

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



Maryam Ghiasi^{1*} , Matin Shakoori¹ 

1. Caspian Sea Ecology Research Center, Iranian Fisheries Science Research Institute (IFSRI), Agricultural Research, Education and Extension Organization (AREEO), Sari, Iran.



Citation Ghiasi M, Shakoori M. *Spirulina platensis* as a Dual-action Functional Agent to Improve Aquaculture Outcomes and Promote Human Health: A Review Study. Research in Molecular Medicine. 2025; 13(2):77-94. <https://doi.org/10.32598/rmm.13.2.1303.1>

 <https://doi.org/10.32598/rmm.13.2.1303.1>

Article Type:

Review Paper

Article info:

Received: 05 Feb 2025

Revised: 25 Feb 2025

Accepted: 12 Mar 2025

Keywords:

Spirulina platensis,
Aquaculture, Antibiotic
resistance, Fish immunity,
Human health

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.

* Corresponding Author:

Maryam Ghiasi, Assistant Professor:

Address: Caspian Sea Ecology Research Center, Iranian Fisheries Science Research Institute (IFSRI), Agricultural Research, Education and Extension Organization (AREEO), Sari, Iran.

Phone: +98 (11) 33462511

E-mail: ghiasimaryam4@gmail.com



Copyright © 2025 The Author(s);

This is an open access article distributed under the terms of the Creative Commons Attribution License (CC-BY-NC: <https://creativecommons.org/licenses/by-nc/4.0/legalcode.en>), which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

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-phycoerythrin, 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.

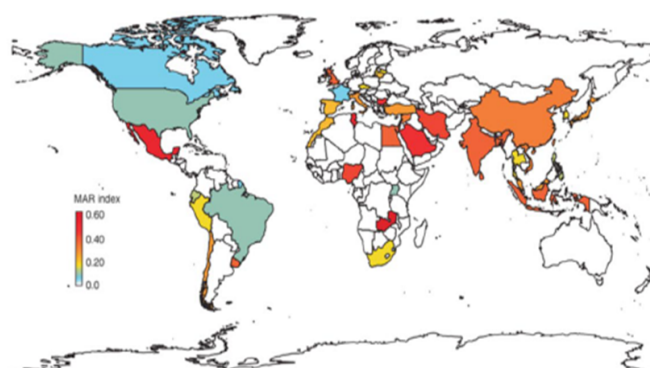


Figure 1. Global MAR index in aquaculture pathogens countries without sufficient data are shown in white [7]



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 de-

toxification 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 ($\geq 60\%$) 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

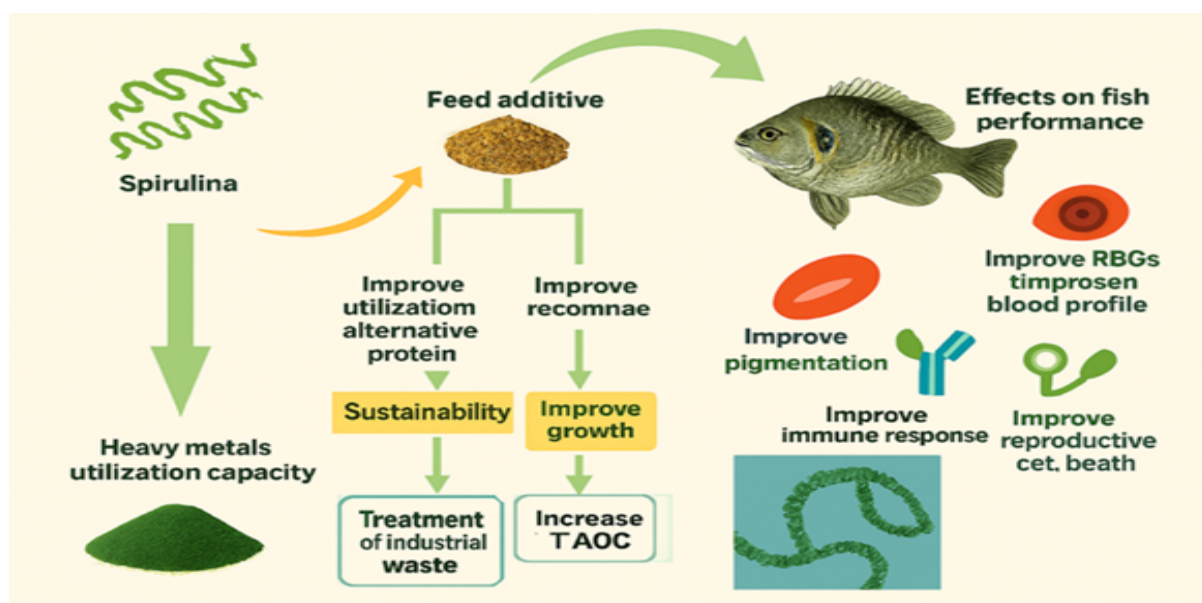


Figure 3. Role of *S. platensis* in aquaculture



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

loids, 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 non-polar 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 (<i>O. niloticus</i>)	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 (<i>L. calcarifer</i>)	56	5–20 (Se-enriched <i>Spirulina</i>)	Numerical ↑ blood indices (not significant); stabilization of physiological status	[27]
Beluga sturgeon (<i>H. huso</i>)	56	5–10	↑ RBC, Hb, HCT; ↓ Chol, TG	[22]
Persian sturgeon (<i>A. persicus</i>)	84–90	2.5–10	↑ hematological indices (Hb ↑ significantly at 10%); ↓ ALT, AST, ALP, Chol, TG	[25, 26]
Rainbow trout (<i>O. mykiss</i>)	56–70	2.5–10	↑ RBC, Hb, HCT (7.5–10%); ↑ TP, Alb; ↓ Glu, Cort	[60]
Caspian brown trout (<i>S. trutta caspius</i>)	70	2–8	(Growth studied – limited hematology data reported)	[24]
Grouper (<i>Epinephelus</i> spp.)	56	2–10	↑ RBC, Hb, HCT (best at 10%); ↓ Chol, TG	[47]
Stinging catfish (<i>Heteropneustes fossilis</i>)	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

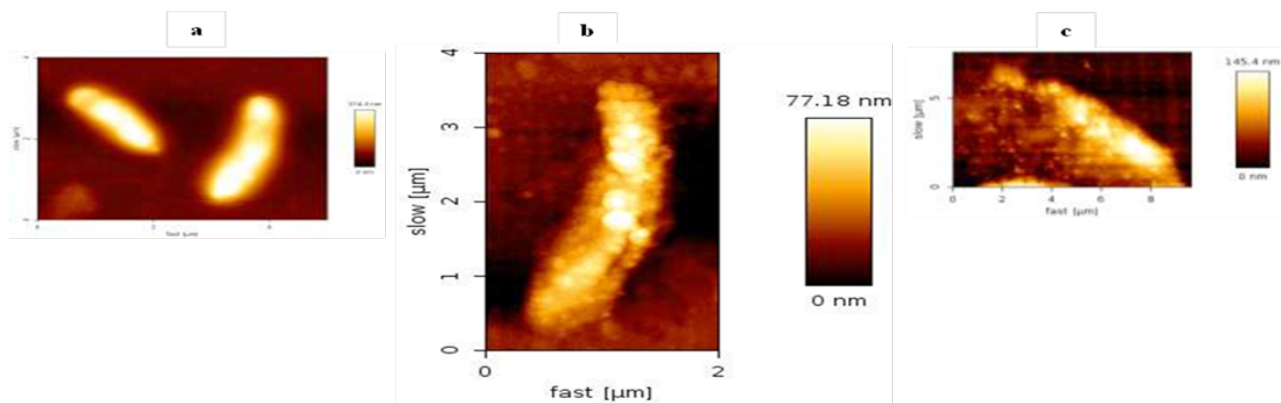
interest in immunostimulants, natural compounds that enhance innate immunity and reduce stress [31]. Fish rely primarily on innate immunity, especially during early development, with defense mechanisms including physical barriers, immune cells, and humoral factors [66, 67]. White blood cells play a key 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*
<i>Staphylococcus aureus</i>	10	25.1	25.1	5	50.2	5
<i>Staphylococcus pyogenes</i>	10	25.1	50.2	10	5	10
<i>Staphylococcus epidermidis</i>	20	25.1	50.2	10	5	10
<i>Proteus mirabilis</i>	5	25.1	25.1	5	50.2	10
<i>Bacillus cereus</i>	10	25.1	25.1	5	50.2	10
<i>Escherichia coli</i>	10	50.2	50.2	10	5	5
<i>Pseudomonas aeruginosa</i>	20	50.2	5	10	10	5
<i>Vibrio cholerae</i>	80	5	10	40	20	20
<i>Salmonella typhi</i>	40	5	5	20	10	20
<i>Klebsiella pneumoniae</i>	10	25.1	50.2	5	50.2	10
<i>Shigella flexneri</i>	5	25.1	25.1	5	50.2	10

*Ampicillin (5 mg).





Rmm

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, $\uparrow$ 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 $\rightarrow$ gene expression of IgM, TNF- α & complement	Rainbow trout, Oscar	[46, 48]

Rmm

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	—	—	<i>Spirulina's</i> 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 (<i>Lactobacilli</i> , <i>Bifidobacteria</i> , lactic acid bacteria); suppression of harmful strains (<i>Enterobacteria</i> , <i>Clostridia</i>)	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 <i>Spirulina</i> 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-phycoerythrin 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	<i>Spirulina</i> 's compounds modulate NADPH/NADH pathways and carbohydrate-metabolizing enzymes (e.g. glucose-6-phosphatase)	[84, 85]
Cancer treatment	Immunomodulatory and anti-cancer 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 μ M (C-phycocyanin & β -carotene, 48 h); 11.3–21.8 μ g/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	<i>Spirulina</i> 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

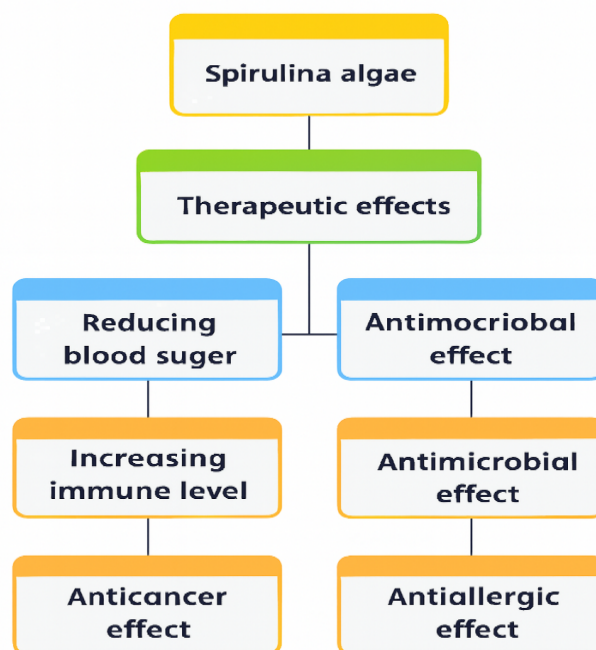


Figure 5. Overview of *Spirulina*'s health benefits in humans



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-phycoerythrin, 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 phytyls, 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 μ M 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 μ g/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 im-

munostimulatory, 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.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

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.

Acknowledgements

The authors acknowledge the general academic support of their home institutions.

References

- [1] Nikolova K, Petkova N, Mihaylova D, Gentsheva G, Gavrilov G, Pehlivanov I, et al. Extraction of phycocyanin and chlorophyll from *Spirulina* by green methods. *Separations*. 2024; 11(2):57. [DOI:10.3390/separations11020057]
- [2] Alotaiby S, Zhao X, Boesch C, Sergeeva NN. Sustainable approach towards isolation of photosynthetic pigments from *Spirulina* and the assessment of their prooxidant and antioxidant properties. *Food Chem*. 2024; 436:137653. [DOI:10.1016/j.foodchem.2023.137653] [PMID]
- [3] Marzorati S, Schievano A, Idà A, Verotta L. Carotenoids, chlorophylls and phycocyanin from *Spirulina*: Supercritical CO₂ and water extraction methods for added-value products. *Green Chem*. 2020; 22(1):92-105. [DOI:10.1039/C9GC03292D]
- [4] Benucci I, Esti M, Liburdi K, et al. *Spirulina*-derived carotenoids and their role in fish reproductive health and mucosal immunity. *Aquac Nutr*. 2023; 29(1):112-24.
- [5] Wu Q, Liu L, Miron A, Klímová B, Wan D, Kuča K. The antioxidant, immunomodulatory, and anti-inflammatory activities of *Spirulina*: An overview. *Arch Toxicol*. 2016; 90(8):1817-40. [DOI:10.1007/s00204-016-1744-5] [PMID]
- [6] Rana N, Singh R, Kumari R, et al. Role of *Spirulina*-derived polysaccharides in gut health and aquaculture nutrition. *Aquac Nutr*. 2024; 30(1):88-102.
- [7] Karkos PD, Leong SC, Karkos CD, Sivaji N, Assimakopoulos DA. *Spirulina* in clinical practice: Evidence-based human applications. *Evid Based Complement Alternat Med*. 2011; 2011:531053. [DOI:10.1093/ecam/nen058] [PMID]
- [8] Finamore A, Palmery M, Bensehaila S, Peluso I. Antioxidant, immunomodulating, and microbial-modulating activities of the sustainable and ecofriendly *Spirulina*. *Oxid Med Cell Longev*. 2017; 2017:3247528. [PMID]
- [9] Deng R, Chow TJ. Hypolipidemic, antioxidant, and anti-inflammatory activities of microalgae *Spirulina*. *Cardiovasc Ther*. 2010; 28(4):e33-45. [DOI:10.1111/j.1755-5922.2010.00200.x] [PMID]
- [10] Metekia WA, Ulusoy BH, Habte-Tsion HM. *Spirulina* phenolic compounds: Natural food additives with antimicrobial properties. *Int Food Res J*. 2021; 28(6):1109-18. [Link]
- [11] Liu Y, Mándi A, Li XM, Meng LH, Kurtán T, Wang BG. Peniciadametizine A, a dithiodiketopiperazine with a unique spiro[furan-2,7'-pyrazino[1,2-b][1,2]oxazine] skeleton, and a related analogue, peniciadametizine b, from the marine sponge-derived fungus *Penicillium adametzoides*. *Mar Drugs*. 2015; 13(6):3640-52. [PMID]
- [12] Chadov BF, Fedorova NB. Ontogenes and the paradox of homologous pairing. *Adv Biosci Biotechnol*. 2021; 12(1):1-14. [DOI:10.4236/abb.2021.121001]
- [13] Xv Z, Zhong Y, Wei Y, Zhang T, Zhou W, Jiang Y, et al. Yeast culture supplementation alters the performance and health status of juvenile largemouth bass (*Micropterus salmoides*) fed a high-plant protein diet. *Aquacult Nutr*. 2021; 27(6):2637-50. [DOI:10.1111/anu.13391]
- [14] Hien TT, Hoa TT, Liem PT, Onoda S, Duc PM. Effects of dietary supplementation of heat-killed *Lactobacillus plantarum* L-137 on growth performance and immune response of bighead catfish (*Clarias macrocephalus*). *Aquacult Rep*. 2021; 20:100741. [DOI:10.1016/j.aqrep.2021.100741]
- [15] Serna-Duque JA, Cuesta A, Sánchez-Ferrer Á, Esteban MÁ. Two duplicated piscidin genes from gilthead seabream (*Sparus aurata*) with different roles in vitro and in vivo. *Fish Shellfish Immunol*. 2022; 127:730-9. [DOI:10.1016/j.fsi.2022.07.013] [PMID]
- [16] Wang Z, Feng Y, Yang N, Jiang T, Xu H, Lei H. Fermentation of kiwifruit juice from two cultivars by probiotic bacteria: Bioactive phenolics, antioxidant activities and flavor volatiles. *Food Chem*. 2022; 373:131455. [DOI:10.1016/j.foodchem.2021.131455]
- [17] Anderson DP, Kumari A, Sahu NP. Growth performance as a health indicator in aquaculture. *Aquac Int*. 2020; 28:137-56.
- [18] Belal EB, Khalafalla MM, El-Hais AM. Use of *Spirulina* (*Arthrospira fusiformis*) for promoting growth of Nile Tilapia fingerlings. *Afr J Microbiol Res*. 2012; 6(35):6423-31. [DOI:10.5897/AJMR12.288]
- [19] Ibrahim MD, Mohamed MF, Ibrahim M. The role of *Spirulina platensis* in growth and immunity of Nile tilapia. *J Agric Sci*. 2013; 5(6):109-117. [DOI:10.5539/jas.v5n6p109]
- [20] El-Sayed H, El-Ghobashy H, El-Kady M. Partial replacement of fishmeal with *Spirulina platensis* in Nile tilapia diets. *Aquac Res*. 2013; 44(5):728-36.
- [21] Velasquez A, Martinez R, Gomez D. Effects of *Spirulina* inclusion on growth and feed efficiency in tilapia. *Aquac Nutr*. 2016; 22(3):543-550.
- [22] Adel M, Yeganeh S, Dadar M, Sakai M. Effects of *Spirulina platensis* on growth performance, immune response and disease resistance of African catfish (*Clarias gariepinus*). *Iran J Fish Sci*. 2016; 15(3):1028-43.
- [23] Teimouri M, Amirkolaie AK, Yeganeh S. Effect of *Spirulina platensis* meal on growth and pigmentation of rainbow trout. *World J Fish Mar Sci*. 2013; 5(2):194-202. [DOI:10.5829/idosi.wjfs.2013.05.02.7223]
- [24] Roohani AM, Abedian Kenari A, Fallahi Kapoorchali M, Borani MS, Zoriezahra SJ, Smiley AH, et al. *Spirulina* as a complementary ingredient in Caspian salmon diets. *Aquac Nutr*. 2019; 25(3):654-64. [DOI:10.1111/anu.12885]

- [25] Akhoundian M, Younesi H, Agh N. Supplementing *Spirulina platensis* to improve survival and hematological parameters of Persian sturgeon (*Acipenser persicus*). Iran J Fish Sci. 2024; 23(1):15–29.
- [26] Akhoundian M, Younesi HA, Gorjian MH, Khan S. *Arthrospira platensis* supplementation: A nutritional boost for enhancing survival and hemato-biochemical indices of Persian Sturgeon (*Acipenser persicus*) larvae. Iran J Fish Sci. 2025; 24(1):69–83. [DOI:10.22092/ijfs.2024.132434]
- [27] Siddik MAB, Vatsos IN, Rahman MA, Pham HD. Selenium-enriched *Spirulina* enhances growth and immunity in Asian sea bass. Antioxidants. 2022; 11(8):1572. [DOI:10.3390/antiox11081572] [PMID]
- [28] Zahan N, Hossain MA, Islam MR, Saha J, Akter T, Fatema UK, et al. Effects of dietary *Spirulina platensis* on growth performance, body composition, haematology, immune response, and gut microflora of stinging catfish *Heteropneustes fossilis*. Aquac Rep. 2024; 35:101997. [DOI:10.1016/j.aqrep.2024.101997]
- [29] Rana M, Mandal S, Kabita S. *Spirulina* in fish immunity development: Find the black box. Rev Fish Biol Fish. 2024; 34(2):623–46. [DOI:10.1007/s11160-023-09832-0]
- [30] Han T, Wang JT, Li XY, Yang YX, Yang M, Tian HL, et al. Effects of dietary phospholipid and cholesterol levels on growth and fatty acid composition of juvenile swimming crab, *Portunus trituberculatus*. Aquac Nutr. 2018; 24(1):164–72. [DOI:10.1111/anu.12544]
- [31] Santos L, Ramos F. Antimicrobial resistance in aquaculture: Current knowledge and alternatives to tackle the problem. Int J Antimicrob Agents. 2018; 52(2):135–43. [DOI:10.1016/j.ijantimicag.2018.03.010] [PMID]
- [32] Vincent AT, Gauthier J, Derome N, Charette SJ. The Rise and Fall of Antibiotics in Aquaculture. In: Derome N, editor. Microbial communities in aquaculture ecosystems. Cham: Springer; 2019. [Link]
- [33] Bhowmik D. Antimicrobial activity of *Spirulina platensis* extracts. J Phytology. 2009; 1(5):20–5.
- [34] Ozdemir G, Karabay NU, Dalay MC, Pazarbasi B. Antibacterial activity of volatile component and various extracts of *Spirulina platensis*. Phytother Res. 2004; 18(9):754–7. [DOI:10.1002/ptr.1541] [PMID]
- [35] Alshuniaber MA, Krishnamoorthy R, AlQhtani WH. Antimicrobial activity of polyphenolic compounds from *Spirulina* against food-borne bacterial pathogens. Saudi J Biol Sci. 2021; 28(1):459–64. [DOI:10.1016/j.sjbs.2020.10.029] [PMID]
- [36] Abdel-Moneim AE, El-Saadony MT, Shehata AM, Saad AM, Aldhumri SA, Ouda SM, et al. Antioxidant and antimicrobial activities of *Spirulina platensis* extracts and biogenic selenium nanoparticles against selected pathogenic bacteria and fungi. Saudi J Biol Sci. 2022; 29(2):1197–209. [DOI:10.1016/j.sjbs.2021.09.046] [PMID]
- [37] Usharani G, Srinivasan G, Sivasakthi S, Saranraj P. Antimicrobial activity of *Spirulina platensis* solvent extracts against pathogenic bacteria and fungi. Adv Biol Res. 2015; 9(5):292–8. [DOI: 10.5829/idosi.abr.2015.9.5.9610]
- [38] Pradhan J, Das BK, Sahu S, Marhual NP, Swain AK, Mishra BK, et al. Traditional antibacterial activity of freshwater microalga *Spirulina platensis* to aquatic pathogens. Aquac Res. 2012; 43(9):1287–95. [DOI:10.1111/j.1365-2109.2011.02932.x]
- [39] Bhuvaneswari R, Murugesan S, Subhashini S. Antibacterial activity of *Spirulina platensis* solvent extracts against fish pathogens. Int J Current Microbiol Appl Sci. 2013; 2(1):34–7.
- [40] Hegazy AM, Chen N, Lin H, Babu VS, Li F, Yang Y, et al. Induction of apoptosis in SSN-1 cells by Snakehead Fish Vesiculovirus (SHVV) via matrix protein dependent intrinsic pathway. Fish Shellfish Immunol. 2021; 113:24–34. [DOI:10.1016/j.fsi.2021.03.010] [PMID]
- [41] Mokhtar DM, Zacccone G, Alesci A, Kuciel M, Hussein MT, Sayed RK. Main components of fish immunity: An overview. Fishes. 2023; 8(2):93. [DOI:10.3390/fishes8020093]
- [42] Dossou S, Koshio S, Ishikawa M, Yokoyama S, El Basuini MF, Zaineldin AI, et al. Effects of replacing fishmeal with fermented and non-fermented rapeseed meal on the growth, immune and antioxidant responses of red sea bream (*Parus major*). Aquac Nutr. 2019; 25(2):508–17. [DOI:10.1111/anu.12876]
- [43] Shan S, Liu R, Jiang L, Zhu Y, Li H, Xing W, et al. Carp toll-like receptor 8 (TLR8): An intracellular TLR that recruits TIRAP as adaptor and activates AP-1 pathway in immune response. Fish Shellfish Immunol. 2018; 82:41–49. [DOI:10.1016/j.fsi.2018.08.001] [PMID]
- [44] Grishin AM, Sokolov AV, Vasilyev VB. Lysozyme: Structure, function, and role in fish immunity. Biochemistry (Moscow). 2020; 85(3):267–79.
- [45] Gabriel NN, Qiang J, He J, Ma XY, Kpundeh MD, Xu P. Dietary Aloe vera supplementation on growth performance, some haemato-biochemical parameters and disease resistance against *Streptococcus iniae* in tilapia (GIFT). Fish Shellfish Immunol. 2015; 44(2):504–14. [DOI:10.1016/j.fsi.2015.03.002] [PMID]
- [46] Mohammadiarzam H, Maniat M, Ghorbanijezeh K, Ghotbeddin N. Effects of *Spirulina platensis* on Oscar fish immunity. Aquac Nutr. 2020; 26(4):1234–45. [DOI:10.1111/anu.13182]
- [47] Zhang W, Sun S, Ge X, Zhu J, Miao L, Lin Y, et al. Effects of dietary lipid sources on growth performance, fatty acid composition and hepatic lipid metabolism of juvenile blunt snout bream, *Megalobrama amblycephala*. Aquac Nutr. 2018; 24(6):1652–63. [DOI:10.1111/anu.12800]
- [48] Sheikhzadeh N, Mousavi S, Oushani AK, Firouzmandi M, Mardani K. *Spirulina platensis* modulates mucosal immune responses in rainbow trout. Aquaculture. 2019; 510:1–8. [DOI:10.1016/j.aquaculture.2019.05.009]
- [49] Saleghizadeh R, Yavari V, Mousavi SM, Zakeri M. Effect of *Spirulina platensis* on immune indices in Binni fish (*Mesopotamichthys sharpeyi*). J Aquat Ecol. 2015; 5(1):44–50.
- [50] Hematyar N, Rustad T, Sampels S, Kastrup Dalsgaard T. Relationship between lipid and protein oxidation in fish. Aquac Res. 2019; 50(5):1393–403. [DOI:10.1111/are.14012]
- [51] Ghanbari M, Kneifel W, Domig KJ. A new view of the fish guts microbiome: *Spirulina* as a prebiotic. Rev Aquac. 2015; 7(1):1–24. [DOI:10.1111/raq.12057]

- [52] Zhu H, He A, Chen L, Qin J, Li E, Li Q, et al. Effects of dietary lipid level and n-3/n-6 fatty acid ratio on growth, fatty acid composition and lipid peroxidation in Russian sturgeon *Acipenser gueldenstaedtii*. *Aquac Nutr*. 2017; 23(4):879-90. [DOI:10.1111/anu.12454]
- [53] Thuong TD, Hoang T. Rearing the spotted seahorse *Hippocampus kuda* by feeding live and frozen copepods collected from shrimp ponds. *Aquac Res*. 2015; 46(6):1356-62. [DOI:10.1111/are.12289]
- [54] Abdel-Warith A, Elsayed A. Effects of dietary *Spirulina platensis* on hematological and serum biochemical parameters of Nile tilapia. *J Sci Ind Res*. 2019; 78(10):681-6. [Link]
- [55] Youssef IMI, Saleh ESE, Tawfeek SS, Abdel-Fadeel AAA, Abdel-Razik AH, Abdel-Daim ASA. Effect of spirulina platensis on growth, hematological, biochemical, and immunological parameters of Nile tilapia (*Oreochromis niloticus*). *Trop Anim Health Prod*. 2023; 55(4):275. [DOI:10.1007/s11250-023-03690-5] [PMID]
- [56] Manera M, Dezfuli BS. Fish histopathology and blood biomarkers as tools for health assessment in aquaculture. *Fish Physiol Biochem*. 2021; 47(2):345-60.
- [57] Mathur S, Gupta N. Phycocyanin as a natural modulator of hematological and antioxidant responses in fish: mechanisms and aquaculture applications. *Fish Physiol Biochem*. 2018; 44(5):1295-305.
- [58] Abdel-Tawwab M, El-Araby IE, Abdel-Rahman AM. Dietary *Spirulina platensis* and its role in enhancing hematological indices and erythropoiesis in Nile tilapia (*Oreochromis niloticus*). *Aquac Int*. 2014; 22(3):567-76.
- [59] Najafpour A, Ghorbani R, Ebrahimi M. Antioxidant and hematoprotective effects of dietary *Spirulina platensis* in common carp (*Cyprinus carpio*). *Iran J Fish Sci*. 2012; 11(2):345-54.
- [60] Teimouri M, Yeganeh S, Mianji GR, Najafi M, Mahjoub S. The effect of *Spirulina platensis* meal on antioxidant gene expression, total antioxidant capacity, and lipid peroxidation of rainbow trout (*Oncorhynchus mykiss*). *Fish Physiol Biochem*. 2019; 45(3):977-86. [DOI:10.1007/s10695-019-0608-3] [PMID]
- [61] Liu JD, Chi C, Zheng XC, Xu CY, Zhang CY, Ye MW, et al. Effect of dietary glutathione supplementation on the immune responses and the fatty acid and amino acid composition in Chinese mitten crab, *Eriocheir sinensis*. *Aquac Rep*. 2019; 15:100217. [DOI:10.1016/j.aqrep.2019.100217]
- [62] Youssef AM, El-Sayed A, El-Gamal AE. Selenium-enriched *Spirulina* improves immunity and stress resistance in Nile tilapia. *Aquac Nutr*. 2023; 29(2):234-45.
- [63] Gabriel U, Akinrotimi OA, Orok EJ. Hematological indicators of fish health in aquaculture. *J Aquac Res Dev*. 2019; 10(3):1-6.
- [64] Zhang Q, Li Y, Sun X, Zhang J, Gui JF. Grass carp reovirus induces apoptosis and immune responses in CIK cells through mitochondrial and death-receptor pathways. *Fish Shellfish Immunol*. 2020; 98:105-13.
- [65] Mokhtar DM, El-Gamal AE, El-Morshedy HA. Immunological responses of Nile tilapia to dietary *Spirulina* under stress. *Aquac Int*. 2023; 31(2):567-78.
- [66] Pang Y, Bai X, Zhang L, Wang H, Shi Y, Yang G. Molecular characterization and expression analysis of TLR3 in common carp (*Cyprinus carpio*) following poly(I:C) challenge. *Fish Shellfish Immunol*. 2012; 33(3):632-40.
- [67] Magnadóttir B. Innate immunity of fish (overview). *Fish Shellfish Immunol*. 2006; 20(2):137-51. [PMID]
- [68] Sun H, Jiang Z, Mao M, Huo Y, Han Y, Zhang S. Cloning and expression analysis of interferon regulatory factor 7 in the Pacific cod, *Gadus macrocephalus*. *Fish Shellfish Immunol*. 2016; 49:7-15. [DOI:10.1016/j.fsi.2015.12.020]
- [69] Cavalcante RB, Telli GS, Tachibana L, de Carla Dias D, Oshiro E, Natori MM, et al. Probiotics, prebiotics and synbiotics for Nile tilapia: Growth performance and protection against *Aeromonas hydrophila* infection. *Aquac Rep*. 2020; 17:100343. [DOI:10.1016/j.aqrep.2020.100343]
- [70] Yu L, Zhang Y, Li X, Luo Y, Xu H, Zhang W. Dietary *Spirulina platensis* improves growth performance, antioxidant capacity and immune response in grouper (*Epinephelus coioides*). *Aquac Nutr*. 2018; 24(6):1802-12.
- [71] Ding Z, Zhao X, Cui L, Sun Q, Zhang F, Wang J, et al. Novel insights into the immune regulatory effects of ferritins from blunt snout bream, *Megalobrama amblycephala*. *Fish Shellfish Immunol*. 2019; 87:679-87. [DOI:10.1016/j.fsi.2019.01.045] [PMID]
- [72] Ghaeni M, Roomiani L. Effects of dietary *Spirulina platensis* on immune parameters and lysozyme activity in common carp (*Cyprinus carpio*). *Iran J Fish Sci*. 2014; 13(2):456-66.
- [73] Mostafa SS, El-Gendy NS. Antioxidant potential of *Spirulina platensis* and its applications in aquaculture. *J Appl Phycol*. Ibrahim MD, Mohamed MF, Ibrahim MA.
- [74] Rurangwa E, Verdegem MC. Microorganisms in recirculating aquaculture systems and their management. *Rev Aquac*. 2015; 7(2):117-30. [DOI:10.1111/raq.12057]
- [75] Ibrahim MD, Mohamed MF, Ibrahim MA. The role of *Spirulina platensis* (*Arthrospira platensis*) in growth and immunity of Nile tilapia (*Oreochromis niloticus*) and its resistance to bacterial infection. *J Agric Sci*. 2013; 5(6):109-17. [DOI:10.5539/jas.v5n6p109]
- [76] Pavan Kumar RS, Sibi G. Replacing fish meal with *Spirulina* (*Arthrospira platensis*): nutrigenomic modulation of growth, reproductive performance, and metabolism in zebrafish. *World J Fish Mar Sci*. 2020; 12(1):47-52.
- [77] DiNicolantonio JJ, Bhat AG, O'Keefe J. Effects of spirulina on weight loss and blood lipids: A review. *Open Heart*. 2020; 7(1):e001003. [DOI:10.1136/openhrt-2018-001003] [PMID]
- [78] Lak M, Karimi M, Akhgarjand C, Ghotboddin Mohammadi S, Pam P, Ashtary-Larky D, et al. Effects of spirulina supplementation on body composition in adults: A GRADE-assessed and dose-response meta-analysis of RCTs. *Nutr Metab*. 2025; 22(1):61. [DOI:10.1186/s12986-025-00959-4] [PMID]
- [79] AlFadhly NKZ, Alhelfi N, Altemimi AB, Verma DK, Cacciola F, Narayanankutty A. Trends and technological advancements in the possible food applications of spirulina and their health benefits: A review. *Molecules*. 2022; 27(17):5584. [DOI:10.3390/molecules27175584] [PMID]

- [80] Sayed R, Sayed AE-D. Protective role of *Spirulina platensis* against oxidative stress and metabolic disturbances in zebrafish (*Danio rerio*). *Aquac Res*. 2020; 51(12):5462–73.
- [81] Li TT, Huang ZR, Jia RB, Lv XC, Zhao C, Liu B. *Spirulina platensis* polysaccharides attenuate lipid and carbohydrate metabolism disorder in high-sucrose and high-fat diet-fed rats in association with intestinal microbiota. *Food Res Int*. 2021; 147:110530. [DOI:10.3389/fnut.2021.734812]
- [82] Gutierrez E, Metcalfe JJ, Prescott MP. The relationship between fluid milk, water, and 100% juice and health outcomes among children and adolescents. *Nutrients*. 2022; 14(9):1892. [DOI:10.3390/nu14091892] [PMID]
- [83] Visioli F, Poli A. Fatty acids and cardiovascular risk. Evidence, lack of evidence, and diligence. *Nutrients*. 2020; 12(12):3782. [DOI:10.3390/nu12123782] [PMID]
- [84] Zhang X, Lv S, Zhang W, Jia Q, Wang L, Ding Y, et al. Shenmai injection improves doxorubicin cardiotoxicity via miR-30a/Beclin 1. *Biomed Pharmacother*. 2021; 139:111582. [DOI:10.1016/j.biopha.2021.111582] [PMID]
- [85] Fukunaga E, Hirao Y, Ogata-Ikeda I, Nishimura Y, Seo H, Oyama Y. Bisabololoxide A, one of the constituents in German chamomile extract, attenuates cell death induced by calcium overload. *Phytother Res*. 2014; 28(5):685–91. [DOI:10.1002/ptr.5041] [PMID]
- [86] Matos J, Cardoso C, Bandarra NM, Afonso C. Microalgae as healthy ingredients for functional food: A review. *Food Func*. 2017; 8(8):2672–85. [DOI:10.1039/D0FO01200G]
- [87] World Health Organization (WHO). Cardiovascular diseases (CVDs) fact sheet. Geneva: World Health Organization; 2023. [Link]
- [88] Rtibi K, Selmi S, Jabri MA, El-Benna J, Amri M, Marzouki L, et al. Protective effect of *Ceratonia siliqua* L. against a dextran sulfate sodium-induced alterations in liver and kidney in rat. *J Med Food*. 2016; 19(9):882–9. [DOI:10.1089/jmf.2016.0020] [PMID]
- [89] Cho CY, Bureau DP. A review of diet formulation strategies and feeding systems to improve growth and nutrient utilization in fish. *Aquac Res*. 2001; 32(s1):349–360. [DOI:10.1046/j.1355-557x.2001.00027.x]

This Page Intentionally Left Blank
