oncologists, particularly in therapeutic interventions for head and neck cancer medicine. This condition not only restricts chemotherapy and radiation therapy but also has a detrimental influence on the life quality and efficacy of therapy. Therapy for oral mucositis is complicated and focuses on palliative care (64).

Fucoidan and deoxycholic acid can be combined to generate nano-micelles, which are ultramicroscopic globular structures with an outer hydrophilic polar head and an inner hydrophobic fatty acyl chain. Nano-micelles reportedly have the capacity to deliver less water-soluble medications while also protecting drug molecules. In this approach, cannabidiol, a hydrophobic anti-inflammatory medication, can be introduced to the hydrophobic part of the nano-micelles. In a murine model simulating oral mucositis, intravenous injection increased cannabidiol accumulation and retention. These nano-micelles not only accelerated the healing of oral mucositis but also inhibited the infiltration of lymphocyte antigen 6 complex locus G6D (Ly6G) inflammatory cells and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) nuclear transcription. The therapy showed greater anti-inflammatory properties than cannabidiol after local or systemic administration. The competitive inhibition test demonstrated the involvement of P-selectin, an adhesion

protein found prominently in endothelial and platelet cells during inflammatory states. P-selectin is a potential biomarker for inflammatory responses and plays a role in mediating the anti-inflammatory targeting ability of fucoidan nano-micelles (65).

Utilizing the powerful binding affinity of fucoidan to P-selectin has been employed to enhance the effectiveness and safety profile of current cancer therapies. Due to the focused P-selectin mechanism, fucoidan-based nanoparticles promote more binding to cancer cells than healthy cells (66). Additionally, it functions as a polymer sensitive to pH changes, as its components incorporate acidic groups while the negative charges can adjust to the surrounding environmental acidity. Using chitosan-fucoidan in the form of pH-responsive nanoparticles demonstrated resistance in the gastrointestinal tract as well as mucoadhesive properties (67). Furthermore, the electrostatic relations among the negative charge ($-SO_3^-$) in fucoidan and the positive charge ($-NH_3^+$) in chitosan resulted in the creation of nanoparticles with pH sensitivity. This characteristic makes them appropriate for administering oral drugs that have low water solubility and may degrade under highly acidic conditions (68).

The negative charges found in fucoidan can also interact with the positive charges on the surface of zein nanoparticles, thereby improving their stability. The derived nanoparticles show better drug-loading efficiency and photochemical stability (69). Fucoidan additionally exhibits hypoglycemic effects and guards against complications associated with diabetes. Moreover, it can be combined with trimethyl chitosan, which has excellent mucoadhesive properties, to create multifunctional nanoparticles aimed at improving the transepithelial permeation of insulin across the intestinal epithelial cell barrier and suppressing α-glucosidase (70).

Oral submucous fibrosis therapy

Oral submucous fibrosis (OSF) is an established, persistent inflammatory disorder that most commonly affects the buccal mucosa. One of the symptoms is aberrant collagen deposition beneath the mouth mucosal epithelium. This disease causes symptoms such as submucosal fibrosis, xerostomia, and difficulty in opening the mouth, all of which negatively impact the quality of life. According to a previous study, OSF is also considered a precancerous lesion (71).

Several therapies have been suggested, including habit control (areca nut chewing cessation), physical therapy, as well as medical and surgical interventions (72). The use of natural substances or herbal medications with antioxidant capabilities (such as curcumin and *Salvia miltiorrhiza*) for the therapy of OSF is currently being investigated (73,74).

Fucoidan as a natural compound has also been studied for its potential in OSF therapy showing significant ability to suppress maternally expressed gene 3 (MEG3), and related to myofibroblast markers. MEG3 deficiency can impair myofibroblast activity, while also acting as a competitive endogenous ribonucleic acid (ceRNA) that targets microRNA-181a (miR-181a), blocking early growth response protein 1 (Egr1) and translational suppression by miR-181a (75).

Tooth movement restriction following orthodontic therapy

The orthodontic retention stage marks the completion of orthodontic therapy, aiming to stabilize the teeth in the correct position and avoid repositioning (76). Mechanical forces produce tooth movement during orthodontic therapy, which is an aseptic inflammatory reaction. The orthodontic force causes an immediate inflammatory reaction in the periodontal ligament and alveolar bone, resulting in absorption on the compression section and the formation of new bone in the tension section. Several cell types are related to this complex process including cytokines and various signals/pathways (77).

Injections of fucoidan into mice have been shown to inhibit the movement of teeth subjected to orthodontic stresses and enhance the density of bone minerals. Fucoidan raised the amount of F4/80 cluster of differentiation 206 ($^+CD206^+$) macrophages, and prompted the messenger RNA expression of arginase 1 (Arg-1), CD206, and interleukin 10 (IL-10) expression, while decreasing tumor necrosis factor-α (TNF-α), IL-1b, IL-6, and F4/80 $^+CD11c^+$ cells expression. As stated in a previous study, tooth stability was increased following orthodontic movement by strengthening restorative macrophages through the signal transducer and activator of the transcription 3 (STAT3) pathway (78). Table 1 shows the therapeutic potentials of fucoidan.

Conclusion

In conclusion, fucoidan, a substance with a variety of bioactivities, is widely utilized in the pharmaceutical and health fields, especially dentistry. Investigation into its application spanned both preventive and curative purposes. The potential of fucoidan for regenerative therapy in dentistry was explored, but only a few studies have been published on this subject. This provided opportunities for expanding the application of fucoidan in dentistry, particularly considering the abundance of brown seaweed as the main source. The majority of studies presented in this literature review were still in the early stages, both in vitro and in vivo. Therefore, further study and development efforts are required to optimize the health advantages of fucoidan clinically.

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Table 1. Summarized therapeutic potentials of fucoidan

Therapeutic potential	Tested sample	Study design	Study method	Study results	Ref.
Antimicrobial	Fucoidan, ampicillin, and gentamicin. The cariogenic bacterial strain used were *S. Sanguinis*, *S. mutans*, *S. sobrinus*, *S. criceti, S. ratti*, *S. anginosus*, as well as *S. gordonii*. The periodontopathogen bacterial strains employed for periodontal pathogenicity included *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*	*In vitro*	MBCs as well as MICs assay	Fucoidan exhibited potent antimicrobial effects against all examined cariogenic and periodontopathogen bacteria. Its most robust antimicrobial activity was observed against the anaerobic bacteria, specifically *P. gingivalis*.	(38)
			Chequerboard assay	The combination of fucoidan and ampicillin produced synergistic effects, as did the mixture of fucoidan and gentamicin. The additive effect was found in *S. sobrinus* and *S. anginosus* for combinations of fucoidan and ampicillin, as well as in *P. intermedia and A. actinomycetemcomitans* for combinations of fucoidan and gentamicin.	
Pulp protection	Experimental MTA (portland cement and zirconium oxide) (PZ), fucoidan, PZ added by fucoidan 5 wt% (PZF5), PZ added by fucoidan 10 wt% (PZF10), and a commercial MTA.	*In vitro*	Evaluation of mechanical properties	The incorporation of fucoidan led to a reduction in both the initial and final setting times. In comparison to the PZ group, PZF5 exhibited a lower compressive strength. However, PZF10 demonstrated a higher compressive strength compared to PZF5.	(46)
			Biological evaluation	Cell viability remained comparable across groups at both 3 and 7 days. After 12 hours of culture, PZF5 exhibited greater cell migration compared to the other groups. After 14 days, the ALP activity was elevated in the PZF5 and PZF10 groups compared to the others.	
Bone regeneration	β-TCP-Ch-Fu scaffold and TCP-Ch scaffold.	*In vitro*	Biomineralization of scaffolds	After 7 days of incubation in SBF, TCP-Ch-Fu scaffolds exhibited a greater deposition of the apatite layer on the surface compared to TCP-Ch scaffolds.	(32)
	Fucoidan with chitosan hydrogel and CGF.	RCT	Clinical parameters: plaque index, gingival index, periodontal pocket depth, and clinical attachment loss	The hydrogel resulted in decreased scores for all other clinical parameters at 3, 6, and 9 months, as compared to the baseline, in both groups. The two groups were comparable at 9 months.	(47)
			Radiographic parameters: CEJ to base, CEJ to bone level, intra-bony defects, and defect fill	At 9 months, the fucoidan-chitosan group exhibited increased defect fill, accompanied by a reduced CEJ-base measurement.	

Table 1. Continued

Therapeutic potential	Tested sample	Study design	Study method	Study results	Ref.
Oral inflammatory disease therapy	Calcium alginate (CA) hydrogel, CA- *Lactobacillus rhamnosus* (CA-L.rha) hydrogel, CA-2.5% Fucoidan-L.rha (CA-2.5FD-L.rha) hydrogel, CA-5% FD-L.rha (CA-5FD-L.rha), and CA-7.5% FD-L.rha (CA-5FD-L.rha). A commercial chitosan patch was used in the *in vivo* study.	*In vitro* and *in vivo*	Probiotic release	The hydrogel could release probiotics within one hour. After 6 hours, the release of probiotics from the CA/7.5FD/L.rha hydrogel exceeded that from the other hydrogels.	(51)
			Antimicrobial activities	Hydrogel groups with higher FD content exhibited superior antibacterial activity compared to CA.	
			Cell migration	Following 24 hours of incubation, the area recovery of CA/2.5FD/L.rha hydrogel was 17.4%, surpassing that of CA hydrogel (12.6%). Nevertheless, hydrogels with 5 and 7.5 mg/mL FD impeded cell migration.	
			In vivo evaluation	In animal experiments, the CA/2.5FD/L.rha hydrogel demonstrated superior efficacy in promoting ulcer healing compared to the commercial oral ulcer patch.	
Oral cancer therapy	A cocktail consisting of about 20% mixed vegetable juice, 10% of mixed mulberry juice, 65% of wheatgrass juice, and 5% of fucoidan powder extract of *F. vesiculosus* (VMW-FC)	*In vitro* and *in vivo*	In vitro evaluation	VMW-FC led to approximately 50% or greater cell death in all three oral cancer cell lines, reduced the invasion capability of oral cancer cells, and triggered apoptosis and G2/M cell cycle arrest.	(55)
			In vivo evaluation	VMW-FC resulted in a decrease in tumor size and weight, without inducing any additional adverse effects on the liver and kidney.	
	Fucoidan	*In vitro*	Biological activities of CAL27 cells	Fucoidan decreased the invasion capability of CAL27 cells and attracted macrophages.	(56)
Salivary gland radioprotection	Radioiodine (RI) and fucoidan	*In vivo*	Measurements of salivary gland functions	The fucoidan group exhibited enhancements in salivary flow rates and lag times compared to the group treated with RI.	(63)
			Morphological analysis of tissues	In the fucoidan group, the salivary glands displayed parenchymal regions rich in mucin and reduced periductal fibrosis. Additionally, there was a higher count of salivary epithelial and myoepithelial cells, along with a lower presence of apoptotic cells compared to the RI group.	
Oral mucositis therapy	Fucoidan and the hydrophobic deoxycholic acid (FD nano-micelles), Cannabidiol (CBD)-loaded FD nanomicelles (CBD/FD nanomicelles)	*In vitro* and *in vivo*	*In vitro* evaluation	The targeting of inflammation by FD nano-micelles was facilitated through P-selectin mediation. The presence of CBD/FD led to a reduction in the levels of TNF-α and IL-1β.	(65)
			In vivo evaluation	Following intravenous administration, CBD/FD nano-micelles resulted in a significantly lower degree of ulceration compared to PBS or free CBD. In situ, dripping administration of CBD/FD nano-micelles demonstrated outstanding healing and anti-inflammatory impacts.	

Table 1. Continued

Therapeutic potential	Tested sample	Study design	Study method	Study results	Ref.
OSF therapy	Fucoidan	*In vitro*	Examination of the anti-fibrotic result of fucoidan on the myofibroblast actions of fBMFs	Fucoidan suppressed the wound healing, migration, and collagen gel contraction capabilities of fBMFs. Moreover, fucoidan demonstrated a downregulation of myofibroblast biomarkers, which included the reduction in the secretion of TGF-β1 and the expression of COL1A1, α-SMA, and p-Smad2.	(75)
			RNA-sequencing and qRT-PCR	The OSF specimen exhibited an elevated expression of MEG3. The suppression of MEG3 resulted in a decrease in the secretion of TGF-β1 and IL-6. Additionally, an upregulation in the expression of microRNA-181a (miR-181a) was observed following MEG3 silencing.	
Tooth Movement Restriction Following Orthodontic Therapy	Fucoidan	*In vivo*	Micro-computed tomography scanning and analysis	Fucoidan treatment decreased both the distance and rate of OTM. Additionally, over time, fucoidan led to an increase in the density of periodontal bone.	(78)
			RT-PCR analysis	The injection of fucoidan in mice resulted in the suppression of proinflammatory factors' expression, including TNF-α, IL-1β, iNOS, and IL-6, in the alveolar bone. Conversely, the levels of anti-inflammatory factors, including IL-10, Arginase-1 (Arg-1), and cluster of differentiation 206 (CD206), were elevated.	
			Flow cytometry	The presence of reparative CD206+ macrophages in periodontal tissues saw an increase from day 5 to 14 following fucoidan injection during OTM, accompanied by a notable decrease in the proportion of proinflammatory CD86+ macrophages. Following fucoidan therapy, there was a reduction in the expression of Ly6C in CD11b+ cells. Additionally, fucoidan led to a decrease in the ratio of F4/80+CD11c+ macrophages.	

RCT, Randomized Clinical Trial; CGF, concentrated growth factor; MBC, Minimum bactericidal concentrations; MICs, minimum inhibitory concentrations; SBF, simulated body fluid; TCP-Ch-Fu, Tricalcium phosphate-chitosan-fucoidan; CEJ, cementoenamel junction; CA, Calcium alginate; OSF, Oral submucous fibrosis; TNF alpha, tumor necrosis factor-α; IL-1β; interleukin 1 beta; fBMFs, fibrotic buccal mucosa fibroblasts; TGF-β1, transforming growth factor; COL1A1, collagen type 1 alpha 1; α-SMA, alpha-smooth muscle actin; p-Smad2, phosphorylated Smad 2; OTM, orthodontic tooth movement; iNOS, inducible nitric oxide synthase; MEG3, maternally expressed gene 3; qRT-PCR, real-time quantitative polymerase chain reaction; PBS, phosphate-buffered saline.

Authors' contributions

Conceptualization: Alim Isnansetyo, Maya Hudiyati.
Data curation: Maya Hudiyati.
Formal analysis: Maya Hudiyati.
Funding acquisition: Siti Sunarintyas.
Investigation: Maya Hudiyati.
Methodology: Maya Hudiyati, Siti Sunarintyas, Retno Ardhani, Alim Isnansetyo.
Project administration: Maya Hudiyati.
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Validation: Siti Sunarintyas, Retno Ardhani, Alim Isnansetyo.
Visualization: Maya Hudiyati.
Writing-original draft: Maya Hudiyati.
Writing-review & editing: Maya Hudiyati, Siti Sunarintyas, Retno Ardhani, Alim Isnansetyo.

Conflict of interests

There is no conflict of interest.

Ethical considerations

The authors have diligently addressed ethical considerations, including plagiarism, data fabrication, and double publication.

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