Research in Molecular Medicine

# *Spirulina platensis* as a Dual-action Functional Agent to Improve Aquaculture Outcomes and Promote Human Health: A Review Study

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## ABSTRACT

**Background:** In 2015, the World Health Organization (WHO) urged member states to develop national action plans to address the growing threat of antimicrobial resistance in humans. A key recommendation was to reduce the use of antibiotics in livestock, poultry, and aquaculture sectors where overuse contributes significantly to the emergence of resistant pathogens. In aquaculture, the prophylactic and therapeutic use of antibiotics has led to the emergence of antibiotic-resistant bacterial strains that can enter the food chain and pose serious risks to human health.

**Materials and Methods:** This narrative review synthesizes findings from original and peer-reviewed articles published between 2010 and 2025, retrieved from reputable scientific databases: PubMed, Scopus, Web of Science, and Google Scholar. Sources were selected based on their relevance to immunomodulatory strategies as alternatives to antibiotics in aquaculture and public health. Particular emphasis was placed on studies investigating the molecular mechanisms and functional outcomes of *Spirulina platensis* bioactive compounds, especially their immunostimulatory and antimicrobial effects in fish and human health contexts.

**Results:** *S. platensis*, a filamentous cyanobacterium rich in protein, carbohydrates, essential fatty acids, vitamins, pigments (chlorophyll, beta-carotene, phycocyanin), phenolic compounds, and antimicrobial peptides, has demonstrated positive effects on fish growth, immunity, hematobiochemical parameters, and disease resistance. Its natural antimicrobial and immunostimulatory properties suggest that *Spirulina* can serve as a sustainable alternative to antibiotics in aquaculture. Moreover, recent studies have highlighted its beneficial effects in humans, including modulation of gut microbiota, enhancement of immune function, antioxidant and anti-inflammatory activity, and potential roles in weight management and metabolic regulation.

**Conclusion:** *S. platensis* holds promise as a natural, eco-friendly solution to antibiotic overuse in aquaculture. Its integration into fish diets may support global efforts to neutralize antimicrobial resistance and promote safer food production systems. Additionally, its health-promoting effects in humans position *Spirulina* as a valuable functional food with potential applications in preventive nutrition and public health.

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## Introduction

Aquaculture is not only a vital source of income but also a key contributor to food security and social development in many countries. According to data from the Food and Agriculture Organization (FAO) and the World Bank, global fish consumption has nearly doubled over the past 2 decades and is projected to double by 2050 [1]. To meet this growing demand, current strategies have focused on intensive and semi-intensive farming systems and the commercialization of aquaculture products. However, such systems often compromise environmental conditions, leading to stress-induced immunosuppression in fish and increased susceptibility to viruses, bacteria, parasites, and fungi, resulting in substantial economic losses for the industry [2, 3].

The overuse of antibiotics in aquaculture has raised serious concerns, including the emergence of antimicrobial-resistant (AMR) bacteria, increased production costs, environmental disruption, and health risks to consumers [4, 5]. A key indicator of this issue is the multiple antibiotic resistance (MAR) index, which reflects the extent of antibiotic contamination. Based on data from 40 countries representing 93% of global aquaculture production, 28 countries showed MAR values above 0.2, indicating high-risk zones. The global average MAR index was 0.25. The highest values were reported in Zambia (0.56), Mexico (0.55), and Tunisia (0.53), while the lowest were observed in Canada (0.02), France (0.03), and the United States (0.08) (Figure 1) [6, 7].

These alarming trends underscore the urgent need for natural, bioactive alternatives to antibiotics. Among them, *Spirulina platensis* has gained attention for its unique antimicrobial and immunostimulatory properties, offering a promising solution to mitigate AMR risks in aquaculture. Despite efforts to improve water quality, invest in health management, enhance biosecurity, and adopt preventive measures, such as specific pathogen-free stocks and vaccination, these interventions have not sufficiently reduced the industry's reliance on antibiotics or addressed the associated risks to consumer health in line with World Health Organization (WHO) standards [5]. One of the most promising strategies to reduce antibiotic use in aquaculture is the incorporation of immunostimulant feed additives. Numerous studies have shown that dietary supplementation with microalgae, such as *S. platensis*, not only improves growth and reproductive performance but also enhances the immune systems of cultured aquatic species, primarily due to their high levels of bioactive compounds. Certain components, such as phlorotannins, laminarin, phycobiliproteins, and C-phycocyanin, exhibit antibacterial activity, while others, including butylated hydroxytoluene, amphidinolide, and phycobiliproteins, possess antifungal properties. These compounds also stimulate immune responses, increasing resistance to infectious agents and reducing the need for antibiotic treatments [8–10].

Moreover, the high levels of vitamins C and E, carotenoids (α-carotene, β-carotene, astaxanthin), chlorophylls, and phenolic compounds found in microalgae such as *S. platensis* contribute significant antioxidant and anti-inflammatory effects, further supporting immune function and overall health in fish [11, 12]. Essential minerals such as calcium, magnesium, phosphorus, iron, iodine, and zinc also play crucial roles in growth and immunity, making microalgae ideal candidates as natural feed additives in aquaculture. Additional advantages include their ability to grow in simple environments without special conditions, high biomass yield at low cost, and the production of diverse bioactive compounds [13]. The global market value of microalgae-based products was estimated at 1.548 billion USD in 2021 and is projected to reach 2.811 billion USD by 2028 [14]. In aquaculture alone, global demand for *Spirulina* reached 3.4 billion USD by 2020 and is expected to grow by approximately 3.4% by 2027 [15].

This review critically examines the bioactive compounds of *S. platensis*, their molecular mechanisms, and their role in reducing antibiotic use and AMR risks in aquaculture. These compounds not only enhance immune responses but also improve growth, hematological, and serum indices, boosting resistance to bacterial infections and reducing the need for antibiotics. With its direct antimicrobial properties, *Spirulina* is a promising natural alternative to conventional antibiotics in future aqua feeds.

## Bioactive compounds of *S. platensis* and their functional roles

*S. platensis* is a filamentous cyanobacterium (Figure 2) widely recognized for its rich biochemical profile and health-promoting properties in aquaculture. Its bioactive compounds span several functional categories, each contributing to enhanced growth, immune modulation, and disease resistance in aquatic species [16]. By enhancing innate and adaptive immune responses, *Spirulina*'s bioactive compounds reduce the incidence and severity of infections in aquaculture species. This immunomodulatory effect reduces reliance on prophylactic and therapeutic antibiotics, thereby lowering the risk of antimicrobial resistance.

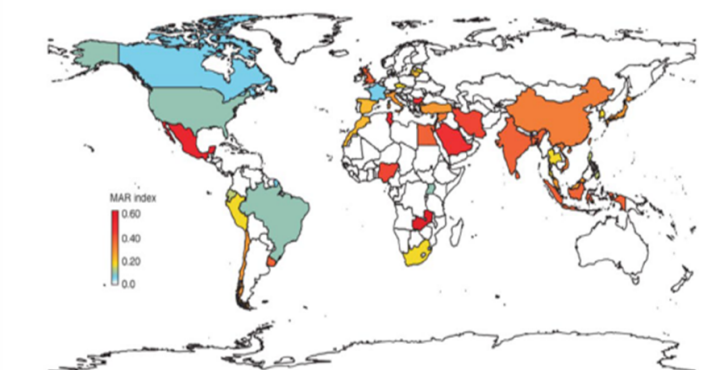


**Figure 1.** Global MAR index in aquaculture pathogens countries without sufficient data are shown in white [7]

## Proteins and peptides

*Spirulina* contains up to 60–70% protein by dry weight, including all essential amino acids required for fish growth and tissue repair. Among its proteinaceous components, phycobiliproteins such as phycocyanin and allophycocyanin exhibit strong antioxidant and immunostimulatory properties. C-phycocyanin, in particular, has been shown to mitigate oxidative stress and enhance immune responses in zebrafish models [17]. Additionally, antimicrobial peptides derived from *Spirulina* have demonstrated inhibitory effects against pathogenic bacteria and fungi [16].

## Pigments

*Spirulina* is notably rich in biologically active pigments that contribute to its health-promoting properties in aquaculture. Among these, phycocyanin stands out as a blue pigment with potent antioxidant, anti-inflammatory, and immunomodulatory effects [18]. It plays a key role in enhancing immune responses and protecting aquatic organisms against oxidative stress. Chlorophylls, another major pigment group in *Spirulina*, support detoxification processes and promote gut health by improving intestinal function and microbial balance [19]. In addition, carotenoids such as β-carotene and astaxanthin act as effective free radical scavengers. These compounds not only strengthen mucosal immunity but also contribute to reproductive health and overall resilience in fish [20, 21].

## Polysaccharides

*Spirulina*-derived polysaccharides, particularly sulfated forms, have demonstrated significant immunostimulatory effects by activating innate immune cells such as macrophages and neutrophils. These bioactive compounds enhance the production of pro-inflammatory cytokines and nitric oxide, thereby strengthening the host's defense mechanisms [22]. In addition to their immunomodulatory role, *Spirulina* polysaccharides support gut microbiota balance and enhance nutrient absorption, which are essential for maintaining intestinal health and optimizing feed efficiency in aquaculture species [23].

**Figure 2.** Macroscopic and microscopic views of *S. platensis*

Note: Commercial forms (powder) exhibit a filamentous spiral structure under light microscopy.

## Vitamins and minerals

Among the various nutritional attributes of *S. platensis*, its abundance of essential vitamins and minerals is pivotal in promoting the health and physiological resilience of aquatic organisms. Notably, it contains high levels of vitamin C, vitamin E, and B-complex vitamins, with vitamin B12 being particularly important for antioxidant defense, cellular metabolism, and neurological function [24, 25]. These vitamins help reduce oxidative stress and enhance energy production, especially under intensive aquaculture conditions. In addition to its vitamin profile, *Spirulina* also provides a broad spectrum of minerals, including iron, calcium, magnesium, phosphorus, iodine, and zinc. These micronutrients are indispensable for hematopoiesis, enzymatic regulation, osmoregulation, and optimal immune cell function [26].

## Phenolic and flavonoid compounds

Among its diverse bioactive constituents, *S. platensis* contains significant levels of phenolic acids and flavonoids, which contribute to its therapeutic potential in aquaculture. These compounds exhibit strong antioxidant, anti-inflammatory, and antimicrobial properties, helping to mitigate oxidative stress and enhance resilience against environmental challenges [16, 27]. By modulating immune responses and inhibiting pathogenic microorganisms, phenolic and flavonoid compounds from *Spirulina* support fish health and food safety, making them valuable candidates for natural feed additives in sustainable aquaculture systems.

## Essential fatty acids

The lipid profile of *S. platensis* includes valuable polyunsaturated fatty acids (PUFAs), most notably γ-linolenic acid (GLA), which plays essential roles in maintaining cellular and physiological homeostasis. These fatty acids contribute to membrane fluidity, hormone biosynthesis, and the modulation of inflammatory responses, thereby enhancing stress tolerance and immune competence in aquatic species [28, 29]. Moreover, PUFAs are particularly important for preserving skin integrity, promoting growth performance, and supporting reproductive health in fish, making *Spirulina* a promising functional ingredient in aquafeeds [30].

## Role and applications of *S. platensis* in aquaculture

*S. platensis*, with its high-quality protein and essential amino acids, meets FAO criteria for a balanced protein source. Its rich nutritional profile, including vitamins, minerals, pigments, essential fatty acids, and phenolic compounds, alongside its rapid biomass production, positions it as a promising solution to global protein shortages. In aquaculture, *Spirulina* has shown potential as a plant-based alternative to animal proteins, with positive effects across various fish species depending on dietary inclusion levels [31]. Beyond growth enhancement, it contributes to improved antioxidant status, immune stimulation, and disease resistance. It may help mitigate the impact of aquatic pollutants such as algal toxins, pesticides, and heavy metals [32]. The following section reviews its effects on growth performance, hematological and biochemical parameters, immune function, and resistance to bacterial infections in farmed fish (Figure 3).

## Enhancement of growth performance in aquatic species

Growth performance is widely recognized as a key indicator of fish health and product quality in aquaculture [33]. Numerous studies have demonstrated that dietary supplementation with *S. platensis* can enhance growth performance in various cultured fish species, particularly Nile tilapia (*Oreochromis niloticus*), which has been the most extensively studied (Table 1). Inclusion levels as low as 1% have shown significant improvements in growth parameters [34, 35], while moderate replacement of fishmeal (30%–50%) also yielded positive outcomes [36, 37]. However, excessive inclusion (≥60%) often led to reduced performance, likely due to palatability or nutrient imbalance. Similar trends were observed in African catfish (*Clarias gariepinus*), with enhanced growth and digestive enzyme activity at 10% inclusion [38]. Rainbow trout (*Oncorhynchus mykiss*) and Caspian salmon (*Salmo trutta caspius*) responded positively to 6–10% *Spirulina*, attributed to improved nutrient digestion and modulation of the gut microbiota [39, 40]. In contrast, Persian sturgeon (*Acipenser persicus*) showed no significant growth changes, highlighting species-specific responses [41, 42]. In Asian sea bass (*Lates calcarifer*), selenium-enriched *Spirulina* improved growth at 5%–10%, but higher inclusion (20%) reduced performance, possibly due to feed palatability issues [43]. Thorny catfish (*Mystus cavasius*) showed optimal growth at 7.5%–10%, linked to improved digestion, energy balance, and the production of bioactive compounds [44]. Overall, *Spirulina* efficacy depends on species, inclusion level, feed formulation, and culture conditions [45]. Based on the results presented in Table 1, dietary supplementation with *S. platensis* generally improves growth performance across cultured fish species. Notable enhancements were observed in weight gain, specific growth rate

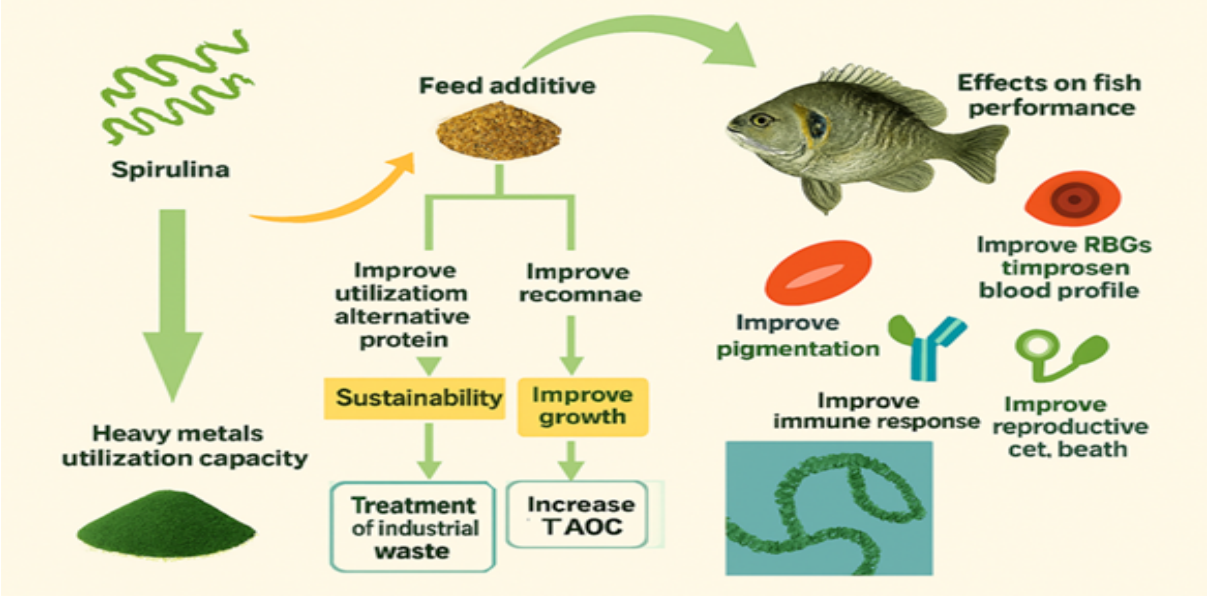


**Figure 3.** Role of *S. platensis* in aquaculture

(SGR), and feed conversion ratio (FCR), particularly at higher inclusion levels.

## Improvement of hematological and serum biochemical parameters in aquatic species

Blood is a primary tissue for evaluating fish health, with the oxygen-carrying capacity reflected in red blood cell (RBC), hemoglobin (Hb), and hematocrit (HCT), which serve as key physiological indicators [22]. Dietary supplementation with *S. platensis* may improve hematological and serum biochemical parameters, though responses vary by species, dosage, and duration (Table 2). In Nile tilapia (*O. niloticus*), inclusion levels ranging from 0.5% to 30% have produced both significant improvements and neutral effects in RBC, Hb, HCT, and related indices such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) [35, 46, 47]. These outcomes are largely attributed to *Spirulina*'s richness in bioavailable iron and B-complex vitamins, especially B12 [48, 49]. In Asian sea bass (*L. calcarifer*), selenium-enriched *Spirulina* led to numerical but non-significant increases in blood indices [43].

Supplementation with *S. platensis*, especially when enriched with selenium, has shown a stabilizing effect on physiological homeostasis in fish, even at higher inclusion levels where growth performance may decline. In beluga sturgeon (*Huso huso*), optimal hematological outcomes were observed at 5% and 10% inclusion, indicating improved metabolic health. Persian sturgeon (*A. persicus*) exhibited a dose-dependent increase in blood indices, with Hb significantly elevated at 10%. Grouper (*Epinephelus* spp.), rainbow trout (O. *mykiss*), and thorny catfish (*Clarias gariepinus*) also demonstrated enhanced hematological parameters at 7.5–10% inclusion levels. These effects are largely attributed to *Spirulina*'s phycocyanin content, which stimulates erythropoiesis by activating bone marrow and increasing erythropoietin production [50, 51].

Additionally, *Spirulina*'s antioxidant properties may protect RBCs from oxidative damage, enhancing their stability and abundance [52, 53]. Beyond hematological parameters, blood serum contains key compounds that reflect fish health, including total protein, liver enzymes, glucose, cortisol, cholesterol, and triglycerides. Total serum protein, comprising albumin and globulins, is a marker of metabolic function and immune status. Enzymes such as alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) indicate liver health, while glucose and cortisol levels reflect stress responses. Cholesterol and triglycerides are linked to metabolic and hepatic function [54]. Dietary supplementation with *S. platensis* has consistently improved serum biochemical profiles across species. In tilapia, *Spirulina* increased total protein, albumin, and globulin levels, while reducing cholesterol, triglycerides, glucose, and liver enzymes [34, 37, 46, 47, 55]. Similar benefits were observed in rainbow trout, grouper, beluga sturgeon, Persian sturgeon, and grey mullet, with optimal effects at 7.5–10% inclusion levels. These improvements are attributed to *Spirulina*'s bioactive compounds,

**Table 1.** Effects of *S. platensis* supplementation on growth performance in various fish species

| Fish Species | Feeding Duration (Days) | Dietary Dose (%) | Growth Performance Changes | Ref. |
|---|---|---|---|---|
| Nile tilapia (*O. niloticus*) | 84 | 1 | FCR↓, WG, SGR, PER↑ | [18] |
| Nile tilapia (*O. niloticus*) | 90 | 2, 1.5, 1, 0.75, 0.5 | WG, SGR, CF↑ | [19] |
| Nile tilapia (*O. niloticus*) | 77 | 100, 75, 50, 25 | FCR↓, FW, WG, SGR, PER↑ | [20] |
| Nile tilapia (*O. niloticus*) | 60 | 75, 60, 45, 30 | FCR↓, FW, WG, SGR, PER↑ | [21] |
| Nile tilapia (*O. niloticus*) | 56 | 10, 5, 2.5 | FCR↓, WG, SGR, PER↑ | [62] |
| Nile tilapia (*O. niloticus*) | 84 | 1, 0.75, 0.5, 0.25 | FW, WG, SGR↑ | [13] |
| Nile tilapia (*O. niloticus*) | 84 | 2, 1 | FCR, WG, SGR | [30] |
| Nile tilapia (*O. niloticus*)* | 84 | 30, 20, 10 | FCR, FW, WG, SGR, PER | [54] |
| Nile tilapia (*O. niloticus*)* | 90 | 20 | FCR, WG, SGR | [61] |
| Asian sea bass (*L.calcarifer*)* | 56 | 20, 10, 5 | FCR, FW, WG, SGR | [27] |
| Beluga (*H. huso*) | 56 | 10, 5, 2.5 | FCR↓, WG, SGR↑ | [22] |
| Persian sturgeon (*A. persicus*)* | 90 | 10, 7.5, 5, 2.5 | FW, SGR, CF | [25] |
| Persian sturgeon (*A. persicus*)* | 84 | 7.5, 5, 2.5 | FW, SGR, CF, SGR | [26] |
| Rainbow trout (*O. mykiss*) | 70 | 10, 7.5, 5, 2.5 | FCR↓, FW, WG, SGR↑ | [23] |
| Caspian brown trout (*S. trutta caspius*) | 70 | 8, 6, 4, 2 | FCR↓, FW, WG, SGR↑ | [24] |
| Leopard coral grouper (*Plectropomus leopardus*) | 56 | 8, 10, 6, 4, 2 | FCR↓, FW, WG, SGR, CF↑ | [47] |
| Stinging catfish (*Heteropneustes fossilis*) | 70 | 10, 7.5, 5, 2.5 | FCR↓, FW, WG, SGR, PER↑ | [28] |

Abbreviations: FCR: Feed conversion ratio; FW: Final weight; WG: Weight gain; SGR: Specific growth rate; CF: Condition factor; PER: Protein efficiency ratio.

*No significant change in growth indicators.

including carotenoids, polysaccharides, vitamins, minerals, and linoleic acid, which also act as immune stimulants [56].

## Antimicrobial properties of *Spirulina* and its bioactive compounds

In aquaculture, excessive use of antibiotics has raised concerns about drug residues in fish muscle, antibiotic resistance, disrupted microbial balance, and weakened fish immunity. These challenges, along with rising consumer demand for eco-friendly products, highlight the need for safe, natural alternatives in intensive farming systems [57, 58]. *S. platensis* has gained attention for its antimicrobial properties. Studies have shown its inhibitory effects against both gram-positive and gram-negative bacteria, as well as *Candida albicans* [59, 60]. These effects are attributed to bioactive compounds such as polyphenols, fatty acids, glycolipids, terpenoids, alkaloids, and bacteriocins [61, 62]. Extraction of *S. platensis* using various solvents has revealed its antimicrobial potential, with hexane and methanol extracts showing the most pronounced inhibitory effects against bacterial and fungal pathogens—highlighting its promise as a natural alternative to conventional antibiotics (Table 3) [63].

Studies have shown that ethanolic, methanolic, and acetone extracts of *S. platensis* exhibit strong antimicrobial activity against fish pathogens, including Pseudomonas, Aeromonas, Vibrio, and Edwardsiella species, whereas aqueous extracts show no inhibitory activity. This finding suggests that the active compounds are likely nonpolar and poorly soluble in water (Figure 4) [64, 65].

**Table 2.** Effects of *S. platensis* supplementation on hematological and serum biochemical parameters in various fish species

| Fish species | Feeding Duration (Days) | Dietary Dose (%) | Hematological/Serum Changes | Ref. |
|---|---|---|---|---|
| Nile tilapia (*O. niloticus*) | 84–90 | 0.5–30 | ↑ RBC, Hb, HCT, MCV, MCH, MCHC; ↑ TP, Alb, Glob; ↓ Chol, TG, Glu, ALT, AST, ALP | [18, 19, 21, 30, 54, 55] |
| Asian sea bass (*L. calcarifer*) | 56 | 5–20 (Se-enriched *Spirulina*) | Numerical ↑ blood indices (not significant); stabilization of physiological status | [27] |
| Beluga sturgeon (*H. huso*) | 56 | 5–10 | ↑ RBC, Hb, HCT; ↓ Chol, TG | [22] |
| Persian sturgeon (*A. persicus*) | 84–90 | 2.5–10 | ↑ hematological indices (Hb ↑ significantly at 10%); ↓ ALT, AST, ALP, Chol, TG | [25, 26] |
| Rainbow trout (*O. mykiss*) | 56–70 | 2.5–10 | ↑ RBC, Hb, HCT (7.5–10%); ↑ TP, Alb; ↓ Glu, Cort | [60] |
| Caspian brown trout (*S. trutta caspius*) | 70 | 2–8 | (Growth studied – limited hematology data reported) | [24] |
| Grouper (*Epinephelus* spp.) | 56 | 2–10 | ↑ RBC, Hb, HCT (best at 10%); ↓ Chol, TG | [47] |
| Stinging catfish (*Heteropneustes fossilis*) | 70 | 2.5–10 | ↑ hematological indices at 7.5–10% | [28] |

Abbreviations: RBC: Red blood cells; Hb: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; TP: Total serum protein; Alb: Albumin; Glob: Globulin; Chol: Cholesterol; TG: Triglycerides; Glu: Glucose; Cort: Cortisol; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase.

## Dietary *Spirulina* and its impact on immunity and disease resistance in aquatic species

As aquaculture intensifies, factors such as water scarcity, overcrowding, and poor feed quality increase fish's susceptibility to bacterial infections. While antibiotics and vaccines are commonly used, their limitations have prompted interest in immunostimulants, natural compounds that enhance innate immunity and reduce stress [31]. Fish rely primarily on innate immunity, especially during early development, with defense mechanisms including physical barriers, immune cells, and humoral factors [66, 67]. White blood cells play a key role in pathogen elimination through phagocytosis and cytokine release. One consistent

**Table 3.** MIC of *S. platensis* extracts against various bacterial strains using different solvents (mg/mL) [37]

| Bacteria | Hexane | Methanol | Acetone | Ethanol | Petroleum Ether | Positive Control* |
|---|---|---|---|---|---|---|
| *Staphylococcus aureus* | 10 | 25.1 | 25.1 | 5 | 50.2 | 5 |
| *Staphylococcus pyogenes* | 10 | 25.1 | 50.2 | 10 | 5 | 10 |
| *Staphylococcus epidermidis* | 20 | 25.1 | 50.2 | 10 | 5 | 10 |
| *Proteus mirabilis* | 5 | 25.1 | 25.1 | 5 | 50.2 | 10 |
| *Bacillus cereus* | 10 | 25.1 | 25.1 | 5 | 50.2 | 10 |
| *Escherichia coli* | 10 | 50.2 | 50.2 | 10 | 5 | 5 |
| *Pseudomonas aeruginosa* | 20 | 50.2 | 5 | 10 | 10 | 5 |
| *Vibrio cholerae* | 80 | 5 | 10 | 40 | 20 | 20 |
| *Salmonella typhi* | 40 | 5 | 5 | 20 | 10 | 20 |
| *Klebsiella pneumoniae* | 10 | 25.1 | 50.2 | 5 | 50.2 | 10 |
| *Shigella flexneri* | 5 | 25.1 | 25.1 | 5 | 50.2 | 10 |

*Ampicillin (5 mg).

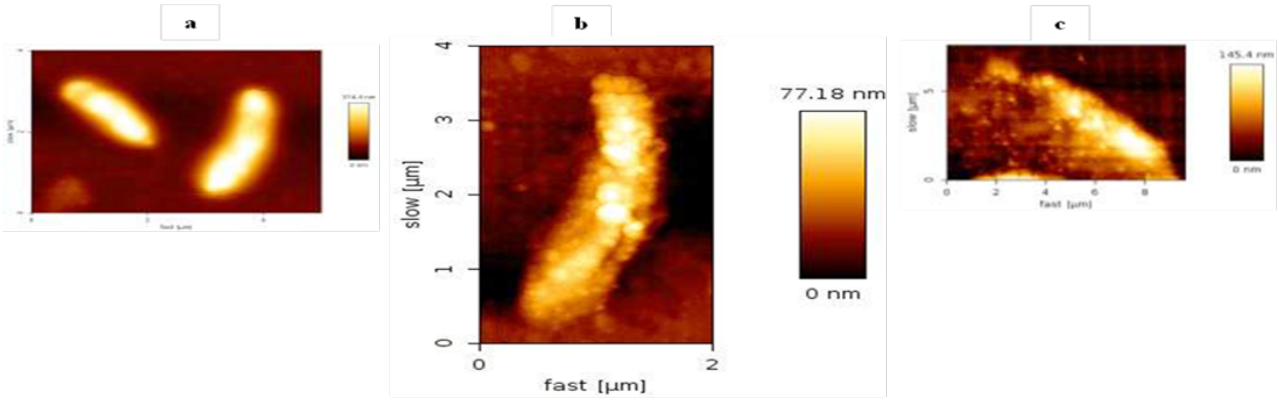


**Figure 4.** Atomic force microscopy (AFM) images showing the morphological changes in *Aeromonas hydrophila* cells at 0 h (a), 1 h (b), and 2 h (c) following exposure to the acetone extract of *Spirulina* [39]

effect of *S. platensis* supplementation is an increase in leukocyte counts across multiple species, including Nile tilapia, beluga sturgeon, rainbow trout, grouper, and armored catfish. This response is often dose-dependent, even when growth performance remains unchanged [41, 44, 55].

*Spirulina* supplementation has been shown to increase total leukocytes and neutrophils, key innate immune cells that eliminate pathogens via phagocytosis and the release of reactive oxygen species (ROS). This outcome suggests a strong immunostimulatory effect, potentially mediated by phycocyanin [45, 68]. Humoral immunity also benefits, with elevated lysozyme, immunoglobulin, and complement activity. Lysozyme, produced in organs like the kidney and spleen, breaks down bacterial cell walls and supports immune function [69]. The complement system enhances pathogen clearance through multiple activation pathways [70].

*Spirulina* has consistently increased lysozyme activity and ROS production in Nile tilapia, beluga sturgeon, and armored catfish, often in a dose-dependent manner [38, 44, 56]. *Spirulina* supplementation has consistently enhanced immune parameters in various fish species. In grouper and Oscar fish, lysozyme activity, complement levels (C3, C4), immunoglobulin concentration, and ROS production increase in a dose-dependent manner, likely due to bioactive compounds such as β-carotene, phycocyanin, and polysaccharides [71, 72]. In rainbow trout, dietary *Spirulina* (2.5–5%) upregulated immune-related genes, including lysozyme, C3, TNF-α, and IgM, in mucosal tissues [73]. Asian sea bass showed improved lysozyme and immunoglobulin levels, though the response was not dose-dependent [45]. In binni fish, a 10% inclusion level significantly increased lysozyme activity [74] (Table 4).

**Table 4.** Immunomodulatory mechanisms of *Spirulina* in aquatic species

| Mechanism | Result | Fish Species | Ref. |
|---|---|---|---|
| Lysozyme | Breaks down gram-positive bacteria, enhances immune cell function, produced in the kidney, spleen, gills & skin | Nile tilapia, beluga sturgeon, grouper, catfish, Oscar, rainbow trout | [22, 23, 28, 42, 46, 47] |
| Immunoglobulins (IgM) | Key biomarkers of immune response, ↑ serum and mucosal levels | Rainbow trout, beluga sturgeon, grouper, Asian sea bass | [22, 47, 48, 76] |
| Complement (C3, C4) | Activated via classical, lectin, or alternative complement pathways; works with phagocytes | Oscar, grouper, rainbow trout | [46-48] |
| Respiratory burst (ROS) | Rapid release of ROS by neutrophils, macrophages & dendritic cells through TLRs | Nile tilapia, beluga sturgeon, grouper | [22, 42, 47] |
| Immune-related gene expression | Phycocyanin, β-carotene, polysaccharides → gene expression of IgM, TNF-α & complement | Rainbow trout, Oscar | [46, 48] |

**Table 5.** The nutritional effects of *Spirulina* in humans

| Topic | Effect | Study Model/ Population | Dose and Duration | Observed Outcomes | Proposed Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Weight regulation | Weight regulation and metabolic improvement | Obese adults | 1–2 g/d for 3 months | Significant reduction in body weight, BMI, and waist circumference | Antioxidant and anti-inflammatory effects may enhance metabolic activity | [77] |
| Weight regulation | Reduction of body fat and weight | Overweight and obese individuals | 4 g/day for 12 weeks | Decreased body weight, body fat percentage, and waist circumference; stronger effect in obese participants | May act through increased energy expenditure and inhibition of adipocyte formation | [78] |
| Weight regulation | Biochemical mechanisms of weight control | Review study | — | — | *Spirulina*'s antioxidant compounds increase cholecystokinin secretion, promoting satiety; inhibit lipase activity and adipogenesis. | [79] |
| Gut microbiota | Modulation of gut microbiota and correction of dysbiosis | (General and in vitro findings) | — | Promotion of beneficial bacteria (*Lactobacilli*, *Bifidobacteria*, lactic acid bacteria); suppression of harmful strains (*Enterobacteria*, *Clostridia*) | Biostimulatory compounds (xylose, galactose, oligosaccharides, resistant starch) enhance the growth of probiotic bacteria and suppress pathogens. | [79, 80] |
| Gut microbiota | Antioxidant and antibacterial properties of *Spirulina* extracts | In vitro (alcoholic extracts: methanol, acetone, hexane) | — | High antioxidant and antibacterial activity correlated with phenolic content | Polyphenolic compounds contribute to antimicrobial and antioxidant effects | [78, 80] |
| Immune system enhancement | General immune and nutritional support | — | — | Improved immune resilience and nutritional balance | Rich in proteins, essential fatty acids, vitamins, minerals, and bioactive pigments | [82] |
| Immune system enhancement | Immune cell activation and modulation | (In vitro and clinical findings) | — | Activation of T and B lymphocytes, macrophages, and NK cells; increased cytokine and antibody production | Strengthens defense mechanisms and maintains intestinal epithelial integrity | [83, 67] |
| Immune system enhancement | Antioxidant and anti-inflammatory immune support | Nile tilapia and human studies | — | Improved antioxidant capacity and balanced immune response | Phycobiliproteins, vitamins, and polyphenols compensate for deficiencies and reduce inflammation | [30] |
| Immune system enhancement | Polysaccharide "Immulina" immune stimulation | Human volunteers | 400 mg/d for 7 days | Enhanced activity of immune cells targeting cancer cells | High-molecular-weight, negatively charged sugar polymers (Immulina) act as immunomodulators | [79] |
| Immune system enhancement | Antiviral and systemic protection | In vitro and review studies | — | Antiviral effect against HSV-I and HSV-II; protection against hepatitis; reduced cholesterol | Ca-spirulan (sulfated polysaccharide) exhibits antiviral activity and systemic protection. | [30, 79] |
| Blood pressure & cholesterol | Antihypertensive effect | Human clinical studies | 4.5 g/d for 6 weeks | Significant reduction in diastolic BP; mild increase in systolic BP | Vasodilation, potassium-rich & sodium-poor content, improved cardiovascular metabolism | [67] |
| Blood pressure & cholesterol | Antihypertensive and Vascular Protection | — | — | Inhibition of platelet aggregation, modulation of calcium mobilization, neutralization of free radicals | C-phycocyanin antioxidant and bioactive peptides | [30] |
| Blood pressure & cholesterol | Cholesterol and triglyceride regulation | — | — | Decreased triglycerides & LDL; maintained or increased HDL | Phycocyanin, phenolic antioxidants, γ-linolenic acid, niacin; inhibition of pancreatic lipase | [30, 67] |
| Blood pressure & cholesterol | Anti-atherosclerotic Effects | — | — | Protection against LDL oxidation; prevention of platelet aggregation | Phenolic compounds, phycocyanin, calcium modulation, antioxidant activity | [82, 83] |

| Topic | Effect | Study Model/ Population | Dose and Duration | Observed Outcomes | Proposed Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Diabetes treatment | Regulation of glucose and lipid metabolism | Type 2 diabetic individuals | — | Lowered fasting blood glucose, improved lipid profile, and reduced inflammatory markers | Bioactive compounds (phytols, phenolic antioxidants, and fatty acid methyl esters) reduce oxidative stress and support pancreatic/hepatic function. | [83, 67] |
| Diabetes Treatment | Antioxidant and Anti-inflammatory Support | Diabetic rats | — | Reduction of oxidative stress | *Spirulina*'s compounds modulate NADPH/ NADH pathways and carbohydrate-metabolizing enzymes (e.g. glucose-6-phosphatase) | [84, 85] |
| Cancer treatment | Immunomodulatory and anticancer effects | Human and in vitro studies | — | Enhanced immune surveillance (NK cells, antibody, and cytokine production); cytotoxicity against cancer cells | Bioactive compounds (γ-linolenic acid, phycocyanin, β-carotene, lutein, chlorophyll) reduce oxidative stress, DNA damage, and tumor cell proliferation. | [30, 83, 67] |
| Cancer treatment | Direct cytotoxicity | K562 cells; colon and liver cancer cell lines | 50 µM (C-phycocyanin & β-carotene, 48 h); 11.3–21.8 µg/mL (extracts) | Reduced cell growth by ~49%; inhibition of cancer cell lines | Antioxidant pigments inhibit proliferation and promote cytotoxicity | [82, 86] |
| Cardiovascular disease | Cardioprotective effects | Human clinical studies and the general population | — | Lowered total cholesterol, LDL, and triglycerides; increased HDL; improved blood pressure and fasting glucose; reduced inflammatory markers | Phycocyanin, phenolic compounds, and PUFAs (EPA, DHA) act as antioxidants, improve lipid metabolism, reduce oxidative stress, and inflammation. | [82, 83, 67, 86] |
| Cardiovascular disease | Antioxidant protection | In vitro studies | — | Prevention of oxidative damage to plasma proteins and vascular tissues; reduced cardiovascular risk | Phycocyanin exhibits antioxidant properties similar to bilirubin. | [88] |
| Cardiovascular disease | Lipid and metabolic support | Survey-based and supplementation studies | — | Improvement in lipid profile and cardiovascular outcomes | *Spirulina* supplementation contributes to metabolic regulation and CVD prevention. | [83, 89] |

*S. platensis* has proven to be a potent natural immunostimulant in aquaculture, enhancing disease resistance and survival across diverse fish species. Supplementation levels ranging from 2% to 10% have significantly improved survival rates against pathogens such as *Vibrio harveyi, Pseudomonas fluorescens, Streptococcus iniae, Yersinia ruckeri,* and *Aeromonas hydrophila* in species, including Asian sea bass, Nile tilapia, grouper, beluga sturgeon, rainbow trout, and African catfish [35, 44, 45, 55, 71, 73]. These protective effects are attributed to *Spirulina*'s rich profile of bioactive pigments (e.g. C-phycocyanin, phycoerythrin, xanthophylls) and antioxidants (e.g/ carotenoids, flavonoids, tocopherols), which support immune function and reduce stress [44, 75]. Additionally, its polysaccharide content promotes beneficial gut microbiota, enhancing mucosal immunity through prebiotic-like mechanisms [76].

## Potential health benefits of *Spirulina* in human nutrition, biology, and medicine

In the preceding sections, we discussed the beneficial effects of *Spirulina* supplementation in aquaculture, including enhanced growth performance, improved immune responses, and increased disease resistance in fish. These outcomes contribute to reduced antibiotic usage and the production of safer, more sustainable aquatic food. Beyond its applications in aquaculture, *Spirulina* also offers a range of health-promoting effects in humans, which are explored in the following section (Figure 5). The nutritional effects of *Spirulina* in humans are summarized in Table 5.

### *Spirulina* and weight regulation

Several clinical studies have demonstrated *Spirulina*'s potential in supporting weight loss and metabolic health in humans. Obese adults who consumed 1–2 g of *Spirulina* daily for 3 months experienced significant reductions in body weight, body mass index (BMI), and waist circumference [77]. Supplementation with 4 g/d

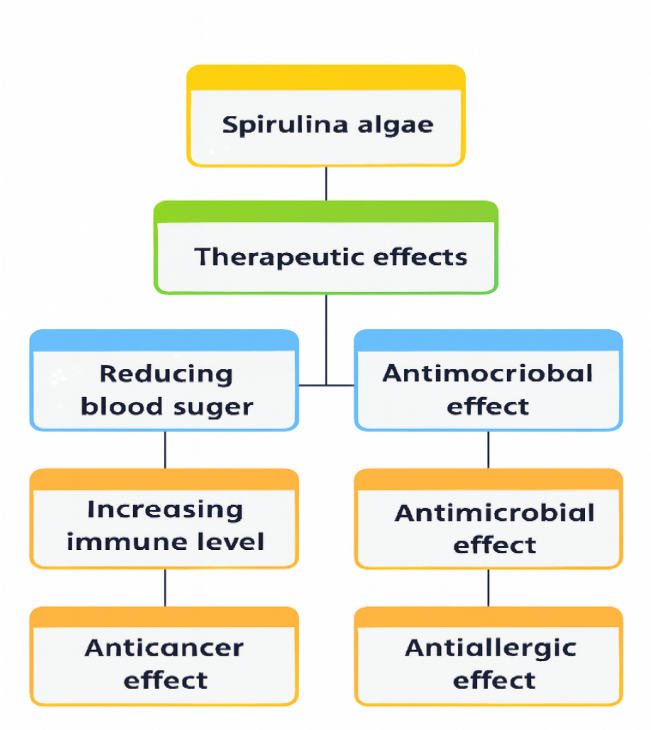


**Figure 5.** Overview of *Spirulina*'s health benefits in humans

for 12 weeks notably decreased body weight, body fat percentage, and waist circumference, with stronger effects observed in obese individuals than in overweight individuals [78]. Furthermore, *Spirulina*'s antioxidant compounds may enhance energy expenditure, inhibit adipocyte formation and lipase activity, and promote satiety by increasing cholecystokinin secretion, a hormone known to suppress appetite [79].

## *Spirulina* and gut microbiota

*Spirulina* has shown promising potential in modulating gut dysbiosis, an imbalance in intestinal flora, by promoting the growth of beneficial microorganisms. Its aqueous extract is rich in biostimulatory compounds, such as xylose, galactose, oligosaccharides, and resistant starch, which enhance the proliferation of probiotic bacteria, including *Lactobacilli, Bifidobacteria*, and lactic acid bacteria, while suppressing harmful strains such as *Enterobacteria* and *Clostridia* [79, 80]. This microbial modulation contributes to improved immune and metabolic health and may help reduce the risk of disorders such as inflammatory bowel disease. *Spirulina* consumption has been associated with restoring balance between beneficial probiotic genera and anaerobic bacteria, particularly *Bacteroides* spp., *Eubacterium* spp., and *Lactobacillus* spp. [79, 81]. Additionally, alcoholic extracts of *Spirulina* (methanol, acetone, hexane) exhibit strong antioxidant and antibacterial properties, with high phenolic content correlating with biological activity [78, 80].

## *Spirulina* and immune system enhancement

*S. platensis* has gained recognition for its powerful role in supporting the human immune system. Thanks to its high concentration of natural nutrients, including proteins, essential fatty acids, vitamins, minerals, and bioactive pigments, it offers a wide range of biological activities that support immune resilience and overall nutritional balance [82].

One of *Spirulina*'s most notable effects is its ability to modulate immune responses. It activates both T and B lymphocytes, enhances macrophage function, stimulates antibody and cytokine production, and increases the presence of natural killer (NK) cells in tissues [83]. These actions help strengthen the body's defense mechanisms and maintain the integrity of the intestinal epithelium, which serves as the first line of protection against infections [67].

*Spirulina* is also a rich source of antioxidants and anti-inflammatory compounds, which not only support immune function but also contribute to brain and nervous system health. These compounds help compensate for nutritional deficiencies and promote a balanced immune response [30].

Several studies have highlighted *Spirulina*'s immunological and antioxidant effects, particularly its high polysaccharide content. Among these, a group of high-molecular-weight, negatively charged sugar polymers known as "Immulina" has shown promising pharmaceutical potential. When consumed at a dose of 400 mg per day for 7 days, Immulina was found to enhance the activity of immune cells capable of targeting cancer cells [79].

In addition, *Spirulina* contains Ca-spirulan, a sulfated polysaccharide composed of rhamnose, methyl rhamnose, methyl xylose, uronic acids, and sulfates, which has demonstrated antiviral activity against herpes simplex virus types I and II [79].

*Spirulina* also produces phycobiliproteins, which are used as natural colorants and fluorescent markers in clinical diagnostics and immunological assays. These pigments have a wide range of applications in medicine, including therapeutic and diagnostic uses. Moreover, *Spirulina* intake has been linked to reduced blood cholesterol levels and protective effects against hepatitis, further reinforcing its role in systemic health regulation [30].

Taken together, these findings underscore *S. platensis* as a potent immunonutritional agent. Its ability to stimulate immune cells, regulate inflammation, and offer antiviral and anticancer support makes it a valuable candidate for integrative health strategies and functional food development.

## Effects of *S. platensis* on blood pressure and cholesterol

Supplementation with *S. platensis* has shown promising effects on blood pressure regulation. Clinical observations indicate a significant reduction in diastolic blood pressure (DBP), alongside a mild increase in systolic blood pressure (SBP), which may reflect improved cardiovascular metabolism and safety. Oral intake of 4.5 g/d over 6 weeks was associated with reductions in both SBP and DBP, attributed in part to vasodilatory mechanisms and the presence of potassium-rich, sodium-poor mineral content [67].

The pigment C-phycocyanin, abundant in *Spirulina*, contributes to these effects by inhibiting platelet aggregation, modulating calcium mobilization, and neutralizing the actions of free radicals, which help prevent atherosclerosis and support vascular health [30]. Additionally, phycocyanin has demonstrated lipid-lowering properties and contains ACE-inhibitory peptides, both of which contribute to antihypertensive outcomes.

*S. platensis* has demonstrated beneficial effects on lipid metabolism, particularly in lowering triglycerides and low-density lipoprotein (LDL) cholesterol while supporting high-density lipoprotein (HDL) levels. These outcomes are largely attributed to its bioactive compounds, including phycocyanin, phenolic antioxidants, γ-linolenic acid, and niacin [30, 67].

Phycocyanin helps reduce fat absorption by inhibiting pancreatic lipase and prevents platelet aggregation through calcium modulation and antioxidant activity [82]. Phenolic compounds protect against LDL oxidation, a key factor in atherosclerosis. Additionally, γ-linolenic acid and niacin contribute to cholesterol regulation and vascular health [83].

## *Spirulina* and diabetes treatment

Diabetes is a widespread metabolic disorder with serious public health implications. *S. platensis* has shown potential to regulate glucose and lipid metabolism, making it a promising candidate for dietary support in individuals with diabetes [83]. Analyses of *Spirulina* extracts have revealed a rich profile of bioactive compounds, including phytols, phenolic antioxidants, and fatty acid methyl esters, which act synergistically to reduce blood glucose and cholesterol levels [84]. These compounds contribute to *Spirulina*'s antioxidant and anti-inflammatory properties, which help mitigate oxidative stress and support pancreatic and hepatic function. Clinical observations suggest that *Spirulina* supplementation may lower fasting blood glucose, improve lipid profiles, and reduce inflammatory markers in people with type 2 diabetes [30, 67]. Its effects are partly attributed to the modulation of NADPH/NADH pathways and enzymes involved in carbohydrate metabolism, such as glucose-6-phosphatase, which helps balance energy production and lipid synthesis [85].

## *Spirulina* and cancer treatment

*S. platensis* has emerged as a promising source of natural anticancer compounds, largely due to its high concentration of antioxidant molecules and PUFAs, particularly γ-linolenic acid [83, 67]. These bioactive constituents contribute to a wide range of pharmacological activities, including immunomodulatory, anti-inflammatory, and cytotoxic effects against cancer cells. *Spirulina* enhances immune surveillance by stimulating antibody and cytokine production and activating NK cells, which play a key role in tumor suppression [30]. It also influences human myeloid progenitors and NK cell function through direct and indirect mechanisms [67].

Pigments such as phycocyanin, β-carotene, lutein, and chlorophyll naturally present in *Spirulina* have demonstrated anticarcinogenic properties. These compounds inhibit oxidative stress, reduce DNA damage, and suppress tumor cell proliferation. For instance, C-phycocyanin and β-carotene reduced cell growth by 49% in chronic myeloid leukemia (K562) cells at 50 µM over 48 hours [82]. Similarly, cytotoxicity assays have shown that *Spirulina* extracts can inhibit colon and liver cancer cell lines, with $LC_{50}$ values ranging from 11.3 to 21.8 µg/mL [86].

### *Spirulina* and cardiovascular disease treatment

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, with the WHO estimating over 17 million deaths annually, a number projected to exceed 23 million by 2030 [87]. Major contributors to CVDs include dyslipidemia, oxidative stress, and chronic inflammation [30].

*S. platensis*, a blue-green alga widely consumed in Asia, has been associated with reduced incidence of cardiovascular and metabolic disorders. Its cardio-protective effects are largely attributed to its rich content of phycocyanin, phenolic compounds, and PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [67, 86].

Clinical studies suggest that *Spirulina* supplementation can lower total cholesterol, LDL, and triglycerides, while increasing HDL levels, thereby improving lipid profiles and reducing atherosclerotic risk [83]. Additionally, it has shown beneficial effects on blood pressure, fasting glucose, and inflammatory markers, without reported adverse effects [82].

Phycocyanin, a key pigment in *Spirulina*, exhibits antioxidant properties similar to bilirubin. It helps neutralize ROS and prevents oxidative damage to plasma proteins and vascular tissues, contributing to vascular protection and reduced cardiovascular risk [88]. Recent studies suggest that consuming *Spirulina*-fed fish species, such as tilapia, may enhance human nutritional status and improve cardiovascular and metabolic health outcomes [89]. The nutritional effects of *Spirulina* in humans are summarized in Table 5.

## Conclusion

*S. platensis* stands out as a multifunctional biological resource with profound implications for both aquaculture and human health. In aquaculture systems, its immunostimulatory, antioxidant, and antimicrobial properties offer a natural alternative to antibiotics, reducing the risk of antimicrobial resistance while enhancing fish immunity, growth performance, and overall product quality. This condition not only improves the sustainability of aquaculture practices but also elevates the nutritional value and safety of aquatic products destined for human consumption. Importantly, the consumption of *Spirulina*-fed aquatic species may indirectly contribute to human health by reducing the risk of chronic conditions such as diabetes, hyperlipidemia, hypertension, cancer, and cardiovascular disease. This food-chain effect highlights *Spirulina*'s role in bridging aquatic nutrition and public health outcomes. In addition to its indirect benefits, *Spirulina* itself, when consumed directly by humans, has demonstrated a wide spectrum of therapeutic effects. Its rich profile of bioactive compounds, including phycocyanin, phenolic antioxidants, γ-linolenic acid, and essential micronutrients, supports immune modulation, metabolic regulation, antioxidant defense, and disease prevention. These properties position *Spirulina* as a potent functional food with applications in integrative medicine, preventive nutrition, and chronic disease management. Taken together, *S. platensis* offers a dual-action strategy to improve aquaculture outcomes and promote human well-being. Its integration into feed formulations and human diets represents a sustainable, science-backed approach to enhancing food quality, reducing dependency on synthetic drugs, and advancing global health resilience. Future research should explore optimized formulations, dosage strategies, and synergistic combinations of *S. platensis* with other natural immunostimulants to enhance its efficacy in aquaculture and human health applications.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Authors contribution's

Conceptualization, validation, resources, writing the original draft, supervision and project administration: Maryam Ghiasi; Software, formal analysis, data curation, and visualization: Matin Shakoori; Methodology, investigation, review and editing: All authors.

## Conflict of interest

The authors declared no conflict of interest.

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