Effectiveness of Fucoidan Extract from Brown Algae to Inhibit Bacteria Causes of Oral Cavity Damage

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Effectiveness of Fucoidan Extract from Brown Algae to Inhibit Bacteria Causes of Oral Cavity Damage

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ABSTRACT
Introduction: Dental caries is a disease in the hard tissue of teeth damaged by enamel and dentin which is caused by the activity of microorganisms such as mutant Streptococcus. Periodontal disease is an inflammatory condition that affects the tissue around the teeth, one of the causes of which is microorganisms such as Porphyromonas gingivalis. Various antibacterial compounds that have been effective can be found in the extraction process, one of which is fucoidan extract in brown algae. To inhibit bacterial growth, fucoidan compounds contained in brown algae can be used.
Objective: To determine the ability of fucoidan extract from brown algae to inhibit the growth of bacteria that cause oral cavity damage.
Method: Literature review method. Literature searches are obtained from several literature study sources related to the topics to be discussed. Synthesize information from literature / journals which will be used as a reference by making a table. After that, conduct a literature review and analyze the similarities and differences of the literature.
Result/ Discussion: Fucoidan extract from brown algae has the ability to inhibit bacteria that cause oral cavity damage, namely Streptococcus mutans, Porphyromonas gingivalis and Fusobacterium. **Conclusion**: Fucoidan extract from brown algae can reduce oral pathogens and have antibacterial activity.

Keywords: Brown algae, Fucoidan, Caries, Periodontal disease, Streptococcus mutan, Porphyromonas gingivalis, Fusobacterium nucleatum.

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INTRODUCTION

Dental caries is a disease in the hard tissue of teeth characterized by the destruction of enamel and dentin caused by microorganism activity in plaque which causes demineralization due to interactions between microorganism products, saliva, and parts derived from food and enamel. Plaque that results from the activity of microorganisms can also cause periodontal disease.[1,2] Periodontal disease is an inflammatory condition that affects the tissues surrounding the teeth. Periodontal disease is divided into two, namely gingivitis and periodontitis. The main cause of periodontal disease is the presence of microorganisms that colonize the dental plaque. Plaque can cause gingivitis. Dental plaque is a structured, soft, yellow substance that adheres to the surface of the tooth. Plaque containing pathogenic microorganisms plays an important role in causing periodontal tissue infections. [3]

According to Riskesdas 2007 and 2013 the percentage of Indonesians who have oral and dental problems has increased from 23.2% to 25.9%. Riskesdas in 2013, there was an increase in the prevalence of dental caries in Indonesia, namely patients with active dental caries increased by 9.8% from 43.4% in 2007 to 53.2% in 2013. Caries sufferers increased by 5.1% from 67, 2% in 2007 increased to 72.3% in 2013.Based on the Basic Health Research (RISKESDAS) in 2007, the prevalence of periodontal disease reached 23.5% and an increase in 2018 which showed that the percentage of periodontal disease cases in Indonesia was 74, 1% (Ministry of Health, 2018). [4]

The main cause of dental caries is Streptococcus mutans which is a gram-positive bacterium with the ability to withstand acidic conditions on the tooth surface and can also produce acid. The bacteria that cause caries are also bacteria that cause periodontal disease, namely Porphyromonas gingivalis, Prevotella intermedia, Actinobacillus, actinomycetemcomitans and Fusobacterium nucleatum which are gram-negative bacteria. These gram-negative bacteria are commonly found in dental plaque, so that the periodontal tissue undergoes pathological changes by activating the host's immune and inflammatory responses and the periodontium cells are directly affected. [5,6,7]

Several studies that have been conducted by experts in the field of dentistry have shown that the antibacterials used so far have been efficient and effective. Various antibacterials that have been used and used in the form of mouthwash, gum, toothpaste and so on have different levels to inhibit the growth of bacteria that cause oral cavity damage. Mouthwash containing chlorhexidine has antibacterial properties due to its bactericidal and bacteriostatic properties. Chewing gum that is generally on the market contains xylitol with antibacterial properties. Meanwhile, toothpaste contains various substances that can inhibit the growth of caries-causing bacteria, such as fluoride. Various effective antibacterial compounds can also be obtained in the extraction process, one of which is fucoidan extract in brown algae. To inhibit bacterial growth, fucoidan compounds contained in brown algae can be used.

Brown algae such as Sargassum sp, Turbinaria sp, and Padina sp contain compounds such as alginate, laminarin, and fucoidan. Fucoidan compounds present in brown algae can be exploited by extracting them. The fucoidan compounds contained in brown algae can be extracted using acid solvents, water and calcium salts. Fucoidan is a type of sulfate polysaccharide that is soluble when extracted and shows strong biological activity. Fucoidan with antibacterial properties has a chemical structure and a varied composition which is useful for inhibiting the growth of microorganisms.

Research conducted by Chotigeat in 2004 stated that crude fucoidan extract from Sargassum polycystum showed antibacterial activity. Then, research conducted by Zhao in 2018 stated that the antibacterial activity of fucoidan has been tested and proven effective. On this basis, a review literature study was carried out with the title of the effectiveness of brown algae fucoidan extract against the inhibition of bacteria that cause oral cavity damage. [8,9,10]

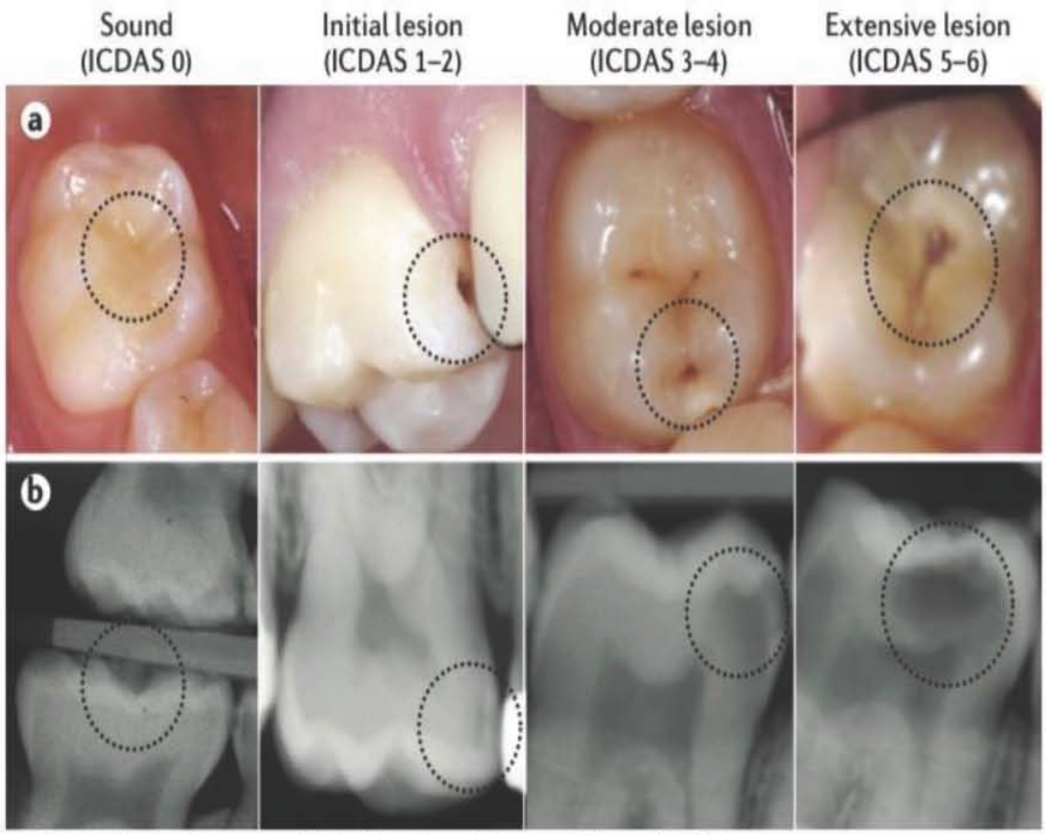
METHOD

Literature review method. Literature searches are obtained from several literature study sources related to the topics to be discussed. Synthesize information from literature / journals which will be used as a reference by making a table. After that, conduct a literature review and analyze the similarities and differences of the literature.

The journals used in the literature review come from reliable sources or databases, for example Scopus, Sciendirect, Ebsco, Pubmed, Willey Online Library, etc. The obvious source is one result from the quality of the literature research or systematic review. The selected articles must be relevant to the topics previously determined.

DISCUSSION

Caries

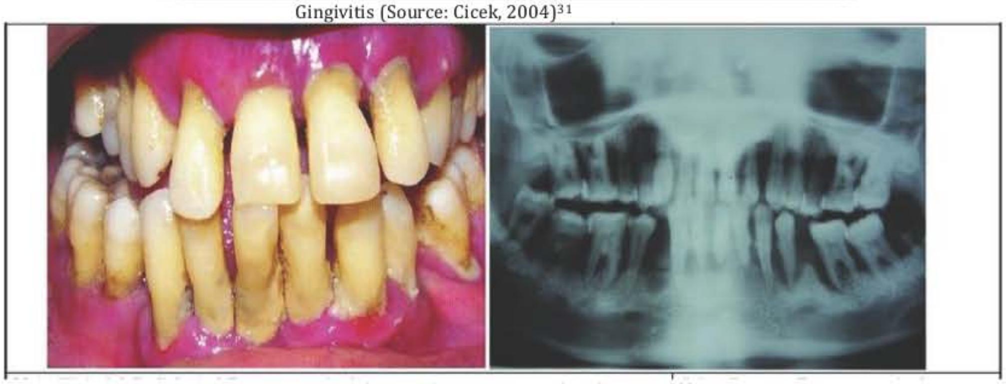


Dental Caries (Sumber: International Caries Detection and Assessment System, 2017)[30]

Dental caries is a disease found in the hard tissues of the teeth, namely enamel, dentin, and cementum, which is a chronic regressive process. Dental caries occurs due to the interaction between bacteria on the surface of the teeth, plaque or biofilm and diet, especially the carbohydrate components that can be fermented by plaque bacteria to become acidic, especially lactic and acetic acids.[11,12] Which is characterized by demineralization of tooth hard tissue and damage to organic matter due to disruption of the balance of enamel and its surroundings, causing the occurrence of bacterial invasion and irreversible of pulp and the bacterial can develop into the periapex tissue, causing pain in the teeth. [13,14]

Periodontal Disease

Gingivitis (Source: Cicek, 2004)[31]



Periodontitis (Source: Ramachandra, 2017)[32]

Periodontal disease is a chronic bacterial infection characterized by persistent inflammation, damage to connective tissue and damage to the alveolar bone. Periodontal disease includes a wide range of chronic inflammatory conditions of the gingiva (or gum, the soft tissue that surrounds the surface of teeth), the bones and ligaments that support the teeth.

The main cause of periodontal disease is the presence of microorganisms that colonize the dental plaque. The content of dental plaque is various types of microorganisms, especially the remaining bacteria are viruses, fungi and protozoa. Plaque containing pathogenic microorganisms plays an important role in causing and aggravating infection in the periodontal tissue.

Dental plaque is a bacterial biofilm that causes chronic gingivitis and chronic periodontitis. Conceptually, one can think of periodontal disease as a host-microbial interaction in which the host factor and bacteria determine the outcome, so that a change in the balance between the host factor and bacteria can result in a change from healthy to disease. The balance can be altered, with an increase in plaque biofilm or an increase in bacterial prevalence and a reduction in host resistance.[15,16]

Periodontal disease begins with gingivitis, which is local inflammation of the gingiva due to the presence of bacteria in dental plaque, which is a microbial biofilm that forms on the teeth and gingiva. In this primary stage, the term gingivitis refers to plaque-induced gingivitis. Chronic periodontitis occurs when untreated gingivitis progresses to loss of the gingival bone and ligaments, which are characteristic of the disease and can eventually lead to tooth loss. [15,16,17]

Bacteria that cause damage to the oral cavity and Periodontal

Streptococcus mutans

Streptococcus mutans is a Gram-positive, nonmotile cocci, anaerobic facultative microorganism that can metabolize carbohydrates and is considered a forming agent for dental caries. These bacteria are widespread in nature and some of them are normal flora found in the human body. In culturing Streptococcus mutans bacteria form long chains and have anaerobic metabolism, but they also live in anaerobic facultative. Streptococcus mutans bacteria on solid media are rough, pointed, and have mucoid colonies. These bacteria grow optimally at a temperature of 18 ° C-40 ° C. Gram-positive bacteria are characterized by a thick (15-80 nm) cell wall structure and single-layered. Streptococcus mutans bacteria are usually found in the cavities of injured human teeth and are the most conducive bacteria to cause dental caries. The bacterium Streptococcus mutans is acidogenic, that is, it produces acid, is acidoduric, is able to live in an acidic environment, and produces a sticky polysaccharide called dextran. [18,19]

Porphyromonas gingivalis

Porphyromonas gingivalis is anaerobic obligate gram-negative black pigmented bacteria. Gram-negative bacteria have cell wall layers that are more complex than gram-positive bacteria both structurally and chemically. Structurally, the wall of gram-negative bacteria contains two external layers on the cytoplasm. The gram-negative cell wall contains three components located on the outer layer, namely peptidoglycan, lipoprotein, outer membrane and lipopolysaccharide.

The main habit of P.gingivalis is the subgingival sulcus of the human oral cavity. It relies on amino acid fermentation for energy production and is necessary for its survival in the periodontal pocket, where sugar availability is low. As an obligate anaerobic bacteria, P.gingivalis functions as a secondary colony of dental plaque. [20]

Fusobacterium nucleatum

Fusobacterium nucleatum is a gram-negative anaerobic bacterium that has a role in the process of forming dental plaque. These bacteria appear in high numbers after 24 hours and multiply for 48 hours in dental plaque. Increasing the number of Fusobacterium nucleatum bacteria can cause gingival inflammation, increased pocket depth and periodontal tissue damage. These bacteria are often found in chronic gingivitis and chronic periodontitis because they play a role in shutting down normal proliferation of fibroblast cells in periodontal tissue. [20,21]

Brown Algae

Brown algae is a type of seaweed from the Phaeophyceae group that has various shapes but mostly brown or blonde. Thallus of the class Phaeophyceae are not unicellular, in the form of branched filaments. The length of the thallus is several millimeters to approximately 50mm. Phaeophyta has one class, namely Phaeophyceae. Phaeophyceae generally live in shallow waters. Most of the phaeophyceae are the main elements that make up the vegetation in the Arctic and Antarctic oceans, but some genera such as Dictyota, Turbinaria and Sargassum are the most typical algae for tropical oceans. [24,25]

Brown algae contains carbohydrates, protein, ash, water, vitamins and minerals in the form of macro and micro elements, namely potassium (K), sodium (Na), magnesium (Mg), phosphate (P), iodine (I) and iron (Fe). The most important components of secondary bioactive compounds such as phlorotannin, fucosterol, fucoidan, alginic acid, fucoxanthin and phycocolloid have been found in brown algae which exhibit significant biological properties including antidiabetic, anti-inflammatory, antioxidant and antibacterial activity.[26,27]

Fucoidan

Fucoidan was first isolated in 1913 from brown seaweed and given the name "fucoidin". Fucoidan is a name that fits the IUPAC nomenclature, although it can also be called fucan, fucosan or fucan sulfate. Fucoidan is included in the homo- and heteropolysaccharide sulfate family and has been studied extensively and deeply because it has various biological activities for example, anticoagulants, anti-inflammatory, anti-tumor, antiviral. [26,27]

Fucoidan is a water-soluble polysaccharide substance found in brown algae. Fucoidan is a complex heterogeneous group of polysaccharides, which function as intracellular sap. The fucoidan content can be determined by measuring the three main components, namely sugar, sulfate and uronic acid. This component makes fucoidan a potential antiviral agent. Fucoidan has been known for more than a century, however, its chemical structure has not been determined with certainty, because of its high heterogeneity. This is probably due to the ability of brown seaweed to synthesize complex polysaccharides, where the structure and proportions vary depending on the specific taxonomic position.[27]

Fucoidan has been isolated from several types of brown algae and has been shown to have antiviral active components and also has antioxidant and antibacterial activity. [28,29,30] Naturally, fucoidan is a component of the cell wall that plays a role in keeping brown algae in moist conditions and protecting it from microorganisms. It has been found that the fucoidan content is higher when seaweed grows in deep waters because it shows an important effect in protecting the seaweed. Similar to other natural substances, the high bioactivity and low toxicity of fucoidan have attracted attention from the health-related industry in search of new substances that are beneficial to health.

Fucoidan has many benefits including anti-inflammatory, anti-coagulant, anti-cancer, anti-immunoregulatory and antibacterial. The antibacterial compound fucoidan in a study conducted by Chotigeat in 2004 stated that crude fucoidan extract from Sargassum polycystum showed antibacterial activity. Then research conducted by Zhao in 2018 stated that the antibacterial activity of fucoidan had been tested and proved effective. Fucoidan can reduce oral pathogens and improve oral hygiene, inhibit oral bioflm formation with anti-adhesion activity of tooth surfaces, and prevent endotoxin-mediated systemic inflammation due to oral pathogens by neutralizing endotoxins and then releasing from oral bioflm.[28,29,30]

Fucoidan is a sulfated polysaccharide that is primarily extracted from brown seaweeds which has been broadly studied in recent years due to its numerous biological properties, including anticoagulant, antithrombotic, antitumor, and antiviral activities. The effects of fucoidan on microbiome is an emerging area of focus. Global concern regarding the increase of drug-resistant superbugs and the lack of new antibiotics for treating human and animal diseases has led to a call for new approaches. In agriculture, there is an urgent need to develop strategies to replace antibiotics for food-producing animals, especially poultry and livestock. In human health, there is increasing awareness of a connection between the microbiome and disease conditions. [38]

Fucoidans have bacteria-inhibiting qualities against the ulcer-causing *Helicobacter pylori* and modulate the growth and biofilm-forming properties of other types of bacteria. Additional antiviral activity and the anti-inflammatory nature of fucoidans make them suitable for a wide range of digestive tract applications. In particular, fucoidans can attenuate inflammation generated by lipopolysaccharides produced by Gram-negative bacteria. New research demonstrates activity against norovirus, for which there are no current treatments. Perhaps much of the biological activity ascribed to fucoidans may be due their effects on modulating microbiome and inflammation from the oral cavity and throughout the length of the gut. [38]

In another research, fucoidan was evaluated against clinic isolated methicillin-resistant Staphylococcus aureus (MRSA) 1 - 20, either alone or with antibiotics, via broth dilution method and checkerboard and time kill assay. Minimum inhibitory concentrations (MICs)/Minimum bactericidal concentrations (MBCs) values for the fucoidan against all the tested bacteria ranged between 64 - 512/256 - 2048 microg/mL, for ampicillin 32 - 1024/64 - 1024 microg/mL and for oxacillin 8 - 64/16 - 256 microg/mL respectively. Furthermore, the MIC and MBC were reduced to one half-eighth as a result of the combination of the fucoidan with antibiotics. 2 - 6 hours of treatment with 1/2 MIC of fucoidan with 1/2 MIC of antibiotics resulted from an increase of the rate of killing in units of CFU/mL to a greater degree than was observed with alone. These results suggest that fucoidan could be employed as a natural antibacterial agent against multi-drug bacteria. Fucoidan exerted synergistic effects when administered with oxacillin or ampicillin and the antimicrobial effect and resistant regulation of fucoidan against MRSA might be useful for potential application as a natural product agent. [38]

Synthesis Table:

No	Authors and Title of Journal	(Year)	Result / Conclusion
1.	Min S., *et al* Synergistic antibacterial efficacies of chlorhexidine digluconate or protamine sulfated combined with *Laminaria japonica* or *Rosmarinus officinalis* extracts against *Streptococcus mutan* Journal of Biocontrol Science	(2020)	The results obtained from the brown algae extract L.japonica combined with chlorhexidine digluconate was 62.5 µg / ml against S. mutant bacteria.
2.	anos Jonathan M., *et al* Antimicrobial properties of sargassum spp (Phaeophyceae) against selected aquaculture pathogens International Journal of Current Microbiology and Applied Sciences	(2017)	The antimicrobial activity of Sargassum oligocystum and Sargassum crassifolium using six different solvents was tested against S. mutants. The results obtained for the aqueous extract of Sargassum oligocystum were the lowest inhibition (5.33 ± 3.06 mm) against S. mutant bacteria. While moderate activity was also seen in the ethyl acetate extract and water of Sargassum crassifolium against S. mutants (6.33 ± 2.08 mm, 6.33 ± 0.58)
3.	Oka S., *et al* Properties fucoidans beneficial to oral healthcare Journal of Odontology	(2019)	The antimicrobial activity of fucoidan against oral pathogens, S. mutants and P.gingivalis which was carried out by the disc diffusion method resulted in the largest zone of inhibition (5.67 ± 0.21 mm) against S. mutants. Whereas for P.gingivalis the largest inhibition zone was obtained (5.33 ± 0.33 mm).
4.	Je H Anti-bacterial effect of marine algae against oral borne pathogens Journal of Medicinal Plant	(2014)	The antibacterial activity of the marine algae extract was evaluated by agar well diffusion test. Antibacterial extract of Sargassum micracanthum showed the strongest anti-bacterial activity with an inhibition zone of 6.0 ± 1.4 mm against S. mutant bacteria.
5.	Kyung Y., *et al* Synergistic effect of fucoidan with antibiotics against pathogenic bacteria Journal of Archives Oral Biology	(2013)	The results obtained were MIC (Minimum Inhibitory Concentration) and KBM (Minimum Bactericidal Concentration) of fucoidan against bacteria: a) P.gingivalis yielded 0.125 / 0.25 mg ml-1 b) F.nucleatum obtained 0.25 / 0.50 mg ml-1 results.

The first (first) literature study of a study conducted by Min Seok Yoo., *Et al* in 2020 regarding the synergistic antibacterial properties of chlorhexidine digluconate or protamine sulfate combined with ethanol extract of brown algae laminaria japonica or rosmarinus officinalis against mutant Streptococcus. The Minimum Inhibitory Concentration (MIC) of the brown algae extract of laminaria japonica or rosmarinus officinalis was determined using the broth dilution method. The synergistic effect is determined by the fractional inhibitor concentration index. This index shows the synergistic effect of various combinations of antibacterial agents. The results obtained from the brown algae extract L.japonica combined with chlorhexidine digluconate were 62.5 µg / ml against S. mutant bacteria. The conclusion of this study is that the ethanol extract of brown algae laminaria japonica is a moderate antibacterial concentration. [34]

Further literature studies from research by Oka Shunya., *Et al* in 2019 regarding the properties of fucoidan which are beneficial for oral health. The results of the study can be seen in Table 4.3, namely the antimicrobial activity of fucoidan against oral pathogens, S. mutants and P.gingivalis which was carried out by the disc diffusion method.The results showed the largest zone of inhibition (5.67 ± 0.21 mm) against S. mutants. Whereas for P.gingivalis the largest inhibition zone was obtained (5.33 ± 0.33 mm). The conclusion of this study is the fucoidan extract of brown algae F.vesiculosus is a high antibacterial concentration. 36

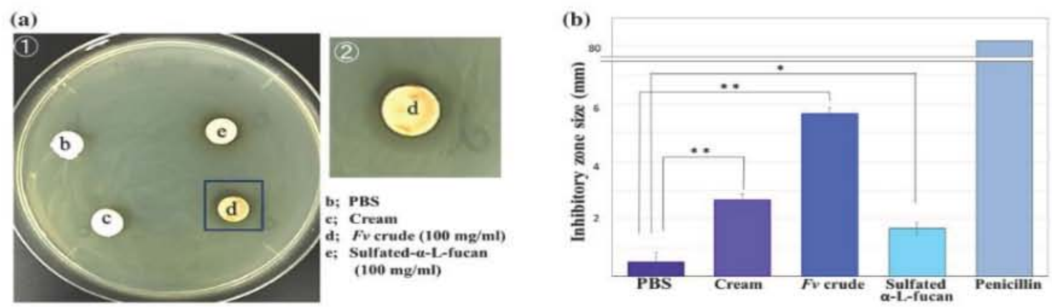


Fig. 2 Antimicrobial activities of fucoidans against *S. mutans*, assessed using the disc diffusion method. **a** Typical inhibitory zone against *S. mutans* (①), and enlarged image of the region in the blue square (②). There was a clear inhibitory zone around *Fv* crude disc (①-d, ②). For the positive control, Penicillin 10 U disc completely inhibited *S. mutans* on the plate medium, thus no inhibition circles were formed (data not shown). **b** Inhibitory zone size was calculated by subtracting 8 mm, the diameter of paper disc, from the overall diameter. $^{**}p<0.01$. $^{*}p<0.05$

(**Fig. 2**: The antimicrobial activity of fucoidan against S. mutants was tested using the disc diffusion method. A. The zone of inhibition against S. mutants can be seen in Figure 1, namely the area around the blue box. There is a clear zone of inhibition around the course Fv disc. For positive control., Penicillin U discs completely inhibited S. mutant in the petri dish, so that no inhibition loop was formed (data not shown). B. Inhibition zone size was calculated by subtracting 8mm, the diameter of the paper disc of the overall diameter.)

** p <0.01. * p <0.05

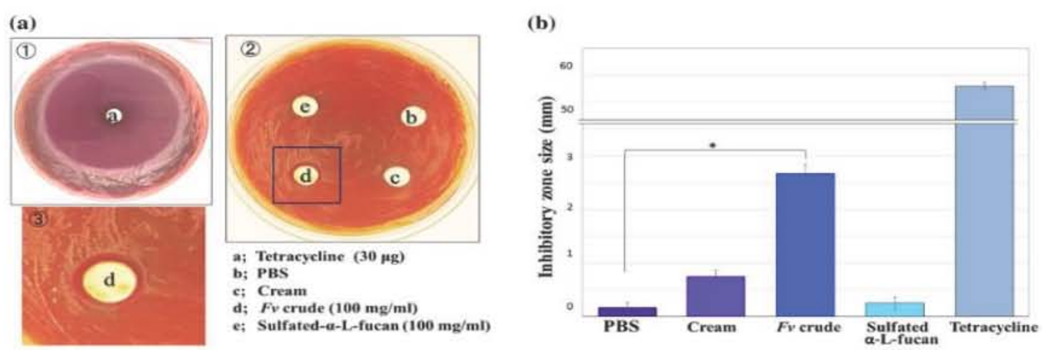


Fig. 3 Antimicrobial activities of fucoidans against *P. gingivalis*, assessed using the disc diffusion method. **a** Typical inhibitory zone against *P. gingivalis* (①, ②). Photograph "③" shows enlarged view of the region in the blue square "②". Tetracycline 30 µg discs were used as the positive control (①-a). There was a clear inhibitory zone around *Fv* crude disc (②-d, ③). **b** Inhibitory zone size was calculated by subtracting 8 mm, the diameter of paper disc, from the overall diameter. $^{**}p<0.01$. $^{*}p<0.05$

(**Fig. 3:** The antimicrobial activity of fucoidan against P.gingivalis was tested using the disc diffusion method. A. The typical zone of inhibition against P.gingivalis can be seen in Figure 2, namely the area around the blue box. 30-disc tetracycline was used as a positive control. around the rough Fv.b.The size of the drag zone is calculated by subtracting 8mm, the diameter of the paper disc from the overall diameter.)

** p <0.01. * p <0.05

Based on this, it is known that the minimum inhibitory concentration of fucoidan antimicrobial activity against oral pathogens, S. mutants and P. the zone of greatest inhibition (5.33 ± 0.33 mm). Fucoidan extract of the brown algae F.vesiculosus undergoes binding with other proteins and molecules. This is what causes fucoidan to have antibacterial activity by inhibiting microbial cell walls.[35] Research conducted by Lee Je Hyuk in 2014 on the antibacterial effect of marine algae against oral pathogens. The results obtained were the antibacterial activity of the brown algae extract Sargassum micracanthum showed the strongest anti-bacterial activity with an inhibition zone of 6.0 ± 1.4 mm against S. mutant bacteria. The conclusion of this study is that the brown algae extract of Sargassum micracanthum has moderate antibacterial concentrations [36]

Subsequent research conducted by Lee Kyung Yeol, *et al* in 2013 regarding the synergistic effect of fucoidan with antibiotics against oral pathogenic bacteria. The results obtained were that fucoidan showed the strongest antimicrobial activity against anaerobic bacteria, both fucoidans showed similar MIC / MBC values for each bacterial species, ranging from 0.25 / 0.25 to 0.50 / 1.00 mg ml 1. The conclusion of this study is the fucoidan extract of brown algae Laminaria japonica has moderate antibacterial concentration. [37]

In the new present study also have similar purpose to evaluate the antibacterial capability of fucoidan from *Sargassum wightii* against the chosen human bacterial pathogens. The major chemical constituents of the extracted fucoidan were analyzed by biochemical methods. It showed that the extracted fucoidan contains 52.86 ± 0.64% of fucose and 29.26 ± 0.83% of sulphate. The antibacterial efficacy was performed by agar well diffusion, minimum inhibitory concentration (MIC) and minimum inhibitory concentration (MBC) method. The maximum antibacterial activity 18.6 ± 0.32 mm was obtained for *Vibrio cholera* and the minimum activity 8.6 ± 0.26 mm was obtained for *Salmonella typhi*. Result of this manifested the considerable antibacterial potentiality of fucoidan against human bacterial pathogens. The study concluded that fucoidan might be used as natural and safe antibiotics in curing many bacterial diseases[39]

CONCLUSION

Based on the literature review and literature analysis studied, it can be concluded that brown algae fucoidan extract can reduce oral pathogens and have antibacterial activity. Fucoidan extract of brown algae can also inhibit mutant Streptococcus, Fusobacterium nucleatum and Porphyromonas gingivalis bacteria with different minimum inhibitory concentrations and zones of inhibition.

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