Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

Spirulina as a multisystem protective nutraceutical: Molecular mechanisms and therapeutic potential across major organs

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ARTICLE INFO

Article type:
Review

Article history:
Received: May 24, 2026
Accepted: Aug 2, 2026

Keywords:
Anti-inflammatory Agents
Anti-oxidant
Phycocyanin
Protective agents
Spirulina

ABSTRACT

Spirulina has emerged as a promising multisystem nutraceutical with protective potential against organ injury mediated by oxidative stress and inflammation. Extensive experimental evidence and emerging clinical data suggest that *Spirulina* and its bioactive constituents, including phycocyanin, phenolic compounds, polysaccharides, vitamins, minerals, and essential fatty acids, exert protective effects on the nervous, cardiovascular, hepatic, renal, and reproductive systems. However, existing reviews have largely addressed these organ systems in isolation, without a structured search strategy or an integrated mechanistic view. To address this gap, relevant studies were identified through a structured search of Google Scholar, PubMed, Scopus, and Web of Science (2010–2026) and critically evaluated to synthesize mechanistic and translational evidence on *Spirulina*'s organ-protective properties across five organ systems within a single framework. Across diverse experimental models, Spirulina consistently attenuates tissue damage induced by environmental toxins, pharmaceuticals, heavy metals, radiation, metabolic stress, and age-related processes. These effects are mediated by coordinated antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, including activation of the Nrf2/HO-1, AMPK, and PI3K/Akt signaling pathways, suppression of NF-κB-mediated inflammation, modulation of apoptotic cascades, and preservation of mitochondrial integrity. These mechanisms converge across organ systems. In addition, *Spirulina* has demonstrated the ability to improve biochemical, histological, and functional parameters associated with organ injury in numerous preclinical studies. However, heterogeneity in study design, dosing regimens, *Spirulina* formulations, and intervention duration limits the interpretation and generalizability of the findings. Overall, *Spirulina* is a promising nutraceutical with potential applications in disease prevention and as an adjunctive therapy. Well-designed future clinical trials are warranted to determine optimal dosing strategies, long-term safety, and organ-specific efficacy.

▶ Please cite this article as:
Torkashvand S, Nazari Taloki Z. *Spirulina* as a multisystem protective nutraceutical: Molecular mechanisms and therapeutic potential across major organs. Iran J Basic Med Sci 2026; 29:

Introduction

The rising global burden of chronic diseases, driven by oxidative stress, inflammation, environmental toxicants, and metabolic dysregulation, has intensified interest in nutraceuticals that offer broad, multi-organ protection (1). Among natural functional foods, Spirulina, a filamentous cyanobacterium in the genus Arthrospira, has emerged as a leading candidate because of its exceptional nutritional density and diverse bioactive composition.

Spirulina contains high-quality proteins, essential amino acids, polyunsaturated fatty acids, vitamins, minerals, and a wide range of bioactive compounds, including phycocyanin, carotenoids, phenolic compounds, and polysaccharides. These constituents collectively confer potent antioxidant, anti-inflammatory, and cytoprotective properties, positioning Spirulina as more than a simple dietary supplement and rather as a multifunctional nutraceutical with therapeutic relevance (2).

Over the past two decades, extensive experimental studies have demonstrated that Spirulina supplementation attenuates tissue injury and functional decline in multiple organs exposed to chemical toxins, pharmaceuticals, heavy metals, radiation, and metabolic stressors (3-7). Notably, protective effects have been consistently reported in the reproductive system, liver, cardiovascular system, kidneys, and central nervous system organs that are particularly vulnerable to oxidative and inflammatory damage (8-14). These organ-specific benefits are mediated through overlapping molecular mechanisms, including activation of endogenous antioxidant defenses, suppression of pro-inflammatory signaling pathways, modulation of apoptosis and autophagy, and preservation of mitochondrial and cellular homeostasis.

Despite the growing body of evidence, the literature remains relatively fragmented, with studies often focusing on single organs, specific toxicants, or isolated bioactive

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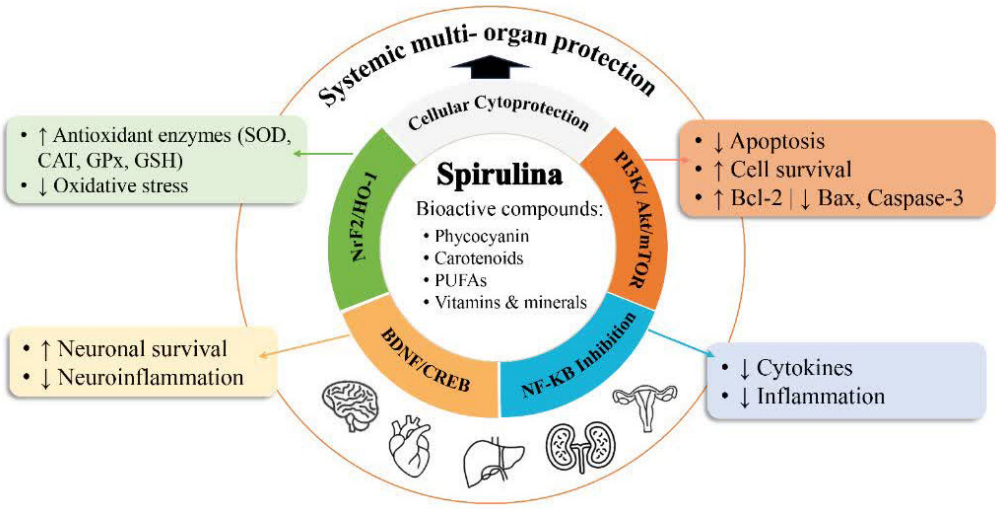

Figure 1. Multi-organ protective signaling pathways of Spirulina

compounds. Several prior reviews have examined Spirulina's health-promoting properties. Still, each has typically been limited in scope, focusing on a single organ system, a single toxicant class, or general nutritional composition without an integrated mechanistic framework. Consequently, the field lacks a synthesis that maps convergent molecular mechanisms such as Nrf2/Keap1 antioxidant signaling, NF-κB-mediated inflammation, and Bcl-2/caspase-3-dependent apoptosis across multiple organ systems simultaneously. Accordingly, this narrative review aims to (1) map experimental and clinical evidence on Spirulina's protective effects across the neurological, cardiovascular, hepatic, renal, and reproductive systems using a structured search strategy; (2) identify convergent molecular mechanisms shared across these organ systems; and (3) critically evaluate the translational barriers that should be addressed to facilitate future clinical application (Figure 1).

Methods

This narrative review summarizes and critically synthesizes available experimental and clinical evidence on the organ-protective effects of Spirulina and its bioactive constituents, with particular focus on its antioxidant, anti-inflammatory, and anti-apoptotic properties across the neurological, cardiovascular, hepatic, renal, and reproductive systems.

Relevant studies were identified through searches of Google Scholar, PubMed, Scopus, and Web of Science, covering literature published predominantly between 2010 and 2026, with a limited number of earlier foundational studies included where they remained the primary source for a specific mechanism not superseded by more recent work. The search combined the keywords "Spirulina," "Nutraceutical," "Antioxidant," "Anti-inflammatory," "Organ protection," "Phycocyanin," "Neuroprotective," and "Hepatoprotective," using Boolean operators (AND/OR). Organ-specific terms ("cardio protective," "nephroprotective," "reproductive toxicity") were additionally applied to ensure balanced coverage of all five organ systems addressed in this review. Reference lists of retrieved articles and prior related reviews were also hand-searched to identify additional eligible studies not captured by the primary search. Titles and abstracts were first screened for relevance, followed by full-text assessment of potentially eligible articles. Studies were included if they were (a) peer-reviewed original research articles (*in vitro, in vivo*, or clinical) or systematic reviews/meta-analyses; (b) focused on Spirulina, *Arthrospira platensis*, or its bioactive constituents (particularly phycocyanin) in the context of organ injury, toxicity, oxidative stress, or inflammation; and (c) published in English. Conference abstracts without full text, non-peer-reviewed sources, and studies lacking a clearly defined intervention or outcome measure were excluded (15).

Neuroprotective role of Spirulina in the central nervous system

Spirulina (primarily *Spirulina platensis, Spirulina maxima,* and *Spirulina fusiformis*) is a nutrient-dense cyanobacterium rich in phycocyanin, carotenoids, polyunsaturated fatty acids, vitamins, phenolics, and essential minerals. It has emerged as a promising neuroprotective nutraceutical (16, 17). Extensive preclinical and emerging clinical evidence indicates that Spirulina mitigates stress- and anxiety-related behaviors, counters neurotoxicity induced by environmental toxins and drugs, and serves as an adjuvant strategy in both chronic neurodegenerative and acute neurological insults (12, 17, 18). At the mechanistic level, Spirulina exerts its neuroprotective actions primarily through potent antioxidant, anti-inflammatory, anti-apoptotic, and immunomodulatory pathways, thereby enhancing neuronal survival and functional integrity (13, 19). At the systemic level, Spirulina has been shown to restore endogenous antioxidant defense systems and reduce oxidative damage markers, thereby limiting neuronal injury across diverse experimental conditions (20-22). These antioxidant effects are closely coupled with suppression of neuroinflammatory responses by modulating key inflammatory signaling pathways and reducing microglial activation, which contributes to attenuation of secondary neuronal damage (21, 23, 24). In neurodegenerative disease models such as Alzheimer's and Parkinson's disease, Spirulina has demonstrated significant neuroprotective efficacy, including improvement in cognitive and motor functions, modulation of amyloid- and dopamine-related pathology, and enhancement of neurotrophic signaling pathways

Table 1. Protective effects of Spirulina on the central nervous system

Organ/System	Injury/Disease model	Key mechanisms of Spirulina	Ref.
Brain (CNS)	Alzheimer's disease models (Aβ, scopolamine)	↓Oxidative stress, ↑BDNF/CREB signaling, ↓APP/BACE1, anti-apoptotic effects, improved antioxidant defenses	(21, 25, 26)
	Parkinson's disease models (6-OHDA, rotenone, reserpine, α-synuclein)	Preservation of dopaminergic neurons, ↓oxidative & nitrosative stress, microglial modulation, improved dopamine levels	(22, 23, 27, 28)
	Cerebral ischemia (MCAO)	Antioxidant, anti-apoptotic, reduction of neuronal injury and neurological deficits	(20)
	Intracerebral hemorrhage	Protection of peri-lesional neurons, improved long-term motor function	(31)
	Traumatic brain injury (TBI)	Reduced histopathological damage, attenuation of neuronal injury markers	(32)
	Autism spectrum disorder model (valproic acid)	↓Oxidative stress & neuroinflammation, normalization of PI3K/Akt/mTOR, ↑BDNF, behavioral improvement	(29)
	Fibromyalgia model (reserpine)	Restoration of antioxidant balance, ↓neuroinflammation, normalization of neurotransmitters	(30)
	Neurotoxicity by heavy metals, drugs, toxins	Antioxidant activation, inhibition of apoptosis, mitochondrial protection, improved neuronal viability	(33-41)

Summary of experimental models, observed neuroprotective outcomes, and proposed molecular mechanisms. Symbols: ↑ indicates increased levels, activity, or expression; ↓ indicates reduced levels, activity, or expression.

(21-28). Similarly, in models of neurodevelopmental and neuropsychiatric disorders, including autism spectrum disorder and fibromyalgia, Spirulina has been associated with improvement in behavioral outcomes alongside normalization of neuroinflammatory and neurotransmitter-related disturbances (29, 30). Furthermore, Spirulina has shown protective effects in acute neurological injury models, including cerebral ischemia, intracerebral hemorrhage, and traumatic brain injury, where it reduces neuronal damage and supports functional recovery (20, 31, 32). In cellular and toxicological models, Spirulina protects neuronal cells against a wide range of insults, including heavy metals, pharmacological toxins, and environmental neurotoxicants, primarily through enhancement of cellular viability, mitochondrial protection, and inhibition of apoptosis (33-41).

Mechanistically, these neuroprotective effects converge on restoration of antioxidant defenses (SOD, CAT, GPx, GSH), suppression of NF-κB driven neuroinflammatory cytokines (TNF-α, IL-1β, IL-6), and activation of neurotrophic/pro-survival signaling (BDNF/CREB, PI3K/Akt/mTOR), alongside model-specific effects including reduced APP/BACE1 expression and PARP-1 cleavage (Alzheimer's), preserved dopaminergic markers (TH, DAT) and microglial modulation (CX3CR1, MHC-II) in Parkinson models, and mitochondrial preservation with suppression of NOX4/SOD2-related oxidative pathways at the cellular level. A detailed, model-specific summary of these mechanisms is provided in Table 1.

Collectively, these findings support a broad neuroprotective profile that converges on redox regulation, neuroinflammation control, and neuronal survival pathways. However, despite strong preclinical evidence, further large-scale and well-controlled clinical trials are still required to validate its therapeutic efficacy, determine optimal dosing strategies, and establish long-term safety in human neurological disorders.

Cardioprotective effects of Spirulina

Growing experimental and emerging clinical evidence supports the role of Spirulina (*A. platensis*) as a cardioprotective nutraceutical with potential benefits in reducing myocardial injury, preserving cardiac function, and improving cardiometabolic risk profiles. Across diverse preclinical models, Spirulina has demonstrated consistent protective effects against ischemic, toxic, and inflammatory cardiac injury, highlighting its multi-target biological activity (42-52). A summary of the principal experimental models and outcomes is provided in Table 2. In large-animal

Table 2. Protective effects of Spirulina on the cardiovascular system

Organ/System	Injury/Disease model	Key mechanisms of Spirulina	Ref.
Cardiovascular system	Ischemia–reperfusion injury (pig LAD occlusion model)	Infarct size ↓, LV function ↑; PI3K/AMPK/iNOS/Bcl-2/COX-2 ↑; MCP-1, oxidative DNA damage & apoptosis ↓	(42, 43)
	Doxorubicin-induced cardiotoxicity	SOD, GPx, CAT, GSH ↑; lipid peroxidation, inflammation, apoptosis & fibrosis ↓; myocardial structure preserved	(44-46)
	Drug and poisoning-induced cardiotoxicity (multiple agents)	CK-MB, troponin, LDH ↓; antioxidant defense ↑; infarct size & tissue injury ↓; TLR4/NLRP3/NF-κB, Bax, caspase-3 ↓; Bcl-2 & connexin-43 ↑	(47-52)
	Cyclophosphamide cardiotoxicity (nano-Spirulina)	Autophagy markers (Beclin-1, LC3II) ↑; p-AKT/eNOS ↓; antioxidant & anti-apoptotic signaling ↑	(53)
	Anthracycline/Trastuzumab cardiotoxicity (combined nutraceutical)	Cardiac function ↑; fibrosis, inflammasome activation & cytokine release ↓	(54, 55)
	Cardiac dysfunction in thalassemia major (clinical)	Hemoglobin ↑; transfusion need ↓; LV strain ↑; iron overload–related damage ↓	(56)
	Cardiometabolic risk factors (meta-analysis of RCTs)	Glycemia, lipids, BP, inflammation, body weight & insulin resistance ↓ ; CVD risk ↓	(57)
	Hypertension, diabetes, dyslipidemia	BP, glucose & lipid levels ↓ via phycocyanin, PUFAs & micronutrients	(9, 10)
	Comparative nutraceutical cardio protection	Oxidative stress & inflammation ↓; cardio protection comparable to resveratrol	(58)
	Radiation-induced cardiotoxicity	Limited benefit when dose/duration insufficient; protocol optimization needed	(59)

Summary of experimental and clinical studies, observed neuroprotective outcomes, and proposed molecular mechanisms. Symbols: ↑ indicates increased levels, activity, or expression; ↓ ind;icates reduced levels, activity, or expression. SOD: Superoxide dismutase; GPx: Glutathione peroxidase; CAT: Catalase; GSH: Glutathione; LDH: Lactate dehydrogenase; CK-MB: Creatine kinase-MB; TLR4: Toll-like receptor 4; NLRP3: NOD-like receptor protein 3; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Bcl-2: B-cell lymphoma 2; CVD: Cardiovascular disease; PUFAs: Polyunsaturated fatty acids

ischemia-reperfusion models, Spirulina supplementation significantly reduced infarct size and improved post-ischemic cardiac performance (42, 43). In multiple drug- and toxin-induced cardiotoxicity models, including doxorubicin, cyclophosphamide, and other cardiotoxic agents, Spirulina consistently attenuated biochemical and histopathological markers of myocardial injury (44-52). In several studies, its efficacy was comparable to or greater than standard antioxidant or pharmacological comparators, while advanced formulations and combination therapies further enhanced cardioprotective effects (44, 45, 53-55). Clinical evidence, although still limited, provides supportive findings. In children with thalassemia major, Spirulina supplementation improved hematological parameters and cardiac function indices, suggesting protection against iron overload–related cardiac dysfunction (56). Importantly, echocardiographic assessment demonstrated improvement in diastolic function parameters rather than strain-specific indices. In adults, a meta-analysis including 35 randomized controlled trials reported that Spirulina supplementation favorably influences major cardiometabolic risk factors, including glycemic control, lipid profile, blood pressure, inflammatory markers, body weight, and insulin resistance, thereby contributing to reduced cardiovascular risk (57). These findings are consistent with previous reviews highlighting its antihypertensive, antidiabetic, and lipid-lowering effects (9, 10).

These cardioprotective effects are primarily mediated by activation of pro-survival kinase signaling (PI3K, AMPK, p-AKT/eNOS) and restoration of antioxidant defenses (SOD, GPx, CAT, GSH), alongside suppression of inflammatory and apoptotic pathways (MCP-1, TLR4/NLRP3/NF-κB, Bax/caspase-3) and enhancement of anti-apoptotic and structural mediators (Bcl-2, iNOS, COX-2, connexin-43), with induction of autophagic pathways (Beclin-1, LC3II) observed in advanced formulations. A detailed, model-specific summary of these mechanisms is provided in Table 2.

Overall, Spirulina appears to confer broad cardioprotective effects across multiple experimental and clinical settings. Although preclinical evidence is robust, clinical data remain limited, underscoring the need for further trials.

Protective effects of Spirulina on liver

Extensive experimental and clinical investigations demonstrate that Spirulina species, particularly *S. platensis* and *Spirulina maxima* (*S. maxima*), possess pronounced hepatoprotective properties against liver injuries induced by chemical toxins, pharmaceuticals, heavy metals, metabolic disorders, and oxidative stress. These effects have been demonstrated across diverse formulations, including powder, aqueous and ethanolic extracts, phenolic-enriched biomass, mineral-enriched Spirulina, nano-formulations, and functional foods, and across a wide range of hepatotoxicity models spanning classical toxicants (e.g., TAA, CCl_4, acetaminophen, diclofenac, methotrexate, cisplatin, ethanol) and heavy metal exposures (lead, cadmium, aluminum, iron oxide, arsenic) (60-76). Across these models, Spirulina consistently attenuated biochemical, oxidative, inflammatory, and histopathological markers of liver injury through coordinated antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, summarized in Table 3. Notably, phenolic-enriched Spirulina preparations exhibited superior hepatoprotective efficacy compared with low-phenolic forms, underscoring the importance of bioactive composition (77, 78), and combination with other nutraceuticals (whey protein concentrate, thymoquinone, vitamin C) produced synergistic protection beyond single-agent treatment (79-81). Importantly, these preclinical findings are supported by human evidence: supplementation with *S. maxima* or *A. platensis* (≈6 g/day for 3–6 months) in NAFLD patients significantly reduced liver enzymes, improved lipid profiles and insulin sensitivity, and enhanced quality of life (82), representing one of the few organ systems in this review with direct clinical confirmation. Beyond direct hepatocellular effects, Spirulina supplementation also modulated gut

Table 3. Protective effects of Spirulina on the liver

Organ/System	Injury/Disease Model	Key mechanisms of Spirulina	Ref.
Liver	Toxicant-induced liver injury (TAA, CCl_4, acetaminophen, diclofenac, methotrexate, cisplatin, ethanol, etc.)	ALT, AST, ALP ↓; MDA/TBARS & NO ↓; TNF-α, IL-6, IL-1β, NF-κB ↓; oxidative stress & necrosis ↓; antioxidant defense ↑; liver histology improved	(60-64, 66-68)
	TAA hepatotoxicity (Spirulina-fortified foods)	Oxidative stress & inflammation ↓; metabolic profile & liver structure ↑	(65)
	Heavy metal–induced hepatotoxicity (Pb, Cd, Al, Fe oxide, As)	SOD, CAT, GPx, GSH ↑; lipid peroxidation & inflammation ↓; mitochondrial damage & apoptosis ↓; liver histology improved	(69-73, 75)
	Transgenerational lead hepatotoxicity	Hepatic biochemical imbalance & oxidative stress ↓; antioxidant status ↑ in offspring	(73)
	General hepatoprotection (mechanistic studies)	Nrf2/AMPK ↑; TNF-α, IL-6, COX-2, NF-κB ↓; Bax & caspase-3 ↓; Bcl-2 ↑; DNA damage & abnormal proliferation markers ↓	(60, 64, 74, 76)
	Phenolic-enriched Spirulina formulations	Antioxidant & hepatoprotective efficacy ↑ compared with low-phenolic forms	(77, 78)
	Combined nutraceutical therapy (with whey protein, thymoquinone, vitamin C)	Oxidative stress, inflammation & tissue damage ↓; hepatoprotection ↑ (synergistic effect)	(79-81)
	NAFLD (clinical studies)	ALT, AST ↓; lipid profile & insulin sensitivity ↑; body weight ↓; liver function & quality of life ↑	(82)
	Age-related liver inflammation & gut dysbiosis	Gut microbiota balance ↑; hepatic inflammation & oxidative stress ↓	(83)
	Broad hepatoprotective evidence (systematic reviews)	Oxidative stress, inflammation, apoptosis & lipid dysregulation ↓; gene-regulatory & metabolic protection ↑	(84, 85)

Summary of experimental and clinical studies, observed neuroprotective outcomes, and proposed molecular mechanisms. Symbols: ↑ indicates increased levels, activity, or expression; ↓ indicates reduced levels, activity, or expression. ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; MDA: Malondialdehyde; TBARS: Thiobarbituric acid reactive substances; NO: Nitric oxide; TNF-α: Tumor necrosis factor alpha; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; CAT: Catalase; GSH: Glutathione; Nrf2: Nuclear factor erythroid 2-related factor 2; AMPK: Adenosine monophosphate-activated protein kinase; COX-2: cyclooxygenase-2; Bcl-2: B-cell lymphoma 2; NAFLD: Non-alcoholic fatty liver disease

microbiota composition and reduced age-related hepatic inflammation, suggesting a contributory gut–liver axis mechanism (83).

At the molecular level, hepatoprotection is largely driven by activation of antioxidant and metabolic regulatory pathways (Nrf2/Keap1, AMPK) and suppression of inflammatory signaling (TNF-α, IL-6, COX-2, NF-κB), alongside inhibition of apoptosis through down-regulation of Bax and caspase-3 and up-regulation of Bcl-2, and modulation of proliferation/DNA damage markers (p53, Ki-67, PCNA), with additional contribution from gut–liver axis modulation. A detailed, model-specific summary of these mechanisms is provided in Table 3.

Collectively, these findings support Spirulina as a safe, multifunctional hepatoprotective agent with translational relevance as a functional food or adjunct therapy for liver disease (84, 85).

Nephroprotective effects of Spirulina

A substantial body of experimental evidence demonstrates that Spirulina species, particularly *S. platensis*, *S. maxima*, and *S. fusiformis*, exert pronounced nephroprotective effects against a wide spectrum of drug-, toxin-, metal-, radiation-, and diabetes-induced renal injuries, primarily through antioxidant, anti-inflammatory, anti-apoptotic, and metabolic regulatory mechanisms, summarized in Table 4. Across aminoglycoside (gentamicin and amikacin), chemotherapy and immunosuppressant (cyclophosphamide, cisplatin, cyclosporine A), and heavy metal/environmental toxin–induced (chromium, mercury, aluminum, lead, arsenic) models of nephrotoxicity, Spirulina supplementation consistently restored antioxidant defenses, attenuated oxidative and nitrosative stress, and preserved renal histoarchitecture, with prophylactic regimens generally showing superior protection compared with concurrent or post-treatment approaches (14, 48, 85-101). Notably, Spirulina preserved the antitumor efficacy of cisplatin while protecting kidney tissue, and combined nutraceutical strategies (e.g., Spirulina with camel milk) produced synergistic protection beyond either intervention alone (87, 88, 99, 100).

These nephroprotective effects are largely mediated by restoration of antioxidant defenses (GSH, SOD, CAT, GPx) and suppression of oxidative and nitrosative stress, together with inhibition of caspase-3-mediated apoptosis and up-regulation of anti-apoptotic mediators (Bcl-2, SIRT). These effects are further supported by normalization of renal injury biomarkers (KIM-1, NGAL) and correction of nephrotoxicity-associated microRNA dysregulation (miR-1, miR-146a). A detailed, model-specific summary of these mechanisms is provided in Table 4.

Collectively, this evidence positions *Spirulina* as a safe, multi-target nephroprotective nutraceutical with potential application as a preventive or adjunct strategy against nephrotoxic drugs, metabolic disorders, and environmental toxicants; however, as emphasized in translational reviews, well-designed clinical trials remain essential to validate dosing, long-term safety, and efficacy in human renal disease (102).

Protective effects of Spirulina on the male and female reproductive systems

Accumulating experimental evidence indicates that *S. platensis* and its bioactive constituents, particularly phycocyanin, polysaccharides, selenium-enriched forms, and nano-formulations, exert robust protective effects against a broad spectrum of male and female reproductive toxicities induced by environmental pollutants, chemotherapeutic agents, heavy metals, radiation, and oxidative stressors, summarized in Table 5. In male reproductive models, exposure to pesticides, chemotherapeutic drugs, heavy metals, nanoparticles, and radiation consistently impaired sperm parameters, disrupted the hypothalamic-pituitary-gonadal axis, and induced oxidative and apoptotic testicular damage (103-115). Spirulina supplementation consistently restored sperm quality and reproductive hormone levels while enhancing antioxidant capacity, with phycocyanin and enriched formulations frequently outperforming whole Spirulina (113, 114, 116), and selenium-enriched Spirulina additionally counteracting endocrine disruption through regulation of steroidogenic and spermatogenic gene expression (117). In female reproductive models, Spirulina similarly alleviated ovarian toxicity, hormonal imbalance, and follicular depletion induced by chemotherapeutic agents, heavy metals, and hyperglycemia, preserving follicular reserves and normalizing estrous and fertility indices (118-122). Beyond toxicity mitigation, Spirulina supplementation improved puberty traits, libido, and semen

Table 4. Protective effects of Spirulina on the renal system

Organ/System	Injury/Disease model	Key mechanisms of Spirulina	Ref.
Kidney	Gentamicin & Amikacin -induced nephrotoxicity	Urea & creatinine ↓; MDA/TBARS & NO ↓; GSH, SOD, CAT, GPx ↑; tubular necrosis & renal injury ↓; kidney histology improved	(14, 85, 86, 101)
	Combined therapy (Spirulina + camel milk) in nephrotoxicity	Oxidative stress & renal injury ↓; biochemical & histological recovery ↑ (synergistic protection)	(87)
	Chemotherapy/immunosuppressant-induced nephrotoxicity (cyclophosphamide, cisplatin, cyclosporine A)	Renal biomarkers ↓; lipid peroxidation & apoptosis ↓; antioxidant enzymes ↑; renal morphology preserved	(88, 89, 99, 100)
	Potassium dichromate-induced renal injury (mechanistic studies)	Caspase-3 ↓; Bcl-2 & SIRT ↑; injury markers KIM-1 & NGAL ↓	(102)
	Chemical and environmental toxin–induced nephrotoxicity (Cr, Hg, Al, Pb, CCl_4, arsenic, etc.)	Oxidative stress, inflammation & renal tissue damage ↓; antioxidant defense ↑	(48, 90-97)
	Nephrotoxicity-associated microRNA dysregulation	miR-1 & miR-146a dysregulation ↓; epigenetic/post-transcriptional balance restored	(98)

Summary of experimental models, observed neuroprotective outcomes, and proposed molecular mechanisms. Symbols: ↑ indicates increased levels, activity, or expression; ↓ indicates reduced levels, activity, or expression. MDA: Malondialdehyde; TBARS: Thiobarbituric acid reactive substances; NO: Nitric oxide; GSH: Glutathione; SOD: Superoxide dismutase; CAT: Catalase; GPx: Glutathione peroxidase; NGAL: Neutrophil gelatinase-associated lipocalin; Bcl-2: B-cell lymphoma 2; SIRT1: Sirtuin 1; KIM-1: Kidney injury Molecule 1

Table 5. Protective effects of Spirulina on the reproductive system

Organ/System	Injury/Disease model	Key mechanisms of Spirulina	Ref.
Male reproductive system	Drug-, pesticide-, and radiation-induced reproductive toxicity	Sperm count, motility & morphology ↑; testosterone, LH, FSH ↑; MDA, NO, inflammation & apoptosis ↓; antioxidant defenses ↑	(103-106, 112-115)
	Heavy metal and nanoparticle-induced testicular toxicity (Pb, Cd, Al, As, AgNPs)	Spermatogenesis & testicular structure ↑; oxidative stress & apoptosis ↓; steroidogenic gene function ↑; antioxidant enzymes ↑	(107-115)
	Mechanistic reproductive protection	Nrf2/HO-1 & PPAR-γ/IL-10 ↑; NF-κB ↓; Bcl-2–mediated anti-apoptotic signaling ↑	(103, 107)
	Phycocyanin or enriched Spirulina formulations	Lipid peroxidation ↓; sperm DNA integrity & testicular architecture ↑; efficacy > whole Spirulina	(113, 114, 116)
	Selenium-enriched Spirulina (zebrafish model)	Steroidogenesis & spermatogenesis gene regulation ↑; oxidative & endocrine disruption ↓	(117)
Female reproductive system	Drug- and toxin-induced ovarian toxicity (doxorubicin, cyclophosphamide, lead, hyperglycemia)	Follicular reserve & fertility indices ↑; oxidative stress, inflammation & apoptosis ↓; hormonal balance restored	(118-121)
	Mechanistic ovarian protection	Nrf2, SIRT1 & steroidogenic gene expression ↑; inflammatory & apoptotic signaling ↓	(121, 122)
Reproductive performance (animals/ART)	Livestock fertility & sperm preservation models	Puberty traits, libido & semen quality	(123, 124)

Summary of experimental models, observed neuroprotective outcomes, and proposed molecular mechanisms. Symbols: ↑ indicates increased levels, activity, or expression; ↓ indicates reduced levels, activity, or expression. MDA: Malondialdehyde; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1: Heme oxygenase-1; PPAR-γ: Peroxisome proliferator-activated receptor gamma; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Bcl-2: B-cell lymphoma 2; SIRT1: Sirtuin 1; ART: Assisted reproductive technology

quality in livestock, and enhanced post-thaw sperm quality in assisted reproductive applications (123, 124).

These reproductive protective effects are largely mediated by activation of Nrf2/HO-1 antioxidant signaling and modulation of PPAR-γ/IL-10 anti-inflammatory pathways, together with inhibition of NF-κB and up-regulation of Bcl-2-dependent anti-apoptotic mechanisms in male models. In female models, comparable protection is associated with up-regulation of Nrf2 and SIRT1 signaling and normalization of ovarian steroidogenic gene expression. A detailed, model-specific summary of these mechanisms is provided in Table 5.

Collectively, these findings support S. platensis as a multi-targeted, natural reproductive protectant. Its antioxidant, anti-inflammatory, anti-apoptotic, and gene-regulatory properties make it a promising adjunct for preventing or attenuating environmentally and therapeutically induced reproductive dysfunction.

Discussion

The present review demonstrates that Spirulina exerts protective effects across five major organ systems through a strikingly convergent mechanistic framework. Despite the diversity of insults, including chemical toxins, pharmaceuticals, heavy metals, radiation, and metabolic stress, the protective actions uniformly converge on three interconnected pathways: activation of Nrf2-driven antioxidant defenses (60, 74, 76), suppression of NF-κB-mediated inflammation (29, 61, 64, 103), and regulation of Bcl-2/caspase-3 apoptotic cascades (44, 104). This cross-organ consistency supports Spirulina as a systemic cytoprotective agent rather than a tissue-specific intervention (9, 10). However, organ-specific nuances exist: neurotrophic support via BDNF/CREB in the brain (21, 25), mitochondrial preservation in the heart (42, 43), and enhanced efficacy of fractionated formulations in the reproductive system (113, 114) highlight opportunities for targeted applications.

The consistent superiority of prophylactic over concurrent treatment across multiple models (14, 85, 99) implies that Spirulina primarily preconditions cellular defenses through up-regulation of endogenous antioxidants and heat-shock proteins rather than acting as a direct toxin scavenger. This distinction has important implications for clinical timing: the protective window may depend on pre-exposure rather than post-injury intervention. Notably, Spirulina preserved the antitumor efficacy of cisplatin while protecting kidney tissue (100), a dual benefit of particular relevance in oncology settings where dose-limiting nephrotoxicity remains a major clinical challenge.

Several major knowledge gaps remain unresolved. The poor oral bioavailability and gastric instability of phycocyanin, coupled with the limited availability of human pharmacokinetic data, represent critical translational barriers. No standardized, bioactivity-linked quality markers exist for product comparison, and phycocyanin content varies considerably across strains and commercial products (101). Long-term safety of high-dose Spirulina (>6–8 g/day), potential drug-nutraceutical interactions (especially with anticoagulants or immunosuppressants), and the role of gut microbiota in mediating systemic effects (83) require systematic investigation. In addition, the absence of mechanism-based dosing strategies for different organ-specific applications remains an important translational gap. It requires further investigation through dose–response studies and well-designed clinical trials. Epigenetic modulation (miRNA-1, miR-146a), currently demonstrated only in renal models, represents an unexplored frontier across other tissues (98). In summary, this synthesis provides a robust mechanistic foundation for Spirulina's multisystem protective effects. Still, it simultaneously highlights that clinical translation requires overcoming critical bioavailability, standardization, and knowledge gaps that must be addressed in future rigorously designed trials.

Conclusion

The extensive preclinical evidence reviewed here supports Spirulina as a multi-target cytoprotective agent with remarkable cross-organ mechanistic convergence, consistently attenuating oxidative and inflammatory damage across the nervous, cardiovascular, hepatic, renal, and

reproductive systems. However, substantial translational gaps, particularly the lack of standardized formulations, poor phycocyanin bioavailability, limited human pharmacokinetic data, and the absence of mechanism-based dosing strategies, remain major barriers to clinical application. Until these challenges are addressed through rigorously designed, well-powered randomized controlled trials that incorporate validated quality markers, optimized dosing approaches, and clinically meaningful endpoints, the promising preclinical benefits of Spirulina cannot be confidently translated into evidence-based therapeutic strategies in humans.

Acknowledgment

None.

Ethical Statement

Not applicable.

Funding

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

Authors' Contributions

Z NT contributed to conceptualization, methodology, validation, investigation, resource provision, original draft writing, supervision, and project administration. S T handled visualization. Both Z NT and S T conducted formal analysis, data curation, and review and editing of the writing.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Declaration

This manuscript was solely prepared and edited by the authors, with artificial intelligence used only for language correction.

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