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Bioactive Compounds from Microalgae: Mechanistic Insights into the Regulatory and Therapeutic Potential of the Gut Microbiota

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ABSTRACT: Targeting gut microbiota dysbiosis—a key driver in chronic disease—has become a major research focus. Microalgae-derived bioactive compounds, such as polysaccharides, *ω*-3 PUFAs, carotenoids, and phenolics, represent promising candidates owing to their structural diversity and multi-functional properties. They operate through a dual mechanism: serving as metabolic substrates for beneficial gut bacteria and directly modulating host signaling pathways. This review first systematically analyzes the epidemiological associations between gut dysbiosis and various chronic diseases. It then focuses on the multi-target regulatory potential of microalgal bioactive compounds in mediating gut microbiota-host interactions. Furthermore, it examines key strategies to enhance the production of these functional metabolites, from optimizing photobioreactor design and cultivation conditions to applying induction techniques. Despite promising prospects, challenges remain in enhancing compound bioavailability, overcoming individual heterogeneity in microbiota responses, and establishing standardized clinical evaluation systems. By integrating multi-omics technologies with synthetic biology tools, this review aims to provide innovative perspectives for developing microalgae-based functional foods and precision therapeutics, thereby bridging microbial ecology with personalized nutrition to offer sustainable solutions for chronic disease prevention and management.

Keywords: Microalgae bioactive compounds; Gut microbiota; Microbial dysbiosis; Metabolic-immune regulation

1. Introduction

The human gastrointestinal (GI) tract, as the largest and core component of the digestive system, serves not only as the primary site for nutrient breakdown and absorption but also contains extensive lymphoid tissues that form a critical immune barrier[1]. This unique environment harbors a complex symbiotic ecosystem - the gut microbiota - comprising bacteria, archaea, and fungi. The gut microbiota consists of over

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10^{14} microorganisms representing more than 35,000 bacterial species[2], which establish a profound symbiotic relationship with the host. These microbes are essential for food digestion, energy metabolism, and vitamin synthesis, while also playing a central role in immune system development, mucosal barrier maintenance, and host-microbe signaling[3]. Under homeostasis, the microbiota maintains a balanced ecosystem by reinforcing mucosal barrier integrity, establishing metabolic networks, and regulating immune responses. Key genera such as *Faecalibacterium* modulate Treg cell differentiation and anti-inflammatory cytokine (e.g., IL-10, TGF-β) secretion, suppressing c-mediated inflammation while promoting intestinal epithelial regeneration and metabolic regulation[4]. Additionally, the glycosylated mucus layer acts as a physical barrier, limiting pathogen-epithelial contact while providing metabolic substrates for commensal bacteria, fostering a mutualistic host-microbiota relationship. Disruption of this homeostasis leads to dysbiosis, characterized by increased mucosal permeability, release of pro-inflammatory cytokines (IL-6, TNF-α), and metabolic disturbances, ultimately triggering systemic inflammation and chronic diseases via the "gut-organ axis"[5].

However, modern dietary patterns such as dietary fiber deficiency, high-sugar and high-fat diets, industrialized food intake, and the abuse of antibiotics are causing "dysbiosis" by disrupting the diversity and functional balance of the microbiota[6]. Epidemiological studies demonstrate that this microbial imbalance, marked by depletion of beneficial taxa (e.g., *Faecalibacterium*, *Bifidobacterium*) and enrichment of pathobionts (e.g., *Proteobacteria*, *Enterococcus*), shows significant positive correlations with increased incidence of diabetes, cardiovascular diseases, neurodegenerative disorders, and chronic obstructive pulmonary disease (COPD)[7,8]. For instance, inflammatory bowel disease (IBD) patients exhibit reduced gut microbiota *β*-diversity and overgrowth of pro-inflammatory bacteria such as adherent-invasive *Escherichia coli* (AIEC), which exacerbates intestinal inflammation through NF-κB pathway activation. In diabetic and hypertensive patients, increased abundance of endotoxin-producing bacteria (e.g., *Enterobacteriaceae*) triggers insulin resistance and vascular endothelial dysfunction via CD14/TLR4 signaling[6,9]. These perturbations not only alter the gut microenvironment but also systemically modulate host immunity and metabolism through microbial-derived metabolites (e.g., disrupted secondary bile acid and short-chain fatty acid profiles), ultimately establishing a bidirectional "microbiota-host" pathogenic network[10].

As one of Earth's earliest photosynthetic organisms, having originated approximately 3 billion years ago, microalgae have evolved diverse and unique secondary metabolic pathways throughout their prolonged evolutionary history[11]. The functional bioactive compounds they synthesize - including carotenoids and polyunsaturated fatty acids not only modulate gut microbiota diversity through dietary intake, but also mediate microbiota-host metabolic interactions, demonstrating significant biomedical value in maintaining immune homeostasis and energy balance[12,13]. Microalgae have gained significant research attention as a promising dietary intervention for modulating gut microbiota and mitigating chronic diseases, owing to their rich profile of bioactive compounds including polysaccharides, *ω*-3 polyunsaturated fatty acids (PUFAs), carotenoids, and phenolic compounds [14]. Their growing prominence is underpinned by several inherent

advantages: microalgae exhibit an exceptional biosynthetic capacity to produce unique metabolites seldom found in terrestrial plants; they offer sustainable scalability through cultivation on non-arable land using seawater or wastewater, thereby avoiding competition with conventional agriculture; and their complex chemical composition enables multi-targeted, synergistic modulation of the gut ecosystem and host physiology, often resulting in efficacy superior to that of isolated compounds [15] (Fig. 1).

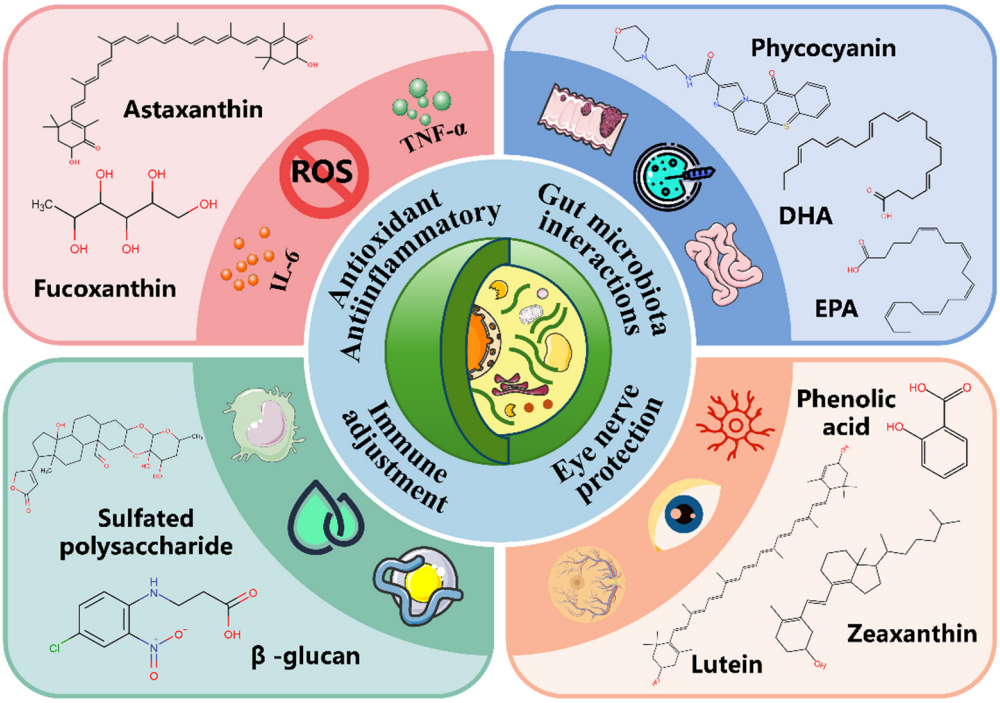

Fig. 1 Multi-target health-promoting mechanisms of microalgal bioactive compounds: Synergistic antioxidant and anti-inflammatory effects, gut microbiota modulation, immune regulation, and eye nerve protection.

Although initial studies have shown that microalgae-derived bioactive compounds regulate the gut microbiota, the specific mechanisms, such as direct interactions between the compounds and microorganisms, mediation of host signaling pathways, and synergistic effects of different compounds, still need to be thoroughly investigated. In this study, we focus on bioactive compounds derived from microalgae and examine their potential in preventing and treating chronic diseases through the modulation of gut microbiota. By reviewing pathologies associated with gut dysbiosis, we integrate current knowledge regarding how these compounds influence microbial composition, metabolic activity, and host immune-metabolic signaling pathways. The present work aims to address the existing research gap on microalgae-derived compounds in gut microbiome regulation and to provide a theoretical foundation for developing novel microalgae-based functional foods and therapeutic agents.

2. Disease spectrum associated with gut microbiota imbalance

The gut microbiota, as a central regulator of host physiological homeostasis, has been demonstrated to have its compositional and functional imbalance closely associated with the development of various chronic diseases. Such imbalance triggers pathological cascades across multiple levels including metabolism, immunity, neurology, and tumorigenesis by disrupting the microbiota-host interaction network, thereby contributing to complex disease spectra (Fig. 2).

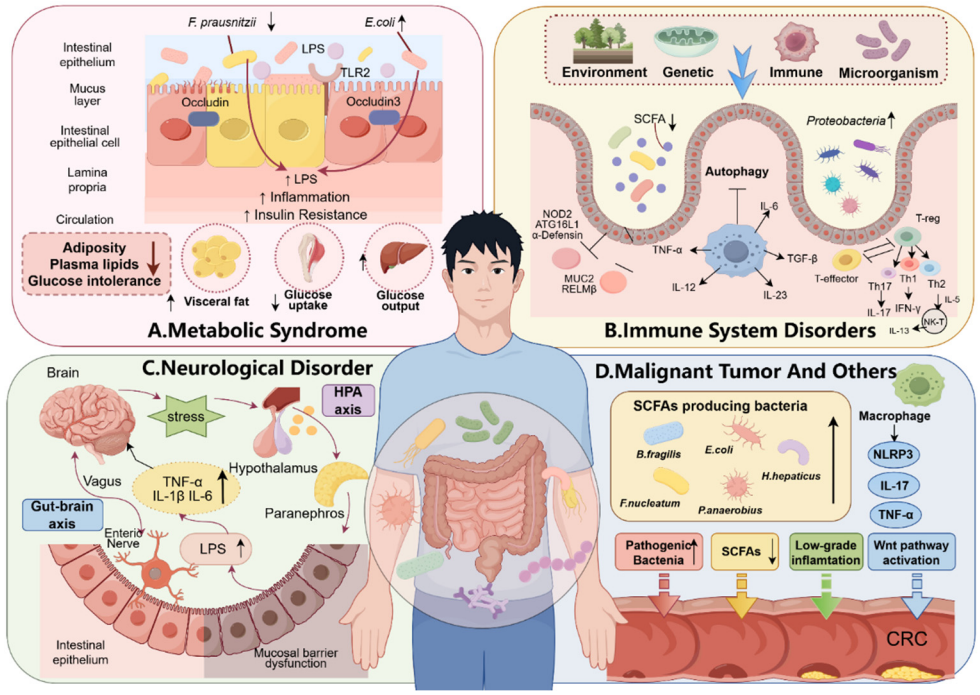

Fig. 2 Schematic representation of gut microbiota dysbiosis in multifactorial diseases through metabolic, immune, neurodegenerative, and oncogenic pathways. (A) Metabolic syndrome: Gut microbiota imbalance (*e.g.*, elevated *Firmicutes*/*Bacteroidetes* ratio) induces increased intestinal permeability, enabling lipopolysaccharide (LPS) translocation and subsequent activation of Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) signaling. This cascade promotes systemic release of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), exacerbating insulin resistance and driving obesity/type 2 diabetes mellitus (T2DM) pathogenesis. (B) Immune system disorder: In inflammatory bowel disease (IBD), pro-inflammatory *Proteobacteria* activate nucleotide-binding oligomerization domain-containing protein 2 (NOD2)/NF-κB pathways (upregulating C-X-C motif chemokine ligand 8 [CXCL8]), while T-helper 1/17 (Th1/Th17) cell polarization (*via* interleukin-23 (IL-23)/signal transducer and activator of transcription 3 (STAT3)-mediated IL-17A/interferon-gamma (IFN-γ) production) sustains chronic mucosal inflammation.(C) Neurological disorders: Gut-brain axis communication (*via* vagal neurotransmission and hypothalamic-pituitary-adrenal axis activation) amplifies neuroinflammatory responses through circulating TNF-α, IL-6, and interleukin-18 (IL-18), compromising blood-brain barrier integrity and accelerating β-amyloid (Aβ) plaque deposition in Alzheimer's disease.(D) Malignant tumors: Pathogens including *Bacteroides fragilis* and *Fusobacterium nucleatum* dysregulate *Wnt*/β-catenin signaling and activate NLR family pyrin domain-containing 3 (NLRP3) inflammasomes, establishing pro-tumorigenic microenvironments in colorectal cancer (CRC). IL-17/TNF-α-mediated immune suppression further facilitates tumor progression, with dietary metabolites potentially modulating this process. This figure was generated using FigDraw (http://www.figdraw.com).

Abbreviations: Aβ, β-amyloid; CRC, colorectal cancer; IFN-γ, interferon-gamma; IL, interleukin; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain-containing 3; NOD2, nucleotide-binding oligomerization domain-containing protein 2; STAT3, signal transducer and activator of transcription 3; Th, T-helper; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; T2DM, type 2 diabetes mellitus.

2.1 Metabolic syndrome: the gut microbiota basis of obesity and diabetes

The gut microbiota plays a central role in the pathogenesis of metabolic syndrome through the regulation of energy metabolism and induction of chronic inflammation. Obese individuals commonly exhibit an elevated *Firmicutes/Bacteroidetes* ratio, a microbial signature that exacerbates lipid accumulation by enhancing dietary energy absorption and reducing short-chain fatty acid (SCFA) production[16]. SCFAs, such as butyrate and propionate, activate G protein-coupled receptors (GPR41/43), thereby enhancing glucagon-like peptide-1 (GLP-1) secretion and modulating insulin sensitivity and satiety signaling. Notably, high-fat diet-induced gut dysbiosis increases intestinal permeability, facilitating the translocation of

lipopolysaccharide (LPS) into the circulatory system. This process triggers Toll-like receptor 4 (TLR4) signaling, leading to chronic low-grade inflammation and insulin resistance[17].

In type 2 diabetes mellitus (T2DM), gut microbiota dysbiosis manifests as reduced microbial diversity and abnormal enrichment of specific bacterial taxa. Abundance analyses reveal that T2DM patients exhibit moderate gut microbial dysbiosis, characterized by a deficiency in butyrate-producing bacteria - a key subgroup of short-chain fatty acid (SCFA)-producing microbiota[18,19]. Reduced abundance of *Faecalibacterium prausnitzii* (a butyrate producer) alongside increased pro-inflammatory Proteobacteria (e.g., *Escherichia coli*) disrupts the intestinal mucosal barrier, exacerbating chronic inflammation caused by endotoxin translocation[20]. This imbalance subsequently interferes with insulin signaling pathways. Studies demonstrate that impaired gut barrier function allows bacterial products such as lipopolysaccharide (LPS) to enter systemic circulation, activating the immune system and promoting the release of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines suppress insulin signaling, reduce insulin sensitivity, and impair normal glucose metabolism, thereby elevating diabetes risk[16].

2.2 Immune system disorders: from intestinal inflammation to systemic immune imbalance

The interaction between gut microbiota and the immune system is particularly prominent in inflammatory bowel disease (IBD) and allergic disorders[21]. Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), represents a disorder characterized by localized immune dysregulation that is driven by intestinal microbial dysbiosis. Patients with IBD exhibit significantly reduced β-diversity in their gut microbiota, characterized by diminished protective commensal bacteria and aberrant proliferation of pathogenic species. In Crohn's disease, adherent-invasive *Escherichia coli* (AIEC) directly activates the NOD2 receptor in ileal epithelial cells through type III secretion system effector proteins (e.g., OmpC), triggering the NF-κB signaling cascade and stimulating CXCL8 secretion. This recruits neutrophils, leading to the formation of transmural granulomas[22,23]. This process is closely linked to Th1/Th17 immune polarization, marked by sustained activation of the IL-23/STAT3 pathway, which drives T cells to overproduce IL-17A and IFN-γ. In contrast, ulcerative colitis is distinguished by the abnormal proliferation of hydrogen sulfide-producing bacteria such as *Desulfovibrio*[24]. Their metabolites inhibit mitochondrial complex IV activity, depleting ATP levels in colonic epithelial cells. Simultaneously, activation of the TLR4/MLCK pathway induces abnormal phosphorylation of the tight junction protein occludin, ultimately resulting in goblet cell depletion and the development of continuous superficial ulcers[25].

Gut microbiota imbalance is closely linked to the pathogenesis of systemic allergies. During allergic responses, dysbiosis may disrupt immune regulatory functions[26]. Studies indicate that reduced abundance of beneficial bacteria (e.g., *Lactobacillus* and *Bifidobacterium*) alongside increased proportions of harmful bacteria (e.g., *Escherichia coli* and *Salmonella*) can compromise the gut immune system's ability to induce tolerance to allergens, thereby elevating susceptibility to allergic reactions[27]. For example, infants with low

gut microbiota diversity and high Proteobacteria abundance exhibit an increased risk of childhood atopic dermatitis and food allergies. Additionally, gut microbiota influences dendritic cell differentiation and regulatory T cell (Treg) function, disrupting the Th1/Th2 immune balance[28]. This imbalance promotes excessive production of allergen-specific IgE, triggering systemic allergic reactions. These findings highlight the critical regulatory role of gut microbiota in systemic allergic pathogenesis[29].

2.3 Neurological disorder: Imbalance in the bidirectional regulation of the gut-brain axis

The gut-brain axis, a bidirectional communication system connecting the central nervous system and gastrointestinal tract, plays a critical role in neurological disorders such as depression and Alzheimer's disease (AD)[30]. This axis achieves bidirectional regulation through neural, endocrine, and immune mechanisms, influencing both gastrointestinal function and central nervous system health: (1) The vagus nerve serves as the primary afferent pathway, directly activated by gut microbiota metabolites: *Lactobacillus rhamnosus* induces γ-aminobutyric acid (GABA) release from vagal nerve terminals, upregulating GABA(B1b) receptor expression in the prefrontal cortex, thereby suppressing amygdala hyperactivity and improving anxiety-related behaviors[31]. (2) Gut microbiota critically modulates stress responses through hypothalamic-pituitary-adrenal (HPA) axis remodeling. Clinical studies demonstrate that depressed patients exhibit HPA axis hyperactivation characterized by elevated cortisol levels and glucocorticoid receptor resistance, which strongly correlates with gut dysbiosis[32]. (3) Immune-neural crosstalk dysfunction represents another core mechanism of gut-brain axis dysregulation. Gut microbiota influence pathogen-associated molecular pattern (e.g., lipopolysaccharide, LPS) translocation by regulating intestinal barrier integrity, subsequently triggering systemic inflammatory responses[33].

In AD, gut microbiota dysbiosis disrupts intestinal barrier function, allowing bacteria and their metabolites (e.g., lipopolysaccharide, LPS) to translocate into systemic circulation. This activates the immune system, triggering the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)[34]. These cytokines not only induce local intestinal inflammation but also enter the brain via circulation. This compromises blood-brain barrier (BBB) integrity, exacerbating neuroinflammation, and promoting neuronal damage - key drivers of AD progression. Concurrently, gut microbiota-derived amyloid proteins, such as curli produced by *Escherichia coli*, exhibit structural mimicry with host amyloids[35]. Through molecular mimicry, curli acts as a template for misfolding, facilitating the abnormal aggregation of β-amyloid (Aβ). The accumulation of Aβ, a core pathological feature of AD, generates neurotoxic oligomers and fibrillar deposits, further impairing neuronal function[36].

2.4 The occurrence and development of malignant tumors: from the intestinal microenvironment to systemic carcinogenesis

Emerging evidence demonstrates that gut microbiota contributes to tumorigenesis through diverse mechanisms, including genotoxic metabolite production, immune modulation, and epithelial barrier disruption. In colorectal cancer (CRC), specific pathogenic bacteria synergistically drive carcinogenesis via distinct pathways[37]: *Fusobacterium nucleatum* activates the β-catenin signaling pathway via its FadA

adhesin, upregulating oncogenes (e.g., c-myc, cyclin D1), while suppressing natural killer cell activity through the MyD88-dependent IL-23/IL-17A axis[38]. Polyketide synthase (pks)-producing *Escherichia coli* generates colibactin, a genotoxin that induces DNA double-strand breaks, impairs mismatch repair, promotes KRAS mutations, and inhibits apoptosis by upregulating Bcl-2/XL. *Bacteroides fragilis* secretes the metalloprotease toxin BFT, which cleaves E-cadherin to activate the TLR/NF-κB/STAT3 pathway, amplifying pro-inflammatory cytokine release (e.g., IL-17, TNF-α) and accelerating adenoma-to-carcinoma progression[39]. Additionally, *Enterococcus faecalis* triggers macrophage-mediated "bystander effects" by disseminating pro-inflammatory signals via extracellular vesicles, leading to chromosomal instability[40]. These pathogens collectively disrupt mucosal integrity through adhesion, toxin secretion, and immune reprogramming, perpetuating chronic inflammation and amplifying genotoxic stress. Together, they establish a carcinogenic network at the host-microbe interface, driving CRC development[41,42].

Also, gut microbiota dysbiosis is implicated in systemic tumorigenesis. In hepatocellular carcinoma (HCC), microbiota-derived tryptophan metabolites activate the aryl hydrocarbon receptor (AhR) signaling pathway, upregulating sterol regulatory element-binding protein 2 (SREBP2) to promote cholesterol biosynthesis and hepatocyte malignant transformation[39,43]. Pancreatic cancer-associated dysbiosis suppresses carnitine palmitoyltransferase 1A (CPT1A)-mediated fatty acid oxidation, leading to lipid accumulation and mechanistic target of rapamycin (mTOR)-driven tumor proliferation[44]. Preclinical studies demonstrate that microbiota modulation enhances the efficacy of programmed cell death protein 1 (PD-1) inhibitors, underscoring the therapeutic potential of targeting microbial communities. These findings position the gut microbiota as a cross-cancer biomarker and actionable target in precision oncology[45].

2.5 Other systemic diseases: cross-organ interactions

The gut microbiota exhibits close associations with multiple systemic diseases, including cardiovascular disorders and liver diseases, through mechanisms involving microbial metabolites, immune responses, inflammatory regulation, and neuroendocrine interactions. In cardiovascular health, gut microbiota-derived metabolites such as trimethylamine N-oxide (TMAO) and short-chain fatty acids (SCFAs) play pivotal roles[46]. TMAO promotes atherosclerosis by inducing macrophage foam cell formation and activates platelet CD40L release, elevating thrombosis risk. Conversely, SCFAs contribute to myocardial repair and blood pressure homeostasis. Dysbiosis-induced endotoxin release further triggers systemic inflammation, exacerbating cardiovascular risks[47]. Clinical evidence highlights significant correlations between gut microbiota imbalance and hypertension, coronary artery disease, and heart failure[48]. In non-alcoholic fatty liver disease (NAFLD), gut-derived acetate promotes hepatic de novo lipogenesis via acetyl-CoA synthetase (ACSS2), while butyrate suppresses hepatic stellate cell activation through PPAR-γ signaling, delaying fibrosis progression[49]. In chronic kidney disease, dysbiosis-generated uremic toxins (e.g., p-cresyl sulfate, indoxyl sulfate) - produced from microbial metabolism of aromatic amino acids - accumulate due to impaired renal clearance[50]. These toxins activate renal interstitial fibrosis

and endothelial damage, accelerating disease progression. Additionally, in rheumatoid arthritis, overgrowth of *Prevotella copri* activates Th17 responses via molecular mimicry, targeting synovial tissues[51].

In summary, gut microbiota dysbiosis is closely linked to the development and progression of diverse diseases spanning metabolic, immune, neurological, and oncological systems. Elucidating the mechanistic roles of microbiota imbalance across disease spectra may provide novel targets and strategies for diagnosis, treatment, and prevention. Future research should prioritize large-scale clinical studies and mechanistic investigations to establish causal relationships between gut microbiota and disease pathogenesis. Such efforts will advance precision medicine by offering evidence-based interventions targeting microbial-host interactions.

3. Biological characteristics and resource development of microalgal

3.1 Classification of microalgal systems

Microalgae, as photosynthetic unicellular organisms, exhibit chemical diversity in microalgal metabolites directly shaped by their phylogenetic diversity. Based on cellular structure, photosynthetic pigment profiles, and molecular phylogenetics, microalgae are classified into two major evolutionary lineages: prokaryotic and eukaryotic[52]. The prokaryotic lineage is represented by Cyanobacteria, characterized by the absence of membrane-bound nuclei. Eukaryotic microalgae encompass diverse groups, including Chlorophyta (green algae), Bacillariophyta (diatoms), and Dinophyta (dinoflagellates)[53]. Modern taxonomic frameworks integrate ultrastructural features, biochemical markers, and molecular phylogenomic data. For instance, the carotenoid biosynthesis pathway in *Haematococcus pluvialis* and the phycobilisome architecture of *Arthrospira platensis* exemplify divergent secondary metabolic strategies evolved under horizontal gene transfer and habitat-driven selection pressures in eukaryotic and prokaryotic microalgae, respectively[54,55].

Microalgae across distinct phyla produce diverse bioactive compounds through unique metabolic pathways and ecological adaptations. In Chlorophyta (e.g., *Chlorella* and *Haematococcus*), carotenoids such as lutein and astaxanthin are synthesized via the non-mevalonate pathway, with their production under nitrogen-limited conditions reaching 5% - 8% of cellular dry weight, demonstrating potent antioxidant and anti-inflammatory properties[56–58]. Diatoms (*Phaeodactylum tricornutum*) utilize C4 photosynthesis and lipid reallocation mechanisms to accumulate medium-chain fatty acids (C16-C18, up to 44.6% of dry weight) under stress, with eicosapentaenoic acid (EPA) shown to alleviate metabolic syndrome by modulating the *Firmicutes*/*Bacteroidetes* ratio in gut microbiota[59,60]. Cyanobacteria employ polyketide synthase (PKS) and non-ribosomal peptide synthetase (NRPS) gene clusters to produce hepatotoxins like microcystins and nodularins, which at low doses specifically inhibit intestinal pathogens (e.g., *Clostridium difficile*)[61,62]. Notably, symbiotic dinoflagellates (*Symbiodinium*) synthesize dimethylsulfoniopropionate (DMSP), which gut microbiota convert to the anti-inflammatory mediator hydrogen sulfide (H_2S), offering novel insights for microbiome-based therapies in inflammatory bowel disease[63,64]. This metabolic diversity

reflects both phylogenetic divergence among microalgae and their potential as targeted modulators of gut microbiota through specific molecular mechanisms (Table 1).

Table 1 Influence of microalgae-derived bioactive compounds on gut microbiota composition and health outcomes.

Microalgae Species	Dosage	Target	Affected Gut Microbiota	Health Benefits	References
Lobosphaera incisa	2% BW/d, twice daily × 1 month2% BW/d, twice daily × 1 month	Gut	↓ *Bacteroides*, *Plesiomonas*, *Shewanella*; ↑ *Fusobacteria*	Enhanced gut barrier integrity and reduced bacterial infection susceptibility.	[65]
Chlorophyceae* & *Eustigmatophyceae	1 mg/g mouse BW/d (oral)	Small Intestine	↓ *Bacillus badius*, *B. galactosidilyticus*, *B. clausii*, *B. pumilus*, *B. safensis*, *Escherichia coli*, *E. fergusonii*	Improved systemic inflammatory status.	[66]
***Scenedesmus* sp.**	2.0% stocked biomass/d, four times daily × 45 days	Entire intestine	Homogenized bacterial community structure	Increased fillet nutritional quality (e.g., n-3 polyunsaturated fatty acids [PUFAs], docosahexaenoic acid [DHA]).	[67]
***Schizochytrium* sp.**	Phase-dependent: 5% (50-100 g fish), 4% (100-500 g), 2% (>500 g)	Distal intestine	↑ *Firmicutes*	Immunomodulatory effects.	[68]
Chlorella pyrenoidosa	150 mg/(kg·d)	Caecum	↑ *Alistipes, Prevotella, Alloprevotella, Ruminococcus;* ↓ *Turicibacter, Lachnospira*	Alleviated dyslipidemia.	[69]
Chlorella pyrenoidosa* & *Spirulina platensis	150 mg/(kg·d)	Cecal	↑ *Parasutterella;* ↓ *Turicibacter*	Anti-diabetic effects.	[70]
Spirulina platensis	150 mg/(kg·d)	Cecal	↑ *Prevotella*, *Alloprevotella*, *Porphyromonadaceae*, *Barnesiella*, *Paraprevotella*; ↓ *Turicibacter*, *Romboutsia*, *Phascolarctobacterium*, *Olsenella*, *Clostridium* XVIII	Hypolipidemic effects.	[71]

3.2 Strategies for Enhanced Production of Bioactive Compounds

The core challenge in microalgae cultivation lies in balancing biomass accumulation with the induction of target bioactive compounds, often through the strategic application of environmental stresses[65,66]. Closed photobioreactors (PBRs), such as tubular and column-shaped designs, are central to this process, providing superior control over growth conditions and reduced contamination risk compared to open ponds, thereby supporting large-scale production of consistent quality[67-69].

Cultivation strategies are selected based on the target product. Autotrophic growth, driven by photosynthesis, is often used for light-dependent pigments. Heterotrophic metabolism, utilizing organic carbon sources, enables high-density biomass production[70]. Mixotrophic cultivation combines both light and organic carbon assimilation, facilitating synergistic biomass and metabolite accumulation[71]. To induce

valuable compounds, key stressors are applied: nutrient limitation (e.g., nitrogen deprivation) significantly enhances lipid and carotenoid synthesis, while high-light exposure can effectively boost antioxidant pigment production such as astaxanthin[72,73](Fig. 3).

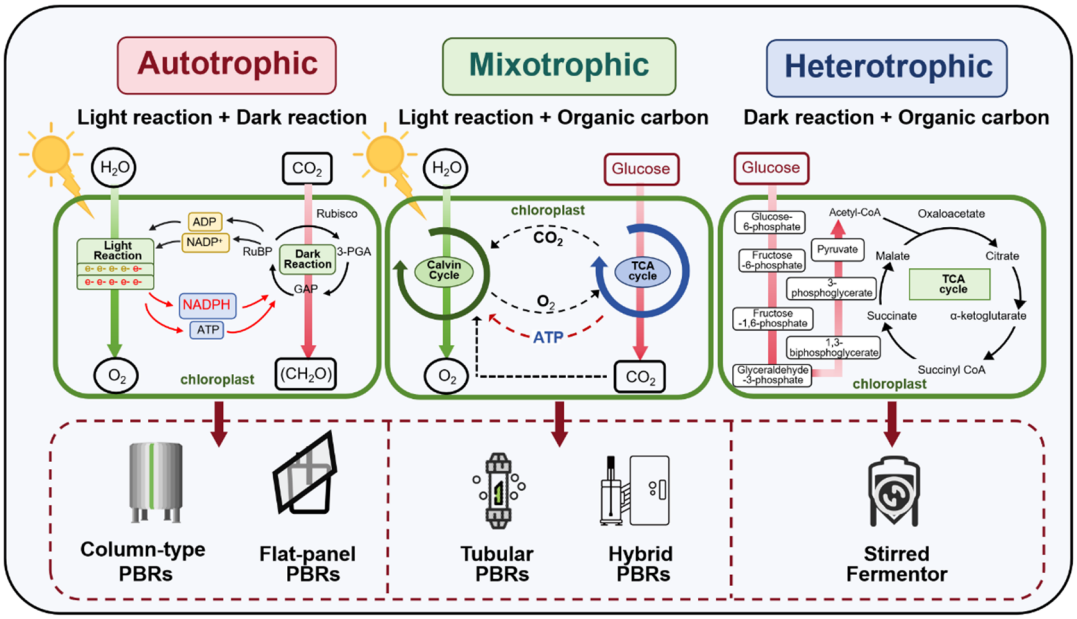

Fig. 3 Schematic diagram of the comparison of algal nutrition patterns and their correlation with the culture system. Autotrophic cultivation synthesizes organic compounds (CH_2O) through light reactions ($H_2O \rightarrow O_2$ with ATP/NADPH generation) and the Calvin cycle (Rubisco-mediated CO_2 fixation to 3-phosphoglycerate, 3-PGA), optimally implemented in columnar or flat-panel photobioreactors[74][75]; Mixotrophic cultivation synergistically integrates light reactions with organic carbon metabolism (glucose → acetyl-CoA), coordinating chloroplast and cytoplasmic pathways (Calvin cycle coupled with tricarboxylic acid cycle (TCA) intermediates), and is achieved in tubular or hybrid photobioreactors[76][77]; Heterotrophic cultivation exclusively relies on organic carbon catabolism (glucose → glycolysis-TCA cycle-derived oxaloacetate and succinate) without light-dependent processes, and is adapted to stirred fermentor[78][79].

The biosynthesis of bioactive compounds in microalgae is synergistically regulated by environmental factors and cultivation strategies, necessitating balanced optimization between biomass accumulation and metabolite induction for industrial production [80,81]. Light, temperature, and nutrient limitations activate specific signaling pathways to drive lipid and carotenoid synthesis, though these stress conditions often incur growth suppression [82]. Innovative photobioreactor designs address this challenge through dynamic regulation of light environments and culture parameters[83,84], offering viable solutions to reconcile photosynthetic efficiency with metabolic productivity[85].

Light regulation strategies precisely control light intensity and spectral parameters to directionally induce high-value compound synthesis in microalgae [86]. High-intensity light (> 500 μmol photons m^{-2} s^{-1}) significantly enhances astaxanthin production in *Haematococcus pluvialis*, while reactor-integrated light gradient designs mitigate concomitant photoinhibition[87,88]. Blue light (450-470 nm) mediates light-nutrient coupling in *Nannochloropsis oceanica* through the BlueLight-NobZIP77-NoDGAT2B signaling module: DGAT2B expression is suppressed under nitrogen-replete conditions, whereas blue light exposure during nitrogen depletion doubles triacylglycerol (TAG) yield[89]. Engineering implementations demonstrate industrial viability: flat-panel photobioreactors achieve 8.3% photonic conversion efficiency through wavelength switching (white/blue light alternation) and < 5 cm light paths[90], while pulsed illumination (10

- 100 Hz) enhances fucoxanthin accumulation by modulating PSII electron transport rates[91]. These findings provide dual molecular and engineering foundations for developing dynamic light-driven cultivation systems, advancing industrial microalgae bioprocessing through coordinated photo-regulation and metabolic engineering[92].

Nutrient stress significantly enhances microalgae lipid biosynthesis through metabolic pathway regulation. Nitrogen limitation (< 5 mg/L) redirects carbon flux toward lipid metabolism via mTOR signaling activation, elevating eicosapentaenoic acid (EPA) content to 5.2% of dry cell weight in *Nannochloropsis* sp.[93,94]. Conversely, phosphorus limitation increases acetyl-CoA carboxylase activity through NADPH/ATP ratio modulation, boosting lipid content from 15% to 42% in *Phaeodactylum tricornutum*[95,96]. The two-phase cultivation strategy spatially and temporally decouples biomass accumulation from product synthesis, as demonstrated in tubular photobioreactors for *Chlorella vulgaris* production[97]. Initial high-density cultivation (> 10 g/L biomass) in airlift reactors is coupled with subsequent nitrogen/light stress in open ponds, achieving 4.5% astaxanthin yield by dry weight[98]. This integrated system demonstrates the synergistic potential of metabolic regulation and engineered cultivation for industrial lipid production[99].

Mixotrophic cultivation enhances microalgae production resilience through synergistic integration of phototrophic and heterotrophic metabolism[83]. The core mechanism involves cooperative activation of the Calvin cycle by photochemical ATP and PPP-derived NADPH from organic carbon, elevating carbohydrate productivity by 30% in *Scenedesmus obliquus*[100,101]. Engineering strategies employing gradient carbon supply (initial 5 g/L glucose) and 12 h/12 h light-dark cycling in tubular photobioreactors effectively balance photoautotrophic-heterotrophic competition while mitigating acetate accumulation-induced TCA cycle inhibition[102,103]. Industrial implementation using wastewater-derived organic carbon (e.g., citric acid residue) reduces feedstock costs, with Fe/Mg cofactors synergistically improving chloroplast light-harvesting efficiency by 19%[104]. This system demonstrates the dual advantages of mixotrophy in metabolic flux redistribution and industrial adaptability, providing a scalable pathway for high-value compound production through rational integration of carbon partitioning and photobioreactor engineering[104,105].

4. Functional analysis of microalgal bioactive compounds

4.1 Polysaccharides: gut microbial substrate and barrier repair

Microalgae-derived sulfated polysaccharides demonstrate structure-dependent modulation of gut microbiota composition and intestinal barrier restoration through distinct molecular mechanisms[106]. Structural parameters including sulfation degree, monosaccharide ratio, and molecular weight, critically determine bioactivity[107]. Highly sulfated κ-carrageenan from red algae (30% sulfation) enhances *Bifidobacterium* spp. proliferation by 2.1-fold through electrostatic binding with bacterial surface protein[108]. *Haematococcus pluvialis* polysaccharides elevate butyrate-producing *Roseburia intestinalis* abundance by 180% via optimized sulfation patterns[109]. Conversely, low-sulfated alginates form mucoadhesive hydrogels

that reduce LPS permeability by 42%, with mannuronic/guluronic acid ratios modulating TLR4 affinity to suppress TNF-α expression by 58%, particularly when 6-O-sulfation dominates spatial configurations[110].

Molecular weight-sulfation synergy governs functional specialization: Low-MW fucoidans (< 10 kDa) penetrate mucus layers to stimulate Bacteroides thetaiotaomicron β-glucosidase activity, elevating SCFA production by 61.85%[111]. Whereas, high-MW counterparts (120 kDa) enhance tight junction integrity via ZO-1 upregulation through GEF-H1/TBK1-mediated mechanotransduction[112]. This dual functionality is complemented by sulfation pattern-mucin structural complementarity, where sulfated galactans competitively inhibit pathogen adhesion while activating Nrf2/ARE antioxidant pathways to mitigate oxidative barrier damage[113]. Low-sulfated alginates further restore epithelial ion selectivity through Claudin-2/occludin phosphorylation regulation[114].

Monosaccharide composition directs species-specific microbial cross-talk, as evidenced by Chlorella polysaccharides with acetyl-sulfate modifications selectively enriching *Parabacteroides distasonis* 3.2-fold while suppressing Enterobacteriaceae[115]. Metagenomic analyses reveal Muribaculaceae GH105 hydrolases specifically degrade mannuronic-rich alginates into oligosaccharides for subsequent Lachnospiraceae metabolism into SCFAs[116]. These structure-specific interactions establish microalgae polysaccharides as precision modulators of microbiome-host dynamics[112], providing molecular rationale for their therapeutic application in inflammatory bowel diseases through concurrent microbial manipulation and multi-target barrier reinforcement[113] (Fig. 4).

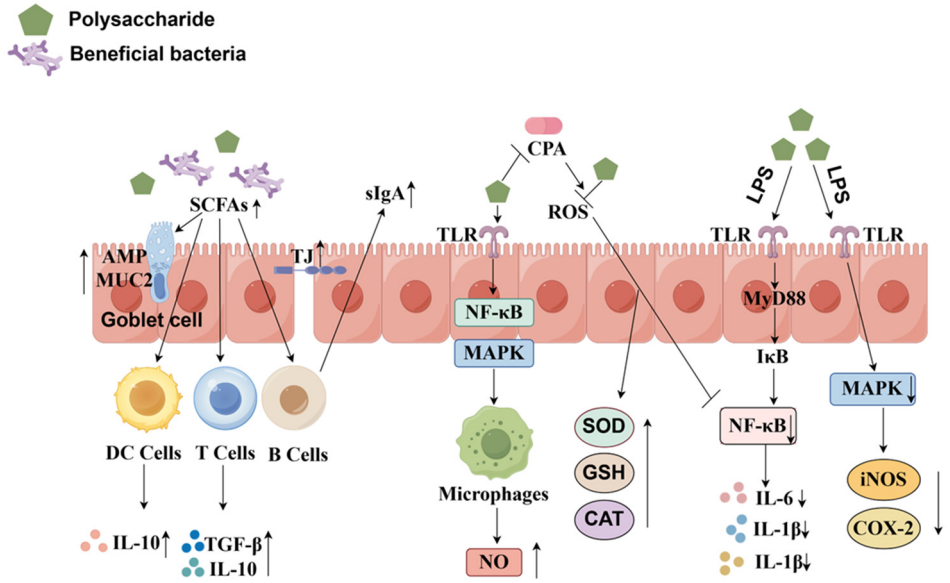

Fig. 4 Microalgae polysaccharides alleviate intestinal injury through triple-barrier synergy and dual-pathway inhibition mechanisms. Up-regulating TJ proteins (ZO-1/occludin) strengthens the intestinal physical barrier, promoting goblet cells to secrete MUC2 and increasing the abundance of beneficial bacteria through prebiotic effects, while driving the synthesis of SCFAs to maintain the chemical barrier. Meanwhile, it stimulates the DC-T-B cell axis to secrete anti-inflammatory factors such as IL-10/TGF-β, activating the immune barrier. By inhibiting phosphorylation of the NF-κB/MAPK pathway (blocking the activation of IKKβ and generation of ROS) to reduce expression of IL-6/TNF-α and enhancing activity of SOD/GSH, it achieves synergistic regulation of antioxidant and anti-inflammatory effects, ultimately repairing intestinal injury induced by LPS or chemotherapeutic drugs. This figure was generated using FigDraw (http://www.figdraw.com).
Abbreviations: DC-T-B, dendritic cell-T cell-B cell; GSH, glutathione; IKKβ, IκB kinase beta; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MUC2, mucin 2; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SOD, superoxide dismutase; TGF-β, transforming growth factor-beta; TJ, tight junction; TNF-α, tumor necrosis factor-alpha; ZO-1, zonula occludens-1.

4.2 ω-3 PUFAs: inflammation regulation and membrane homeostasis

Microalgae-derived *ω*-3 polyunsaturated fatty acids (PUFAs) exhibit dual therapeutic advantages in inflammation and metabolic disorder management through unique structural and targeted regulatory mechanisms. *ω*-3 PUFAs (e.g., DHA, EPA) competitively inhibit *ω*-6-derived pro-inflammatory eicosanoid synthesis, remodeling inflammatory microenvironments[117]. Structurally, DHA (C22:6) with extended carbon chains and double bond configuration potently suppresses TLR4/MyD88 signaling via allosteric inhibition of TLR4 dimerization and lipid raft recruitment, reducing IL-6 and TNF-α secretion by 58% and 43%, respectively, while blocking NF-κB nuclear translocation[117]. Compared to fish oil, *Schizochytrium* spp. oil contains 52.4% DHA (vs. 18.3% in fish oil), exerting dual anti-inflammatory actions[118]: (1) inhibiting TAK1-TAB1 complex-mediated JNK/NF-κB activation; (2) ameliorating adipose inflammation via microbial metabolite 10-hydroxy-cis-12-octadecenoic acid (HYA)-dependent free fatty acid receptor activation. Concurrently, DHA-derived resolvins (RvDs) enhance macrophage phagocytic efficiency by 2.3-fold, accelerating inflammation resolution[119].

The synergistic metabolism between microalgae PUFAs and gut microbiota underpins their functional efficacy. *Chlorella pyrenoidosa* extracts enrich *Lactobacillus reuter* (+ 280%) and *Bifidobacterium longum* (+ 190%), reducing hyperlipidemic rat LDL-C by 32% through bile acid hydroxylation and SCFA-axis modulation. *Schizochytrium* spp. oil (SMO) suppresses sulfate-reducing *Desulfovibrio* (- 320%) while promoting butyrogenic *Roseburia* (+ 210%), decreasing obese mouse visceral fat by 39%. When *ω*-3/*ω*-6 ratios reach 4.7:1, coordinated PPAR-γ activation and *Akkermansia muciniphila* proliferation enhance insulin sensitivity by 27%[118–120]. This microbiota-PUFA crosstalk reveals trans-system regulatory properties of microalgae metabolic interventions[121].

Synthetic biology breakthroughs enable precise optimization and scalable production of microalgae PUFAs. CRISPR-Cas9-mediated overexpression of fatty acyl-ACP thioesterase (FAT) elevates DHA production in *Haematococcus pluvialis* by 4-fold, while engineered *Yarrowia lipolytica* strains expressing heterologous eukaryotic PUFA synthases achieve 16.8% DHA yield under phosphate limitation[122]. Modular photobioreactor configurations achieve synergistic effects through electromagnetic field modulation and co-cultivation strategies, boosting PUFA productivity in *Isochrysis galbana* by 15%[123]. These innovations enhance PUFA bioavailability and establish molecular foundations for precision therapeutic strategies integrating anti-inflammatory and metabolic regulatory functions[124] (Fig. 5).

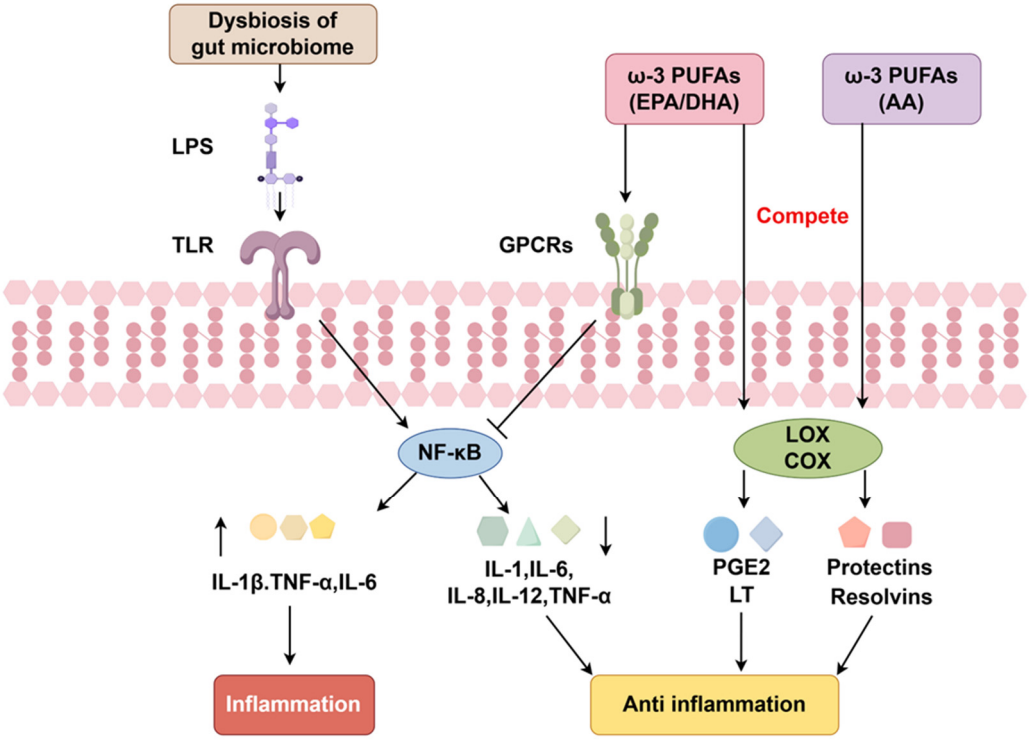

Fig. 5 *ω*-3 PUFAs (e.g., EPA and DHA) exert anti-inflammatory effects through competitive inhibition and signaling pathway regulation: On the one hand, *ω*-3 PUFAs compete with AA for binding to COX and LOX, thereby not only reducing the production of pro-inflammatory eicosanoids (e.g., PGE2 and LT) but also generating anti-inflammatory mediators (e.g., resolvins and protectins) via the same enzymatic systems; on the other hand, *ω*-3 PUFAs suppress the activation of transcription factors such as NF-κB by binding to cell membrane receptors, leading to downregulation of pro-inflammatory cytokines including TNF-α and IL-8.This figure was generated using FigDraw (http://www.figdraw.com).
Abbreviations: PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid; COX, cyclooxygenase; LOX, lipoxygenase; PGE2, prostaglandin E2; LT, leukotriene; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor-alpha; IL-8, interleukin-8.

4.3 Carotenoids: immunomodulatory effect

Microalgal carotenoids exhibit multidimensional mechanisms in antioxidant defense and immune homeostasis through their conjugated double-bond systems and functional group configurations[125]. Representative compounds (e.g., astaxanthin, lutein, fucoxanthin) achieve cross-system regulation via reactive oxygen species (ROS) scavenging and key signaling pathway modulation[126]. Astaxanthin, with 13 conjugated double bonds and a C8-keto group, demonstrates 10-fold stronger antioxidant capacity than β-carotene[127]. It suppresses mast cell degranulation by inhibiting Lyn/Fyn kinase phosphorylation and downregulates TLR4/MyD88 signaling through PPARγ activation, reducing TNF-α secretion by 40%-60%[128]. In alcoholic fatty liver models, astaxanthin (10-20 mg/kg) enhances intestinal barrier protein ZO-1 expression by 60% via *Akkermansia muciniphila*-mediated short-chain fatty acid production, confirming its microbiota-host synergistic regulation[129,130].

Lutein and fucoxanthin regulate immunity through distinct mechanisms. In LPS-induced models, lutein bidirectionally modulates redox homeostasis by inhibiting p38/JNK phosphorylation to block NF-κB nuclear translocation, while concurrently activating the ERK1/2-Nrf2 axis to elevate HO-1 expression by 2.1-fold, reducing microglial ROS levels by 40%-60%[131,132]. Fucoxanthin (≤6.25 μmol/L) dually suppresses NLRP3 inflammasome activity - blocking NF-κB priming and caspase-1 activation - thereby decreasing IL-1β

maturation by 55% - 70%.[133,134]. Its unique allyl bond configuration confers 3.2-fold higher PPARα activation capacity than β-carotene, inducing 2.1-fold *Desulfovibrionaceae* proliferation and 25% butyrate production in high-fat models[129], concurrently ameliorating metabolic inflammation and intestinal barrier function[135].

Multi-omics studies elucidate core mechanisms underlying carotenoid-microbiota interactions[136]. Lutein remodels microbial tryptophan metabolism, reducing serum trimethylamine N-oxide (TMAO) by 30% while elevating neuroprotective indole-3-propionic acid 2.5-fold[137]. Fucoxanthin alters bile acid profiles via microbiota-mediated 7α-dehydroxylation, activating intestinal farnesoid X receptor (FXR) signaling for mucosal immunity regulation. Notably, *Bacteroides*-dominated enterotypes exhibit 1.5-fold higher plasma lutein levels than *Prevotella*-enriched counterparts, revealing microbiota-dependent carotenoid bioavailability[138]. These findings systematically decipher how microalgae carotenoids achieve multidimensional regulation through structure-specific actions and microbial metabolic reprogramming, providing theoretical foundations for developing microbiota-targeted microalgae interventions via metabolic-immune network modulation[139] (Fig. 6A).

4.4 Phenolic compounds: antagonistic to oxidative stress

Microalgae-derived phenolic compounds exhibit synergistic antioxidant and microbiota-modulatory effects through their unique chemical configurations and multi-target mechanisms[140]. As secondary metabolites, these phenolics primarily include caffeic acid derivatives (e.g., *Chlorella* spp.) and flavonoid glycosides (e.g., *Phaeodactylum tricornutum*), with antioxidant capacity stemming from phenolic hydroxyl electron transfer and catechol-mediated metal chelation[141]. Salt-stressed *Desmodesmus* spp. phenolic extracts inhibit TLR4/NF-κB signaling, reversing macrophage M1/M2 polarization ratios by 1.8-fold and reducing colitis model IL-6/TNF-α levels by > 40%[142]. Structure-activity analyses reveal pyrogallol-type compounds exhibit 3.2-fold higher Fe^{2+} chelation capacity than monophenols, effectively blocking Fenton reaction cascades, while caffeoylquinic acid derivatives activate the Nrf2/ARE pathway to enhance SOD and GPx activities by 2.1-fold and 1.7-fold, respectively[143].

Microalgae phenolics exert their core functions through metabolic crosstalk with gut microbiota. *In vitro* digestion simulations reveal *Spirulina platensis* phenolics achieve intestinal release rates of 73-124 mg/100 g DW, with metabolite 3,4-dihydroxyphenylacetic acid selectively enriching butyrogenic *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* to enhance antioxidant enzyme expression via the SCFA-Nrf2 axis[144]. These compounds concurrently reshape microbiota through dual mechanisms: disrupting pathogen membrane integrity (e.g., inhibiting *Escherichia coli* biofilm formation by 65%) and promoting probiotic proliferation via siderophore competition. In disease models, *Chlorella* spp. phenolics reduce the Firmicutes/Bacteroidetes ratio (0.83 to 0.51), decreasing intestinal permeability by 42% while upregulating tight junction protein ZO-1 expression 1.6-fold, demonstrating microbiota-host co-regulation[145,146].

Advanced extraction and cultivation technologies significantly enhance the bioefficacy of microalgae phenolics. Subcritical water extraction (175℃, 5 min) boosts DPPH radical scavenging activity of *Chlorella* spp. by 2.3-fold through cell wall polysaccharide degradation and phenolic isomerization[143]. Surfactant-modified foam-bed photobioreactors regulate metabolic flux via membrane polarity modulation, achieving 58% increased syringic acid production. Molecular docking reveals hydrogen bonding between the C3-hydroxyl group of microalgae phenolics and Cys413 in Keap1 (binding energy: -8.2 kcal/mol), providing structural insights for rational design of high-activity phenolic derivatives[142]. These technological innovations establish a foundation for developing microalgae-based interventions with dual antioxidant and microbiota-modulatory functions[147] (Fig. 6B).

4.5 Sterols: regulation of metabolic pathways

Microalgae phytosterols demonstrate structural diversity and multi-target regulatory properties in cholesterol metabolism and gut microbiota modulation. Compared to terrestrial phytosterols, microalgae variants exhibit species-specific carbon chain configurations and double bond distributions: *Nannochloropsis oceanica* predominantly synthesizes campesterol (62% total sterols), while *Dunaliella tertiolecta* produces ergosterol (58%)[148]. This structural divergence stems from evolutionary adaptations in cytochrome P450-dependent C-24 methylation pathways, conferring superior cholesterol-competitive inhibition. microalgae sterols exhibit stronger binding affinity to NPC1L1 receptors, reducing intestinal absorption by 38% through steric hindrance-mediated inhibition of cholesterol-clathrin complex formation[149]. Molecular docking reveals C25-hydroxyl groups form hydrogen-bond networks with the NPC1L1 N-terminal domain (NTD), mechanistically blocking cholesterol endocytic pathways[150,151].

Microalgae sterols achieve systemic regulation through gut microbiota-metabolic network remodeling[152]. *Phaeodactylum tricornutum* sterols (200 μg/mL) elevate *Bifidobacterium adolescentis* abundance by 2.7-fold while suppressing sulfate-reducing *Desulfovibrio* in colonic models[153]. This microbial restructuring directly correlates with bile acid etabolic reprogramming: conversion efficiency of primary bile acid chenodeoxycholic acid (CDCA) to ursodeoxycholic acid (UDCA) increases by 45%. Genome-scale metabolic models (GEMs) confirm metabolic flux redistribution in butyrogenic *Faecalibacterium prausnitzii* enhances butyrate production to 1.8 mmol/g, thereby reinforcing intestinal barrier function[154]. Mechanistically, sterol metabolites activate PPARγ signaling in enterocytes, upregulating tight junction protein occludin expression by 1.6-fold and significantly reducing lipopolysaccharide permeability[155].

The bidirectional regulation of the sterol-bile acid axis constitutes the core mechanism of metabolic modulation. microalgae sterols suppress bile salt hydrolase (BSH) activity in gut microbiota, reducing free bile acid generation and subsequently downregulating hepatic CYP7A1 expression (38% inhibition), establishing an FXR/FGF19-mediated negative feedback loop. Concurrently, sterol metabolites stimulate intestinal L-cell secretion of glucagon-like peptide-1 (GLP-1, 1.9-fold increase), activating PGC-1α - a key mediator of white adipose tissue browning[156]. In metabolic syndrome models, this multi-target action

reduces serum LDL-C by 28% and increases fecal neutral sterol excretion 1.5-fold, demonstrating synergistic lipid homeostasis regulation through microbiota-host interaction networks[157] (Fig. 6C).

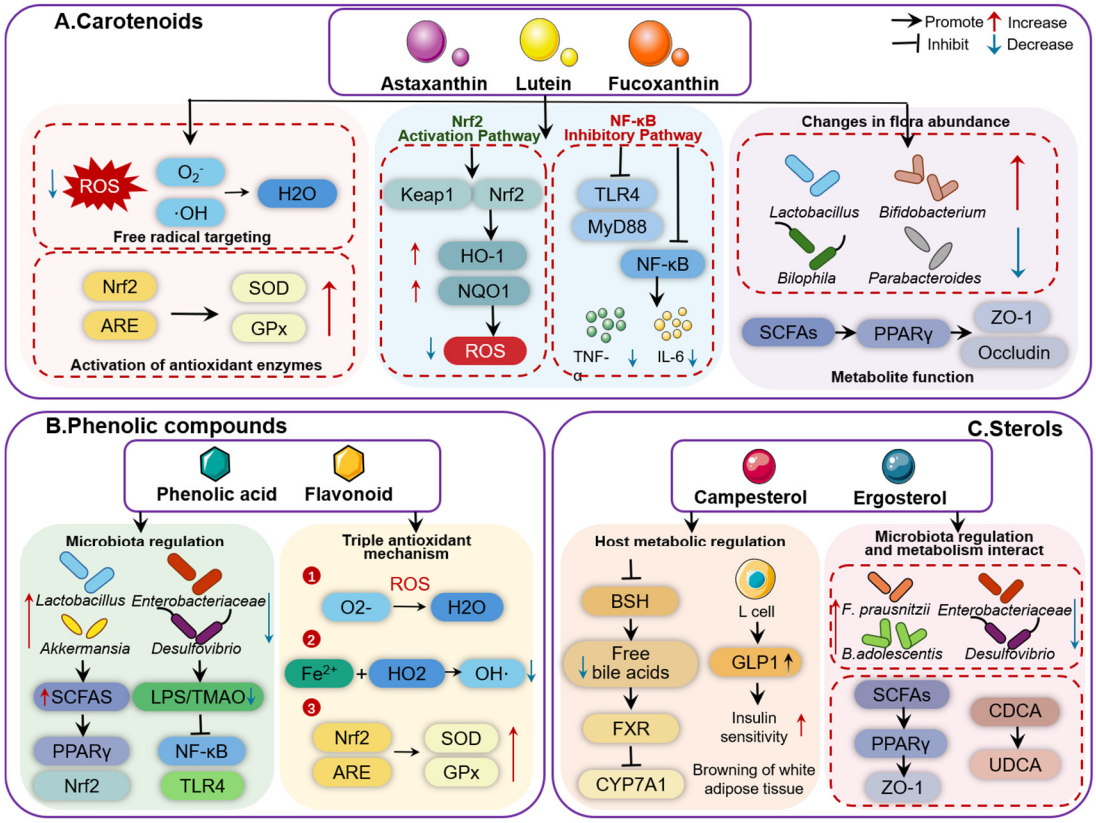

Fig. 6 Molecular mechanisms underlying the multimodal regulation of gut microbiota and host metabolism by microalgae-derived bioactive compounds. This figure systematically illustrates the molecular network through which microalgal active components (carotenoids, phenolic compounds, and sterols) coordinately regulate gut microbiota and host metabolism via multi-target mechanisms. (A) Carotenoids, including astaxanthin, lutein, and fucoxanthin, mediate their biological effects through tripartite mechanisms of action: the left pathway scavenges ROS through electron transfer while activating the Keap1/Nrf2-ARE axis (upregulating SOD, GPx, HO-1) to enhance antioxidant defenses; the central pathway mediates anti-inflammatory effects by suppressing the TLR4/MyD88-NF-κB signaling axis (downregulating pro-inflammatory cytokines TNF-α/IL-6); the right pathway improves intestinal barrier integrity through microbiota modulation (promoting *Lactobacillus*/*Bifidobacterium* while inhibiting *Bilophila*/*Parabacteroides*), thereby driving the SCFAs-PPARγ axis to enhance ZO-1/occludin expression. (B) Phenolic compounds (phenolic acids/flavonoids) improve metabolic homeostasis by regulating microbial metabolism (enriching SCFA-producing bacteria including *Akkermansia* and *F. prausnitzii* while suppressing *Enterobacteriaceae* and *Desulfovibrio*) and implementing triple antioxidant strategies: direct ROS scavenging, ferroptosis inhibition, and Nrf2/ARE pathway activation. (C) Sterols (campesterol/ergosterol) modulate gut microbiota composition (promoting *B. adolescentis* and *F. prausnitzii* proliferation while inhibiting *Enterobacteriaceae*/*Desulfovibrio*), concurrently reducing bile acid synthesis via bacterial BSH activity inhibition and FXR-mediated downregulation of hepatic CYP7A1 expression. They also enhance insulin sensitivity through GLP-1 secretion and induce white adipose browning via PPARγ pathway activation.

Note: Black arrows indicate promotion; black T-bars indicate inhibit; red arrows indicate increase; blue arrows indicate decrease.

Abbreviations: ARE, antioxidant response element; BSH, bile salt hydrolase; CYP7A1, cytochrome P450 7A1; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GPx, glutathione peroxidase; HO-1, heme oxygenase-1; IL, interleukin; Keap1, Kelch-like ECH-associated protein 1; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; ZO-1, zonula occludens-1.

4.6 Synergistic Interactions Among Microalgal Bioactive Compounds

The health-promoting effects of microalgae are not merely the sum of individual bioactive compounds but arise from potent synergistic interactions among their diverse constituents. These interactions enhance

bioavailability, amplify biological activity, and enable multi-target modulation of both the gut microbiome and host physiology.

Synergy in bioavailability and absorption: The co-ingestion of lipids and carotenoids significantly enhances the intestinal absorption of these lipophilic compounds [118]. Microalgal lipids facilitate the emulsification and micellization of carotenoids such as astaxanthin and lutein, improving their solubilization and uptake. Concurrently, carotenoids help protect PUFAs from oxidative degradation during digestion, thereby increasing the bioaccessibility and stability of both compounds [126,131]. This mutualistic interaction results in a higher proportion of bioactive molecules reaching systemic circulation and target tissues.

Amplified antioxidant and anti-inflammatory activity: Microalgal extracts frequently demonstrate greater antioxidant capacity than the sum of their isolated components due to redox interactions among molecules. For example, phenolics can regenerate oxidized carotenoids, thereby restoring their antioxidant potential and forming a more resilient and sustained defense system against oxidative stress [134]. Similarly, the anti-inflammatory effects of ω-3 PUFAs are enhanced by concomitant antioxidant actions from carotenoids and phenolics, which scavenge reactive oxygen species (ROS) that propagate inflammatory signaling pathways [123].

Multi-target modulation of the gut ecosystem: A key aspect of microalgal synergy is their multifaceted influence on gut health. Soluble polysaccharides serve as prebiotics, selectively promoting the growth of beneficial bacteria such as Bifidobacterium and Lactobacillus [107]. These bacteria ferment dietary fibers to produce SCFAs like butyrate, which strengthens the intestinal barrier. This effect is complemented by the direct barrier-stabilizing properties of ω-3 PUFAs and carotenoids. Additionally, phenolic compounds exhibit anti-pathogenic activity, helping to shape a microbial environment favorable for probiotic colonization [140]. Together, these compounds target complementary mechanisms—modulating microbial composition, SCFA production, epithelial integrity, and local immune responses—to collectively promote gut homeostasis.

5. Application Prospects and Challenges

As a novel sustainable biogenic platform, microalgae have garnered significant attention in precision nutrition, metabolic syndrome intervention, and translational medicine due to their unique photosynthetic carbon fixation efficiency and diversified metabolite profiles. However, critical technical barriers - including bioavailability regulation, personalized microbiota modulation, clinical translation challenges, and standardization framework development - persist across the research-to-industrialization pipeline. Deciphering molecular interaction networks between algal bioactive spatiotemporal delivery systems and gut niche adaptation may provide interdisciplinary solutions to overcome biomanufacturing bottlenecks in microalgae-based product commercialization.

5.1 Development of Microalgal Functional Foods

Microalgae have emerged as a pivotal sustainable resource for functional food development owing to their high-density microalgal bioactive compounds, including proteins, polyunsaturated fatty acids

(EPA/DHA), carotenoids (astaxanthin, *β*-carotene), and phycocyanin. These photosynthetic microorganisms not only enhance the nutritional quality of conventional foods but also exhibit unique techno-functional properties, offering innovative solutions to global nutrition and sustainability challenges[158].

In functional food systems, microalgae demonstrate multi-dimensional applicability: their nutrient-dense components (e.g., phycocyanin, carotenoids, and polyphenols) improve protein quality, mineral content, and antioxidant capacity in baked goods and dairy products while extending shelf life through texture modulation[159]. In bakery matrices, the water-binding capacity of microalgae proteins and the gelling properties of their dietary fibers positively influence dough texture; however, incorporation at levels exceeding 5% (w/w) may lead to color alterations and changes in digestibility [160,161]. In dairy applications, polysaccharides from microalgae help stabilize emulsions and act synergistically with antioxidants to enhance functionality, although careful management of pigment migration and texture modification remains essential [159].

Current challenges—such as the thermal instability of bioactive compounds, flavor-matrix incompatibility, and controlled nutrient release during large-scale production—require interdisciplinary approaches. Strategies including microencapsulation to protect sensitive components, co-fermentation techniques, and smart delivery systems are being developed to overcome these barriers and facilitate the commercial translation of microalgae-based biotechnology into functional food products [162,163].

5.2 Personalized Microbiota intervention strategies

Microalgal bioactives have gained prominence in precision medicine for personalized microbiota modulation, leveraging their structural diversity and functional specificity to restore gut homeostasis through host-microbiota crosstalk[164]. This regulatory capacity stems not only from direct biological effects but also multidimensional interventions on microbial composition, metabolic function, and host immunity[165].

Individualized intervention strategies must account for host genetics, baseline microbiota profiles, and metabolic phenotypes. Population-specific responses are evident: fucoxanthin (320 mg/kg) increased *Lachnospiraceae* abundance improving obesity in high-fat diet mice, while activating bile acid metabolism in normodiet individuals—differences potentially linked to initial β-diversity and bile salt hydrolase gene distribution[166]. Artificial intelligence models integrating multi-omics data (metagenomics, metabolomics, host genomics) enable response prediction[163], exemplified by machine learning algorithms optimizing phaeophycean polysaccharide dosage based on butyrate synthesis gene (e.g., *but* operon) abundance to maximize SCFA production in hypobutyryl-CoA patients. In preclinical models, *Chlorella pyrenoidosa* polypeptides (< 3 kDa) suppressed adipogenesis via AMPK activation, reducing hepatic TG by 22.98% in NAFLD mice while increasing Firmicutes/Bacteroidetes ratio to 2.04, demonstrating metabolic-microbial dual regulation[167]. A randomized controlled trial for diabetic nephropathy showed microalgae polysaccharide prebiotics elevated gut *Lactobacillus* 8.4-fold while decreasing serum IL-1β and TNF-α levels, outperforming conventional interventions[168]. Dose optimization remains critical - excessive lipid extracts may inhibit beneficial bacteria via pH alteration, while prolonged polysaccharide supplementation

risks iodine dys-regulation. Pharmacokinetic model-guided dynamic dosing (e.g., MIC-based regimens) is proposed to balance efficacy and safety. To overcome the bioavailability hurdle, established techniques such as microencapsulation (e.g., using polysaccharide-protein complexes to protect compounds during digestion) and nanoemulsification (which enhances the solubility and absorption of lipophilic compounds like carotenoids and ω-3 PUFAs) can be employed to ensure efficient delivery to the gut microbiota and systemic circulation[169].

Despite therapeutic potential, clinical translation faces three bottlenecks: (1) Limited validation beyond preclinical models[109]; (2) Unclarified synergistic effects (e.g., polyphenol-polysaccharide complexes) on microbiota-host networks[170]; (3) Standardized biomanufacturing challenges, where light-regulated carotenoid synthesis causes 30% content variability[171]. Addressing these requires interdisciplinary integration of synthetic biology for pathway optimization and nano-delivery systems for targeted release, This will ultimately enable precise and accessible personalized microbiota interventions[172].

5.3 Construction of standardized evaluation system

The standardization of microalgae bioactive evaluation requires multidimensional integration of component characterization, bioactivity validation, and manufacturing control to address inherent challenges posed by chemical complexity and bioresponse heterogeneity[173]. Central to this framework is the development of precision analytical platforms[174]: HPLC-MS/MS coupled with NMR fingerprinting achieves ± 5% quantification accuracy for phycocyanin subunit ratios (α/β) in *Arthrospira*, while supercritical fluid chromatography (SFC) enhances lipid-soluble component resolution with 0.1 ng/mL detection limits for astaxanthin isomer discrimination[175]. These methodological breakthroughs establish technical foundations for global harmonization of microalgae bioactive databases.

Bioactivity validation requires integrated in vitro-in vivo models. The Simulator of Human Intestinal Microbial Ecosystem (SHIME) accurately predicts colonic fermentation kinetics of microalgae polysaccharides by regulating microbial composition and metabolism[176], with butyrate production rates (0.8-1.2 mmol/L/h) showing strong clinical correlation ($r = 0.89$). Genetically modified zebrafish enable simultaneous assessment of lipid metabolism and gut barrier function, demonstrating transcriptomic alignment with human metabolic markers (IL-6, LDL-C)[177]. 13C-tracing quantifies bioactive compound transport efficiency (1.2%-3.8%) across biological barriers, supporting dynamic dose-response modeling[177].

Safety assessment and manufacturing standardization are critical for ensuring product quality in microalgae biotechnology. Photobioreactor systems achieve controlled fucoxanthin production with ± 8% content variation through optimized photosynthetic active radiation (PAR: 100-300 $\mu mol \cdot m^{-2} \cdot s^{-1}$) gradients and nitrogen stress timing[178]. Thus, 100 kDa ultrafiltration membranes enhance phycocyanin purification to 95% purity[179]. Current limitations include the lack of standardized tools for evaluating component synergies (e.g., antioxidant synergy indices) and real-time quality control technologies in industrial-scale operations[180]. Future development requires artificial intelligence-powered platforms that decode nonlinear

relationships between bioactive components, functional efficacy, and safety parameters through machine learning algorithms, thereby advancing data-driven innovation in microalgae-based functional foods[171,181].

6. Conclusion and prospect

Microalgae-derived bioactive compounds, through their multifaceted interactions with the gut microbiota and host metabolism, present a transformative approach for managing chronic diseases. This review has synthesized the mechanistic insights into how these compounds—ranging from polysaccharides and ω-3 PUFAs to carotenoids and phenolics—modulate microbial composition, reinforce intestinal barrier integrity, and dampen inflammatory pathways. The cultivation and induction strategies discussed herein further underscore the potential to tailor these natural products for enhanced efficacy. However, the translation of this potential into clinical and commercial reality is hampered by challenges in bioavailability, personalization, and scalable production.

To bridge these critical gaps, future research could integrate disruptive technologies with innovative conceptual frameworks through three key avenues: (1) Advancing the engineering of smart delivery systems such as gut-microbiota-responsive nanocapsules with pH- or enzyme-triggered mechanismsfor targeted colonic release, and developing microalgae-based synbiotics that use microalgae as a prebiotic shield to enhance the survival and synergistic function of co-delivered probiotics [182]; (2) Establishing causal mechanisms via synthetic ecology approaches by utilizing synthetic microbial communities (SynComs) in gnotobiotic models to precisely dissect the effects of defined microalgal metabolites on specific bacterial taxa and metabolic outputs, thereby elucidating the causal pathways linking intervention to host phenotype [183]; and (3) Enabling precision nutrition through AI-driven platforms that integrate multi-omics data—including metagenomic, metabolomic, and host genetic information—to predict individual responses to microalgae supplements and reverse-engineer optimal strain formulations and chemical profiles to correct specific dysbiotic patterns, thereby guiding personalized nutritional therapeutics [184]. By championing these integrated innovative strategies, the scientific community can accelerate the translation of microalgae from promising functional ingredients into evidence-based, precision therapeutics for gut health and broader applications.

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Declaration of Competing Interest

All the authors listed have approved this manuscript and agreed to authorship and submission of the manuscript for peer review.

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