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Microalgae and the gut microbiome: Insights from animal models to human trials

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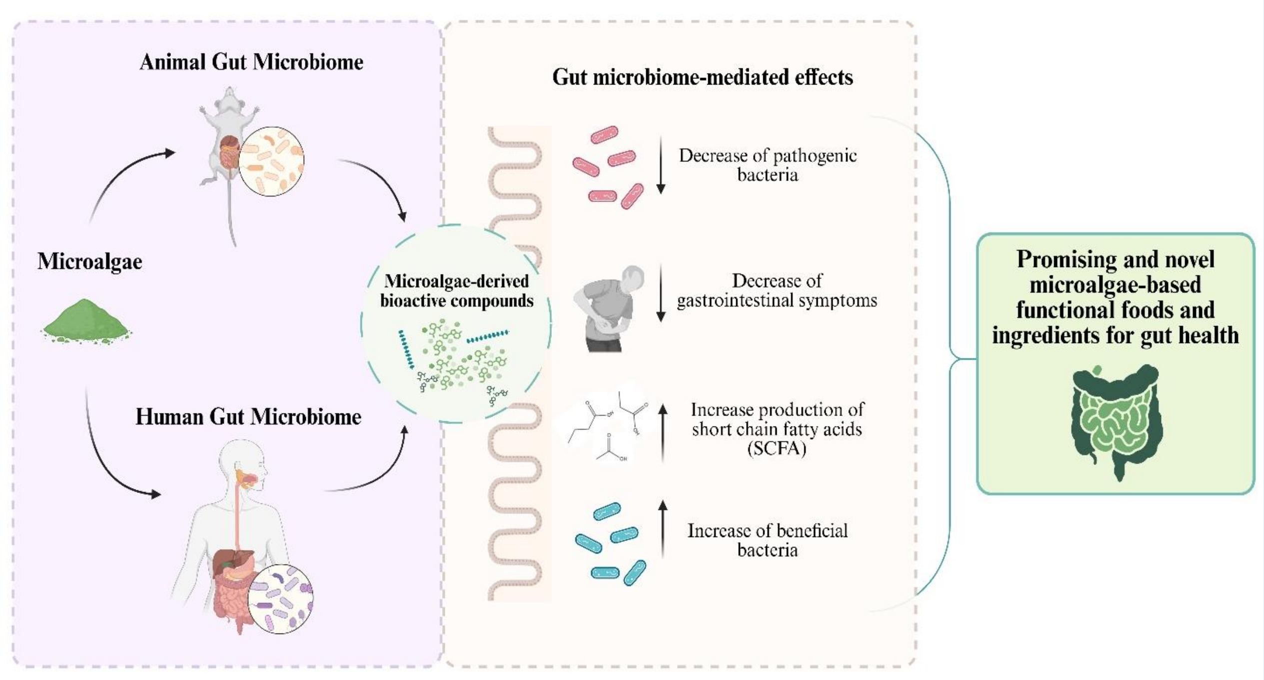
ABSTRACT: The gut microbiota is a vast consortium of microorganisms living in the gastrointestinal tract that plays essential roles in host metabolic, nutritional, and immune functions. However, this delicate ecosystem is susceptible to disruptions, or dysbiosis, which have been associated with conditions such as inflammatory bowel disease, obesity, and metabolic syndrome. The consumption of Western diets disrupts gut function; however, functional foods are essential for healthy microbiota. Microalgae, known for their ecological sustainability and rich nutritional profile, are increasingly considered promising sources of bioactive compounds, with growing evidence suggesting they may support the growth of beneficial gut microbes and help restore microbial balance. Microalgal-rich diets have shown promise by modulating fatty acid metabolism, inhibiting gut inflammation, and improving gut health. Despite previous investigations, the specific effects of microalgae on the gut microbiome remain underexplored, and the available data are dispersed. This review aims to unite and apprise the current scientific literature on the effects of microalgae-based dietary interventions on the gut microbiome by examining studies conducted in animal models, evidence from human-based approaches, including *in vitro* gut models and clinical trials, and identifying critical knowledge gaps in this research area. By highlighting the most relevant findings and outlining areas requiring further investigation, this review underscores the emerging potential of microalgae as microbiome-modulating agents and their promising role in next-generation functional foods for human health.

Keywords: microalgae, gut microbiome, animal models, clinical trials, prebiotics



Graphical abstract: Microalgae and the gut microbiome: insights from animal models to human trials

INTRODUCTION

In recent years, the intricate interplay between human health and the gut microbiome has gathered significant attention as a cornerstone in the prevention and management of various diseases. The gut microbiota, an expansive community of trillions of microorganisms inhabiting the gastrointestinal tract, plays a role in biological functions such as metabolic and nutritional regulation [1]. Given its complexity, the composition and functionality of the gut microbiome are susceptible to both intrinsic and extrinsic factors. Disruptions in this balance, termed dysbiosis, have been linked to chronic inflammatory disorders, including ulcerative colitis, Crohn's disease, and obesity [2]. Among the external influences, diet stands out as a primary modulator of microbiome structure and, by extension, systemic homeostasis.

The growing interest in diet as a preventive health strategy has highlighted the role of functional foods in reducing the risk of chronic conditions such as diabetes, cardiovascular disease, and inflammatory bowel disease [3]. Driven by a greater focus on health and diet, the food industry is turning to microalgae for new functional ingredients, prized for their sustainability and richness in nutritional and bioactive compounds [4]. Among these compounds, polysaccharides have attracted attention due to their potential prebiotic properties, which may foster the growth of beneficial gut microbiota and help restore microbial balance [5].

Advances in high-throughput sequencing and multi-omics technologies have greatly enhanced our understanding of the gut microbiome composition and function, especially in response to dietary inputs. Techniques such as 16S rRNA gene sequencing, metagenomics, and metabolomics are frequently used to study how food-derived prebiotics and probiotics modulate microbial communities and metabolic pathways [6]. However, despite this progress, the mechanisms by which unconventional and alternative food sources translate into microbiome-mediated health benefits remain poorly explored, especially for microalgae, for which available data are scattered. Therefore, this review aims to provide an update on scientific findings, as well as microalgae-based interventions in the animal and human gut microbiome, a promising intersection in the development of novel microbiome-modulating approaches for human health.

METHODS

A literature search was conducted across PubMed, Scopus, Web of Science, and the Functional Foods in Health and Disease Journal (FFHDJ.com) to identify studies examining interactions between microalgae and the gut microbiome, ranging from animal models to human trials. The search covered publications from January 2000 to November 6, 2025 (last search date), with a focus on recent publications. Search strings combined controlled vocabulary and free-text terms such as: "microalgae" or "*Arthrospira*" or "*Chlorella*" or "*Nannochloropsis*" or "*Tetraselmis*" or "*Schizochytrium*" and "gut microbiota" or "gut microbiome" or "fecal microbiota" and "animal model" or "human" or "clinical trial". Focusing mainly on experimental articles, data were extracted on microalgae species or compounds, study design (*in vitro*, animal, or human), intervention details, microbiota analysis method, and primary microbial and host outcomes. Study quality was appraised qualitatively, considering sample size, control design, and robustness of microbiome characterization (e.g., 16S rRNA vs. microbial plate count). Evidence was synthesized narratively, grouping studies by experimental model. However, the main limitations included methodological heterogeneity, variable reporting standards, and limited human trial data, which prevented meta-analysis and constrained cross-study comparisons.

Effects of microalgae on the animal gut microbiome: Several studies have shown the impact of microalgal species on the gut microbiome in rabbit, piglet, mouse, rat, chicken, fish, and dog models (Table 1). Ethanol extracts, oil, polyunsaturated fatty acids (PUFA), pectin, and polysaccharides from the microalgal species were used in the studies. The was administered at doses of 50 to 400 mg/kg body weight (BW) via oral gavage. Microbiome analysis was investigated in cecal and fecal samples. Of all the studies, only two (Guo et al., 2021 [7] and Azad et al., 2025 [8]) assessed the effects of C. pyrenoidosa and C. vulgaris on colonic and fecal short-chain fatty acids (SCFA), respectively, using gas chromatography-mass spectrometry (GC-MS).

Across all studies, the microalgal species showed beneficial effects on gut microbiota and lipid metabolism, as evidenced by their impact on SCFA levels. Only the report by Bordignon et al. (2014) [9] showed that C. vulgaris did not significantly affect the levels of caecal bacteria, including Eubacteriaceae, Christensenellaceae, and Ruminococcaceae, in rabbits. Similarly, dietary *C. vulgaris* supplemented with lysozyme did not significantly affect microbial diversity in the piglet intestine. However, supplementation with these microalgae and lysozyme reduced the abundance of *Megasphaera* A. and increased the abundance of *Phascolarctobacterium*_A.

Table 1. *In vivo* studies on the effect of microalgae on animal microbiota.

Authors	***In vivo* model**	**Microalgae/dosis**	**Methods**	**Study outcome**
[7]	High-fat-fed mice's gut microbiota	*C. pyrenoidosa* and *A. platensis* polysaccharides (400 mg/kg BW)	Fecal samples (16s RNA sequencing analysis)	↓ Firmicutes *Bacteroidota* ratio ↓ Relative abundance of the *Actinobacteria* and *Verrucomicrobia* Restored the HFD-induced depletion of *Clostridia* Prevented enrichment of *Erysipelotrichia* ↑ Fecal levels of acetate, propionate, and butyrate
[8]	Weaned piglets' microbiota	*C. vulgaris (*5%) and 100 mg/kg lysozyme	Colonic microbial DNA and 16sRNA sequencing analysis and GC-MS characterization (SCFA levels)	↓ Firmicutes ↑ Bacteroidota and Proteobacteria ↑ *Phascolarctobacterium_A* ↓ Acetate, propionate, butyrate, and valerate concentrations ↑ Isobutyrate and isovalerate levels
[9]	Rabbit caecum's microbiota	*C. vulgaris* (2%)	Caeca microbial analysis (16sRNA sequencing)	No significant changes in caecal *Eubacteriaceae, Christensenellaceae, Ruminococcaceae*
[10]	Mice with ulcerative colitis	*Chlorella vulgaris* (oral gavage, 3 weeks)	16sRNA analysis from mouse stool	↑ *Actinobacteria* phylum ↑ Relative abundance of *Coriobacteriaceae* UCG 002, *Bifidobacterium,* and *Eubacterium xylanophilum* ↑ Acetic and propionic acid Alleviation of colitis symptoms
[11]	Mouse gut's microbiota	*A. platensis* (80 µg/mL)	Fecal samples analysis (16sRNA sequencing)	Enhanced recovery of bacterial community diversity ↓ *Bacteroidetes*/*Firmicutes* ratio to normal levels ↓ *Proteobacteria* ↑ *Tenericutes* and *Actinobacteria* Reversed *Ruminococcaceae*_UCG-014, *Lactobacillus, Ruminiclostridium*_9, *Bifidobacterium*, *Roseburia*, and *Rom boutsia* to normal levels
[12]	Gut microbiota from Wistar male rats with nonalcoholic fatty liver disease	*A. platensis* (5% and 10% enriched diet, 20 g/day for 18 weeks)	Fecal samples analysis (16sRNA sequencing)	↑ *Prevotellaceae* and *Lactobacillaceae* families, and decreasing effect on the ratio of *Firmicutes: Bacteroidetes* Decrease liver fat weight, serum TNF-α, and urea levels
[13]	High-fat-fed rats gut microbiota	*C. pyrenoidosa* polysaccharide (150 and 300 mg/kg/day)	Cecal samples analysis (16sRNA sequencing)	↓ *Lachnospira* and *Ruminococcus_gauvreauii*_group. ↑ *Turicibacter, Lactobacillus,* and *Ruminococcus_1*
[14]	High-fat-fed rats gut microbiota	*Schizochytrium* sp. oil (100 mg/kg BW)	Cecal samples analysis (16sRNA sequencing)	↑ Relative abundance of Firmicutes ↑ *Clostridiales, Ruminococcaceae,* and *Lachnospiraceae* ↓ *Parasutterella* expression
[15]	High-fat-fed rats' gut microbiota	*A. platensis* PUFAs (150 mg/kg/day)	Cecal samples analysis (16sRNA sequencing)	↓ Firmicutes and Bacteroidetes ↑ *Ruminococcaceae*, *Porphyromonadaceae*, *Prevotella*, *Desulfovibrionaceae*, *Bacteroides*, *Alloprevotella*, *Helicobacter*, *Paraprevotella*, *Oscillibacter*, and *Barnesiella* expression ↓*Lachnospiraceae_unclassified*, *Romboutsia*, *Allobaculum*, *Roseburia*, *Clostridium_XlVa*, *Erysipelotrichaceae*, *Coprococcus*, *Turicibacter*, *Escherichia/Shigella*, *Clostridiales*, *Phascolarctobacterium*, and *Desulfovibrio* expression

Authors	***In vivo* model**	**Microalgae/dosis**	**Methods**	**Study outcome**
[16]	Nile tilapia fish *(Oreochromis niloticus)*	*C. vulgaris* (0.5% and 2% additives in regular diets for 30 days)	Intestine – 16s RNA sequencing	*Paracoccus, Thiobacillus, Dechloromonas,* and *Desulfococcus* were enriched under 2% *C. vulgaris* treatment *Afipia, Ochrobactrum, Polymorphum, Albidovulum, Pseudacidovorax,* and *Thiolamprovum* were more abundant in the 2% *C. vulgaris*-treated fish
[17]	Tilapia Fry fish (*Oreochromis niloticus*)	*A. maxima* 5%, 10% and 15% enriched diet for 8 weeks	Intestine 16S sRNA sequencing	Microbial composition was characterized by *Cetobacterium, Pseudomonas,* and *Aeromonas* genus, and a predominance of beneficial metabolic pathways
[18]	European seabass *(Dicentrarchus labrax)* juveniles' gut microbiota	Diet containing a blend of *A. platensis* and *N. gaditana* (2.5% microalgae and 500, 1,000, 2,000, or 10,000 phytase units/kg/day	Intestine samples (16s RNA sequencing V6-V8 analysis)	Improves their growth performance without affecting their gut microbial diversity. An increase in *Vibrio* and *Ochrobactrum* and a decrease in minority genera were observed in fish fed 2.5% microalgae
[19]	Sea bream *(Sparus aurata)* juveniles' intestinal gut microbiota	Diet blend of *Tisochrysis lutea, N. gaditana,* and *Scenedesmus almeriensis* (5%, 15% and 25% enriched diet for 30 days)	Sequencing of V6-V8 regions from 16S rDNA	The 25% enrichment promoted appropriate microbial diversity, favoring the presence of probiotic bacteria, such as *Lactobacillus*, and significantly influencing the fatty acid composition and lipid metabolism of the fish
[20]	Sea bream (Sparus aurata) midgut microbiota	Diet blend of *M. gaditana* + *Isochrysis* sp., *Tisochrysis lutea* + *Phaeodactylum tricornutum* + *Isochrysis* sp., and *Schizochytrium* sp. + *P. tricornutum* (67% enriched diet for 80 days)	16S rRNA amplicon sequencing	↑ Bacteria with potential probiotic abilities in the fish gut, belonging to the *Pseudoalteromonas, Pseudomonas, Bacillus,* and *Rhodopseudomonas* genera. ↑ Expression of pathways related to the metabolism of fucose
[21]	Atlantic salmon (*Salmo salar*) gut microbiota	*C. vulgaris* (2% or 14% enriched diet for 8 weeks)	16S rRNA amplicon sequencing from intestinal mucosa-associated bacterial communities	↑ *Paenarthrobacter* and *Trichococcus* ↓ Lactic acid bacteria *Lactobacillus, Weissella, Floricoccus* ↑Transcriptional resilience towards oxidative stress
[22]	Healthy beagle dog's gut microbiota	*C. vulgaris, N. oceanica,* and *T. obliquus* (0.5,1, and 1.5% enriched diet for 10 days)	16S rRNA amplicon sequencing (V1-V2) from fecal samples	↑ *Turicibacter* and *Peptococcus* are associated with gut health and activation of the immune system at 1.5% of supplementation
[23]	Healthy beagle dog's gut microbiota	Macroalgae *(Ulva rigida* and Fucus vesiculosus*)* + *C. vulgaris* blend (1.5% enriched diet)	16S rRNA amplicon sequencing (V1-V2) from fecal samples	Microbiota diversity and abundance were mostly unaffected by algae blend supplementation, with health-promoting genera *Turicibacter* and *Blautia* being the most abundant ↑ SCFA
[24]	Healthy lamb's rumen microbiota	High-fat diet supplemented with 3% *A. platensis*	16S rRNA amplicon sequencing (V3-V4) from rumen samples	Significant change in microbial composition ↓ Richness and diversity, specifically, the groups of *Prevotella 9* and *Megasphaera,* in contrast with the high-fat diet
[25]	Healthy lambs' intestinal microbiota	Control diet supplemented with 3% *A. platensis*	16S rRNA amplicon sequencing (V3-V4) from intestinal samples	No significant microbial changes, with Prevotella being the primary genus, followed by *Lachnospiraceae_NK3A20, Olsenella, Succinivibrionaceae_UCG-001,* and *Ruminococcus*

Authors	*In vivo* model	Microalgae/dosis	Methods	Study outcome
[26]	Broiler chickens' gut microbiota	Inclusion of *C. vulgaris* diet (0, 0.25, 0.5, and 1%)	16S rRNA amplicon sequencing (V4) from intestinal samples	Firmicutes was the most abundant group, followed by Bacteroidetes and Proteobacteria ↑ *Bifidobacterium spp* in 1% microalgae group
[27]	Heat-stressed broiler chickens' gut microbiota	Basal diet enriched with *A. platensis* (1 g/kg diet) or (1 g *A. platensis*/kg +200 mg garlic powder/kg diet)	Microbial plate counts from cecal samples	Significant improvement of gut morphology, increasing the intestinal lactobacilli, and reducing the coliform contents when microalgae were added
[28]	Female sow pigs and their piglets' gut microbiota	Standard diet supplemented with 1 g/sow/day of *E. gracilis* from day 85 of gestation until day 21 of lactation	Metagenomic analysis and 16S rRNA amplicon sequencing (V3-V5) from fecal samples	Sows: ↑ Bacteroidetes *(Prevotella* and *Bacteroidales*) and Spirochaetes (*Treponema*), while ↓ Firmicutes *(Clostridium* and *f_Peptostreptococcaceae)* during the lactation period Piglets: ↑ Bacteroidetes (*Bacteroides*) and Proteobacteria (*Escherichia*), but ↓Firmicutes (*Lactobacillus*) during the suckling period, than those nursed by control sows

Increased levels of *Phascolarctobacterium* would promote the growth of symbiotic bacteria in the intestine, which play a major role in the protection against intestinal disorders. The study linked by Azad et al. (2025) [8] revealed that C. vulgaris supplementation had a causal effect on pathogenic bacteria associated with SCFA production. Moreover, *C. pyrenoidosa* polysaccharide ameliorated impaired lipid metabolism and intestinal flora by selectively regulating the levels of beneficial bacteria, specifically increasing the abundance of *Coprococcus*_1, *Peptococcus,* and *Turicibacter*, and reducing the levels of *Ruminococcus_gauvreauii*_group [13]. *A. platensis* PUFAs and *Schizochytrium* sp. oil showed beneficial effects on gut microbial profile in high-fat-fed rats [14,15]. While PUFAs from *A. platensis* increased the abundance of beneficial bacteria such as *Prevotella*, *Alloprevotella*, *Porphyromonadaceae*, *Barnesiella*, and *Paraprevotella*, they significantly reduced the levels of Turicibacter, Romboutsia, Phascolarctobacterium, Olsenella, and Clostridium XVIII, which were positively correlated with serum triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels. Similarly, *Schizochytrium* sp. oil showed beneficial effects on dysregulated gut microbiota of high-fat-fed rats by increasing the abundance of SCFA-producing bacteria and attenuating the growth of obesity-promoting *Desulfovibrio* and other pathogenic organisms. These results suggest that the PUFAs and oil from these microalgae species exhibit therapeutic effects and may be explored to prevent gut dysbiosis and intestinal disorders associated with hyperlipidemia.

Effects of microalgae on the human gut microbiome: *In vitro* simulation methods for the human gut fermentation process are widely used worldwide to evaluate the impact of dietary components on the human gut ecosystem. These models facilitate high-throughput screening of compounds, enabling detailed analyses of microbial composition, fermentation profiles, and metabolite production [29]. Their cost-effectiveness and reproducibility make them ideal for preliminary investigations and therefore represent a key first approach. For microalgae, several in vitro approaches to study their effects on the gut microbiome have been previously described and are detailed in Table 2. These studies highlight the growing interest in microalgae as modulators of the human gut microbiome. Regarding microbial composition, a common finding across these studies is the promotion of beneficial gut bacteria. For instance, *A. platensis*, *C. vulgaris*, and *C. pyrenoidosa* were consistently associated with increases in the genera *Bifidobacterium*, *Faecalibacterium*, *Roseburia*, and *Lactobacillus,* which have often been linked to anti-inflammatory effects and improved gut health [30].

Moreover, in the case of metabolite production, most microalgae species stimulate the production of the major SCFA, which are nowadays considered key intestinal health biomarkers [31]. Still, while the microalgae species of *D. maximmus* and *C. pyrenoidosa* stimulated butyrate and propionate production, the addition of *A. platensis* in the dynamic simulator of human intestinal microbial ecosystem (SHIME) led to a reduction in propionate and ammonium, without significant acetic or butyric acid production.

These outcomes might be linked to differences in experimental setups, microalgae species, doses used, and controls selected, all of which are not globally harmonized. Moreover, some studies revealed specific compositional or donor-dependent outcomes. In the work of Van der Linder et al. 2021 [32], *C. pyrenoidosa* showed differential effects depending on the host's health status, with microbial and SCFA profiles diverging in healthy individuals, in contrast to coeliac donors. This underscores the importance of host-specific microbiome baselines when assessing functional impacts of microalgal components. In addition, specific microalgal-derived compounds (e.g., fucoxanthin-enriched or PLE extracts) demonstrated functional interactions with gut microbes, suggesting selective bioactive effects that could be overlooked when using whole microalgae biomass. Overall, the *in vitro* approaches collectively reveal significant trends in microbial shifts and metabolite production driven by microalgal substrates, which reinforces the potential use of microalgae as gut health modulators.

Table 2. *In vitro* studies focused on the effects of microalgae on the human gut microbiome.

Authors	Microalgae	Fermentation model	Microbial Analysis	Results
[32]	Cell wall disrupted *C. pyrenoidosa*	Three-stage continuous gut model using fecal samples from a healthy vs. a coeliac 30-year-old female volunteer	16S amplicon sequencing (V3-V4) + inferred metagenomics	Healthy donors: ↑ *Prevotella, Ruminococcus, Faecalibacterium*; ↑ butyric and propionic acids; ↓ acetic acid Coeliac donors: ↑ *Faecalibacterium, Bifidobacterium, Megasphaera*; ↓ *Enterobacteriaceae*
[33]	*In vitro* digested *C. vulgaris, Desmodesmus maximus, Chlorococcum* sp. *cf hypnosporum,* and *A. platensis*	48 h badge fermentation using fecal samples from 4 healthy volunteers	FISH, combined with flow cytometry, enabled hybridization of 16S rRNA regions in selected bacteria	↑ *Lactobacillus-Enterococcus* ↑ *Bifidobacterium* ↓ *Prevotellaceae-Bacteroidaceae* ↓ *C. histolyticum* ↓ *E. rectale* ↓ *C. coccoides* ↑ Acetic and propionic acids (*A. platensis*) ↑ Butyric and propionic acid (*D. maximus*)
[34]	*Lb. acidophilus* *VS* *Lb. acidophilus + A. platensis*	SHIME using five healthy medium-aged volunteers	16S amplicon sequencing (V3-V4)	↑ *Erysipelatoclostridium, Roseburia, Enterococcus, Bifidobacterium, Coriobacteriaceae UCG-03, Enterobacter,* and *Paraclostridium* ↓ Propionic acid and NH_4^+ (*A. platensis*)
[35]	*In vitro* digested *C. vulgaris, C. protothecoides*, and *Schizochytrium* sp.	48 h batch fermentation with fecal samples from three healthy donors (20–30 years)	16S amplicon sequencing (V3-V4)	↑ *Bacteroides* and *Dialister* ↑ Propionic acid
[36]	*In vitro* digested *C. vulgaris*	48 h batch fermentation with fecal samples from three healthy donors (20–30 years)	16S amplicon sequencing (V3-V4)	↑ *Faecalibacterium, Dialister, Megasphaera, Dorea, Odoribacter, Roseburia, Bifidobacterium, Butyricmonas,* and *Veillonella* ↑ Major SCFAs

Authors	Microalgae	Fermentation model	Microbial Analysis	Results
[37]	*In vitro* digested fucoxanthin-enriched extract from *Nitzschia laevis*	72 h batch fermentation with fecal samples from three healthy donors (20–30 years)	None	Degradation of fucoxanthin, suggesting gut microbiota-mediated metabolism
[38]	*In vitro* digested *Arthrospira*, *Chlorella*, and *Phaeodactylum tricornutum* extracts obtained by PLE	48h batch fermentation with fecal samples from six healthy donors	Targeted microbial quantification by qPCR analysis	Inhibited pathogenic bacteria, promoted *Lactobacillus* and *Bifidobacterium*, and increased major SCFAs
[39]	*In vitro* digested and extracted polysaccharides from *C. pyrenoidosa*	48h batch fermentation with fecal samples from five healthy donors	16S amplicon sequencing (V3-V4)	↓ Ratio of Firmicutes *to* Bacteroidetes ↑ *Parabacteroides distasonis* and SCFA
[40]	*In vitro* digested *N. gaditana* biomass	72 h static fermentation with fecal sample from a healthy donor	16S amplicon sequencing (V2, V3, V4, V6–7, V8, and V9)	↑*Akkermansia, Butyricicoccus, Eisenbergiella, Lachnoclostridium,* and *Marvinbryantia* ↑ Mainly butyric and valeric acids
[41]	*In vitro* digested *T. chuii* biomass	72 h static fermentation with fecal sample from a healthy donor	16S amplicon sequencing (V2, V3, V4, V6–7, V8, and V9)	↓ *Clostridium, Staphylococcus* and *Enterobacteriace* ↑ *Akkermansia* and *Butyricimonas* ↑Major SCFA
[42]	*In vitro* digested *C. vulgaris* biomass	72 h static fermentation with fecal sample from a healthy donor	16S amplicon sequencing (V2, V3, V4, V6–7, V8, and V9)	↓*Enterobacteriaceae, Enterococcus* spp.*,* and *Staphylococcus* spp. ↑ *Akkermansia* and *Lactobacillus* ↑Major SCFA

Although the consumption of some microalgae species such as *A. platensis*, *C. vulgaris* and *T. chuii* as novel foods themselves or as food ingredients has been already approved by the European Food Safety Authority (EFSA) and the United States Department of Agriculture (USDA), where the average amount of microalgae incorporated into functional foods typically ranges from 0.5% to 3% of the product’s weight [43], only two clinical trials have recently focus on the effects of microalgae on gut health (Table 3).

These studies provide compelling evidence that microalgae may provide significant health benefits and could be used as functional food products to mitigate gut dysbiosis and gastrointestinal disorders. This is evident by their ability to modulate microbial diversity associated with gut health, inhibit gut inflammation, trigger the production of short-chain fatty acids, and regulate lipid metabolism. These biological effects exhibited by different microalgae species may be attributed to the diversity of bioactive compounds, such as PUFAs, carbohydrates, and polyphenols, present in these species. However, the molecular mechanisms remain to be fully elucidated. Studies have also demonstrated the safety and potential efficacy of minimally processed microalgal products. Some microalgal species, such as Schizochytrium, Chlorella, Dunaliella, Arthrospira, and Haematococcus, have been approved by regulatory authorities for incorporation into food products. Hence, it is critical to ensure that microalgal biomass regulations are in accordance with regulatory standards to ensure safety and quality.

Table 3. Clinical human trials focused on the effects of microalgae on the gut microbiome.

Authors	Microalgae	Study design	Results
[44]	1 g or 3 g of *Chlamydomonas reinhardtii* biomass	51 participants divided into four groups by gastrointestinal symptoms frequency (low/high) and daily algae dose (1 or 3 g) 16S amplicon sequencing(V4)	Individuals with frequent GI symptoms reported less discomfort with regular *C. reinhardtii* intake Gut microbiome remained complex across all groups, with no signs of dysbiosis
[46]	*Tetradesmus obliquus* Mi175.B1 extract (20-35% w/w) + coconut oil (65–80% w/w) + mix of non-GMO tocopherols E 306 (0.45–0.55% w/w) in a 250 mg capsule *VS* Maltodextrin placebo control	56 healthy-weight adults 4-week randomized, double-blind, placebo-controlled trial 16S amplicon sequencing (V4)	The supplement was safe and well-tolerated ↓ Gastrointestinal symptoms ↑ Shannon's index ↓ Butyrate level ↓ Chromogranin A No adverse effects on cardiovascular health markers
[47]	*C. vulgaris CK5* tablets (3 g/day)	Patients with type 2 diabetes (n = 12, 5 < 60 years old, 7 ≥ 60) for a period of 30 days (baseline vs final day) 16S amplicon sequencing (V3, V4)	↓Bacteroidetes and ↑Firmicutes. ↑ *Akkermansia, Coprococcus, Dorea, Lachno-spira, Lachnospira, Phascolarctobacterium,* and *Ruminococcus* genera ↓*Paraprevotella, Prevotella, Klebsiella,* and *Sutterella*. *C. vulgaris* induced a significant reduction in perceived stress scores, negatively correlated with ↑ Akkermansia, Coprococcus, Dorea, Lachnospira, Phascolarctobacterium, and Ruminococcus, and positively correlated with ↓Paraprevotella, Prevotella*, Klebsiella,* and *Sutterella*.

While the evidence for the therapeutic potential of some microalgal species is promising, several research areas remain. Firstly, most trials to date have focused on healthy individuals, which limits the generalizability of the findings to clinical populations such as those with irritable bowel syndrome, inflammatory bowel disease, or diabetic disorders. Moreover, all of them have focused on adult or elder groups, leaving behind the potential beneficial effects the incorporation of microalgae, specifically A. platensis and Schizochytrium sp., could have in infant or children's gut health [48]. What is more, the duration of interventions has generally been short (e.g., 4 weeks), and longer-term studies are needed to evaluate sustained microbiota shifts and potential systemic effects. Therefore, future clinical work should aim to directly compare the efficacy of different microalgal species and formulations (e.g., whole biomass vs. extract) using standardized endpoints, including microbiome structure, functional metabolites, intestinal permeability, and host inflammatory responses.

Knowledge gaps and future directions: Research on how microalgae affect the gut microbiome employs various models, each with complementary strengths and limitations in translatability and mechanistic insight [49,50]. Nevertheless, the microalgae-gut microbiome axis is a rapidly emerging field with many layers of complexity that should also be taken into consideration. This field faces unique challenges that distinguish microalgae from conventional prebiotics or probiotics. A primary challenge is their inherent biochemical variability, which demands strain-specific standardization for reproducibility [51,52]. Furthermore, study designs must clearly distinguish between whole biomass, which serves as a fermentable fiber, and purified extracts (e.g., lipids, carotenoids), which may directly modulate host functions, such as immunity [53-55].

Microalgae do not always behave like classical prebiotics. Their effects may be indirect, via anti-inflammatory signaling or bioactive peptides, and may enrich microbial taxa not typically associated with standard prebiotics [56-58]. Consequently, research must move beyond traditional metrics like *Bifidobacterium* growth, incorporating metagenomic and metabolomic techniques to capture functional shifts.

A critical technical limitation for 16S rRNA sequencing studies is the co-amplification of residual chloroplast DNA from ingested microalgae, which can skew diversity metrics and inflate bacterial abundances. Mitigation requires bioinformatic filtering, careful primer design, or complementary metagenomic approaches [59,60].

Host interactions are also key. Effects may occur through reduced intestinal permeability or gut-brain axis signaling without significant taxonomic changes, underscoring the need to measure host physiological markers alongside microbial data [46]. Similarly, SCFA production can follow atypical patterns (e.g., increased diversity with reduced butyrate), necessitating functional analyses beyond absolute concentration measurements [46].

Finally, the duration of the intervention and the delivery strategy are crucial. As novel substrates, microalgae may require adaptation periods of 3–4 weeks or longer. Their bioavailability is also heavily influenced by encapsulation, digestibility, and cell wall structure, which determine if active compounds reach the colon.

In summary, while microalgae represent a promising dietary strategy to modulate gut health, their unique biological complexity demands carefully tailored study designs, and addressing these considerations will be essential to harness their full potential as functional ingredients targeting the gut microbiome.

CONCLUSION

The integration of microalgae into gut microbiome research reveals a compelling intersection between nutrition, microbial ecology, and human health. Findings across animal models, *in vitro* fermentations, and preliminary clinical trials suggest that microalgal compounds can selectively modulate microbial communities, enrich health-associated taxa, such as SCFA. These properties position microalgae as promising candidates in the formulation of next-generation functional foods. Nonetheless, the diversity of microalgal species, variability in cultivation and processing methods, and host-specific responses introduce significant complexity. In addition, challenges such as interference from chloroplast DNA in microbiome sequencing and limited human data hinder the establishment of clear mechanistic pathways. Moving forward, interdisciplinary research integrating systems biology, nutrition science, and microbiome analyses will be critical. Therefore, a harmonized framework across studies will be essential to validate the therapeutic potential of microalgae and translate their bioactive promise into safe, effective dietary interventions for gut and systemic health.

Abbreviations: BW: Body weight; DNA: Deoxyribonucleic acid; EFSA: European Food Safety Authority; FISH: Fluorescence in situ hybridization; GC-MS: Gas chromatography–mass spectrometry; GI: Gastrointestinal; GMO: Genetically modified organism; PLE: Pressurized liquid extraction; PUFA: Polyunsaturated fatty acids; qPCR: Quantitative polymerase chain reaction (real-time PCR); RNA: Ribonucleic acid. rRNA: Ribosomal ribonucleic acid. SCFA: Short-chain fatty acids. SHIME: Simulator of human intestinal microbial ecosystem. USDA: United States Department of Agriculture.

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