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Microalgae-derived compounds against *Helicobacter pylori*: antibacterial, antioxidant, and anti-inflammatory evidence

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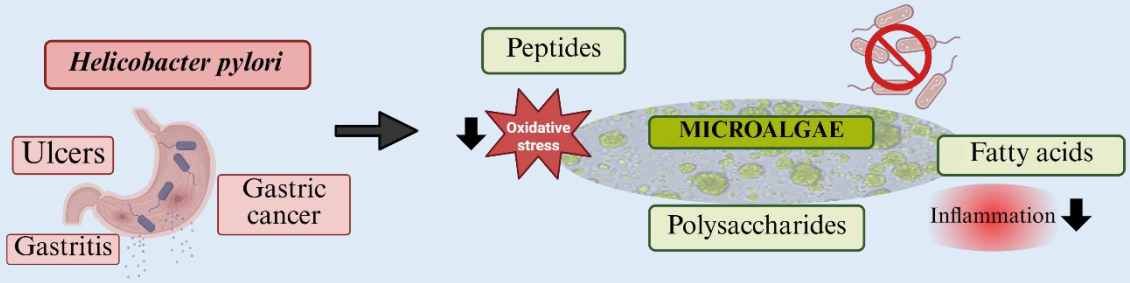
ABSTRACT

Helicobacter pylori is a Gram-negative bacterium that colonizes the human gastric mucosa and affects more than half of the world´s population. It is associated with gastritis, peptic ulcers, and gastric cancers. Despite antibiotics being long effective, increasing multi-resistance to key drugs has led to lower eradication rates, highlighting the need for alternative approaches. Natural bioactive compounds from microalgae have increased attention due to their antioxidant, antibacterial, and anti-inflammatory properties. Microalgae produce a wide variety of metabolites, such as photosynthetic pigments, fatty acids, peptides, and carbohydrates, many of which show promising activity against *H. pylori*. Antioxidants like astaxanthin and polyphenols help neutralize reactive oxygen species, protect gastric epithelial cells, and modulate inflammatory signaling. Sulfated polysaccharides and antibacterial peptides can interfere with bacterial adhesion, damage the cell membrane, and inhibit virulence factors such as *cagA* and *vacA*. Additionally, omega-3 fatty acids (EPA and DHA) and phycocyanin have strong immunomodulatory effects, reducing NF-κB activation and lowering pro-inflammatory cytokines like IL-6 and TNF-α. In contrast to previous reviews that discuss microalgal

bioactivities separately, this article takes an integrated view, connecting specific microalgal compounds with *H. pylori* virulence mechanisms and host inflammatory responses. Using different approaches at once, microalgal metabolites can help limit bacterial growth, reduce oxidative stress, and mitigate chronic inflammation. Overall, microalgae represent a sustainable and innovative source of bioactive compounds that could complement current therapies for *H. pylori* infection. Incorporating these compounds into functional foods or nutraceuticals may improve treatment outcomes, protect the gastric mucosa, and reduce the use of antibiotics. Future work should focus on improving extraction methods, enhancing bioavailability, and confirming their efficacy and safety through preclinical and clinical studies. Microalgal compounds offer a promising, safe, and environmentally friendly strategy for preventing and managing *H. pylori*-related diseases.

Keywords: *H. pylori*, microalgae, bioactive compounds, antibacterial activity, antioxidant activity, anti-inflammatory activity



INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative bacillus that colonizes the human gastric mucosa. Due to the infection of more than 50% of the global population, it is recognized as one of the most prevalent human pathogens worldwide [1]. Its high prevalence is mainly associated with its ability to be transmitted via oral–oral and fecal–oral routes, particularly in environments characterized by overcrowding and lack of access to clean drinking water. Its presence is closely associated with various gastrointestinal disorders, including chronic gastritis, peptic ulcers, and, most notably, gastric cancer [2]. Due to its direct involvement in the development of gastric adenocarcinoma, the World Health Organization (WHO) has classified *H. pylori* as a Group 1 carcinogen, indicating sufficient evidence of its carcinogenicity in humans [3].

In relation to the close association between *H. pylori* and gastric cancer, the eradication of *H. pylori* infection currently requires the administration of a combination of different pharmacological agents. The usual approach includes a mix of antibiotics together with a proton pump inhibitor (PPI). Although these antibiotic-based therapies were highly effective in the past, resistance to key antibiotics such as clarithromycin and metronidazole has increased noticeably in recent years [4]. This rise in resistance has reduced eradication rates and led to more treatment failures [5]. For this reason, current guidelines

advise against using clarithromycin-based triple therapy unless susceptibility is confirmed. Instead, bismuth-based quadruple therapy and regimens that include potassium-competitive acid blockers (PCABs), such as vonoprazan, are now preferred because they show higher efficacy and are less affected by resistance [6].

Considering these limitations, there is increasing interest in alternative or complementary therapeutic strategies that could enhance treatment efficacy while reducing antibiotic resistance. Natural bioactive compounds, particularly those derived from microalgae, have emerged as promising candidates. Microalgae produce a wide range of secondary metabolites, including polyphenols, carotenoids, and polysaccharides, which exhibit antioxidant, anti-inflammatory, and antibacterial activities [7]. Recent *in vitro* studies suggest that specific microalgal extracts can inhibit *H. pylori* growth and modulate host immune responses, highlighting their potential as novel tools in the management of *H. pylori* infection [8].

Mechanisms of pathogenicity: The pathogenicity of *H. pylori* is due to its ability to colonize and persist in the highly acidic environment of the human stomach. This survival is made possible by multiple adaptive mechanisms and virulence factors, among which urease production, flagellar motility, outer membrane proteins, and a type IV secretion system (T4SS) stand out. These traits allow the bacterium to evade host defenses, disrupt epithelial integrity, and induce chronic inflammation, leading to a wide range of clinical manifestations ranging from asymptomatic gastritis to peptic ulcers and gastric cancer [9]. One of the most critical survival strategies employed by *H. pylori* is the secretion of urease. This nickel-dependent enzyme catalyzes the hydrolysis of urea into ammonia and carbon dioxide. The resulting ammonia acts as a buffer, helping to neutralize gastric acid around the bacterium and creating a small, more favorable microenvironment in which it can establish itself. This adaptation is key not only for the initial survival of *H. pylori* but also for its long-term persistence in the gastric mucosa [10]. In addition to acid resistance, *H. pylori* expresses a wide variety of virulent proteins that contribute to its pathogenic profile. Among the most studied are cytotoxin-associated gene A (*CagA*) and vacuolating cytotoxin A (*VacA*). The *CagA* protein is injected into host epithelial cells through the type IV secretion system (T4SS), where it undergoes phosphorylation and interacts with multiple intracellular signaling pathways [11]. These interactions can lead to cytoskeletal rearrangements, disruption of tight junctions, and aberrant cell proliferation, all of which are characteristic features of precancerous transformation [12]. On the other hand, the *VacA* protein induces the formation of intracellular vacuoles, promotes mitochondrial dysfunction, and impairs antigen presentation, thereby modulating immune responses and contributing to the persistence of infection [11,13]. Recent studies have demonstrated an even greater complexity in the interaction between *H. pylori* and the host. It has been observed that the bacterium utilizes host-derived L-lactate as a metabolic source, which increases its resistance to immune responses mediated by the complement system. This not only enhances its survival under immune pressure but also highlights the strategies employed by *H. pylori* to adapt to the continuously changing gastric environment [14]. Due to its high prevalence, genetic variability, and growing resistance to commonly used antibiotics, *H. pylori* remains a major global health concern. Its ability to persist in the human host, along with its association with peptic ulcers, gastric adenocarcinoma, and mucosa-

associated lymphoid tissue (MALT) lymphoma, requires a multifaceted approach to its management. Current research focuses on the development of vaccines and the exploration of bioactive compounds from natural sources, such as those derived from microalgae, to complement conventional treatments. These efforts aim to provide safer, more sustainable, and globally accessible solutions to control and eventually eradicate this persistent pathogen [14].

Methodology: A comprehensive literature search was conducted across major scientific databases, including PubMed, Scopus, Web of Science, and the Functional Foods in Health and Disease Journal ecosystem (www.FFHDJ.com), to uncover studies examining biomolecules from different species of microalgae with antioxidant, antimicrobial, and anti-inflammatory activity against *H. pylori* infection. Studies published between January 2020 and September 2025 (last search date) were considered eligible, focusing on recent publications. Predefined keyword combinations and unrestricted free-text terms were employed in the search, such as: "*Helicobacter pylori*" or "antioxidant, antimicrobial and anti-inflammatory activities" or "microalgae" or "virulence factor". Inclusion criteria focused on peer-reviewed original research and systematic reviews, while conference abstracts and non-scientific sources were excluded. Data extracted from the literature were grouped thematically by the microalgae extract and the effects associated with *H. pylori* pathogenesis and infection. However, the limitation was relevant because of the scarcity of standardized studies on microalgal compounds against *H. pylori,* the predominance of *in silico* or preliminary *in vitro* data, and the methodological heterogeneity among sources.

Bioactive potential of microalgae: Microalgae are photosynthetic unicellular organisms that inhabit a wide variety of aquatic environments, including both marine and freshwater ecosystems. Despite their microscopic size, typically ranging from 2 to 200 µm in diameter, they exhibit remarkable biochemical versatility [15]. This metabolic plasticity enables them to produce a broad range of bioactive compounds with significant therapeutic, nutritional, and industrial potential [16]. According to Borowitzka [17], the ability of microalgae to synthesize high-value metabolites in controlled cultivation systems has made them essential contributors to the advancement of sustainable biotechnology [18]. Their adaptability is largely attributed to their efficient photosynthetic machinery and minimal structural complexity, which allow them to respond quicklbchdy to any changes in their environment. Among the most studied and cultivated species due to their robust growth, high biomass productivity, and capacity to accumulate valuable compounds are *Chlorella vulgaris* (*C. vulgaris*), *Arthrospira platensis* (*A. platensis*), and *Nannochloropsis gaditana* (*N. gaditana*) [19]. Microalgae produce a wide range of secondary metabolites, including carotenoids (e.g., astaxanthin, β-carotene, and fucoxanthin), polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), sulfated polysaccharides, peptides, sterols, and phenolic compounds. These molecules have been widely studied for their antioxidant, anti-inflammatory, antibacterial, immunomodulatory, and anticancer properties (Table 1) [7,20]. EPA and DHA have significant effects on cardiovascular health, neurodevelopment, and immune system regulation. Unlike traditional sources such as fish oil, omega-3 fatty acids derived from microalgae offer a sustainable, contaminant-free, and vegetarian-friendly alternative, aligning with current

trends in environmental management and dietary ethics [21]. In addition, sulfated polysaccharides have shown antiviral activity against herpes simplex virus and influenza, suggesting their potential as natural immunostimulants and antiviral agents [22]. Furthermore, bioactive peptides from microalgae have exhibited antiproliferative, anti-inflammatory, and antioxidant properties, among others [22].

Table 1. Bioactive compounds of microalgae

Microalgae	Biological activity	Bioactive compound	Author
Micractinium sp.	Antioxidant	Lutein, polyphenols	[23]
Chlorella vulgaris	Antioxidant, antibacterial	-	[24]
C. sorokiniana	Antitumor	Pigments, fatty acids, tocopherols, sterols, terpenoids	[25]
Tetradesmus obliquus	Antioxidant, antimicrobial, and anticancer	Carotenoids, PUFAs, sulfated polysaccharides	[26]
Arthrospira platensis	Antimicrobial	Fatty acids, flavonoids, terpenoids	[27]
Dunaliella salina	Antioxidant	-	[28]
Haematococcus pluvialis	Antioxidant, anti-inflammatory	Astaxanthin	[29]
Phaeodactylum tricornutum	Anti-inflammatory, antioxidant	Fucoxanthin, EPA	[30]
Schizochytrium spp.	Antioxidant, antimicrobial	-	[31]
Tetraselmis chuii	Antioxidant	-	[32]
Chaetoceros calcitrans	Antioxidant, antiproliferative	Phenolic and flavonoid components, sulphated polysaccharides	[33]
Coccomyxa onubensis	Anti-inflammatory	Fatty acids, (poly)phenolic compounds and carotenoids	[34]
Tisochrysis lutea	Antioxidant, antimicrobial	Fucoxanthin, DHA	[35]
Nannochloropsis gaditana	Anti-inflammatory, antioxidant	-	[36]
Chlamydomonas reinhardtii	Antioxidant, antimicrobial	Phenolic compounds	[37]
Navicula sp.	Antioxidant, antimicrobial	Fucoxanthin, polyphenols	[38]
Porphyridium cruentum	Antioxidant, anti-inflammatory	Sulfated polysaccharides, phycobiliproteins	[39]
Synechococcus sp.	Antioxidant, antibacterial	Phycobiliproteins, bioactive peptides	[40]
Anabaena sp.	Antibacterial, anticancer potential	Bioactive peptides, toxins	[41]
Spirulina maxima	Antioxidant, immunomodulatory	Phycocyanin, polysaccharides	[42]
Chroococcus turgidus	Antibacterial	Antimicrobial peptides	[43]
Botryococcus braunii	Antioxidant, anticancer potential	Botryococcene, carotenoids	[44]
Chlorella pyrenoidosa	Antioxidant, antibacterial	Lutein, polyphenols, peptides	[45]
Coelastrella sp.	Antioxidant	β-carotene, astaxanthin	[46]

PUFA: polyunsaturated fatty acids, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic Acid

Microalgae are increasingly used in the production of nutraceuticals, functional foods, cosmeceuticals, and biofertilizers. Their cultivation requires relatively little water and land, and they can grow in photobioreactors or open ponds using non-arable land, making them an attractive resource for sustainable bioproduction. Additionally, certain strains have demonstrated phytoremediation capabilities, effectively removing heavy metals, nitrogen, and phosphorus from wastewater, thereby contributing to environmental detoxification and circular bioeconomy models [47].

Microalgae also hold potential in the field of renewable energy. Due to their high lipid content, their biomass can be converted into biodiesel, bioethanol, biogas, and

biohydrogen, offering alternatives to fossil fuels and supporting the transition toward low-carbon energy systems [48].

However, economic and technical challenges remain, particularly in large-scale harvesting, dewatering, and downstream processing, which require further innovation to improve cost-effectiveness and scalability [15].

Bioactivity of microalgal compounds against *Helicobacter pylori*: Due to the presence of bioactive compounds with potential effects against *H. pylori* infection, microalgae have received special attention as a sustainable source. Thanks to their metabolic diversity, microalgae synthesize a wide range of molecules that may contribute to the prevention and control of gastric disorders associated with this pathogen. The biological effects of microalgae are particularly attributed to their antibacterial, antioxidant, and anti-inflammatory activities, which can act synergistically to limit bacterial colonization, reduce oxidative damage, and modulate host inflammatory responses (Figure 1). Together, these complementary activities highlight the relevance of microalgae as a promising natural resource for the development of alternative or adjunct strategies aimed at mitigating *H. pylori*–induced gastric pathology [49].

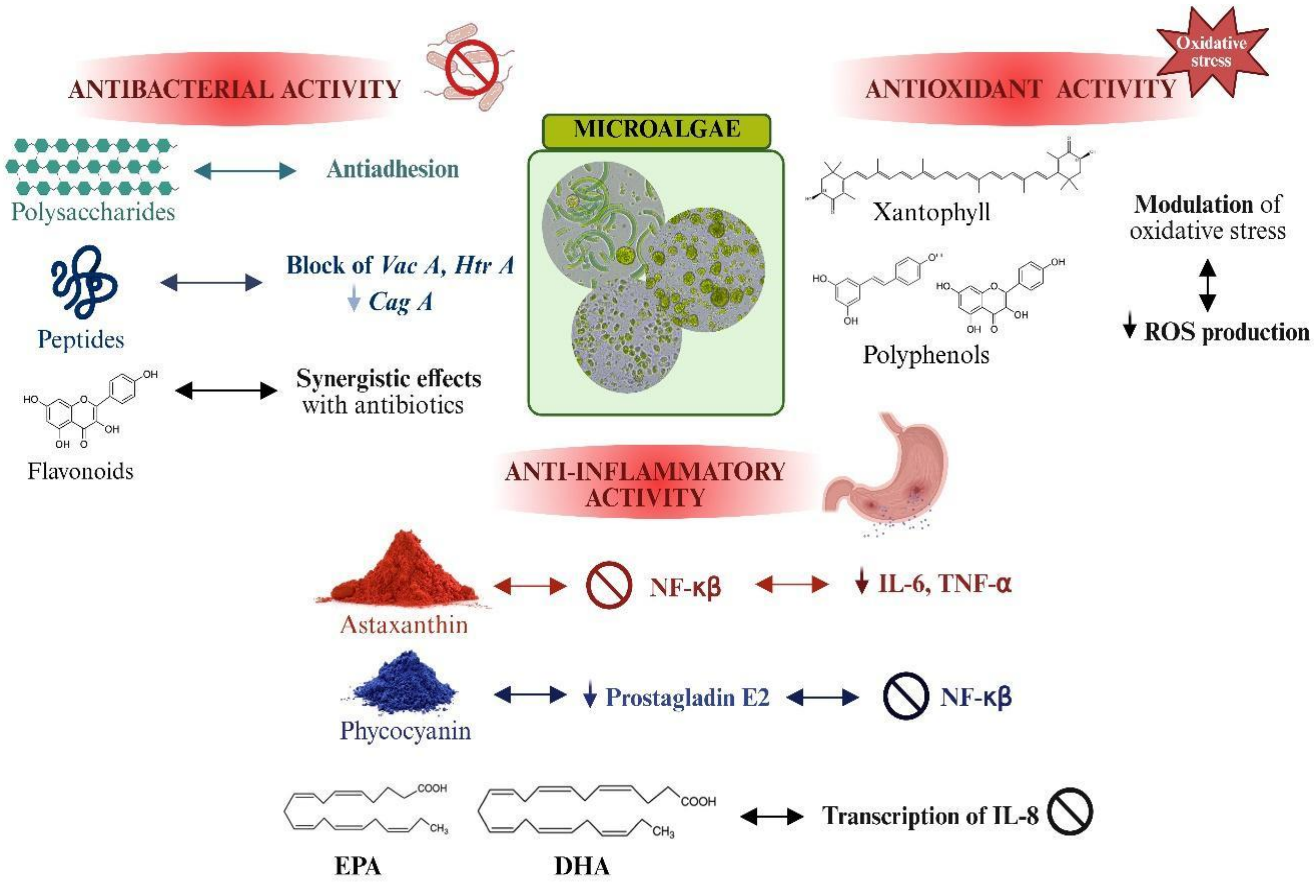


Figure 1. *Potential mechanisms of microalgae against Helicobacter pylori.*

Antibacterial activity: The bioactive compounds present in microalgae have demonstrated significant antibacterial activity against *H. pylori*. These compounds not only inhibit bacterial growth but also interfere with

key pathogenic mechanisms, including adhesion, membrane integrity, and the expression of virulence factors [50].

In addition, sulphated exopolysaccharides produced by microalgal species such as *Porphyridium* sp. and *Chlorella* sp. have been shown to prevent bacterial adhesion to gastric epithelial cells, a critical early step in the colonization process of *H. pylori* [51]. Polysaccharides can reduce host–pathogen interactions by forming a protective layer on the epithelial surface or through competitive binding to bacterial adhesins [51].

Microalgae also produce antibacterial peptides with direct bactericidal effects. The peptide HF-18, identified in microalgae, has been shown to disrupt bacterial membranes and downregulate the expression of virulence factors such as CagA, a protein involved in gastric epithelial transformation and inflammation [52]. These peptides integrate into the bacterial membrane, leading to pore formation and loss of membrane potential, which ultimately results in bacterial death [52]. *In silico* studies have demonstrated a broad repertoire of microalgae-derived peptides with potential anti-*H. pylori* activity [49]. Peptides derived from *Tetradesmus* sp., identified through *in silico* approaches, have shown strong binding affinity to CagA, VacA, and HtrA, three major virulence factors of *H. pylori* involved in epithelial disruption, immune evasion, and tissue degradation. These findings suggest that microalgal peptides could act as inhibitors, reducing bacterial pathogenicity without inducing resistance [50, 53].

Other recent studies have highlighted the potential of flavonoids in combination therapies, enhancing antibiotic efficacy or reducing the required dosage, thereby minimizing side effects and the development of resistance. Yuan et al. [54] demonstrated that plant-derived flavonoids exhibit synergistic effects when combined with antibiotics, particularly those targeting bacterial membranes and ribosomes [55]. This reinforces the relevance of flavonoid-producing microalgae in antibacterial research and suggests their potential as sustainable sources of complementary therapeutic agents.

Antioxidant activity: The central mechanism underlying the pathogenesis of *H. pylori*-induced gastric damage is oxidative stress. This bacterium promotes the overproduction of reactive oxygen species (ROS), causing epithelial cell injury, DNA damage, and chronic inflammation [56]. Conventional antibiotic therapies are aimed at eradicating *H. pylori*, but they often fail to address the oxidative damage that persists in gastric tissues, highlighting the need for complementary antioxidant strategies.

In recent years, microalgae have emerged as an important source of natural antioxidants capable of neutralizing ROS and mitigating the deleterious effects of oxidative stress in gastric tissues [57]. Microalgae synthesize a wide variety of bioactive molecules, including carotenoids, polyphenols, phycobiliproteins, and vitamins, which can scavenge free radicals and modulate oxidative stress pathways. Among these compounds, astaxanthin, a xanthophyll carotenoid produced by *Haematococcus pluvialis*, has attracted considerable attention due to its potent antioxidant and anti-inflammatory activities [58]. This molecule reduces oxidative stress markers such as lipid peroxidation and intracellular ROS accumulation, while also enhancing gastric mucosal integrity [59]. Its molecular structure allows it to traverse cell membranes, providing protection both inside and outside the lipid bilayer, which is particularly relevant in the context of *H. pylori*-induced epithelial damage.

Polyphenolic compounds exhibit strong antioxidant and anti-inflammatory properties, making them

promising candidates for the treatment of *H. pylori*-associated gastric disorders. Recent studies have shown that species such as *T. suecica* and *Phaeodactylum tricornutum* (*P. tricornutum*) produce polyphenols capable of modulating oxidative stress and inflammatory signaling pathways. Furthermore, Mougin et al. [60] demonstrated that extracts from *T. suecica* significantly reduced ROS levels and improved mitochondrial function in gastric epithelial cells exposed to *H. pylori* [61]. Polyphenols from *P. tricornutum* were observed to inhibit nuclear factor kappa beta (NF-κB) activation and downregulate interleukin (IL)-8 secretion, indicating a synergistic anti-inflammatory effect alongside their antioxidant activity [62].

Polyphenols from *N. gaditana* were shown to inhibit ROS production by up to 50% and reduce IL-8 expression in gastric epithelial cells challenged with *H. pylori* [63]. These microalgal compounds often exhibit greater stability under gastric conditions and better bioavailability than their terrestrial counterparts, making them attractive candidates for oral formulations targeting gastric oxidative stress.

In light of increasing antibiotic resistance, the incorporation of antioxidant therapies into the management of *H. pylori* infection is becoming increasingly important. Microalgae-derived compounds, particularly astaxanthin and polyphenols, provide a dual benefit by directly reducing oxidative damage and regulating inflammatory pathways. Their inclusion in functional foods, nutraceuticals, or combination therapies could enhance treatment efficacy and reduce gastric mucosal injury. Future research should focus on standardizing extraction methods, optimizing bioavailability, and conducting clinical trials to assess the long-term effects of microalgal antioxidants in *H. pylori*-infected populations [57,64].

Anti-inflammatory activity: Chronic inflammation is a characteristic of *H. pylori* infection and acts as a crucial aspect in the progression from gastritis to gastric cancer. Beyond the colonization of the gastric mucosa, this bacterium activates immune cells as macrophages and epithelial cells, causing the release of proinflammatory cytokines, including IL-8 and tumor necrosis factor-alpha (TNF-α) [65]. These elements contribute to epithelial barrier disruption, mucus damage, and carcinogenic transformation through sustained activation of the NF-κB and Wnt/β-catenin pathways [66−67].

Different studies have highlighted the potential of microalgae-derived compounds to change these inflammatory responses. Astaxanthin, a potent carotenoid found in *H. pluvialis*, has demonstrated significant anti-inflammatory effects due to the inhibition of NF-κB translocation and activation. Also, it can reduce oxidative stress, and it downregulates inflammatory cytokines such as IL-6 and TNF-α. Moreover, astaxanthin directly attacks IL-6, disrupting its feedback loop and preventing cytokine storms [68].

Omega-3 fatty acids, particularly EPA and DHA, show strong immunomodulatory properties. These fatty acids alter membrane lipid composition, reduce arachidonic acid availability, and promote the synthesis of specialized pro-resolving mediators such as resolvins and protectins. EPA and DHA inhibit NF-κB activation thanks to mechanisms that entail lipid raft disruption and transcriptional regulation, therefore reducing the production of key proinflammatory cytokines, including IL-1β, IL-6, and TNF-α [69]. Additionally, Liu et al. [70] have established that PUFAs, as alpha-linolenic acid (ALA) and DHA, prevent the IL-8 transcription and its protein expression in *H. pylori*-infected cells.

Phycocyanin, a pigment-protein complex extracted from *A. platensis*, has arisen as a promising natural anti-inflammatory agent. It inhibits cyclooxygenase-2 (COX-2)

activity, reduces levels of prostaglandin E2, and suppresses NF-κB signaling. Further, this pigment modulates oxidative stress and activates antioxidant defenses via the Nrf2/HO-1 pathway, reducing the inflammation and improving the protection of gastric epithelial integrity [71].

On the whole, these microalgae-derived bioactives show a multifaceted strategy to prevent *H. pylori*-induced inflammation. Because of the attack key signaling pathways and inflammatory mediators, not only can they mitigate mucosal damage, but also, they can act as supplements to conventional therapies, mostly facing the antibiotic resistance.

CONCLUSION

Microalgae are a sustainable and highly versatile source of bioactive compounds, with great potential to help prevent and manage *H. pylori* infections. Since traditional antibiotic treatments are becoming less effective due to rising resistance and treatment failures, metabolites from microalgae are emerging as promising alternatives for complementary, non-antibiotic approaches. These compounds have antibacterial, antioxidant, and anti-inflammatory properties, allowing them to fight the infection on several fronts at the same time by slowing down bacterial growth and harmful activity, reducing oxidative stress, and helping ease long-term inflammation in the stomach lining.

The distinctive aspect of this review lies in its integration of these bioactivities in a mechanistic framework, illustrating how microalgal compounds exert multi-target effects by modulating both bacterial virulence factors and the host's inflammatory pathways. Instead of looking at just one effect at a time, this approach provides a clearer picture of the biological relevance of microalgae in the context of *H. pylori* infections. Importantly, this perspective highlights microalgae not only as a source of isolated bioactive compounds but also as potential ingredients for functional foods and nutraceuticals that support gastric health. From a food science viewpoint, the ability of microalgal compounds to influence both microbial activity and the host's response is particularly exciting, as it fits with dietary strategies aimed at lowering disease risk and promoting gut balance.

Although increasing evidence from *in vitro* and preclinical studies supports the benefits of microalgal compounds, their translation into functional food applications remains at an early stage. Future research should focus on standardizing cultivation and extraction methods, improving bioavailability and stability in the gut, and testing safety and effectiveness in well-designed human studies. Tackling these challenges will be key to bringing microalgae-based bioactives into evidence-backed functional foods and nutraceuticals for managing *H. pylori*-related stomach disorders.

Abbreviations: *A. platensis: Arthrospira platensis;* ALA: alpha-linolenic acid; *C. vulgaris: Chlorella vulgaris; CagA*: Cytotoxin-associated gene A; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; *H. pylori: Helicobacter pylori;* IL: interleukin; MALT: mucosa-associated lymphoid tissue; *N. gaditana: Nannochloropsis gaditana;* NF-κB: nuclear factor kappa beta; PCABs: potassium-competitive acid blockers; PUFAs: polyunsaturated fatty acids; ROS: reactive oxygen species; T4SS: type IV secretion system; TNF-α: tumor necrosis factor-alpha; *VacA*: Vacuolating cytotoxin A; WHO: World Health Organization.

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