Review Article **Open Access**

Determining the effect of seaweed intake on the microbiota: a systematic review

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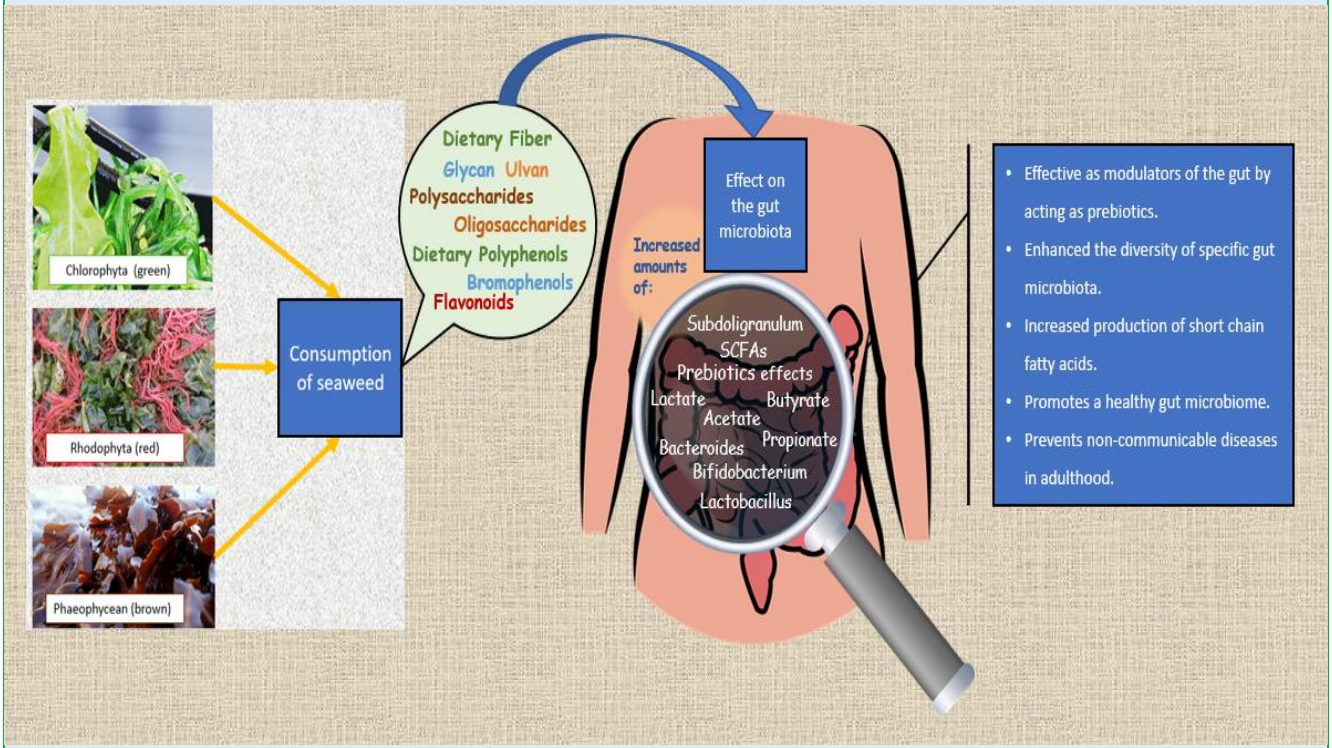
Submission Date: May 20th, 2023; **Acceptance Date:** June 26th, 2023; **Publication Date:** June 27th, 2023

Please cite this article as: Hagan M., Fungwe T. Determining the Effect of Seaweed Intake on the Microbiota: A Systematic Review. *Functional Food Science* 2023; 3(6): 79-92. DOI: https://www.doi.org/10.31989/ffs.v3i6.1117

ABSTRACT

The human gut microbiota is dominated by bacteria, and the host dietary intake is one factor that can modulate the diversity of the gut microbiota to health or diseases. According to the FAO, there is an annual steady decline in agricultural practices of over one percent. There has been an anticipation that algae production will be increased to supplement the use of vegetables from terrestrial land. Seaweed is a sustainable crop that offers a rich source of bioactive compounds, yet its potential is not fully exploited. Seaweeds) has been part of the staple diets of East Asian populations for a long time, and their bioactive compounds have the potential to be functional foods. As such, it has become pertinent to explore how seaweed can modulate gut microbial composition and function to improve host health. The purpose of the study is to conduct an extensive literature review to ascertain what is known about the effects of seaweed on the microbiota. A systematic search was conducted using relevant databases to find studies looking at the effects of green seaweed on the microbiota. From all 8,951 search results, 7 publications were included in this systematic review. The result showed that seaweed has a prebiotic effect in vitro digestive systems and a significant increase in SCFA production. Studies indicated that oligosaccharides and polysaccharides gotten from seaweed can regulate intestinal metabolism and could manage inflammatory bowel disease. The results of this review showed that consumption of seaweed is beneficial to the host and the gut microbiota.

Keywords: Seaweed, algae, marine algae, flora, microbiota



INTRODUCTION

The human gut microbiota is dominated by bacteria, and the host dietary intake is one factor that can modulate the diversity of the gut microbiota to health or diseases [1-3]. Due to the advancements made in understanding the mutualistic interactions between the diet, host, and microbe, efforts have been put in place to explore diets that can maintain health status and overcome or prevent non-communicable diseases [4,5]. According to the Food and Agriculture Organization of the United Nations [6], there is an annual steady decline in agricultural practices of over one percent. It is anticipated that in the next decades, there will be a need to supplement the use of vegetables from terrestrial land with an increase in algae production. Seaweed has several advantages over terrestrial vegetables. Seaweed grows rapidly and does not need land, fertilizers, or fresh water to produce yield [7].

Seaweed is classified as green, brown, or red algae, and diverse bioactive compounds are present for each classification with multiple properties. Seaweed is a sustainable crop that offers a rich source of bioactive compounds including polyphenols, dietary fibers, carotenoids, and fatty acids, yet its potential is not fully exploited. [8,9]. Due to its bioactive compounds, seaweed is considered a nutritious plant possessing beneficial effects for humans. Evidence has correlated seaweed consumption with reduced occurrence of chronic disease [10]. The phytochemical content of seaweed has made the plant act as a functional food and used in nutraceuticals to protect against inflammatory and cardiometabolic risk factors related to diseases such as antihypertensive effects, anti-obesity effects, anti-diabetic effects, antioxidant activities, a combination that could improve overall health outcomes in individuals [8, 11-15]. Humans can benefit from seaweeds either by

consuming whole seaweed or as natural drugs or food supplements to contribute to a healthier lifestyle.

Seaweeds have been eaten as a staple diet by people of East Asian origin, with their recipes written in recipe books across many countries [16]. Seaweed has an abundance of sulfated polysaccharides called ulvan which is used in the biomedicine, pharmaceutical, and cosmetic industries. Ulvan can act as an emulsifier, thickener, and stabilizer in products [17]. Seaweed has been part of the staple diets of East Asian populations for a long time, and its bioactive compounds can serve as functional foods. Recently, seaweed consumption has increased in Western countries due to its beneficial effect on human health. Despite the numerous benefits of seaweed, there is a lack of data available on the effect of seaweed consumption on the human microbiota. As such, it has become necessary to study how seaweed can regulate the composition and function of the gut microbiota to beneficially affect host health.

Purpose of the Study: The purpose of the study is to conduct an extensive literature review to ascertain what is known about the effects of seaweed on the microbiota.

REVIEW OF THE LITERATURE

The Effect of Seaweed Polysaccharides on Gut Bacteria:

The authors Shannon, et al., [18] showed that the total fiber content of seaweed was within the range of 29 to 67% in green seaweed (DW) [19, 9]. The major fibers in green seaweeds are ulvan, arabinogalactans, mannans, and sulfated-rhamnans [20, 21]. The human gut bacteria metabolize fiber (substrate) to confer beneficial effects on the host [22, 23]. In green seaweeds, ulvans account for 38 to 54 percent of the thallus (dry weight) [24]. After twenty-four-hour fermentation of Ulvan, Laminaria, and Pyropia by ethanol extraction in vitro colonic digestion, the result showed a significant increase in Bifidobacterium and Bacteroides with intakes of Laminarin by 8.3%, and 13.8% respectively ($p < 0.05$) compared to the control (fructooligosaccharide (FOS), Lactobacilli increased with intakes of porphyran by 10.7% ($p < 0.05$), and Bacteroides increased with intakes of Ulvan by 6.7% ($p < 0.05$). There was no significant increase at twenty-four-hour in total short-chain fatty acids (SCFA) i.e., lactate, acetate, and butyrate by laminarin, porpyran, or ulvan compared to FOS [25]. Studies have demonstrated Ulvans have potential antiviral, antibacterial, immunoregulatory, and anticoagulant activities in vitro [26-29]. Ulvans demonstrated prebiotic effects in vitro and animal studies [30,31].

The authors Cherry et al., [32] found that complex polysaccharides in seaweed make up 2.97 to 71.4 percent [9, 10], which is made up of xylan and ulvan. Seaweed glycans facilitate substrate cross-feeding of short-chain fatty acids (intermediates), thus causing the indirect rapid growth of specific bacteria. It can also act as a substrate for the fermentation of a specific microbiota population [33-35]. To promote saccharolytic-related fermentation in the colon, the gut microbiome must show within the colonic environment an active carbohydrate enzyme to catabolize the glycans in seaweed as carbon sources. The enzyme exerts specificity for seaweed glycans and highlights the gut bacterial populations which have demonstrable evidence for seaweed glycan utilization. Green seaweed has 8 to 29 percent ulvans (dry weight), a water-soluble polysaccharide. There was no difference in Lactobacillus, Bifidobacterium, and Enterococcus populations in vitro fermentation of Enteromorpha sp. using human fecal inoculum compared to the control. After 24-hour fermentation, there was an increase in Enterobacter. The same was observed after and 48-hour [31]. A study showed that Enteromorpha and its polysaccharides reduced inflammation that was linked with constipated mice that were induced with Loperamide [36]. In seaweed-supplemented mice, Actinobacteria, Firmicutes, and alpha diversity increased in the fecal

microbiota compared to the constipated control. Proteobacteria and Bacteroidetes decreased, while the Bacteroidales genera and Prevotellaceae increased in Enteromorpha and Enteromorpha polysaccharides, respectively.

In a typical diet, polysaccharides come from terrestrial plant origin [37], while other non-terrestrial vegetables like seaweed, are not commonly found in the human diet [7]. Studies have shown that oligosaccharides and polysaccharides gotten from seaweed can regulate intestinal metabolism, including inhibiting disease-causing bacteria to attach and evade cells, promoting fermentation, and managing inflammatory bowel disease [38, 39]. Sulfated or carboxylated structural polysaccharides can influence their capability to ferment [40]. Green seaweed is mostly constituted of sulfated xylans, galactans, mannans, and ulvans (the most abundant i.e., 8 to 29% of dry weight). The human gut microbiome (GM) may not have acquired the efficacy to degrade seaweed polysaccharides, because all through evolution, most humans did not include seaweed as part of their regular diet. Most complex polysaccharides are undigested by humans; however, humans have the enzymes required to digest some algal polysaccharides (e.g., starch) [40, 41]. A study on Japanese participants found that specific genes expressing enzymes with the ability to catabolize seaweed polysaccharides, such as agarases or porphyranases, can be moved from Zobellia galactanivorans to the gut microbiota Bacteroides *plebeius* [42]. Thus, acquiring the capability to digest agarose and porphyran, then the gut microbiota of individuals from North America [42]. Dietary fiber in seaweed is resistant to degradation by enzymes in the human digestive system [10]. Thus, the commensal bacteria feed on the fermented seaweed polysaccharides to stimulate their growth.

Algae demonstrates more prebiotic effects than fructooligosaccharides due to their polysaccharides content in vitro [25, 43]. They demonstrated antioxidant, antitumor, anticoagulant, antibacterial, immunological, antiviral, and anti-inflammatory activities [38, 44]. Green seaweed constitutes sulfated polysaccharides which include ulvans and glycans [38]. Migration of leukocytes to the epithelium of blood vessels can be prevented at the site of inflammation if an individual consumes sulfated polysaccharides from seaweed, as these polysaccharides inhibit their adhesion to sites [45], by stimulating the growth and action of good bacteria thus producing short-chain fatty acid that is beneficial in maintaining health [38]. These sulfated polysaccharides differ in their compositions, specie, and properties [46], as such their benefit on the gut microbiota will also be different.

There was an increase of short-chain fatty acid production observed when seaweeds and their extracted polysaccharides were utilized, thus stimulating the growth of Lactobacillus, Bifidobacterium, and Akkermansia, which are beneficial [47-49] and blocked the growth of disease-causing bacteria [50, 36]. The intake of these polysaccharides also modulated the genes expressing for diabetes in diabetic mice [51], decrease lipopolysaccharide-binding protein in female mice [47], and reduced injury on diseased cells/tissues in the colon [36]. Ulvans are one of the most frequent polysaccharides in green algae. Ulvans contain uronic acids and sulfate which produces indigestible ionic colloids that can bind to bile acids because of their ability to exchange ions. Thus, having more excretion of bile acids with antihyperlipidemic effects [40, 52]. An in vitro analysis was conducted using Enteromorpha and there was no significant diversity in the amounts of Lactobacillus, Bifidobacterium, and Enterococcus compared with controls despite the increasing amount of ulvans in Enteromorpha [31]. However, in vitro fecal analysis, the growth of Lactobacillus and Bifidobacterium population was stimulated with ulvan intake, thus promoting the formation of acetic and lactic acids [25], hence its prebiotic effect. Enteromorpha and its

polysaccharides extract reduced the severity of the inflammation related to constipation that was induced with loperamide in mice [36]. The gut microbiota showed an increase in Actinobacteria and Firmicutes compared with the control and decreased Proteobacteria and Bacteroidetes in mice.

In the study by Shang, et al., [47], Enteromorpha *clathrata* was given to mice which resulted in reducing the amounts of Staphylococcus, Streptococcus, and Enterobacter. The number of Alloprevotella, Bacteroides, Akkermansia *muciniphila*, Blautia, and Ruminococcaceae increased in the intestines of mice and decreased the number of Alistipes, Rikenellaceae, and Peptococcus [53, 47]. Enteromorpha *clathrata* is a specie of green seaweed that contains polysaccharides possessing many bioactivities, such as antioxidant, immunomodulatory, anticoagulant, anti-obesity, and anticancer effects. In female and male mice, E. clathrata exerted prebiotic effects on Bifidobacterium, Lactobacillus, and A. muciniphila because of its polysaccharides content [47]. These prebiotic effects were most evident in the male mice due to the sex hormones influencing the diversity of microorganisms found in the intestine [47]. E. clathrata polysaccharides were given to male mice in another study. The result showed an increase in the number of Eubacterium, Alloprevotella, Peptococcus, Bacteroides, and Prevotella, and a decrease in the ratio of Helicobacter that was related to cancer [47]. The number of Clostridium, Odoribacter, Alistipes sp., and Oscillibacter increased in the female mice, and the ratio of beta-proteobacteria reduced [41].

Shannon et al., [54] "evaluated the prebiotic effect of whole seaweeds and their polyphenol and polysaccharide extracts on human fecal gut bacteria using an in vitro model". The study found that all seaweeds are good sources of minerals, fiber, polyphenols, and protein. The increased fiber content of seaweed improves its prebiotic effect. The short chain fatty acids amount was increased in five out of nine seaweed species used. The individual and total short-chain fatty acids produced after 24 hours by bacteria fermented with U. ohnoi and E. radiata were significantly more than the inulin polysaccharide control and the epigallocatechin gallate (EGCG) polyphenol control. These significant increases in short-chain fatty acids production show the appropriateness of seaweed as a substrate for gut bacteria, especially its polysaccharide extracts and whole seaweed thallus. The seaweed substrates used in the study had notable effects on the number of commensal bacteria.

The Effect of Seaweed Polyphenols on Gut Microbiota*:*

The seaweed thallus is protected against microbial infection, predation from UV damage, oxidation, and herbivores by secondary metabolites called polyphenols [55]. Polyphenols occur in algae and terrestrial plants algae. Green seaweed (dry weight) has 1 to 5% polyphenols [18, 56-58]. In a study involving germ-free animals, there was an absence of bioactive phenolic metabolites in the gut after intake of polyphenols; this finding is atypical [59]. This further emphasizes the role of the gut microbiota in metabolizing polyphenols. Seaweed polyphenols were found to increase post-prandial cognitive function [60], high-density lipoprotein cholesterol [61], and demonstrate anti-hypertensive [62] anti-hyperglycemic [63], and in females, reduced the effect of high blood glucose reducing [64] in human studies.

Seaweed has a chemical defense system such as bromophenols, which protect them from herbivores, oxidation, fungi, and bacteria [65-67]. Bromophenols occur more in green and red and seaweed. It was found that the content of bromophenol in forty-nine seaweeds ranges from 0.9 to 2393 ng/g [68]. Seaweed-derived bromophenols have anti-inflammatory, anti-cancer, antithrombotic, antioxidant, antidiabetic, and antibacterial [69-71]. The results of this study reported that intakes of seaweed and its components exert a

beneficial effect in regulating gut microbiota.

Seaweed is rich in polyphenols, such as flavanols, phlorotannins, and catechins [32]. Green and red seaweed contains phenolic acids, flavonoids, and bromophenols [72]. Studies showed that the biological activities of green and red polyphenols contributed to the reduction of factors related to cardiovascular disease and type 2 diabetes such as oxidative stress, hyperlipidemia, hyperglycemia, anti-microbial activity, and inflammation [73- 76]. About 90 to 95 percent of polyphenols from food migrate to the colon undigested [77], where metabolism and biotransformation occur by the action of the gut microorganism. For a complete biological transformation of polyphenols to occur, a complex array of gut microorganisms is needed. Dietary polyphenol consumption associated with bioactivities may rely on the composition and breakdown ability of the gut microorganisms, because of the activities of the metabolites in the food [78, 79]. However, there may be a collaborative effect between probiotic bacteria and the prebiotic effect of polyphenols occurring [80].

In Lopez-Santamarina et al., [37], flavonoids are present in red, green, and brown seaweed. These compounds have exerted effects against cancer and arteriosclerosis [81] due to their antioxidant characteristics. The flavonoids present in Enteromorpha prolifera affected the balance of the gut microbiota in diabetic mice, growing the presence of Odoribacter, chnospiraceae, and Alistipes [82]. Alistipes sp. is among the most bacterial specie in the intestinal tract of mice that can digest lactic acid and glucose to make acetic, succinic, and propionic acids. These short-chain fatty acids regulate the freeing up of intestinal hormones, thus promoting the stimulation of appetite and insulin. This effect may be the reason E. prolifera is used as an herb to treat inflammation in China [82]. The prebiotic effects of seaweed and its extracts are evidenced in vitro digestion systems that simulate the human colon. This was also evidenced in animal models. However, animals make up differ from humans in several ways e.g., in the gut microbiome constituents, diets, metabolism, and immunity system, thus generalizing the results may not be appropriate for human subjects.

The Effect of Seaweeds on The Diversity of The Microbiome: Noh et al., [83] "investigated relations of long-term intake of both nutrients and foods with the taxonomic composition and diversity of the gut microbiota, and discovered dietary patterns associated with gut microbial within the sample (alpha) diversity". Data from the European Metagenomics of the Human Intestinal Tract (MetaHIT) consortium and the International Human Microbiome Consortium (IHMC) showed that human gut microorganisms can be uniquely grouped into specific enterotypes [84]. The three specific enterotypes were grouped by diverse microbial constituents at the genus level, having significant differences in Prevotella, Ruminococcus, and Bacteroides. Firmicutes, Bacteroidetes, Actinobacteri, and Proteobacteria were the dominant phyla. The Firmicutes: Bacteroidetes ratio was notably more in females than males, with Firmicutes having the most amount (39.8 percent: 32.8 percent, p-value = 0.009) and a reduced amount of Bacteroidetes (53.2 percent: 57.4 percent, p-value = 0.017) in individuals that have never smoked vs to those that smoke. At the nutrient level, intakes of plant protein (r = 0.15) and dietary fiber (r = 0.17) were positively correlated with the F/B ratio.

In the food group study, intakes of fermented legumes (r = 0.16) and vegetables (r = 0.19), were positively correlated with the F/B ratio, but not with the amount of Firmicutes. Intakes of seaweed (r = 0.15), vegetables (r = 0.20), and fermented legumes (r = 0.20) were positively correlated with the Shannon index. This index discovered a dietary pattern that provided an understanding of the alpha diversity of the gut microorganism. This high alpha diversity dietary pattern was characterized by greater intakes of seaweeds,

vegetables, fermented legumes, and minimal intakes of beverages such as sweet and carbonated beverages. High alpha diversity dietary pattern was negatively correlated with Bacteroidetes ($p < 0.001$, $r = -0.17$), but positively correlated with the Firmicutes: Bacteroidetes ratio ($p < 0.001$, $r = 0.24$). The high alpha diversity dietary pattern was negatively correlated with Tannerella ($r = -0.22$), Coenonia ($r = -0.27$), and Prevotella ($r = -0.22$), within the Bacteroidetes classification, but positively correlated with Eubacterium ($r = 0.20$), Lactobacillus ($r = 0.23$), and Ruminococcus ($r = 0.21$). Dietary patterns comprising more intakes of fermented and plant-based foods were beneficial to the gut microorganism's diversity and composition. High alpha diversity dietary pattern was positively associated with Ruminococcus, Eubacterium, and Lactobacillus which are within the Firmicutes phylum. Increasing intakes of fermented plants and the amount of gut microbiota present were not related. Ruminococcus was related to increased consumption of seaweeds, legumes, and vegetables compared to the Bacteroides or Prevotella enterotypes.

Sugimoto et al., [85], "analyzed the relationship between habitual dietary intake surveyed using a food frequency questionnaire (FFQ) and gut microbiota analyzed quantitatively in 354 healthy adults, with the aim of revealing the association between habitual diet and gut microbiota". Based on statistical analysis, there were significant associations with the intake of seaweed, seafood, fruits, mushrooms, and alcoholic beverages. Consumption of seaweed was positively correlated with the number of Subdoligranulum and negatively with the number of Streptococcus. Thus, polysaccharides in seaweed may also influence the number of Subdoligranulum. The β-diversity of gut microbiota was significantly associated with the consumption of seaweed.

Other benefits of seaweeds on overall health: The study by the authors Lomartire et al., [86] "investigated the health benefits of seaweed consumption as whole food". The study showed that marine seaweed is an excellent food ingredient with bioactive compounds that contribute to a healthy diet. Ulva *lactuca* extracts demonstrated photocatalytic and antimicrobial actions [87]. Table 1 summarizes the findings from the literature reviewed on the effect of seaweed intake on the microbiota.

Table 1: Summary of findings: seaweed intake and effect on microbiota

Citation	Intervention/ Comparator Duration	Sample Characteristics	Efficacy Study Summary	Health Outcomes
Shannon et al., [18]	Cross-sectional, Observational Study Seaweed Varied	In vitro, in vivo	Investigated evidence on "the potential therapeutic application of seaweed-derived polysaccharides and polyphenols to regulate the gut microbiota through diet".	With the consumption of ulvan (the major fiber) in seaweed, Bacteroides increased by 6.7% after 24-hour fermentation. At 24 h fermentation, the increase in total SCFA by ulvan was not significant compared to fructooligosaccharide. Seaweed consumption beneficially modulated the microorganisms of the human gut.

Cherry, et al., [32]	Randomized Control Trials. Seaweed Varied	In vitro, in vivo	Investigated the "fermentation and prebiotic effect of seaweed polysaccharides and oligosaccharides".	Complex polysaccharide, such as ulvan is the major component responsible for the prebiotic effects of seaweed.
Lopez-Santamarina et al., [37]	Randomized Control Trials. Seaweeds Varied	In vitro, in vivo	Investigated the "effect of seaweed and seaweed polysaccharides on the human microbiome".	There are a prebiotic effect of seaweed and seaweed extracts.
Lomartire et al., [86]	Prospective Cohort study Seaweed Varied	In vitro, in vivo	Investigated the health benefits of seaweed consumption as whole food.	Seaweed is an excellent food having biological active compounds that encourage a diet that promotes health.
Noh et al., [83]	Cross-sectional study Indigenous diets National Institute of Agricultural Sciences of Korea and the International Agency for Research on Cancer (NAS—IARC)	N= 222 18–60 years Mixed (49% males, 51% females) Koreans	Investigated "relationships between long-term intake of nutrients and food with the taxonomic composition and diversity of the gut microbiota". "Discovered dietary patterns related with gut microbial within sample (alpha) diversity".	Increased intakes of fermented foods and vegetables were beneficial to the gut microorganism constituents and diversity. High alpha dietary pattern was positively associated with Ruminococcus, Lactobacillus, and Eubacterium. Increased consumption of fermented vegetables and the gut microorganism composition was not associated.
Shannon et al., [54]	Randomized Control Trials. Seaweeds/ non seaweed polysaccharide and polyphenol Varied	In vitro, in vivo Australian	Evaluated the "prebiotic effect of whole seaweeds and their polysaccharide and polyphenol extracts on human fecal gut bacteria".	Seaweed is a good source of minerals, protein, fiber, and polyphenols. There was a significant increase in SCFA production in the gut. All seaweeds used in study had significant effect on the number of commensal bacteria.
Sugimoto et. al., [85]	Randomized Control Trials. Indigenous diets Varied	N= 354 20 to 60 years Mixed (51.1% males, 48.9% females) Japanese	Analyzed the "relationship between habitual dietary intake and the quantitative features of gut bacteria".	The intake of seaweed was significantly associated with the beta diversity of gut microbiota. The diversity of the gut microbiota influenced by the usual diet, was strongly associated with the amount of specific gut bacteria.

CONCLUSION

This review was conducted to determine the effect of seaweed consumption on the gut microbiota. Five studies were done in vitro/vivo, except for two studies (Sugimoto et. al., [85]; Noh et al., [83]) which were done in the Asian population i.e., Korea and Japan. The age range for the human population was between 18 to 60 years. Diet is a strong factor that influences the number of gut bacteria and their production of short-chain fatty acids (SCFAs), likewise the action of prebiotics, which ultimately affects the immune system. Shannon et al., [18] showed that the intake of seaweed and/or its extract beneficially modulates the microbiota of the mammalian gut. It was found that seaweed polysaccharides resist the host digestive enzymes, gastric acidity, and gastrointestinal absorption [88]. Cherry et al., [32] provided substantial evidence that ulvan, a green seaweed polysaccharide can interact with the gut microbiota to demonstrate a prebiotic effect. Similarly, Lopez-Santamarina et al., [37] found that seaweed and its extract demonstrated prebiotic effects in vitro digestion. The study by Lomartire et al., [86] showed that the biologically active content of green seaweed has anticancer, antimutagenic, antioxidant, antibacterial, and anticoagulant activities [89], and this antioxidant activity was due to the presence of pheophorbide, a chlorophyll-related compound, implying that seaweed can serve as a functional food. Noh et al., [83] showed that seaweed vegetables are good sources of fiber, which is a good substrate as an energy source for the gut microbiota [90]. Shannon et al., [54] showed that fiber and polyphenol-rich seaweeds can remarkably increase the number of commensal bacteria in vitro and their making of short-chain fatty acids after 24 hours. The study also confirmed that seaweeds and their extracts can be functional food ingredients to support a healthier gut and immune system. Sugimoto et al., [85] showed that there is a relationship between common foods eaten and specific gut bacteria in healthy Japanese adults, which was evident in diets that constituted of seaweed vegetables. The preponderance of evidence in this review showed that intake of seaweed and seaweed extracts can beneficially modulate the gut microbiota toward health. Ulvan, the major polysaccharide in seaweed showed effectiveness as regulators of the gut by working as a prebiotic, which multiplied the amounts of the gut bacteria and the making of short-chain fatty acids. There is a need for recommendations of seaweed and seaweed products to enhance the diversity of specific gut microbiota that promotes the health of the host by policymakers, the Food and Drug Administration (FDA), or other nutritional institutes. There is a need to conduct nutrition education to enhance the knowledge of the population about the nutritional benefits of seaweed. Considering seaweed consumption is not common in Western diets, despite its known benefits and relatively inexpensive cost. Overall, consumption of seaweed can promote a healthy gut microbiome and maintain health status, thus preventing non-communicable diseases. Because most of the studies were done in vitro and on animals, it may not be valid to generalize these findings in humans, considering the uniqueness of the human gut microbial composition, diets, immune function, and metabolism.

Further research: To the best of my knowledge, this review is one of the few publications that assessed the effect of seaweed on gut microbiota as it affects health status. There is a need for human interventional studies with seaweed polysaccharides, and polyphenols to ascertain their metabolism in humans. More experimental studies are needed to explain the mechanism of ulvans and their prebiotic effects in

humans. A standardized method for seaweed polysaccharides extraction should be developed.

Abbreviations: FAO: food and agricultural organization, SCFA: short chain fatty acids, DW: dry weight, FOS: fructooligosaccharide, GM: gut microbiota/microbiome, EGCG: epigallocatechin gallate, FFQ: food frequency questionnaire.

Conflicts of Interest: There are no conflicts of interest associated with this systematic review.

Author's Contributions: The initiation to the closing phases of this review was conducted by MH. MH conducted research, wrote, and edited the manuscript. TF provided supervision when conducting the research as my research advisor.

Acknowledgments: There was no funding supporting this publication. I would like to thank Dr Usher Kareem of Ohio State University, Columbus, Ohio for his mentorship during this research, and Mr. William Hagan for his counsel during this research.

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