Special Article

Potential benefits of dietary seaweeds as protection against COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic in Japan is not as disastrous as it is in other Western countries, possibly because of certain lifestyle factors. One such factor might be the seaweed-rich diet commonly consumed in Japan. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which binds to angiotensin-converting enzyme 2 (ACE2) on the cell surface and downregulates ACE2, likely elevating the ratio of angiotensin-converting enzyme (ACE) to ACE2. The overreaction of the immune system, combined with the cytokine storm and ACE dominance, is purported to cause the condition of COVID-19 patients to deteriorate rapidly. Dietary seaweeds contain numerous components, including ACE inhibitory peptides, soluble dietary fibers (eg, fucoidan, porphyran), omega-3 fatty acids, fucoxanthin, fucosterol, vitamins D_3 and B_{12}, and phlorotannins. These components exert antioxidant, anti-inflammatory, and antiviral effects directly as well as indirectly through prebiotic effects. It is possible that ACE inhibitory components could minimize the ACE dominance caused by SARS-CoV-2 infection. Thus, dietary seaweeds might confer protection against COVID-19 through multiple mechanisms. Overconsumption of seaweeds should be avoided, however, as seaweeds contain high levels of iodine.

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19) pandemic, with 24 854 140 cumulative confirmed cases and 838 924 cumulative deaths reported globally as of August 30, 2020.[1] A comprehensive summary from China indicates that 81% of COVID-19 cases are either asymptomatic or mildly symptomatic. Still, the disease progresses rapidly in the remaining cases, leading to acute respiratory distress syndrome (ARDS) with a cytokine storm.[2] Risk factors for COVID-19 include cardiovascular disease, hypertension, and diabetes, but these cannot fully explain the varying levels of severity of the COVID-19 crisis among high-income countries.

Japan was one of the first countries affected by the COVID-19 pandemic, yet the number of deaths per 100 000 population is much lower than in other Western countries, despite the apparent relaxed and slow response by the Japanese government.[3] It is unclear why the COVID-19 crisis is less severe in Japan than in other countries. The reasons are likely multifactorial and may include Japanese daily customs, such as removing shoes at home, wearing masks in public, and not shaking hands or hugging as frequently.[4,5] Another

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contributing factor might be the traditional Japanese diet, which is rich in seaweeds. Various seaweeds, including *Saccharina* spp (kombu), *Undaria pinnatifida* (wakame), and *Porphyra* spp (nori), are among the major ingredients in traditional Japanese cuisine. Per capita consumption of dietary seaweed consumption in Japan is among the highest in the world.[6] Edible seaweeds have been shown to have various health benefits, which derive from their antihypertensive, anti-inflammatory, and antiviral effects.[7–10] This evidence forms the basis for the hypothesis that dietary seaweeds have contributed to the limited severity of the COVID-19 pandemic in Japan. This review summarizes the pathophysiology of COVID-19 and examines the potential protective effects of dietary seaweeds against COVID-19.

COVID-19

SARS-CoV-2 and SARS-CoV

As the nomenclature implies,[11] the virological characteristics of SARS-CoV-2 are similar to those of severe acute respiratory syndrome coronavirus (SARS-CoV), which caused the SARS outbreak in China and other countries during 2002–2005, with more than 8000 cases, including almost 800 fatal cases.[12] The SARS-CoV-2 genome is 79.6% identical to the SARS-CoV genome.[13] Both viruses bind to the cell-surface protein angiotensin-converting enzyme 2 (ACE2) via the coronavirus spike (S) protein and use ACE2 as an entry receptor. The ACE2 protein is widely expressed in various tissues and organs, including the respiratory system (eg, nasopharyngeal epithelial cells and alveolar type 2 pneumocytes) and the gastrointestinal tract, where expression of ACE2 is highest.[14–16] In addition to SARS-CoV-2 infection of the respiratory system, intestinal infection with SARS-CoV-2 following potential fecal-oral transmission has been suggested.[17,18] The SARS-CoV-2 S protein has a greater affinity for ACE2 than does the SARS-CoV S protein,[19] which presumably accounts for the higher transmissibility of SARS-CoV-2.[20–22] After entering the cell, both SARS-CoV-2 and SARS-CoV generate 3C-like protease ($3CL^{pro}$), one of the two proteases encoded by these viruses (96% sequence identity between SARS-CoV-2 and SARS-CoV) and responsible for processing the nonstructural viral proteins.[23–25]

The clinical features of SARS-CoV and SARS-CoV-2 infections are also similar. As the names imply, both cause have severe acute respiratory syndrome with similar clinical symptoms (respiratory [eg, cough, shortness of breath], inflammatory [eg, fever, myalgia], and gastrointestinal [eg, diarrhea]) and radiological findings. There is also similarity in the laboratory findings of SARS and COVID-19, with lymphocytopenia, increased proinflammatory cytokines (eg, interleukin 6 [IL-6]), and hypercoagulability (eg, D-dimer formation) accompanied by thrombotic events observed in both diseases.[26–33] The lung histology of a COVID-19 autopsy case shows diffuse alveolar damage with multinucleated giant (syncytial) cells and viral inclusion bodies, resembling histological findings of SARS.[34,35]

Several differences between SARS and COVID-19 have been noted. For instance, SARS-CoV-2 infection elicits fewer innate immune responses (induction of interferons and proinflammatory cytokines), which results in higher viral replication in the lung than SARS-CoV infection. This could explain the milder symptoms and lower mortality but higher infectivity of COVID-19 than SARS.[36] Still, the overall similarity in the clinical features, laboratory findings, and pathological characteristics of these two diseases indicates similar pathophysiological processes, and previous research findings for SARS-CoV may be applicable to SARS-CoV-2, at least in part.

Immune overreaction

The alarming feature of COVID-19 is the rapid increase in the severity of the disease, which leads to ARDS. The overreaction of the immune response, called the cytokine storm, plays an essential role in this process. In the cytokine storm, overproduction of proinflammatory cytokines causes widespread vascular hyperpermeability and hypercoagulability, leading to multiorgan damage and ARDS, the leading cause of death in SARS and COVID-19 cases.[28,30,37] The levels of these proinflammatory cytokines are correlated with the severity of disease. The critical role of the cytokine storm is consistent with the favorable outcome of steroid administration in ARDS patients with SAR-CoV-2 infection,[38–40] even though the use of steroids in COVID-19 patients is generally not recommended by the World Health Organization because of concerns over the possible delay in viral clearance and other adverse events.[41]

The initial event of this immune overreaction seems to be the production of massive amounts of reactive oxygen species in the lung in response to the viral infection. The newly formed reactive oxygen species oxidize phospholipids within pulmonary surfactant to generate oxidized phospholipids. This, in turn, causes the lung macrophages to produce a large amount of the proinflammatory cytokine IL-6 via Toll-like receptor 4, shown to lead to acute lung injury in a mouse model.[42] Importantly, the prominent formation of oxidized phospholipids was observed in every SARS-related case of ARDS that the research group evaluated.

Consistent with the findings of this animal study, the levels of IL-6 and other proinflammatory cytokines are elevated in severe cases of SARS and COVID-19.[30,43,44] The presumed central role of IL-6 in severe COVID-19 cases provides a scientific rationale for a clinical trial that investigated the use of the interleukin 6 receptor (IL-6R) antagonist tocilizumab in such cases.[37,45]

Renin-angiotensin system

Another major system that regulates acute lung injury is the renin-angiotensin system (RAS). The RAS is generally known as the master regulatory system of the blood pressure in the body, but it also regulates inflammation and fibrosis of organs locally, via paracrine signaling. It is dually regulated by two enzymes, angiotensin-converting enzyme (ACE) and ACE2. ACE is a carboxypeptidase that positively regulates the RAS by producing angiotensin II (Ang II), which causes vasoconstriction and exerts proinflammatory effects via Ang II receptor type 1 (ATR1).[46,47] On the other hand, ACE2 is another carboxypeptidase that negatively regulates the RAS by converting Ang II to angiotensin 1-7 (Ang 1-7), which causes vasodilation and exerts anti-inflammatory effects via a G-protein–coupled receptor MAS.[48,49] Thus, RAS activity is determined by the balance between the ACE/Ang II/ATR1 and the ACE2/Ang 1-7/MAS axes (Figure 1).

As ACE2 serves as an entry receptor for SARS-CoV-2 and SARS-CoV, it is reasonable to speculate that the levels of ACE2 expression in the lung epithelial cells determine the susceptibility of individuals to these viruses. Since ACE inhibitors (ACEIs) and ATR1 blockers (ARBs) are known to upregulate ACE2 expression, there is a concern that both ACEIs and ARBs might aggravate SARS-CoV-2 infection.[50] However, the sudden cessation of ACEIs or ARBs could cause a rebound increase of blood pressure, elevating the cardiovascular risk of patients with COVID-19. Moreover, ACE2 can be organ protective by counteracting the ACE/Ang II/ATR1 axis (Figure 1). *Ace2* is protective against severe acute lung injury, whereas *Ace* promotes severe acute lung injury in mice models. Furthermore, recombinant *Ace2* and ARBs are also protective against severe acute lung injury in this study.[51] It is currently suggested that neither ACEIs nor ARBs need to be discontinued in patients with COVID-19.[52–54]

Kuba et al[55] also showed that ACE2 downregulation on the surface of lung epithelial cells leads to a dominance of the ACE/Ang II/ATR1 axis in lung tissue, which is crucial in the development of acute lung injury by SARS-CoV infection (Figure 1). In their study, SARS-CoV S protein also produced acute lung injury

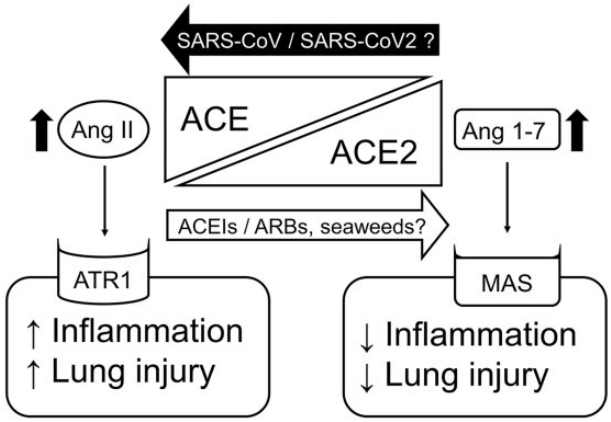

Figure 1 **The roles of ACEIs/ARBs and SARS-CoV/SARS-CoV-2 in the balance between the ACE/Ang II/ATR1 and ACE2/Ang 1-7/MAS axes in regulation of the renin-angiontensin system.** Dietary seaweeds are thought to shift the balance toward the ACE2/Ang 1-7/MAS axis through their possible ACE inhibitory effects. *Abbreviations*: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; ACEIs, ACE inhibitors; Ang II, angiotensin II; Ang 1-7, angiontensin 1-7; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARBs, angiotensin II receptor type 1 blockers; ATR1, angiotensin II receptor type 1.

while downregulating *Ace2* on the cell surface and increasing Ang II in the lung tissue, and the lung injury was rescued by ARB administration in wild-type mice.[55] Because of the similarity in pathophysiological and clinical features between SARS-CoV infection and SARS-CoV-2 infection, this crucial research finding for SARS-CoV infection is likely applicable to SARS-CoV-2 infection. Thus, ACE2 should also be protective against acute lung injury by SARS-CoV-2 infection as well. Consistent with this speculation, two independent studies showed that both ACEIs and ARBs improved the overall clinical outcomes of COVID-19 patients with hypertension.[56,57]

SEAWEEDS IN THE TRADITIONAL JAPANESE DIET

The prevention and management of the COVID-19 pandemic requires the minimization of public exposure to SARS-CoV-2 and curtailment of disease progression to ARDS in people previously exposed to the virus. Daily diets can alter inflammatory processes in the body, as indicated by epidemiological, experimental, and clinical studies.[58,59] The current review focuses on the traditional diet in Japan, where the number of deaths per 100 000 people is much lower than in other Western countries.[60]

The traditional Japanese diet is rich in diverse types of seaweeds. The consumption of edible seaweed in Japan reaches 1 kilogram of dry weight per person

annually[6] or more than 14 wet grams per person per day.[61] Dietary seaweeds are classified into three types: brown seaweeds, which include *Saccharina* (kombu), *Undaria pinnatifida* (wakame), *Cladosiphon okamuranus* (mozuku), and *Sargassum fusiforme* (hijiki); red seaweeds, which include *Porphyra* spp (nori); and green seaweeds, which include *Ulva* spp (sea lettuce or aosa).[62,63] In Japan, *Undaria pinnatifida* (wakame) and *Porphyra* spp (nori) are the two top seaweeds consumed, accounting for 75% of total seaweed consumption.[64] South Koreans also consume dietary seaweeds at a level comparable to that observed in the Japanese.[65] The number of COVID-19 deaths per 100 000 people in South Korea is now even lower than that in Japan.[60]

These edible seaweeds contain numerous and diverse bioactive components with various health benefits, including antihypertensive, antioxidant, and anti-inflammatory effects. These effects appear to counteract the immune overreaction and the dominance of the ACE/Ang II/ATR1 axis in patients with COVID-19, as outlined in the next section. However, these components must be sufficiently bioavailable in order to produce beneficial effects. Bioavailability is dictated by many factors, including digestion and absorption in the gastrointestinal system, hepatic and intestinal metabolism, and composition of the gut microbial flora.[8,9]

NUTRITIONAL COMPONENTS IN DIETARY SEAWEEDS

Protein and peptides

Edible seaweeds are rich in protein. Multiple ACE inhibitory peptides have been isolated from edible seaweeds such as *Undaria pinnatifida* (wakame), *Sargassum fusiforme* (hijiki), and *Porphyra* spp (nori).[66–70] Seaweed proteins are digested in the gastrointestinal tract,[7,8] and the peptides generated through digestion likely contribute to the blood-pressure-lowering effects of seaweeds through ACE inhibition, at least in part.[71] Thus, the peptides in edible seaweeds might function as dietary ACE inhibitors, possibly exerting a protective effect against COVID-19 by reducing the degree of ACE/Ang II/ATR1 axis dominance.

Fucoidan

Dietary fibers are plant-derived carbohydrates that are nondigestible in the gastrointestinal tract. They are classified as either soluble or insoluble fibers.[72] One of the soluble fibers found in brown seaweeds is fucoidan, a sulfated polysaccharide found in the extracellular matrix.[73] Fucoidan is absorbed through the gut epithelium into the systemic circulation, although its oral bioavailability is low.[74,75]

Fucoidan exerts anti-inflammatory effects by reducing the production of proinflammatory cytokines.[76,77] Orally administered fucoidan reduces the levels of proinflammatory cytokines, including interleukin 1β (IL-1β) and IL-6, in patients with advanced cancer.[78] Similarly, orally administered fucoidan has been shown to reduce radiation-induced pneumonitis and lung fibrosis in a mouse model.[79] Orally administered fucoidan also exerts antithrombotic effects by inducing biosynthesis of prostacyclin.[80] The crude extract of the brown seaweed *Cladosiphon okamuranus* (mozuku) consistently exerted antithrombotic effects in rats after 8 weeks of oral administration, likely through the fucoidan in the extract.[81] Another study shows that low-molecular-weight fucoidan prepared in the laboratory has greater antithrombotic activity and oral bioavailability than middle-molecular-weight fucoidan.[82]

Fucoidan has also been shown to have antiviral activity against influenza A virus, hepatitis B virus, canine distemper virus, and human immunodeficiency virus (HIV), mainly in vitro.[73] One study in human volunteers showed that serum/plasma concentrations of fucoidan following oral ingestion of a *Cladosiphon okamuranus* (mozuku) extract were sufficient to exert anti-HIV activity.[83,84] Furthermore, a recent study by Kwon et al[85] showed fucoidan extracted from *Saccharina japonica* (kombu) to have strong antiviral activity against SARS-CoV-2 in vitro. The activity of fucoidan against SARS-CoV-2 was even greater than that of remdesivir. Thus, fucoidan in dietary brown seaweeds might exert antiviral effects against SARS-CoV-2, at least within the intestine.

Porphyran

Porphyran, another soluble dietary fiber in seaweeds, is a sulfated polysaccharide found in the extracellular matrix of red seaweeds, including *Porphyra* spp (nori). Porphyran accounts for more than 40% of the dry weight of red seaweeds.[86] Porphyran was shown to exert antioxidant and anti-inflammatory effects in vitro[87–89] and in vivo after oral administration in a contact hypersensitivity mouse model.[90] Orally ingested porphyran is hydrolyzed by porphyranases in *Bacteroides plebeius*, a bacterium found in the gut microbiota of Japanese and Korean populations.[91–93] It is unclear whether the antioxidant and anti-inflammatory properties of orally ingested porphyran are dependent on the microbiota-mediated hydrolysis of porphyran in the gastrointestinal tract.

Omega-3 unsaturated fatty acids

Seaweeds are also rich sources of omega-3 unsaturated fatty acids, which include eicosapentaenoic acid (EPA; 20:5 omega-3) and docosahexaenoic acid (DHA; 22:6 omega-3) (Figure 2A). The high levels of these omega-3 fatty acids in fish derive from marine plants such as algae and plankton, which are consumed by fish and are rich in omega-3 fatty acids.[62] Because these fatty acids cannot be synthesized in the human body, they are regarded as essential fatty acids for humans. Epidemiological studies support the beneficial health effects of dietary omega-3 unsaturated fatty acids, which are shown to reduce the risk of cardiovascular disease.[94–98] The American Heart Association recommends regular consumption of fish as a way to obtain omega-3 fatty acids via the diet.[98]

The ability of omega-3 unsaturated fatty acids to reduce and resolve inflammation has been demonstrated in both in vitro studies and in animal models of inflammatory disease.[99] Several studies, including a meta-analysis, also support the beneficial effects of omega-3 unsaturated fatty acids in patients with sepsis or ARDS,[100–103] although one clinical trial found no benefit of omega-3 unsaturated fatty acids in patients with ARDS.[104] On the basis of previous studies, the use of omega-3 unsaturated fatty acids is advocated for prophylaxis and treatment of COVID-19.[105,106]

Fucoxanthin (carotenoid)

Fucoxanthin is a xanthophyll-like carotenoid found abundantly in the chloroplasts of brown seaweeds (Figure 2B). Fucoxanthin gives the characteristic brown hue to brown seaweeds. Orally administered fucoxanthin is rapidly hydrolyzed to an active metabolite, fucoxanthinol, in the gut and is further converted into another active metabolite, amarouciaxanthin A, in the liver. Fucoxanthin also provides diverse beneficial health effects, including potent antioxidant activity and anti-inflammatory effects by scavenging oxidants with its allenic bond and reducing the levels of proinflammatory cytokines such as IL-1β and IL-6.[107,108]

Fucosterol

Fucosterol, or 24-ethylidene cholesterol, is a characteristic phytosterol present abundantly all brown seaweeds[109,110] (Figure 2C). Fucosterol exerts both an anti-inflammatory effect by downregulating the generation of proinflammatory cytokines[111,112] and an anti-thrombotic effect by inducing plasminogen activator in endothelial cells in vitro.[113] An antiatopic effect of orally administered fucosterol in mice has also been reported.[114]

Vitamins D_3 and B_{12}

Both brown and red seaweeds are rich dietary sources of vitamin D_3[7,8] (Figure 2D). Most of the epidemiological studies conducted thus far indicate anti-inflammatory effects of vitamin D. Some clinical studies also show that oral vitamin D_3 supplementation decreases levels of proinflammatory cytokines.[115] In vitro studies suggest that vitamin D exerts anti-inflammatory effects by modulating the nuclear factor κB and unfolded protein response pathways.[116,117] Animal and human studies show the significant association between vitamin D deficiency and ARDS or sepsis.[118,119] One recent study also indicates the lung-protective effect of vitamin D supplementation in a mouse model of lipopolysaccharide (LPS)-induced acute lung injury.[120] Interestingly, another animal study shows that vitamin D exerts an organ-protective effect against acute lung injury by minimizing ACE2 downregulation by LPS.[121] There is no report about antiviral effects of vitamin D against SARS-CoV or SARS-CoV-2, even though antiviral effects of vitamin D against multiple types of viruses have been reported.[122] On the basis of previous studies demonstrating the importance of adequate vitamin D in supporting immune function, the use of vitamin D supplementation is advocated for prophylaxis and treatment of COVID-19.[105,123,124]

Red and green seaweeds are also rich dietary sources of vitamin B_{12}[8] (Figure 2D). Interestingly, vitamin B_{12} is ranked fourth among the compounds with possible inhibitory effects against SARS-CoV-2 $3CL^{pro}$ in virtual screening.[24] Another in silico study also indicates that vitamin B_{12} might be able to inhibit the RNA-dependent RNA polymerase activity of SARS-CoV-2.[125]

Phlorotannins

Phlorotannins are tannin derivatives or polyphenolics, compounds that account for 3% to 15% of the dry weight of brown seaweeds.[126,127] They are phloroglucinol (1,3,5-trihydroxylbenzene) oligomers or polymers. Multiple forms of phlorotannins exist, depending on the degree of polymerization (eg, phlorethol is a phloroglucinol dimer, whereas eckol is a phloroglucinol trimer, and dieckol is a phloroglucinol heptamer)[63] (Figure 2E). These compounds exist as either a free form or as a complex form with alginic acid in the physodes (small vesicles) and cell walls to protect the seaweeds from ultraviolet light, herbivores, and bacteria.[128]

Phlorotannins exert anti-inflammatory effects by reducing levels of proinflammatory cytokines (tumor necrosis factor, IL-1β, IL-6) and reactive oxygen species.[63,129] Both direct oxidant-scavenging effects and ACE inhibitory effects are presumed to be the

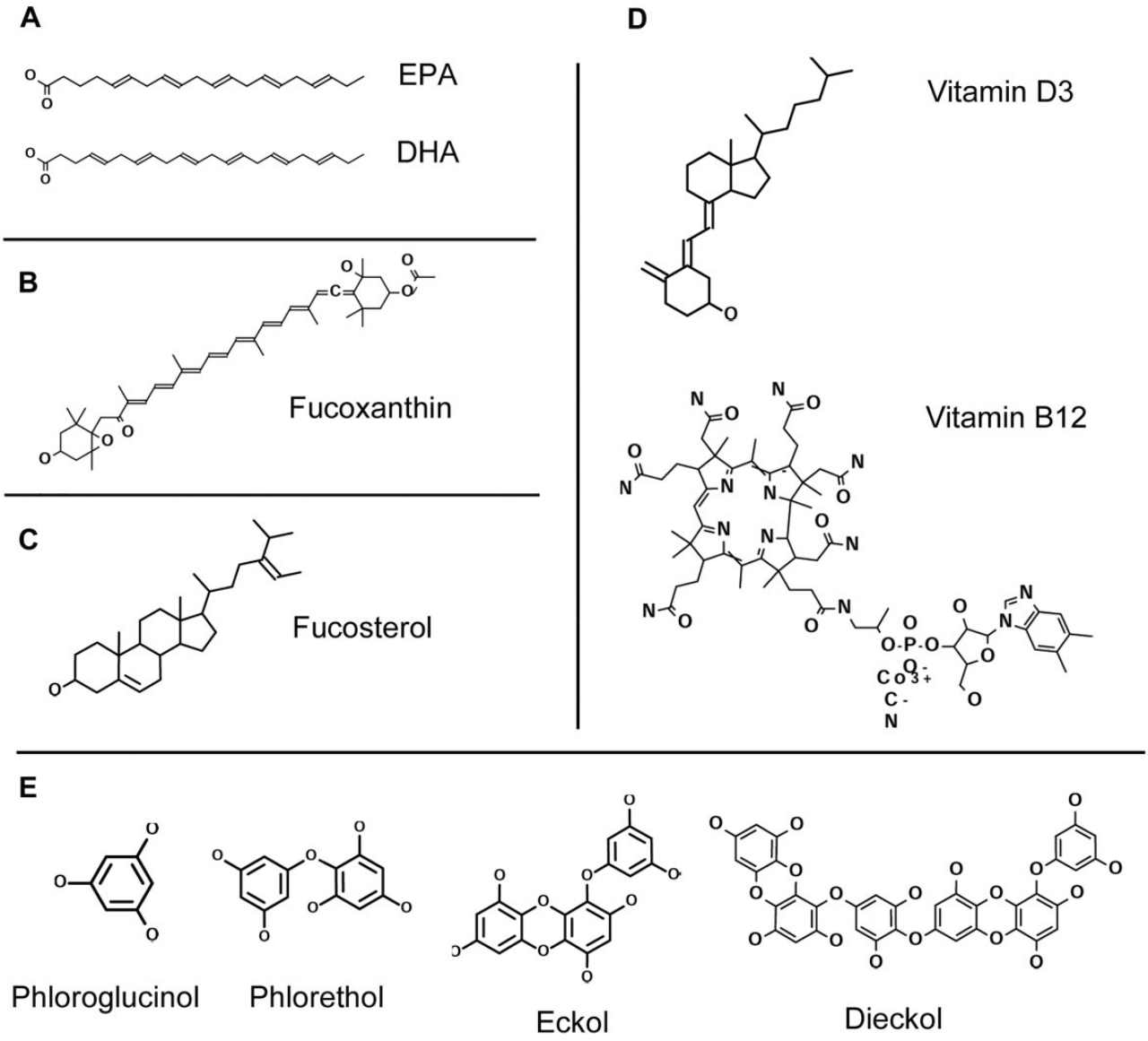

Figure 2 **Chemical structure of seaweed components**. (A) omega-3 unsaturated fatty acids, which include eicosapentaenoic acid (EPA; 20:5 omega-3) and docosahexaenoic acid (DHA; 22:6 omega-3); (B) fucoxanthin; (C) fucosterol; (D) vitamin D_3 (cholecalciferol) and vitamin B_{12} (cyanocobalamin); and (E) phlorotannins, phloroglucinol (1,3,5-trihydroxylbenzene), phlorethol, eckol, and dieckol.

mechanisms underlying the anti-inflammatory action of phlorotannins.[130,131]

Phlorotannins also exert antiviral effects against the influenza virus, HIV, and porcine epidemic diarrhea coronavirus.[132–134] Significantly, with the exception of the monomeric phloroglucinol, phlorotannins inhibit SARS-CoV $3CL^{pro}$. Among the phlorotannins, dieckol has the most potent inhibitory activity against SARS-CoV $3CL^{pro}$.[135] SARS-CoV-2 $3CL^{pro}$ is very similar to SARS-CoV $3CL^{pro}$[24,25]; thus, phlorotannins are expected to inhibit SARS-CoV-2 $3CL^{pro}$ as well.

Phlorotannins undergo enzymatic digestion in the upper gastrointestinal tract and are then fermented by the colonic microbiota to become smaller oligomeric units before being absorbed, predominantly in the colon.[136] Their bioavailability after oral administration is limited. It is unclear whether phlorotannins in brown seaweeds can exert antioxidant, anti-inflammatory, or antiviral effects after oral ingestion.

PREBIOTIC EFFECTS OF DIETARY SEAWEEDS

Daily diets affect the composition of the gut microbiota, and the composition of the gut microbiota, in turn, has profound effects on inflammation and the immune system of the host. Microbial imbalance, or dysbiosis, has been implicated in inflammatory diseases through immune dysregulation.[137–139] Both probiotics (live

microorganisms that produce health-promoting effects after oral ingestion, eg, *Lactobacillus* or *Bifidobacterium*) and prebiotics (food ingredients that improve gut microbiota after oral ingestion) correct dysbiosis by inducing the production of short-chain fatty acids (SCFAs), such as butyrate, through fermentation by the gut microbiota. Short-chain fatty acids are speculated to be key mediators of the anti-inflammatory effects of probiotics and prebiotics.[140]

Soluble dietary fibers provide substrates for the production of SCFAs through fermentation by the gut microbiota. Orally administered fucoidan functions as a prebiotic by increasing the counts of *Lactobacillus* and *Bifidobacterium* organisms in the gut. Other soluble dietary fibers in dietary seaweeds, such as agar, alginate, and laminarin, also serve as prebiotics.[141–144] Furthermore, the omega-3 unsaturated fatty acids in dietary seaweeds might also serve as prebiotics to increase SCFA-producing bacteria within the gut microbiota.[145,146] Together, these findings indicate that dietary seaweeds likely serve as prebiotics.

POTENTIAL RISKS OF DIETARY SEAWEEDS

While seaweed-rich diets may have potential to protect against COVID-19, they are also associated with potential risks.[8] Seaweeds are rich in iodine, a trace element required for thyroid hormone synthesis. The Food and Nutrition Board of the Institute of Medicine in the United States has established the recommended iodine intake as 150 µg/d and the tolerable upper limit as 1.1 mg/d,[147] but the average iodine intake among the Japanese is 3 mg/d, which is the safe upper limit of iodine intake set by the Ministry of Health, Labour and Welfare in Japan.[148] Excessive iodine intake from dietary seaweed consumption can cause both hyper- and hypothyroidism.[149–151] The strong tolerance of the Japanese population to higher iodine intake might be attributable to the various soy products (eg, miso, soy sauce, tofu, etc) commonly used in traditional Japanese cuisine. These products have antithyroid effects through soy isoflavones and are commonly coingested with seaweeds in Japan.[152–154] In other words, dietary soy products raise the amount of iodine required to avoid hypothyroidism. Interestingly, iodine is also known to optimize the innate immune response in the body; thus, high dietary iodine intake was recently speculated to be protective against COVID-19.[155]

Another concern about seaweed consumption is the contamination of seaweed with heavy metals such as arsenic or mercury. The arsenic concentration is highest in the seaweeds within the marine food web, although most dietary seaweeds (*Sargassum fusiforme* [hijiki] being the exception) contain most of their arsenic as organic arsenic compounds such as arsenosugars. Organic arsenic compounds appear to have significantly lower toxicity than inorganic arsenic, the predominant form of arsenic in *Sargassum fusiforme* (hijiki).[156] However, scientific data about organic arsenic compound speciation in seaweeds and in vivo toxicological evaluations of these organic arsenic compounds in humans are limited. Moreover, the effects of food processing and cooking on these organic arsenic compounds have not been evaluated.[156]

The levels of mercury in blood were mildly associated with the amount of various types of foods consumed, including seaweeds, in a Korean study.[157] In a preprint paper, the bioaccumulation of mercury is speculated to be a possible aggravating factor of COVID-19 by inducing hypertension, hypercoagulability, and immune overreaction.[158]

CONCLUSION

Dietary seaweeds contain numerous components that can exert antioxidant, anti-inflammatory, and antiviral effects, directly and indirectly, by improving the gut microbiota. Specifically, orally ingested seaweeds might exert direct antiviral effects against SARS-CoV-2 within the intestine through fucoidan and other components.[85] Several other components of seaweeds might be capable of reducing the degree of ACE/Ang II/ATR1 axis dominance in COVID-19 patients by inhibiting ACE. These potential health benefits of dietary seaweeds might be a contributing factor to the lower severity of the COVID-19 crisis in Japan. The bioavailability of each component after consumption of seaweed varies, and thus each component might not be able to exert these effects alone. It is plausible that these components might work additively or even synergistically, although there is no scientific data to either support or refute this idea.

At this time, it is not possible to propose a global recommendation for the daily dose and frequency of dietary seaweed consumption because the individual tolerance to iodine intake seems to vary, depending on daily dietary habits.[152–154] Further toxicological investigations of organic arsenic compounds in dietary seaweeds are warranted.[156] Because of concerns about excessive intake of iodine and heavy metals, overconsumption of seaweeds is certainly not recommended. The development of seaweed-derived supplements with reduced levels of iodine and heavy metals might be a logical strategy to allow the consumption of greater amounts of dietary seaweeds without adverse effects.

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