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Evaluation of prebiotic, probiotic, and synbiotic potentials of microalgae

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ABSTRACT

Microalgae can be considered an alternative food ingredient thanks to their nutritional composition and bioactive molecules. Microalgae are considered a rich source of sulfated and non-sulfated polysaccharides, and certain types of polysaccharides vary depending on their taxonomic groups. It is thought that valuable bioactive compounds possessed by algae biomass can increase the vitality of probiotic bacteria by stimulating their growth and being a good source for lactic acid production. Probiotics are defined as living, microbial dietary supplements that beneficially affect the human organism with their effects on the intestinal tract when they are consumed adequately. Prebiotics are indigestible or poorly digested food ingredients that stimulate the growth or activity of probiotic bacteria. Synbiotic is a term that expresses the union of probiotics and prebiotics to exert health benefits on humans. Spirulina and Chlorella are good sources of protein and polysaccharides or oligosaccharides that have been suggested as potential prebiotic candidates. These microalgae are thought to have a stimulating effect on the growth of probiotic bacteria. In this study, synbiotic efficacy and prebiotic activity of microalgae on probiotic microorganisms will be discussed and their potential in this area will be revealed.

Keywords: Microalgae, Probiotics, Prebiotics, Bioactive compounds

Introduction

Algae are the primary producers that synthesize organic molecules using luminous energy and carbon dioxide, and they play an important ecological role in the food chain in aquatic environments. Microalgae are microscopic organisms that live in a wide variety of habitats such as marine, freshwater, and extremely salty environments as well as moist soils and rocks (Yalçın Duygu, 2019). These photosynthetic species, encompass several different phyla and classes of organisms that constitute the multi-cellular structure of lengths up to 60 m (Macroalgae) and unicellular organisms with the size of 0.2 µm (Microalgae) (Camacho et al., 2019). Depending on the species, microalgae biomass contains a wide range of biologically active compounds such as proteins, lipids, polyunsaturated fatty acids (PUFAs), pigments, vitamins, and minerals (Schlagermann et al., 2012). Research on the biotechnological usage areas of these microalgae compounds, which were discovered by many studies on microalgae, has been concentrated on these organisms. Nowadays, microalgae are used as raw materials in many areas such as the pharmaceutical and cosmetic industry, health foods, formulation of food and feed, fertilizer, and wastewater treatment due to their high reproduction rate and biochemical structures (Gouveia et al., 2006; Lum et al., 2013; Wang et al., 2015). Eukaryotic microalgae and cyanobacteria are seen as promising organisms for fuel production (Culaba et al., 2020). Studies show that microalgae have anti-inflammatory, antioxidant, anticancer, antimicrobial, and anti-obesity capacities as well as hypocholesterolemic characteristics (Priyadarshani & Rath, 2012). It is thought that the carbohydrates and proteins that algae biomass possess can be a good source for lactic acid production. The lack of lignin in algae biomass compared to plant biomass provides an additional advantage to algae for lactic acid production (Nguyen et al., 2012). In this context, in recent studies, there has been a tendency to add algae biomass to fermented products to increase functional product and nutritional properties by encouraging the viability of probiotics (Varga et al., 2002). Adding algae and probiotics together promotes growth and increases the viability and acid production of probiotic bacteria such as *Lactobacillus* and *Bifidobacterium* (Webb, 1982). Studies have shown that adding algae and lactic acid bacteria to fermented foods can create new opportunities in taste, color, texture, and quality (Omar et al., 2019).

Probiotics refer to beneficial and viable microorganisms that maintain or improve the host's health when adequately consumed (Gupta et al., 2017). This group of bacteria is either natural inhabitants of the gut or can be found in fermented foods (Sornplang & Piyadeatsoontorn, 2016). The growth and activities of probiotics are induced by prebiotics. Prebiotics are selectively fermented by particular strains of resident intestinal microbiota and provide a targeted increase in specific bacteria that deliver health benefits to the host (Wilson & Whelan, 2017). The relationship between prebiotics and probiotics is referred to as synbiotics. As a result, probiotics and prebiotics work together to encourage well-being and the creation of new products. Varieties of algal species have been used in the food and pharmaceutical industries. The microscopic descriptions of these algal species, as well as their prebiotic properties, are described (Gupta et al., 2017). The main purpose of this review is to demonstrate the findings that microalgae can increase the growth and viability of probiotics thanks to their valuable bioactive compounds and examine their potential resources as prebiotic and synbiotic.

Probiotics

Probiotics are described as "nonpathogenic living microorganisms that provide health benefits to the host when adequately consumed" by FAO/WHO (Plaza-Diaz et al., 2019; Sun & Yoon, 2011). These bacteria can be originated from either the gut microbial flora or fermented food. Probiotics consist of lactobacilli *(L. acidophilus, L. amylovorus, L. bulgaricus, L. crispatus, L. casei, L. gasseri, L. helveticus, L. johnsonii, L. pentosus, L. reuteri, L. paracasei, L. plantarum, L. rhamnosus),* Lactococcus species *(Lactococcus lactis, L. lactis, L. reuteri, L. rhamnosus, L. casei, L. acidophilus, L.curvatus, L. plantarum),* Bifidobacterium species *(B. animalis, B. breve, B. infantis, B. bifidum, B. lactis, B. catenulatum, B. longum, B. adolescentis),* Pediococcus species *(P. acidilactici and P. pentosaceus),* Saccharomyces species *(S. cerevisiae, S. boulardii),* and some Streptococcus species *(S. thermophilus, S. sanguis, S. oralis, S. mitis, and S. salivarius*). Probiotics have been known to regulate dysbiosis of gut microflora caused by the overuse of antibiotics or prevent inflammatory bowel diseases, diarrhea, irritable bowel syndrome, gluten intolerance, gastroenteritis, *Helicobacter pylori* infection, prostatitis, colon cancer, urogenital tract disorders, virus infections, and allergies (Kahraman Ilıkkan, 2020; Plaza-Diaz et al., 2019; Sun & Yoon, 2011). This group of bacteria strengthens tight junctions and prevents the entrance of pathogens to host cells. Probiotics also modulate and reinforce the immune system through mucus production, short-chain fatty acid (SCFA) synthesis, macrophage activation, secretory IgA production, stimulation of cytokines, which include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors

(Rodríguez-Lagunas et al., 2017). Therefore, probiotics are also called "immunobiotics".

Prebiotics

Prebiotics were first defined in 1995 as "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and /or activity of one or a limited number of bacteria in the colon, thus improving host health" (Carlson et al., 2018). In 2010 the International Scientific Association for Prebiotics and Probiotics (ISAPP) modified that definition: "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health" (Gibson et al., 2010).

Prebiotics are health-beneficial substrates that are special functionally. These are non-digestible or low digestible foodstuffs (Gupta et al., 2017). Prebiotics are selectively fermented by the intestinal microbiota. Fermentation brings many benefits to the host. These benefits can be listed as follows; increase in the production of short-chain fatty acids, increase in fecal mass, decrease in end products with nitrogen and fecal enzymes, a moderate decrease in colonic PH, and contribution to the development of the immunological system (by providing immune modulation with increased intestinal-specific immunoglobulins) beneficial to the host. Prebiotics promote the growth of beneficial bacteria such as *Bifidobacteria, Lactobacilli*, and *Eubacteria*, which are critical for human health. Selective stimulation of the growth activity of intestinal bacteria is effective in maintaining health (Torun & Konuklugil, 2020; Wilson & Whelan, 2017).

Inulin, oligofructose, galactooligosaccharides, and lactulose are examples of commonly used prebiotics. The prebiotic activity has been demonstrated in vitro and in vivo for a variety of polysaccharides from different sources (O'Sullivan et al., 2010). Prebiotics such as inulin and pectin have a lot of health benefits, including reducing the frequency and length of diarrhea, relieving discomfort and other symptoms associated with irritable bowel syndrome, and preventing colon cancer (Pandey et al., 2015).

Synbiotics

Synbiotic is a term that expresses the union of probiotics and prebiotics to exert health benefits on humans (Pandey et al., 2015; Sataloff et al., 2016). Studies on synbiotics have shown that this association between probiotics and prebiotics increases the persistence and survival of probiotics in the gastrointestinal tract (GIT) and this is the main aim of this union (Omar et al., 2019; Sataloff et al., 2016). The most common prebiotics are fructooligosaccharides (FOS), galactooligosaccharides (GOS), and trans-galactooligosaccharides (TOS). However, synbiotics commonly include GOS, fructans (FOS and inulin) as prebiotics, and *Bifidobacterium, Lactobacilli, S. boulardii, B. coagulans* as probiotics (Davani-Davari et al., 2019; Pandey et al., 2015). Recently, many synbiotic formulas are available in pharmacy markets, but, the discovery of new prebiotics from algae will be an alternative source for the synbiotics (Gupta et al., 2017). Prebiotic potentials of microalgae such as *Spirulina spp*., *Tetraselmis* species, *Dunaliella salina,* and *Chlorella* spp. have been evaluated in many types of research (Table 1). Therefore, the utilization of microalgae together with probiotics will be an emerging approach in terms of synbiotics (Omar et al., 2019).

General Characteristics of Micro and Macroalgae

Algae are unicellular or multicellular photosynthetic organisms containing chlorophylls and other pigments. They transform luminous energy into chemical energy through photosynthesis and perform the critical functions of the energy cycle in natural ecosystems. Algae generally store this energy as starch and carbohydrate. The efficient energy transformation of algae forms an important food network in aquatic ecosystems (Tipnee S., Ramaraj R., 2015). They are grouped based on the pigment types used for photosynthesis, cell wall structure, and carbohydrate compound types stored for energy. Based on the pigments they have, they can also be divided into three groups brown (Phaeophyceae), red (Rhodophyceae), and green (Chlorophyceae) algae (Dawczynski et al., 2007). Today, the number of algae species in the world is estimated to be around ten million, and microalgae constitute the majority of these species. Cyanobacteria differ from other bacteria because they carry out oxygen photosynthesis. As a result of the cyanobacteria's release of oxygen through photosynthesis, they ensured the survival of other life forms on Earth (Chu, 2012). Approximately 70% of algae live in water (seas, lakes, or rivers), but they can also be found in terrestrial environments (lands, trees, and rocks). Algae generally live in environments at 20°C to 30°C, but some strains can live at lower temperatures or in areas full of ice, at higher temperatures (70°C) in spring water, in salty environments, and in lakes and seas where the light intensity level is low and pressure level is high. Different factors such as substrate, temperature, light, turbidity, saltiness, pH, O_2 and CO_2 rates, nutrient salts, oligo-elements, and vitamins affect the distribution of algae to the physical and chemical changes in the environment. The primary and secondary metabolites produced by macro and microalgae include minerals, vitamins, proteins, amino acids, carbohydrates, long-chain polyunsaturated fatty acids, steroids, dietary minerals, halogenated compounds, polyketides, and diverse antioxidants, etc., all of which are used in different fields of industries (Hunt et al., 2010;

Chandini et al., 2008). These industries include the food sector, cosmetics, aquaculture, drug industry, wastewater treatment, and production of anti-tumor, anti-bacterial, and antiviral compounds (Borowitzka & Borowitzka, 1988; Cohen, 1999; Hosikian et al., 2010; Pal et al., 2014). In addition, algae are well known for their renewable bioenergy potentials.

Algae are divided into microalgae and macroalgae based on their sizes. The dimensions of microalgae are expressed in microns, while macroalgae have sizes ranging from 1-2 cm to 40-60 m depending on the species. Macroalgae constitute significant elements of algae groups in aquatic habitats. Moreover, they form environments for feeding, sheltering, and reproducing aquatic animals (Ak et al., 2011). Macroalgae are used in the food and medical sectors but they are also raised in different regions of the world for the extraction of phycocolloids. Macroalgae are rich sources of biologically active metabolites such as minerals, vitamins, protein, and carbohydrates (Chandini et al., 2008). Most of the studies of macroalgae consist of evaluations regarding the amount of macroalgal biomass, the relationship between macroalgal growth and food material, the effects of extreme growth due to external factors, and relative effects that emerge in the environment. Moreover, evidence indicates that macroalgal biomass has the potential for the production of different fluids and solid biofuels through similar conversion (Grayburn et al., 2013). Macroalgae are also rich in polysaccharides that can be utilized as functional compounds of potential prebiotics for both human and animal health applications (O'Sullivan et al., 2010). The prebiotic and indirect probiotic activity of macroalgae compounds can be classified as alginates, laminarin, fucoidans, carrageenan, agar, and porpiran (Torun & Konuklugil, 2020).

Microalgae comprise proteins, amino acids, antioxidant components, Fe and Ca, unsaturated fatty acids, vitamins (A, B2, B6, B8, B12, E, and K). Microalgae are also known and used as a therapeutic and functional food (Gyenis et al., 2005). Some microalgae are a potential source of long-chain polyunsaturated fatty acids (LC-PUFA), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are implied to be useful in preventing cardiovascular disease (Arterburn et al., 2008). Microalgal lipids can be divided into two groups according to their structures. These are defined as follows; polar lipids (phosphoglycerides, glycosylglycerides, and sphingolipids) and nonpolar lipids (acylglycerols, sterols, free fatty acids, wax, and steryl esters) (Borowitzka & Moheimani, 2013). Although the amounts and types of microalgal lipids vary according to the species of algae, environmental factors, and growth conditions, these lipids play important roles in microalgal metabolism. For many microalgae species, the amount of lipid in dry biomass has been determined between 20-50% (Chen et al., 2018; Mata et al., 2010). The carotenoids in microalgae are derived from 5-carbon isoprene units that are enzymatically polymerized to form highly conjugated 40-carbon structures. Microalgal carotenoids are used as an additive for animal feeds, natural food colorants, and cosmetics. Carotenoids have therapeutic value with their anti-inflammatory and anti-cancer activities due to their antioxidant properties, and they also act as B-carotene provitamin A from a nutritional perspective (Chu, 2012).

Carbohydrates have two basic functions in microalgae cells, structural components in cell walls and storage components within the cell. As storage compounds, carbohydrates provide the energy needed for the metabolic processes of organisms (Kromkamp, 1987). Although carbohydrates in algal biomass have the lowest energy content compared to other organic compounds such as protein and lipid (Markou et al., 2012). The carbohydrate content of microalgae in biomass depends on the microalgae species, the growth, and environmental conditions. Algal carbohydrates consist of an extensive category of sugars (monosaccharides) and their polymers (di-, oligo- and polysaccharides), with the most common carbohydrates being glucose, rhamnose, xylose, and mannose (Mussgnug et al., 2010; Nakamura et al., 2005). The polysaccharides that microalgae possess are complex and heterogeneous macromolecules composed of different monosaccharides and sometimes glucuronic acid and sulfate groups. These molecules could be used as prebiotics and probiotics (Sathasivam et al., 2019). Polysaccharides such as laminarin, alginate, and poly-mannuronic acid obtained from micro and macroalgae living in aquatic environments act as prebiotics. Microalgae are considered a rich source of sulfated and non-sulfated polysaccharides and certain types of polysaccharides vary depending on their taxonomic groups.

Microalgae as Probiotics

The emergence of microbiota resistance to antibiotics and traditional drugs has led scientists to find alternative remedies to this issue. Nano-encapsulated multiplex supplements are costly to manufacture, therefore commercially expensive and inconvenient to use (Panghal et al., 2018). With the increase in the human population, the shortage of natural resources has made aquaculture a substantial sector. However, disease outbreaks have become an important problem in this sector and cause economic losses. Chemotherapeutic drugs used for the treatment of these types of diseases are both expensive and some have negative effects on the aquatic environment. Studies have begun to control infectious disease factors and to find alternative therapeutic agents that are environmentally friendly, and the use of probiotics as a food ingredient for the solution to this situation is considered promising (Camacho et al., 2019).

Table 1. Summary of studies conducted with microalgae on probiotics or fermentative products

Microalgae	Prebiotic	Probiotics/ Products	Effects	Reference
S. platensis 945	Extracellular products	*L. lactis* C2, *S. thermophilus* LO1, *L. casei* YK3, *L.acidophilus* JL2, and *L. bulgaricus* YL1	Growth promotion	(Parada et al., 1998)
S. platensis	Biomass	*S. thermophilus* TH4, *L. lactis* C2, and *L. delbrueckii* YL1	Growth promotion	(De Caire et al., 2000)
S. platensis	Biomass	*L. casei* MTCC1423, *Lactobacillus acidophilus* MTCC447, and *S. thermophilus* MTCC1938	Growth promotion	(Bhowmik et al., 2009)
S. platensis and *C. vulgaris*	Biomass	Yoghurt (*Lactobacillus acidophilus* LA-5, *Bifidobacterium lactis* BB-12, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Streptococcus thermophilus*)	Growth promotion	(Beheshtipour et al., 2012)
S. platensis and *C. vulgaris*	Biomass	*L. plantarum* and *E. faecium*	Growth promotion	(Gyenis et al., 2005)
C. vulgaris	Biomass	*L. brevis*	Growth promotion	(Scieszka & Klewicka, 2020)
S. maxima	S. maxima-derived modified pectin	Gut microbiota	Promoted *Bacteroidetes*	(Chandrarathna et al., 2020)
S. platensis	Biomass	*L. acidophilus* /Cheese	Growth promotion	(Mazinani et al., 2016)
Isochrysis galbana	Biomass	*Lactic acid bacteria*	Growth promotion	(Nuño et al., 2013)
Arthrospira platensis (Spirulina) and *Chlorella vulgaris*	Biomass	*Bifidobacterium animalis* and *Lactobacillus casei*	Growth promotion	(Leal et al., 2017)
S. platensis	Biomass	Yoghurt	Growth promotion of total lactic acid bacteria in yoghurt	(Agustini et al., 2017)

The trace elements, vitamins, and bioactive compounds of the microalgae biomass have the characteristics of promoting the growth of the desired bacteria. Some types of microalgae have qualities that can increase the viability of probiotics by stimulating the growth of desired probiotic bacteria in yogurt and fermented milk (Beheshtipour et al., 2012). It has been reported that co-culturing microalgae and probiotics together can stimulate growth and increase the viability of probiotics in the products and also in the gastrointestinal tract due to their alkaline properties and effective compounds (Parada et al., 1998). Parada et al. (1998) demonstrated this statement that by adding products from *S. platensis* to the culture medium, it acted as a nitrogen-depleting photo-autotropic microorganism and releases exopolysaccharides as well as other compounds. This latter case could be responsible for the stimulating effect on LAB. In the other study, it was revealed that using *S. platensis* as algae biomass, significantly stimulated the growth of thermophilic bacteria and acid production (Varga et al., 1999). *C. vulgaris* and *S. platensis* were used together in many studies conducted on the increase in the health and biochemical properties of probiotic bacteria found in yogurt and milk. As a result, the viability of probiotic bacteria in the nutrient medium using these two microalgae were found to be significantly higher (Beheshtipour et al., 2012; Gyenis et al., 2005).

Microalgae as Prebiotics

Microalgae synthesize carbohydrates through photosynthesis, and the chemical profile of carbohydrates (mainly starch and cellulose) varies from species to species. The procedure of partial hydrolysis of polysaccharides in the microalgae cell wall is widely used in the food and feed industry. Studies have shown that microalgal oligosaccharides cannot be completely fermented by the regular intestinal microbiota of humans or animals. However, it is stated that they stimulate the growth and activity of specific beneficial bacteria present in the colon and act like prebiotics (Camacho et al., 2019). The use of microalgae as prebiotics by the food industry has been limited to dairy products. Technological advances could open up an opportunity to develop prebiotics from microalgae for application to foods fermented with lactic acid other than yogurt or cheese.

Polysaccharides and oligosaccharides promote compounds with potential health benefits, notable for prebiotic applications. Algal-derived polysaccharides have prebiotic potential, which has been used for decades to improve animal and human health. Depending on the taxonomic groups of algae, their polysaccharide types are different, and algae are considered a rich source of sulfated polysaccharides. The main function of these high molecular weight polysaccharides is that they are rich in hydroxyl (OH) groups and making them hydrophilic (Gupta et al., 2017). Some microalgae such as *Arthrospira platensis* can stimulate the growth of beneficial bacteria such as *Streptococcus thermophiles*, *Lactobacillus casei,* and *L. acidophilus* (Parada et al., 1998). In the study conducted by (Liu et al., 2015), it was shown that the biomass obtained from microalgae *Chondrus crispus* has prebiotic properties.

Some Algal Species with Probiotic and Prebiotic Potential

Several algal species have been used in the food and pharmacological industries. Recently, various research studies on the prebiotic and probiotic properties of microalgae have shown that aqueous algae extract from *Spirulina platensis, Chlorella, Dunaliella salina, Chlorococcum* are potential sources.

Spirulina

Spirulina is a filamentous blue-green alga, commonly found in many freshwater environments. *Spirulina* has been consumed as food or health food since ancient times due to its high nutritional value. *Spirulina* is produced on a large scale in outdoor pools for commercial purposes to be used as a nutritional supplement in some countries such as Thailand, China, the United States, and India. *S. platensis* contains about 4-7% lipids, 13.6% carbohydrates (glucose, rhamnose, mannose, xylose, and galactose), 78% high-quality proteins, vitamins (A, B2, B6, E, H, and K, more vitamin B12), all essential minerals, trace elements, as well as enzymes and some natural pigments (Parada et al., 1998; Shekharam et al., 1987). *Spirulina* contains essential fatty acids such as γ -linolenic acid (GLA) and linoleic acid (LA). *S. platensis* depletes nitrogen in the growth medium and releases extracellular carbohydrates and other growth agents responsible for stimulating the growth of lactic acid-producing strains. *Spirulina* biomass has a stimulating effect during fermentation and storage of *Lactobacillus casei, Streptococcus thermophilus, Lactobacillus acidophilus, Lactobacillus bulgaricus,* and *Bifidobacterium spp.* (Gupta et al., 2017). The stimulating effect of the extract obtained from *S. platensis* on the growth of three probiotic bacteria (*L. bulgaricus, L. lactis,* and *B. longum*) was shown in the study conducted by Pascal et al. (2011). Galactose and xylose, which are characterized by algal biomass, formed oligosaccharides that function as prebiotic compounds to stimulate probiotic bacteria (Pascal et al. 2011).

Chlorella

Chlorella is another microalga that has been cultured for the commercial production of healthy food. *Chlorella vulgaris* is a single-celled green alga and is widely distributed in freshwater, marine, and terrestrial environments. Thanks to its high photosynthetic property, *Chlorella* can grow rapidly under autotrophic, myxotrophic, and heterotrophic conditions. All these features made it one of the first microalgae to be considered for commercial production and large-scale cultivation (Ru et al., 2020). *Chlorella* is a good source of nutrients such as protein %61.6, lipid %12.5, carbohydrates % 13.7, elements (selenium, magnesium, phosphorus, zinc, calcium, and aluminum), and vitamins (ascorbic acid, thiamine, B1, B2, B6, D, E, and K) (Blas-Valdivia et al., 2011). *Chlorella*, contains β-glucan, an active immunostimulator, and has other useful impacts in scavenging free radicals and reducing blood lipids. It also produces an additional product called "Chlorella Growth Factor" as an agent to improve the growth of lactic bacteria (Chu, 2012).

The most abundant polysaccharide in *C. vulgaris* is starch and cellulose, consisting of amylose and amylopectin, and together with sugars, they act as an energy store for cells. Additionally, one of the most important polysaccharides is β-1,3-glucan, namely as a free radical scavenger with many health and nutritional benefits (Lee et al., 2007). Several studies on the health benefits of consuming *Chlorella* have shown that it can lower blood sugar levels, increase hemoglobin concentrations, and act as hypo-cholesterolemic and hepatoprotective agents during malnutrition (Jeong et al., 2009). *Chlorella* has been reported as an important source of polysaccharides or oligosaccharides that have been suggested as potential prebiotic candidates. Industrially, *Chlorella* has been successfully added to yogurt and cheeses (Jeon, 2006; Beheshtipour et al., 2012).

Conclusion

Probiotics, prebiotics, and synbiotics have all been described and evaluated in terms of their systemic impact on the host's health, metabolism, and immune system. However, studies on new sources such as probiotics and prebiotics are still ongoing. Microalgae have been studied as one of these new sources. Although many studies have revealed that microalgae have a prebiotic effect thanks to the oligo- and polysaccharides contents and it improves the intestinal microflora, there are very few studies in which algae are used together with probiotics as a food product. Microalgae can be potential sources in this regard and it is beneficial to increase the research on the probiotic properties to find more scientific evidence.

Compliance with Ethical Standard

Conflict of interests: The author declares that for this article they have no actual, potential, or perceived conflict of interests.

Ethics committee approval: The author declares that this study does not include any experiments with human or animal subjects; therefore, no ethics committee approval is needed.

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