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Investigating the effect of seaweed bioactive compounds on gut microbiota composition and dysbiosis: a systematic review.

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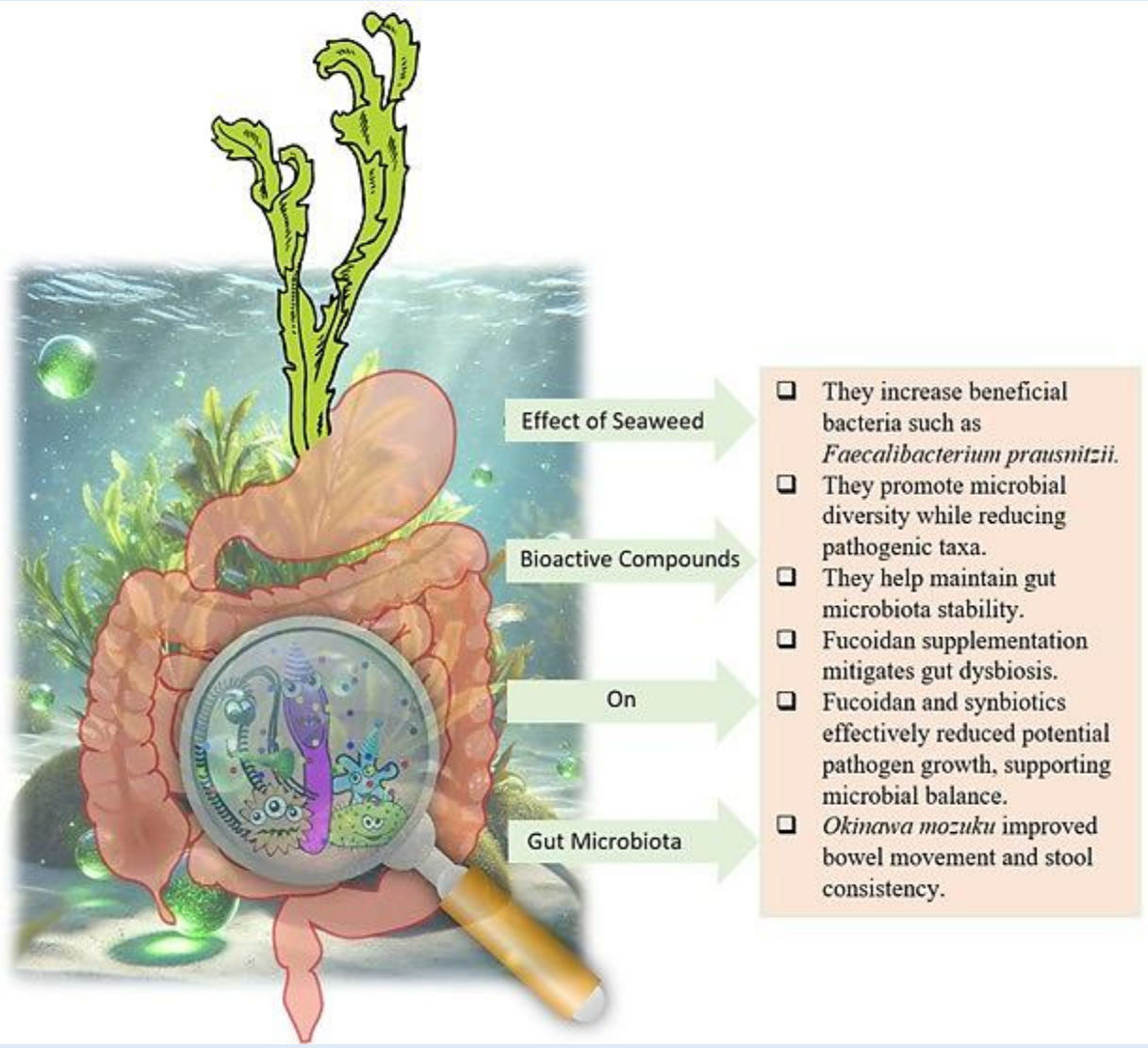
ABSTRACT

The gut microbiota is a complex ecosystem that maintains a symbiotic relationship with the host metabolism, immune development, and intestinal balance. Diet and environmental factors influence the gut microbiota composition, as a disruption in microbiota due to a range of possible diseases may result in dysbiosis. Bioactive compounds, including polysaccharides, polyphenols, and fucoidan, affect gut microbial composition and help balance microflora. Seaweed varieties contain diverse bioactive components with antioxidant, anti-inflammatory, immunomodulatory, and anticancer properties, which makes them valuable for human health. Despite their benefits, their impact on the gut microbiome remains unclear. This research systematically reviewed literature from Google Scholar and Web of Science (2014-2024) to assess seaweed's bioactive compounds' effect on the gut microbiome.

This research yielded seven relevant studies. The studies investigated the effect of fucoidan on *Helicobacter pylori* eradication, gut microbiota, and macrophages. Okinawa mozuku (*Cladosiphon okamuranus)* was used to evaluate bowel movements, the effect of seaweed polysaccharide on fecal weight and microbial imbalance, and the stability of seaweed phlorotannin in the GIT. The data indicate that seaweed components may increase beneficial bacteria such as *Faecalibacterium prausnitzii* to promote microbial diversity, while reducing pathogenic taxa. Fucoidan was beneficial in mitigating the adverse effects of antibiotic-induced dysbiosis during *Helicobacter pylori* eradication therapy, while Okinawa mozuku improved bowel movement and stool consistency. *Fucus vesiculosus* phlorotannin has also been linked

to antioxidant activity. These findings highlight that bioactive seaweed components are potential therapeutic agents for enhancing and sustaining beneficial bacteria in the microbiome. This research supports the application of seaweed compounds in dietary and clinical interventions for gut health.

Keywords: Seaweed; Bioactive compounds; Gut microbiota; Dysbiosis; Fucoidan.



INTRODUCTION

The gut microbiota is a complex and dynamic ecosystem comprising about 100 trillion microorganisms [1-3]. It maintains a symbiotic relationship with its host, benefiting host metabolism, intestinal balance, and immune system development [4-5]. External factors, such as the environment, diet, medications, exercise, and hygiene practices, can influence gut microbiota composition [6]. Dysbiosis may occur when these factors disrupt microbiota beyond its natural capacity for

stability and recovery. This condition alters the balance of microbiota within the gut. Dysbiosis is linked to a growing range of diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), celiac disease, and colorectal cancer (CRC) [7]. Research indicates that microbial imbalance in the gut may weaken the intestinal mucosal barrier and compromise the immune system within the gut, potentially leading to serious gastrointestinal issues [8-10]. Additionally, gut dysbiosis may contribute to conditions beyond the intestines, such as diabetes and obesity, highlighting its role in various systemic diseases [11-14]. Constipation is a common digestive issue, often occurring from inadequate fiber intake. Reduced intestinal peristalsis can lead to irregular bowel movements, while prolonged intestinal stool retention can encourage an overgrowth of putrefactive bacteria. This will eventually diminish beneficial Lactobacillus populations. However, plant- and animal-derived polysaccharides are antioxidants and can support gut health [15,16]. Increasing dietary fiber intake is essential to boost Lactobacillus or Bifidobacteria levels in the gut, which may reduce the production of harmful gases from putrefactive bacteria [17]. Studies have concluded that seaweed polysaccharides could benefit gastrointestinal health and enhance antioxidant capacity [18]. Additional research suggests that compounds such as polyphenols and polyunsaturated fatty acids may positively influence gut microbiota through their selective prebiotic effects and antimicrobial actions against pathogenic bacteria [19-20]. Polyphenol intake has been associated with promoting probiotic bacteria and boosting short-chain fatty acid (SCFA) production, both of which support gut health [21-23]. Therefore, maintaining a balanced gut microbiome is essential for overall health [24-25].

Bioactive compounds such as flavonoids, polyphenols, carotenoids, polysaccharides, fucoidan, anthocyanins, tannins, and alkaloids are phytochemicals found in various plant components and contribute functional benefits essential for health maintenance. Fruits and vegetables are rich sources of these compounds [26]. Through fermentation, microorganisms aid in releasing phytochemicals from foods, enhancing their bioavailability and effectiveness [27]. The gut microbiome is instrumental in modulating these compounds' production, bioavailability, and bioactivity since the gastrointestinal tract has a vast microbial population to facilitate their extraction and metabolic functions [28]. Research indicates a bidirectional relationship between bioactive compounds and the gut microbiome [19]. Colonic microorganisms can transform bioactive compounds into metabolites such as short-chain fatty acids (SCFAs) and bile acids. These products can influence intestinal health and overall host well-being [29,30]. Additionally, bioactive compounds have been shown to affect the gut microbial composition through selective prebiotic actions or with their antimicrobial properties that help balance microflora [19, 31-34].

Seaweed varieties are rich in essential nutrients and bioactive components such as polysaccharides, polyphenols, minerals, vitamins, and polyunsaturated fatty acids, which makes them valuable to human health [35-37]. An increased consumption of seaweed may reduce risk factors associated with non-communicable diseases such as obesity, type 2 diabetes, cardiovascular disease, and cancer [38-42]. Seaweed is high in fiber, as this component makes up to 75% of its dry mass [38]. Seaweed also contains hydrocolloid fibers that exhibit gel-forming and emulsifying qualities, contributing to their health benefits [38]. However, the large molecular structure of these fibers may limit their digestibility and fermentability by gut microbiota [43]. In Asian diets, seaweeds are commonly consumed, whereas in Western countries, they are primarily valued for isolating nutraceutical and therapeutic compounds [44-45]. Seaweeds contain diverse bioactive components, which can vary significantly across different species [46-48].

Fucoidan, a key marine polysaccharide found in the surface mucus and sporophyll of *Undaria pinnatifida*, is rich in fucose sulfate, whose bioactivity depends on the specific placement and amount of sulfate groups present [49-50]. Since fucoidan is not absorbed in the upper digestive tract, it influences gut microbiota in the distal colon [51-52]. Research suggests that fucoidan supplementation may boost gut microbiota diversity through modifying its composition [53]. Fucoidans are known for their broad bioactivity, including antioxidant, anti-inflammatory, immunomodulatory, and anticancer effects [45,54-55]. Studies on animals and cell cultures indicate that fucoidan can prevent *Helicobacter pylori* (H. pylori) adhesion, support gut microbiota health, and reduce mucosal damage [56]. Additionally, fucoidan derived from Okinawa mozuku has shown a beneficial effect in relieving constipation [57,58]. Flavonoids extracted from green seaweed have been shown to raise the Firmicutes-to-Bacteroidetes ratio, lowering blood glucose levels and enhancing insulin sensitivity [19]. Polyphenols from *Enteromorpha prolifera* increase beneficial bacteria such as *Akkermansia* and *Alistipes*, while reducing *Turicibacter* levels [59]. This evidence highlights seaweed's potential to modulate gut microbiota through its bioactive compounds. However, despite these beneficial findings, few studies have explored seaweed's effect on the gut microbiome.

Purpose of the Study: This study aims to investigate the effect of seaweed's bioactive compounds on the gut microbiota.

METHOD

Literature Search: This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [60].

The PICOS (Population, Intervention, Comparator, Outcomes, Study design) criteria were employed to determine the eligibility of studies (Table 1).

Table 1. PICOS criteria for inclusion and exclusion of studies

Parameters	Definition
Population	Adults
Intervention	Seaweeds
Comparator	Non-Seaweed products
Outcome	Any health outcome that influences microbiome health, such as increased beneficial bacteria composition and diversity, gut microbial balance, and mitigation of gut dysbiosis.
Study Design	Original research studies of any interventional or observational design were considered eligible for inclusion. Excluded were narrative reviews, conference or dissertation abstracts, and informational pieces. Only studies published in English between 2014 and 2024 were included.

Search Strategy: A comprehensive search was conducted in the Google Scholar and Web of Science databases for English-language studies indexed between 2014 and 2024. Search terms included "bioactives microbiota," "effect of seaweed bioactive compounds on the microbiome," "bioactives in seaweed," "bioactives seaweed microbiome," and "seaweed." The review included interventional and observational studies examining the effects of seaweed's bioactive compounds on gut microbiota. Observations such as enhanced gut health, improved microbial balance, reduced dysbiosis, and increased beneficial bacteria composition and diversity were noted. Studies were not limited by geographic region. Narrative reviews, conference abstracts, and dissertations were excluded from the study.

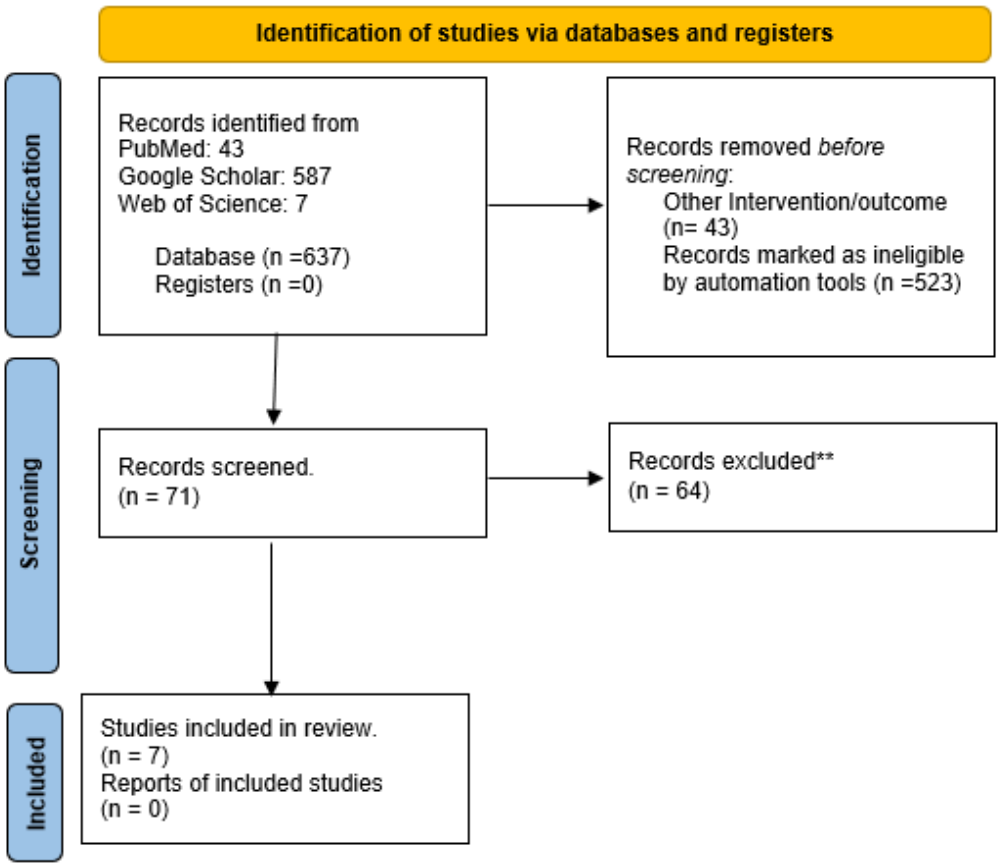


Figure 1. PRISMA Flow diagram

Research Design: This systematic review comprised five randomized controlled trials, one in vitro study, and one simulation study. In each study, subjects were assigned to either an experimental or a control group. The experimental group received a specified amount of seaweed and/or extract over a set timeframe. In contrast, the control group had an alternative diet that did not include seaweed.

Human Participants: The sample size, age, gender, and ethnicity of each study participant varied (see Table 2).

Data Collection: All studies collected their data, meaning this is a primary source of information.

Data Extraction: Key aspects of study design, analytical methods, interventions, outcomes, and primary results were systematically and independently extracted. Titles and abstracts from previous studies were identified through the search strategy explained. Full texts of potentially eligible studies were retrieved for independent assessment. Data from each study were extracted using a standardized form to evaluate study quality and synthesize evidence. Collected information included study design, location, sample size, duration, participant characteristics (such as age, gender, and ethnicity), details of the intervention and comparator, and reported outcomes.

RESULTS

A total of 637 citations were initially retrieved, with 630 excluded due to a lack of seaweed intervention evaluation, absence of an accurate bioactive compound effect measurement, or unrelated health outcomes (see Figure 1). Seven papers proceeded to a full-text review, comprising five randomized controlled trials, one in vitro study, and one simulation study, which are included in this systematic review. Study characteristics and quality ratings are summarized in Table 2.

Table 2. Summary of Findings: Effect of Seaweed's Bioactive Compounds on Human Microbiome

Citation Quality Rating Location	Study Design Duration Intervention	Sample Size Age Gender	Efficacy Study Summary	Health Outcomes
1. Wang et al. [56] Positive China	RCT 12 weeks Fucoidan/Control group	N= 90 Attrition= 0% 18-70yrs Mixed (M= 34; F= 56)	"Examined fucoidan-assisted quadruple therapy for *H. pylori* eradication and gut microbiota improvement".	Beneficial bacteria increased in the FS group ($P < 0.05$). No significant differences in *H. pylori* eradication rate ($P > 0.05$).
2. Stefaniak–Vidarsson et al. [61] Neutral UK	In vitro 24-72h incubation Seaweed/ Control	N=5 concentrations Attrition= N/A N/A N/A	Assessed the effects of Laminaria fucoidan obtained from Laminaria digitata and Laminaria hyperborea on THP–1 macrophage.	No changes in cell viability at low concentrations (0.1-10 µg/ml), but decreased viability at high levels (100 µg/ml). Low-dose fucoidan showed macrophage bioactivity.
3. Matayoshi et al. [62] Positive Japan	RCT 8 weeks Seaweed/Placebo	N= 30 Attrition= 0% 34-56yrs Mixed (M= 22; F= 8)	Evaluated the effects of dried Okinawa mozuku on bowel movement.	Significantly increased stool volume in the treated group (p = 0.0964) Promoted bowel health and regularity.
4. Bannon et al. [63] Positive Ireland	RCT 24 weeks Seaweed /Placebo	N=60 Attrition= not reported 27-45 yrs Mixed (M= 30; F= 30)	"Investigated the effect of alginate and agar LWMPs on gut health markers".	Finding increased *Faecalibacterium prausnitzii* levels in stool samples in the agar LMWP group. Boosted beneficial gut bacteria
5 Mu et al. [64] Positive China	RCT 29 days Seaweed /Cr-induced/Control	N=60 Attrition= N/A 28 days (Mice) Mixed (M= 30; F= 30)	"Explored seaweed's protective effect against chromium-induced gut microbial imbalance"	Significantly improved gut microbiota composition. Maintained gut microbial balance.
6 Wang et al. [65] Positive China	RCT 6 weeks Fucoidan/Control groups	N= 80 Attrition= 0% 27-52yrs Mixed (M= 34; F= 46)	"Assessed fucoidan's effect on gut microbiota during quadruple therapy".	Fucoidan helped mitigate the therapy's harmful effects on microbiota. Reduced microbiota disruption during therapy.
7 Catarino et al. [66] Neutral Not reported	RCT (Simulation) N/A Algal powder	N=30g powder Attrition= N/A N/A	"Evaluated the stability and bioaccessibility of F. vesiculosus phlorotannin-rich extracts in the gastrointestinal tract".	Low bioaccessibility for undigested portions. Linked phlorotannin to antioxidant activity.

REVIEW OF THE LITERATURE

Effect of Seaweed-Derived Bioactive Components on the Gut Microbiota Composition During *H. Pylori* Eradication Therapy: Wang et al. [56] investigated the effectiveness and safety of using fucoidan-enhanced standard quadruple therapy (SQT) to eradicate *Helicobacter pylori* (H. pylori) and improve gut dysbiosis. Fucoidan was sourced from *Undaria pinnatifida*, encapsulated, and administered. Ninety patients with *H. pylori* were randomly assigned to three groups of 30: the SQT-only group (SQ), the SQT with fucoidan group (SF), and the fucoidan-first then SQT group (FS). The SQ group received 14 days of SQT with lansoprazole (30 mg), amoxicillin (1000 mg), clarithromycin (500 mg), and potassium bismuth citrate (600 mg) twice daily. The SF group received the same SQT with added fucoidan (1000 mg twice daily) for 14 days, followed by fucoidan alone (1000 mg twice daily) for an additional four weeks. In the FS group, fucoidan was administered alone for six weeks, with a 13C/14C-UBT test following this intervention to determine if *H. pylori* was eradicated. If not, the 14-day SQT was given. Patients who tested negative for *H. pylori* were followed up for further evaluation. Post-treatment analyses of α-diversity indices in intestinal microbiota showed no significant changes in the SQ group four weeks after completing a two-week course of standard quadruple therapy (SQT) ($P > 0.05$). Similarly, comparisons of β-diversity and the relative abundance of specific Operational Taxonomic Units (OTUs) before and after treatment showed no substantial changes across all three study groups (SQ, SF, and FS). However, at the genus level, the SF group exhibited an increased presence of beneficial bacteria and a reduction in conditional pathogens following fucoidan-assisted SQT. Notably, in the FS group, the abundance of beneficial bacteria gradually rose from baseline to week six. This increase or stabilization continued until week twelve, while pathogen levels progressively decreased ($P < 0.05$). Specific beneficial bacteria, such as *Ruminococcus*, *Lachnobacterium*, *Anaerostipes*, and *Eubacterium*, were more abundant in the FS group than in the SQ and SF groups post-treatment ($P < 0.05$). Interestingly, although *Bifidobacterium* levels showed a declining trend in the SQ group ($P > 0.05$), they remained stable in the SF group and increased in the FS group ($P < 0.05$). This suggests that while fucoidan supplementation does not promote the eradication rate of *H. pylori* among the groups ($P > 0.05$), it may enhance microbial diversity and foster a favorable gut microbiota composition, particularly within the FS group.

Wang et al. [65] evaluated the effects of fucoidan supplementation on *H. pylori* eradication rates and gut microbiota stability in infected patients. Participants were randomized into four treatment groups: (1) the QT group received bismuth quadruple therapy, consisting of bismuth potassium citrate (220 mg), rabeprazole (10 mg), amoxicillin (1000 mg), and minocycline (100 mg), all administered twice daily for two weeks; (2) the QF group received the same quadruple therapy with an additional 1 g of fucoidan daily for six weeks, with fucoidan continuing four weeks beyond therapy completion; (3) the QS group received quadruple therapy plus a daily symbiotic packet for six weeks; and (4) the QFS group combined the quadruple therapy with both 1 g fucoidan and a symbiotic packet daily for six weeks. Fucoidan was derived from *Laminaria japonica*, and the symbiotic contained *Bifidobacterium* and *Lactobacillus* strains, with prebiotics including resistant dextrin (0.5 g), fructooligosaccharides (0.3 g), and inulin (1.0 g). The eradication rates across the QT, QS, QF, and QFS groups were 95%, 90%, 100%, and 95%, respectively, showing no statistically significant differences. When completed, a β-diversity analysis showed a notable shift in the microbiota composition in the QT group from baseline to

week six. This highlights fucoidan's potential to preserve microbial balance during eradication therapy. No significant differences in β-diversity were detected before and after intervention for the QS, QF, and QFS groups. By week six, the β-diversity in both the QS and QFS groups showed some divergence from the QT group. However, these differences were not statistically significant. The relative abundance of the primary bacterial phyla—Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria remained stable from baseline to week six across all groups. In the QF group, notable changes at the genus level were observed. Four genera from the *Ruminococcaceae* family and three from the *Lachnospiraceae* family significantly decreased by week six in both the QT and QF groups. Additionally, *Escherichia-Shigella* levels increased dramatically in the QF group. Unique to the QF group, genera such as *Parabacteroides*, *Akkermansia*, *Blautia*, and *Erysipelatoclostridium* experienced a significant rise by week six, unlike the QT group. Furthermore, *Escherichia-Shigella* significantly increased in the QS group, while this increase was not observed in the QFS group. This discrepancy highlights the combined effects of fucoidan and symbiotics on specific microbial populations. In the QFS group, there was a significant increase in the *Pseudomonadaceae* family and *Pseudomonas* genus at week six, while these decreased significantly in the QS group. The genus *Butyricicoccus*, within the *Ruminococcaceae* family, along with *Ochrobactrum* from the *Rhizobiaceae* family, were significantly more abundant in the QF group by week six, with *Butyricicoccus* levels particularly high in this group. Additionally, the QFS group showed significant increases in the relative abundances of *Ochrobactrum* and *Megamonas*. Statistically, *Ochrobactrum* was more abundant in the QFS group, and *Butyricicoccus* levels were significantly higher in QFS than in the QT group. These findings suggest that both fucoidan and synbiotics contribute to the modulation of specific gut bacterial genera in distinct ways.

Effects of Seaweed Bioactive Components on Bowel Health and Gut Microbiota Composition: Matayoshi et al. [62] conducted a randomized, double-blind, parallel-group study to evaluate the effects of dried Okinawa mozuku on bowel movement in healthy adults with infrequent bowel movements (2–4 times per week). The study included 30 participants divided equally into an Okinawa mozuku group and a placebo group. Each participant consumed daily capsules containing either 2.4 g of Okinawa mozuku (providing 1.0 g of fucoidan) or a starch-based placebo. Both groups exhibited a significant increase in daily bowel movements post-treatment compared to their baselines. However, differences between groups were not initially observed. After eight weeks, the Okinawa mozuku group tended toward a higher frequency of bowel movements than the placebo group ($p = 0.0964$), as their average daily stool volume was significantly greater. Additionally, stool consistency in the Okinawa mozuku group had softened considerably compared to baseline, although this change was not statistically distinct from the placebo group. These findings suggest that Okinawa mozuku may promote improved bowel regularity and stool consistency.

Bannon et al. [63] investigated the effects of seaweed-derived low-molecular-weight polysaccharides (LMWPs), specifically alginate and agar, on fecal weight and gut microbiota composition. In the initial phase, participants were randomly assigned to one of three treatment groups: control (maltodextrin), agar, or alginate. During each treatment phase, participants consumed a 250 mL drink containing 8 g of either low-molecular-weight agar or alginate daily, for four weeks

alongside their regular diet. The control phase included a similar drink with 8 g of maltodextrin, also taken daily for four weeks. Each treatment phase was followed by a four-week washout period without dietary intervention. Results showed significant increases in fecal weight for both the agar ($p = 0.002$) and alginate ($p = 0.02$) treatments compared to the control. These groups experienced increases of approximately 30% and 20%, respectively. These findings suggest a substantial fecal bulking effect from the alginate and agar-based treatments, highlighting their potential as dietary fibers to support gastrointestinal health. Consumption of an agar-based drink in this study led to a small yet statistically significant reduction in fecal pH. Propionic and butyric acid levels rose significantly across all treatment groups. Specifically, propionic acid increased from baseline levels of 0.84 to 1.3 mmoles/L for maltodextrin ($p = 0.006$), 0.86 to 1.18 mmoles/L for agar ($p = 0.001$), and 0.96 to 1.29 mmoles/L for alginate ($p = 0.003$). Notably, agar treatment resulted in a significant rise in *Faecalibacterium prausnitzii* abundance ($p = 0.04$). Alginate showed a similar, though non-significant, increase as the agar treatment. Clostridium histolyticum displayed a non-significant reduction ($p = 0.08$) across treatments compared to baseline for other microbial changes. Alginate consumption led to a significant decrease in lactobacilli numbers ($p = 0.05$). In the maltodextrin group, *Clostridium histolyticum* levels significantly declined ($p = 0.03$), while bifidobacterial counts showed a non-significant increase ($p = 0.1$). No additional bacterial taxa exhibited notable changes post-treatment in any group, indicating selective modulation of the gut microbiota by alginate and agar-based interventions. Differences in microbial communities among participants were more pronounced than any specific changes the three dietary interventions tested. While shifts in fecal microbiota composition occurred, there were no significant differences in Chao1 or Shannon diversity indices between treatment groups. The authors concluded that the substantial increase in fecal weight following the consumption of alginate- and agar-enriched drinks highlights their potential as a functional food ingredient, supporting gastrointestinal health.

Effect of Seaweed Bioactive Compounds on Immune Modulation and Gut Microbial Stability: Mu et al. [64] examined the protective effects of seaweed polysaccharides on gut microbial disturbances induced by hexavalent chromium exposure. Their study also assessed changes in microbial diversity by analyzing the abundance of Operational Taxonomic Units (OTUs) within each sample. Results showed a marked decrease in gut diversity indices in the chromium-exposed group, with ACE (170.75 ± 15.79 vs. 87.00 ± 9.55, $p = 0.00029$), Chao1 (170.75 ± 15.79 vs. 87.00 ± 9.55, $p = 0.00029$), Simpson (0.88 ± 0.060 vs. 0.63 ± 0.15, $p = 0.035$), and Shannon (4.64 ± 0.68 vs. 2.64 ± 0.64, $p = 0.0055$) indices all significantly lower compared to controls. These findings indicate that hexavalent chromium substantially reduced the diversity and abundance of gut microbiota. The administration of seaweed polysaccharides effectively restored these diversity indices, suggesting a protective role in mitigating chromium-induced microbial imbalances in the gut.

The THP-1 macrophage cell model is a widely utilized *in vitro* approach for studying the bioactivity of compounds derived from food sources [67]. Stefaniak–Vidarsson et al. [61] used this model to assess fucoidan bioactivity extracted from *Laminaria digitata* and *Laminaria hyperborea* on human THP-1 macrophages. In their study, THP-1 monocytes were differentiated into macrophages and treated with various concentrations of fucoidan (0, 0.1, 1, 10, and 100 µg/mL), followed by a 24-hour incubation. Polyphenol content was measured for each concentration, with experiments conducted three

times each, to ensure accuracy. No morphological changes were noted in macrophages treated with fucoidan at lower concentrations (0.1–10 µg/mL). However, at the highest concentration of 100 µg/mL, there was a noticeable decrease in cell count and alterations in cell membrane integrity. This change indicates a potential cytotoxic effect when high fucoidan levels are present. The total polyphenol content (TPC) in this fucoidan extract was measured at 27±11 mg GAE/100 g. Even at the lowest concentration (0.1 µg/mL), fucoidan significantly increased TNF–α secretion by macrophages to 658±58 pg/mL compared to the control level of 156±22 pg/mL ($p \leq 0.05$). Higher concentrations of fucoidan led to further TNF–α increases, reaching 551±98 pg/mL, 893±24 pg/mL, and 1895±55 pg/mL for 1, 10, and 100 µg/mL, respectively ($p < 0.001$). TNF–α is essential in immune defense, modulating inflammation by promoting phagocyte migration into tissues [107]. In addition to TNF–α, fucoidan triggered IL–6 secretion at higher concentrations.

While no significant IL–6 increase occurred at 0.1 and 1 µg/mL ($p > 0.1$), substantial increases were noted at 10 and 100 µg/mL, with levels reaching 237±7 and 819±14 pg/mL, respectively, compared to the control at 5.5±1.4 pg/mL ($p < 0.001$). This data highlights fucoidan's concentration-dependent immunomodulatory effects on macrophages, enhancing inflammatory cytokine responses, particularly at higher concentrations. In response to stimulation by TNF-α and IL-6, low levels of the anti-inflammatory cytokine IL-10 were detected in Laminaria fucoidan-treated THP-1 macrophages at concentrations of 0.1 and 1 µg/mL, with levels of 75±4 pg/mL and 69±15 pg/mL, respectively. These values were not significantly different from the control group's 5.4±1.9 pg/mL ($p > 0.1$). However, IL-10 secretion rose significantly ($p < 0.001$) to 378±10 pg/mL at a 10 µg/mL concentration and reached 1900±73 pg/mL at 100 µg/mL. This cytokine secretion pattern highlights the immunostimulatory effects of Laminaria fucoidan on THP-1 macrophages, indicating its bioactive potential. The observed modulation between pro-inflammatory cytokines (TNF-α and IL-6) and the anti-inflammatory cytokine (IL-10) emphasizes the bioactivity of Laminaria fucoidan when influencing immune responses.

Catarino et al. [66] investigated the stability and bioaccessibility of phlorotannin-rich extracts from *Fucus vesiculosus* in the gastrointestinal (GIT) tract and their short-chain fatty acid production potential. To simulate GIT conditions, dried algal powder (30 g) was dissolved in a 70% acetone solution and incubated for 3 hours. Both the crude extract (CRD) and an ethyl acetate fraction (EtOAc) were subjected to simulated GIT digestion, with assessments of total phlorotannin content (TPhC) and antioxidant activity after each compartmental stage. The EtOAc fraction's phlorotannin content decreased progressively through the GIT simulation, while the CRD displayed slightly higher TPhC levels due to its greater stability. During digestion, an initial increase in phlorotannin concentration was observed post-stomach digestion. This concentration decreases when in the intestine. The data indicate that EtOAc phlorotannins are more susceptible to degradation across the GIT than those in CRD, highlighting the influence that extraction methods have on the bioavailability and stability of seaweed-derived bioactive products. After simulated gastrointestinal (GIT) digestion, only a small fraction of the initially loaded phlorotannins from *Fucus vesiculosus* were bioaccessible. The undigested crude extract (CRD) showed a lower total phlorotannin content (TPhC) than the undigested ethyl acetate fraction (EtOAc), with bioaccessibility indices of 14.1% for CRD and 2.0% for EtOAc. The lower bioaccessibility of EtOAc resulted from a faster phlorotannin degradation, which reduced the amount of TPhC available for intestinal absorption.

Antioxidant activity assays showed a strong negative correlation between TPhC and antioxidant measures, linking phlorotannin content at each digestion stage with antioxidant capacity. The crude and ethyl acetate fractions of *F. vesiculosus* positively influenced gut microbiota growth, similar to the prebiotic effects of fructooligosaccharides (FOS). However, FOS did show transient effects when altered from 24 to 48 hours. Additionally, both fractions increased propionate production, as EtOAc enhanced butyrate levels. These products are beneficial short-chain fatty acids with health-promoting effects.

DISCUSSION

This review compiled evidence on the effect of seaweed bioactive compounds on gut microbiota. Four studies focused on individuals with gut microbial imbalances, while others were conducted in vitro, on a mouse model, and through simulation [61,64, 66]. The studies were geographically diverse, with populations from China, the UK, Japan, and Ireland. Fucoidan has been shown to have a beneficial effect on enhancing gut bacteria while reducing harmful taxa. This was observed through mice treated with ciprofloxacin-metronidazole, which suggests its potential to counteract antibiotic-induced dysbiosis. Antibiotic-induced dysbiosis is frequent in *H. pylori* eradication therapy [68]. These findings align with the study by Wang et al. [56]. They are supported by earlier work from Liu et al. [69], which proves that fucoidan can increase microbial diversity and positively influence gut microbiota composition. Adding fucoidan to standard quadruple therapy (SQT) demonstrated effective *H. pylori* eradication and better alleviation of clinical symptoms than SQT alone. This effect may stem from fucoidan's role in modulating inflammation, enhancing microbiota composition, and lowering *H. pylori* load. However, eradication rates did not significantly differ between groups, which may be attributed to treatment duration, sample size, fucoidan dosage, or potential interactions between fucoidan and antibiotics. *H. pylori* eradication was achieved in four patients treated with fucoidan alone, with follow-up tests to confirm the absence of infection. This potentially indicates fucoidan's role in hindering *H. pylori* adherence to the gastric epithelium. Despite these promising outcomes, the sample size did not yield statistically significant differences. Changes in gut microbiota composition following treatment suggest that eradication therapy may help alleviate both local and systemic inflammation, contributing to symptom relief. A*ecalibacterium*, *Roseburia*, *Ruminococcus*, *Clostridium*, *Blautia*, *Dorea*, *Eubacterium*, and *Lachnobacterium* are symbiotic bacteria known for producing short-chain fatty acids (SCFAs), particularly butyric acid, which is essential for maintaining gut health. Gut health is maintained through effects on colon motility, immune regulation, and anti-inflammatory activity [70]. These SCFA-producing bacteria contribute to the stability and resilience of the gut microbiota [71].

In the current study, *Bifidobacterium* levels decreased in the SQ group, remained stable in the SF group, and increased in the FS group. These findings align with Min et al. [72], who also observed a positive influence on *Bifidobacterium* levels in similar interventions. Additionally, in Wang et al. [65], α-diversity was reduced in the QF group compared to the QT group. However, no significant β-diversity changes were observed in QF, which suggests that fucoidan may impact gut microbial composition without major shifts in overall diversity. Supplementation with fucoidan and/or symbiotics supported *Butyricicoccus* growth, significantly increasing all QF, QS, and QFS groups. This reinforces its beneficial effect on gut health. The combined fucoidan-synbiotics treatment (QFS) inhibited *Escherichia-Shigella* growth, as proven through its absence in the QFS group

and presence in the QT, QF, and QS groups. This finding suggests a potential protective role against pathogenic taxa when fucoidan and synbiotics are used simultaneously. Research has identified that specific genera, including *Subdoligranulum*, *Coprococcus*, and *Butyricicoccus*, can produce butyrate, a key short-chain fatty acid beneficial for gut health [73-75]. The reduction in gut microbiota diversity observed following the bismuth-based quadruple therapy was partially restored by adding fucoidan [65]. After the intervention, the QF group showed a significant increase in beneficial genera, indicating fucoidan's potential to mitigate the dysbiotic effects of this treatment on SCFA-producing taxa. Synbiotics, which combine probiotics and prebiotics, help maintain gut microbial stability, potentially countering some negative impacts of bismuth quadruple therapy.

While neither fucoidan nor synbiotics alone prevented the rise in Escherichia-Shigella abundance, their combined use significantly inhibited this pathogen, decreasing Klebsiella levels. This suggests that the combined effects of fucoidan and synbiotics offer a more robust protection against pathogenic bacteria. This data supports their combined use as a strategy to promote a balanced gut microbiota during antibiotic therapy. Fucoidan supplementation alongside standard quadruple therapy (SQT) for *H. pylori* eradication appears to enhance treatment efficacy compared to SQT alone, with pre-treatment fucoidan administration promoting more favorable conditions for gut microbial diversity than its current use. Fucoidan derived from *Laminaria japonica* has a good effect on the preservation of gut microbiota α-diversity, suggesting its role in maintaining microbial health during therapy. Additionally, *Laminaria* fucoidan is active in immune modulation, particularly affecting THP-1 macrophages. Stefaniak–Vidarsson et al. [61] observed changes in cytokine production, with a balance between pro-inflammatory cytokines (TNF–α and IL–6) and anti-inflammatory IL-10 levels, which affirms the immunomodulatory activity of *Laminaria* fucoidan extracts. This dual nature enhances gut microbial stability while modulating immune response, which may support its potential as a beneficial adjunct in *H. pylori* eradication protocols.

Okinawa mozuku offers multiple health benefits, including anticoagulant properties, anti-HIV activity, enhanced intestinal motility, improved gastrointestinal function, and reduced LDL cholesterol, which are all likely due to its high-molecular-weight polysaccharides [58,76-79]. Studies have found that fucoidan extracted from Okinawa mozuku, administered at 810 mg/day over four weeks, may alleviate gastrointestinal symptoms by promoting intestinal motility [58]. Matayoshi et al. [62] reported that Okinawa mozuku directly improved intestinal function, highlighting fucoidan's role in supporting bowel regulation. Additionally, Iraha et al. [80] concluded that fucoidan strengthened the intestinal epithelial barrier by upregulating claudin-1, a protein critical to gut integrity. These findings suggest that fucoidan may be a viable therapeutic option for managing inflammatory bowel diseases due to its capacity to improve gut motility, support barrier function, and enhance gastrointestinal health.

Bannon et al. [63] found that low-molecular-weight polysaccharides (LWMPs) derived from agar and alginate led to increased stool weight, which may be due to increased water retention [81]. This finding aligns with De Vries et al. [106], who observed that dietary fiber increased stool bulk, an essential factor in maintaining healthy gut function and potentially reducing the risk of colon cancer [82-84]. The increased stool bulk associated with LWMPs indicates potential health benefits from incorporating depolymerized agar and alginate into the diet. However, there was no significant increase in fecal

short-chain fatty acids (SCFAs) after LWMP intake, consistent with findings in previous fiber studies. Due to the rapid absorption of SCFAs in the colon, only about 5% is excreted in feces, reducing levels detected distally [85]. Agar LMWP consumption led to a significant increase in *Faecalibacterium prausnitzii*, a prominent anti-inflammatory gut bacterium and a biomarker of gut health often abundant in healthy individuals [86], highlighting the positive microbial impact of agar LMWP on the gut microbiota.

Chromium is a widely used heavy metal in leather processing, fuel production, and steel manufacturing [87,88]. Chromium released from these factories can accumulate in soil, water, and plants, which enter the food chain and pose significant health and safety risks [89-91]. Long-term exposure to hexavalent chromium is particularly harmful, often leading to gut dysbiosis and substantial reductions in microbial diversity. These are critical factors in diarrhea, obesity, and diabetes [92-94]. Lowered gut microbial diversity negatively impacts immune development and compromises the intestinal barrier [95-96]. In the study by Mu et al. [64], hexavalent chromium exposure significantly increased pathogenic bacteria (*Escherichia-Shigella* and *Enterococcus*) while decreasing beneficial microbes such as *Prevotellaceae*, *Alistipes*, *Alloprevotella*, *Lachnospiraceae*, *Rikenellaceae*, and *Bacteroides*. However, treatment with seaweed polysaccharides improved the gut microbiota composition, counteracting chromium-induced dysbiosis. Research has shown that SCFA-producing bacteria like *Alistipes* and *Lachnospiraceae* play a vital role in gut health by reducing oxidative stress and inflammation, while supporting intestinal homeostasis and barrier integrity [97-100]. The results suggest that seaweed polysaccharides may help preserve gut microbial balance and mitigate the negative impacts of heavy metal exposure on gut health.

The observed reduction in total phlorotannin content (TPhC) after oral digestion in the study by Catarino et al. [66] may be due to interactions between phlorotannins and salivary proteins. This is a common reaction with plant tannins, which influences the sensory characteristics of foods [101]. Furthermore, the low pH in the stomach could contribute to the decline observed in EtOAc levels, as extremely acidic conditions often degrade polyphenolic compounds. In contrast, the crude (CRD) samples included other non-phlorotannin compounds that might shield phlorotannins from salivary and acidic degradation. This protective effect has been evaluated in different studies on plant phenolics [102-103]. In related research, a polyphenol-rich extract from *Lessonia trabeculata* was shown to significantly restore the levels of the dominant gut phyla—*Firmicutes*, *Bacteroidetes*, and *Proteobacteria*—in diabetic rats. These studies have found a particular impact on the *Firmicutes*: *Bacteroidetes* ratio, an essential indicator of gut health [104]. A balanced F: B ratio is typically close to 1:1 in healthy individuals, with significant deviations linked to various health issues [105]. In the *Fucus vesiculosus* study, minimal F: B ratio changes were observed with FOS and EtOAc during initial fermentation, stabilizing after 24–48 hours. Meanwhile, the CRD samples maintained a stable F: B ratio, indicating a more consistent influence on gut microbiota composition. Together, these findings support the potential of bioactive compounds in seaweed to modulate the microbiome positively.

CONCLUSION

Fucoidan supplementation offers a promising solution to mitigate gut dysbiosis following *H. pylori* eradication therapy through the preservation of gut microbiota diversity. Fucoidan, particularly when combined with synbiotics, effectively reduces potential pathogen

growth, which supports microbial balance during treatment. Additionally, fucoidan and synbiotics contribute to the abundance of beneficial bacteria, further enhancing gut health. Okinawa mozuku, a functional seaweed, demonstrates regulatory effects on bowel function, improving bowel movement regularity. Seaweed polysaccharides help maintain gut microbiota stability, countering dysbiosis caused by external stressors, such as hexavalent chromium exposure, and increasing fecal bulk through low-molecular-weight polysaccharides. Collectively, the evidence highlights seaweed bioactive components as potential therapeutic agents for enhancing and sustaining beneficial bacteria in the microbiome. This conclusion supports the application of seaweed compounds in dietary and clinical interventions for gut health.

Future research: Further multicenter studies with larger, more diverse sample populations are required to confirm the effectiveness of seaweed's bioactive compounds on gut microbiota composition. Additionally, exploring the impact of higher dosages and extended treatment durations may help determine greater gut microbiota stability and diversity improvements. Such research will provide a stronger basis for the therapeutic application of seaweed bioactive components in microbiome health interventions.

Abbreviations: IBD: inflammatory bowel disease, IBS: irritable bowel syndrome, SCFAs: short-chain fatty acids, 13C/14C-UBT: carbon isotopes (13C or 14C) urea breath test, LMWPs: low-molecular-weight polysaccharides, THP-1: a human monocytic cell line, TNF–α: tumor necrosis factor-alpha, IL-6: interleukin-6, IL-10: interleukin-10, GIT: gastrointestinal tract.

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