Enhanced bioactivity of selenium-enriched *Spirulina platensis* and selenium-containing phycocyanin compared to their non-enriched counterparts: A systematic review

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Received April 24, 2025; Accepted June 20, 2025

DOI: 10.3892/wasj.2025.373

Abstract. Microalgae, particularly *Arthrospira platensis*, commonly known as Spirulina, are recognized for their ability to produce bioactive compounds with significant benefits across industrial, nutraceutical, pharmaceutical, and energy sectors. Spirulina is especially valued for its high content of proteins, vitamins and essential minerals, including phycocyanin and selenium, which contribute to its potent antioxidant properties. The present systematic review was performed by searching major international databases (PubMed, Scopus and Web of Science) following the PRISMA methodology. A total of 12 studies were identified that specifically compared the antioxidant and/or cytotoxic efficacy of selenium-enriched spirulina (Se-SP) or selenium-containing phycocyanin (Se-PC) with their respective non-enriched forms. The findings consistently demonstrated that selenium enrichment enhanced the bioactivity of these compounds. However, future research is required to prioritize the safety of dietary selenium administration by defining clear minimum and maximum daily intake guidelines. Additionally, the health benefits of these compounds need to be examined across diverse population groups, considering variables such as sex, age and pre-existing health conditions that may influence responses to selenium consumption. It is crucial to further investigate the long-term safety of Se-SP and Se-PC intake, with particular emphasis on establishing appropriate dosage limits for various demographic groups to ensure safe and effective use in human health.

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Key words: Spirulina, selenium-enriched spirulina, selenium-containing phycocyanin, selenium, reactive oxygen species, antioxidant activity

Introduction

Unicellular algae, including cyanobacteria, commonly known to the general public as microalgae, have been recognized for their potential in commercial production as functional foods. The most widely utilized species in this category include *Chlamydomonas*, *Chlorella*, *Haematococcus pluvialis* and *Arthrospira platensis*. These organisms are ubiquitous photoautotrophs, thriving in both marine and freshwater environments. They capture solar energy and use CO_2 and mineral salts to synthesize carbohydrates for energy (1,2). Owing to their broad applicability, microalgae are often termed 'green biofactories'. Their increasing use in the production of natural products, nutraceuticals, pharmaceuticals and food ingredients is due to their palatability and rich content of proteins, essential amino acids, vitamins and minerals (3).

Microalgae are a valuable resource, which could be particularly beneficial in developing countries, due to their rapid growth, energy efficiency and rich nutrient profile. They can contain protein levels as high as 60-70% (surpassing those in meat and milk), carbohydrates (up to 30-40%), essential minerals such as iodine, iron and calcium, vitamins, and 10-20% omega-3, omega-6 and omega-9 fatty acids (4). Their versatility has attracted increasing interest from industries aiming to develop healthier and more sustainable products, including natural food colorants and eco-friendly biodiesel. Microalgae are particularly appreciated for their rapid growth, ease of harvesting, efficient drying into powder form and long shelf life (5).

Arthrospira platensis, commonly known as *Spirulina platensis* (SP), is a cyanobacterium that exists in two phases: A green phase under optimal growth conditions and a blue phase when exposed to stress (6). Nutritionally, SP stands out for its high protein content and abundance of vitamins (complexes B, D, E and K), minerals (calcium, magnesium, iron, potassium, zinc, copper, manganese, chromium and selenium), β-carotene, and polyunsaturated fatty acids from the omega-3 and omega-6 series (7). Above all, Spirulina is especially known for its phycocyanin (PC) content, a blue pigment

protein widely recognized for its significant health-promoting properties and frequently used as a dietary supplement. This natural pigment has been shown to exhibit strong antioxidant, anti-inflammatory, hepatoprotective (liver-protecting) and neuroprotective (nerve-protecting) effects in various *in vitro* and *in vivo* studies (8). Due to its extensive therapeutic potential, phycocyanin is increasingly incorporated into health and wellness products aimed at supporting cellular health, reducing oxidative stress and preventing chronic inflammation (9). Its favorable safety and biocompatibility also support further research and application in preventive medicine and nutraceutical development (10). These components are known for their preventive effects on the cardiovascular system and their potent antioxidant properties (11). SP extracts are also used to prevent and manage conditions linked to metabolic syndrome-related disorders (3), oxidative stress, and diseases such as atherosclerosis, cardiac hypertrophy, heart failure and hypertension (12).

Selenium (symbol, Se) is a key trace element present in some microalgae, including, including SP. It plays a crucial role in human nutrition as a structural component of antioxidant enzymes, such as glutathione peroxidase and reductase, which help mitigate oxidative stress (11). Oxidative stress is a major biological event that can negatively affect the health and function of living organisms (13). This imbalance may contribute to conditions, such type 2 diabetes (often associated with hyperlipidemia), ischemia, cardiovascular diseases, neurodegenerative disorders such as Alzheimer's, and cancer; the free radicals produced in these processes can also cause severe organ damage (14). Over the years, research has aimed to identify the most effective selenium sources and, numerous investigations have indicated that selenium nanoparticles derived from Spirulina exhibit significant anti-tumor activity, (15) exhibiting greater efficacy in inducing cell cycle arrest and apoptosis than larger selenium particles (16).

The present systematic review aimed to evaluate the antioxidant and cytotoxic efficacy of selenium-enriched SP (Se-SP) and selenium-containing phycocyanin (Se-PC), a major bioactive component derived from Se-SP, by synthesizing evidence from both *in vivo* and *in vitro* studies. The primary objective was to determine whether selenium enrichment enhances the biological activity of these compounds compared to their non-enriched counterparts (Spirulina or phycocyanin alone). By comparing Se-SP and Se-PC to their respective controls, the present systematic review sought to clarify their potential health benefits and inform future applications in nutritional and therapeutic interventions.

Data and methods

The present systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were included if they met the following criteria: Published in the English language; investigated the antioxidant and/or cytotoxic activities of Se-SP or Se-PC; employed *in vitro* and/or *in vivo* experimental models; included at least one comparative group treated with non-enriched Spirulina or phycocyanin, in order to isolate and assess the specific contribution of the organic selenium component to the observed biological effects. Studies that were reviews, conference proceedings, editorials, articles without available full texts and those published outside the specified time frame were excluded from the review. A comprehensive literature search was conducted using the PubMed, Scopus and Web of Science databases, focusing the search on title and abstract by the use of the following key words: Selenium-containing AND phycocyanin; selenium-enriched AND spirulina. The selection process is detailed in a PRISMA flowchart, including both included and excluded studies with the reasons for exclusion (Fig. 1). The selected studies are summarized in Table I, which outlines the study objectives, the cellular or animal models used, the experimental conditions, and a concise summary of the most effective treatment identified in each case.

Results and Discussion

Included studies. A total of 103 reports were identified, of which 62 articles were excluded due to duplications, 10 articles were excluded as the full text was not available, 18 articles were out of the scope and one article was published in Chinese. The remaining 12 eligible articles were included in the systematic review (Table I).

Se-SP. Se-SP is a biofortified form of the well-known microalga, enhanced with selenium to boost its antioxidant and protective properties (17). This enriched form combines the natural benefits of Spirulina with the potent biological activity of selenium, rendering it a promising agent for health applications involving oxidative stress management, immune support and cellular protection (18).

The protective effects of Se-SP against alcohol-induced liver damage were evaluated in a study involving HL7702 human liver cells and mice exposed to subacute alcohol injury (19). In that study, *in vitro* experiments revealed that Se-SP significantly alleviated ethanol-related cytotoxicity in a concentration-dependent manner. Compared to native SP, Se-SP was more effective in maintaining cell viability, lowering the intracellular levels of reactive oxygen species (ROS) and malondialdehyde (MDA), and boosting the activity of key antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px or GPx). Se-SP also preserved mitochondrial membrane potential (MMP) and reduced apoptosis, as reflected by the lower expression of pro-apoptotic markers (Bax and cleaved caspase-3) and higher levels of the anti-apoptotic protein, Bcl-2. While SP also exhibited some antioxidant and cytoprotective effects, its overall efficacy was consistently lower than that of Se-SP (19). *In vivo*, mice receiving 200 mg/kg Se-SP over a period of 42 days exhibited marked improvement in biochemical indicators of liver injury. Serum alanine aminotransferase and aspartate aminotransferase levels were significantly reduced compared to the alcohol-only group and remained closer to physiological ranges than in animals treated with SP. Similarly, Se-SP was more effective in normalizing lipid profiles, including total cholesterol (TC) and triglycerides, without overshooting the normal values, an effect observed with SP in some parameters. Se-SP also provided superior control over oxidative stress. The activity of SOD and GSH-Px was more significantly enhanced, and the MDA levels were more effectively suppressed in the

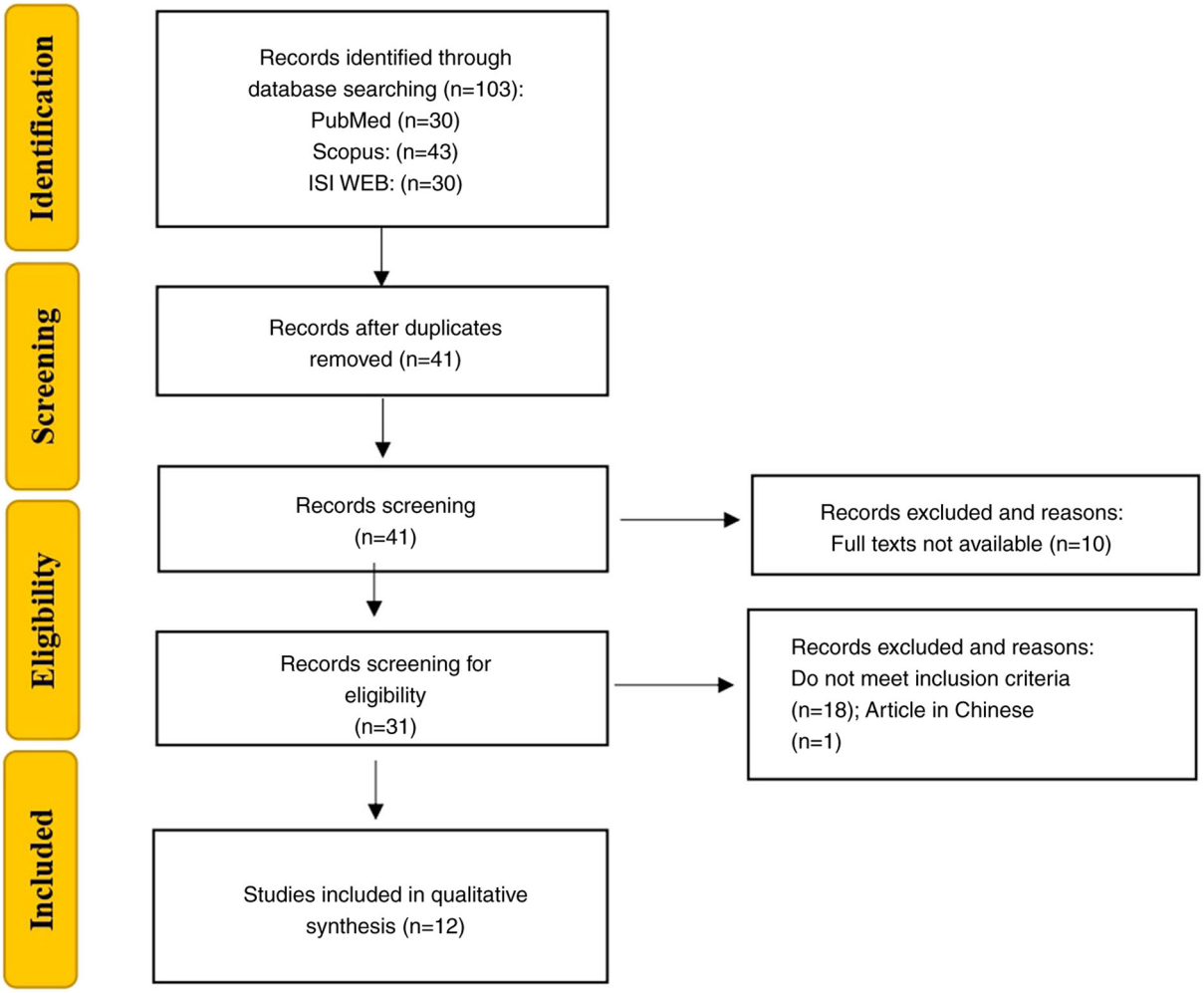

Figure 1. PRISMA flow chart illustrating the study selection process for the present systematic review.

Se-SP-treated animals than in those treated with SP (19). The histological examination of liver tissues further confirmed these findings: Se-SP more effectively preserved hepatic architecture and reduced necrosis and inflammatory infiltration. Immunohistochemical analyses revealed that Se-SP downregulated the levels of key markers of apoptosis (caspase-9), autophagy (LC3) and pyroptosis (caspase-1) more efficiently than SP. These findings underscore the superior protective effects of Se-SP against alcohol-induced liver cell injury, demonstrating greater efficacy than native Spirulina in reducing apoptosis, autophagy and pyroptosis, while enhancing antioxidant enzyme activity. Se-SP emerges as a promising dietary supplement for the prevention and management of oxidative liver damage (19).

The *in vitro* protective effects of Se-SP against cisplatin-induced apoptosis were also previously investigated (20). Cisplatin exposure induced a dose-dependent increase in both early and late apoptosis, accompanied by significant mitochondrial dysfunction, opening of the mitochondrial permeability transition pore (MPTP) and the excessive production of ROS. Pre-treatment with Se-SP effectively mitigated these cytotoxic effects by preserving MMP and restoring the balance between pro- and anti-apoptotic members of the Bcl-2 family. This mitochondrial stabilization limited MPTP opening and prevented the activation of the intrinsic apoptotic cascade. Additionally, Se-SP markedly reduced ROS production and superoxide anion levels, enhanced the activity of endogenous antioxidant systems, such as SOD and GSH-Px, and protected cellular DNA from oxidative damage (20). At the molecular level, Se-SP pre-treatment suppressed the cleavage of PARP and reduced the activation of caspase-3, caspase-7 and caspase-9, key mediators of apoptosis. It also inhibited the phosphorylation of DNA damage response proteins, including ataxia telangiectasia mutated, ataxia telangiectasia and Rad3-related, and tumor protein p53, confirming its role in attenuating oxidative stress-driven apoptotic signaling (20). By contrast, SP without selenium enrichment did not provide significant protection under the same experimental conditions. SP pre-treatment failed to improve cell viability, did not reduce apoptosis, and had negligible effects on oxidative markers. This direct comparison highlights the substantial enhancement of biological activity conferred by selenium incorporation. In summary, Se-SP displayed a markedly superior protective profile compared to its non-enriched counterpart, demonstrating its potential as an effective adjuvant in preventing cisplatin-induced oxidative damage and mitochondrial dysfunction in bone-forming cells (20).

Table I. Selected studies from the scientific literature.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
Yang, 2024	Aim: Investigate the therapeutic potential of selenium-containing protein extracted from Se-enriched Spirulina platensis (Se-SP) in alleviating osteoporosis by modulating inflammation, osteoblast activity, and osteoclasto genesis *in vitro* and *in vivo*. Animal Model: Female C57 mice Cell line: MC3T3-E1	Control group: Mice that underwent a mock surgery without ovariectomy. OVX group (Ovariectomy): Mice that underwent ovariectomy without additional treatment. SP-treated group: OVX mice treated with 10 mg/kg SP via intraperitoneal injections every other day for 2 months. Se-SP-treated group: OVX mice treated with 10 mg/kg Se-SP via intraperitoneal injections every other day for 2 months.	Control group: Cells were cultured in a differentiation medium without any treatment. SP-treated groups: Cells were treated with SP at concentrations of 5 and 10 μg/ml for 14 days in the differentiation medium. Se-SP-treated groups: Cells were treated with Se-SP at concentrations of 5 and 10 μg/ml for 14 days in the differentiation medium	Compared to SP alone, Se-SP demonstrated superior efficacy in reversing bone loss and restoring bone microarchitecture in ovariectomized mice.	(25)
Castel, 2024	Aim: Evaluate the effectiveness of Se-SP in restoring selenium levels and modulating antioxidant enzyme activities and selenoprotein expression in rats fed a selenium-deficient diet. Animal model: Old female Wistar rats	Pre-treatment: 8 weeks with Se deficient diet Control: Se sufficient diet containing 0.3 mg Se/kg of food; Deficient group (D):only water for 4 weeks; SS: SS at adose of 20 μg Se/kg b.w. day in water for 4 weeks. SP: 3 g/kg b.w. day of SP in water for 4 weeks Se-SP: 3 g/kg b.w. day of Se-SP (providing 20 μg Se/kg b.w. day) in water for 4 weeks.	NA	Se-SP ensures better selenium distribution and tissue bioavailability, while SS more effectively enhances antioxidant enzyme activity and certain selenoprotein expressions. SP alone shows only marginal antioxidant benefit without selenium repletion.	(24)
Shen, 2023	Aim: Evaluate the efficacy of Se-PC in photodynamic therapy (PDT) against lung cancer and compare its effects to other treatments, including PC-PDT and PC combined with SS. Animal model: Lung carcinoma-bearing male mice C57BL/6 Cell line: LLC cell	Control: Mice injected with normal saline (0.2 ml), every 3 days and for 11 days. Laser-only: Laser light (630 nm at 100 J/cm^2) for 4 h after receiving 0.2 ml of normal saline, every 3 days and for 11 days. PC-PDT Mice injected with	Control: Cells with no treatment. PC-PDT: Cells treated with 150 μg/ml of PC, then exposed to laser light (26 J/cm^2) for 9 min and incubated for 12 h SS + PC-PDT: Cells treated with a combination of 150 μg/ml PC and 1.14 μg/ml SS (providing an	Se-PC represents the most effective and balanced treatment, offering strong cytotoxicity against tumor cells while preserving antioxidant defenses in normal tissues and minimizing systemic toxicity. Its dual action on tumor inhibition and immune	(30)

Table I. Continued.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
		0.2 ml of PC (15 mg/ml) and exposed to laser light (630 nm at 100 J/cm^2) for 4 h every 3 days and for 11 days. PC + SS-PDT: Mice injected with a combination of 0.2 ml of PC (15 mg/ml) and SS at an equivalent Se dose to the Se-PC group, followed by laser light (630 nm at 100 J/cm^2) for 4 h, every 3 days and for 11 days. Se-PC-PDT: Mice injected with 0.2 ml of Se-PC (15 mg/mll) and exposed to laser light (630 nm at 100 J/cm^2) for 4 h, every 3 days and for 11 days.	equivalent Se content to the Se-PC group) and exposed to the same laser parameters (26 J/cm^2 for 9 min) and incubated for 12 h. Se-PC PDT: Cells treated with 150 μg/ml Se-PC, then exposed to laser light (26 J/cm^2 for 9 min) and incubated for 12 h.	activation makes it the most promising strategy among the three approaches evaluated.	
Castel, 2021	Aim: Evaluate the effects of Se-SP supplementation on sepsis outcomes in selenium-deficient rats. Animal model: female Wistar rats	Pre-treatment: 8 weeks with Se-deficient diet Deficient group (D): Continued to receive Se-deficient food and tap water for 4 weeks. SS: Se supplementation in the form of SS (20 μg Se/kg b.w. day) in drinking water for 4 weeks. SP: SP powder (3 g/kg b.w. day) in drinking water for 4 weeks. Se-SP: Se-SP (3 g/kg b.w. day), providing 20 μg of Se/kg b.w. day in drinking water for 4 weeks. Post-treatment: Sepsis induced in a subgroup of each group	NA	SS remains the most effective option in correcting selenium deficiency and mitigating sepsis-induced oxidative and metabolic disturbances. Se-SP shows promise in upregulating antioxidant genes, but fails to deliver functional protection in the acute setting, likely due to lower bioavailability of organic Se forms (e.g., SeMet) or matrix interactions. SP alone, while theoretically antioxidant, offered no protective effect and may even exacerbate early stress responses in sepsis	(23)

Table I. Continued.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
		using the cecal ligature and puncture (CLP) method. Another subgroup underwent a sham surgery (laparotomy only) to serve as a control.			
Song, 2021	Aim: Neuroprotective effects of selenium-containing protein derived from Se-SP under conditions simulating ischemic injury induced by oxygen-glucose deprivation (OGD). Cell line: Primary hippocampal neurons isolated from Sprague-Dawley (SD) rats	NA	Control: Cells with no treatments. OGD: Cells subjected to oxygen-glucose deprivation (OGD) for 6 h without any additional treatment. SP: Cells treated with 5 or 10 μg/ml of SP during OGD exposure for 6 h. Se-SP: Cells treated with 5 or 10 μg/ml of Se-SP during OGD exposure for 6 h. CsA + OGD: Cells pre-treated with 5 μM CsA (cyclosporine A) for 30 min, followed by OGD exposure for 6 h.CsA + SP + OGD: Cells pre-treated with 5 μM CsA for 30 min, followed by 5 or 10 μg/ml SP treatment during OGD exposure for 6 h. CsA + Se-SP + OGD: Cells pre-treated with 5 μM CsA for 30 min, followed by 5 or 10 μg/ml. Se-SP treatment during OGD exposure for 6 h.	Se-SP showed superior antioxidant and cytoprotective effects compared to SP alone, effectively reducing ROS, preserving mitochondrial function, and preventing neuronal apoptosis under OGD conditions	(22)
Lin, 2020	Aim: Investigate the protective effects and underlying mechanisms of Se-SP against high glucose-induced calcification in mouse aortic vascular smooth muscle cells	NA	Control: Cells cultured with 5 mM glucose. High glucose: Cells exposed to 10-50 mM glucose for 48 h to investigate dose-dependent	Se-SP effectively counteracts high glucose-induced oxidative stress and calcification in vascular cells, showing superior protective and antioxidant	(21)

Table I. Continued.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
	(MOVAS). Cell line: Mouse aortic vascular smooth muscle cells (MOVAS).		effects on proliferation; In calcification assays, cells were exposed to 25 mM glucose for 14 days.SP: Cells treated with 5 or 10 μg/ml SP along with 25 mM glucose for 14 days. Se-SP: Cells treated with 5 or 10 μg/ml Se-SP along with 25 mM glucose for 14 days. GSH pre-treatment: (specific for ROS evaluation): Cells pre-treated with 5 mM glutathione (GSH) for 2 h before exposure to 25 mM glucose. MAPK inhibitor: Cells treated with 10 μM SP600125 (JNK inhibitor) along with 25 mM glucose for 14 days	properties compared to SP alone.	
Sun, 2019	Aim: Investigate the protective effects of Se-SP against cisplatin-induced apoptosis Cell line: MC3T3-E1 mouse preosteoblast cells.		Control: Cells with no treatments. Cisplatin-only: Cells exposed to 20, 40, or 80 μg/ml cisplatin for 24 h. Se-SP: Cells pre-treated with 5, 10, or 20 μg/ml of Se-SP for 24 h before being co-treated with 40 or 80 μg/ml of cisplatin for another 24 h. SP: Cells were with 80 μg/ml SP or Se-SP alone for 48 h in cytotoxicity assays. Co-treatment: Cells treated with 10 μg/ml Se-SP and 80 μg/ml cisplatin.	Se-SP showed strong antioxidant and cytoprotective effects by preventing mitochondrial dysfunction and ROS-mediated apoptosis in cisplatin-injured osteoblasts. Unlike SP, Se-SP preserved cell viability and reduced oxidative stress through mitochondrial stabilization and DNA protection, highlighting its potential in chemoprevention of bone damage.	(20)

Table I. Continued.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
Fu, 2018	Aim: Investigate the protective effects and underlying mechanisms of Se-SP against chronic alcohol-induced liver injury. Animal model: KM mice Cell line: HL7702 human liver cell line.	Control: Mice treated with physiological saline.Model: Mice treated with 30% absolute alcohol (10 ml/kg bw) via gavage for the last 15 days of the experiment. SP: Mice treated with 200 mg/kg bw SP via gavage daily for 42 days, with alcohol gavage during the last 15 days. Low-dose Se-SP: Mice treated with 100 mg/kg bw of Se-SP via gavage daily for 42 days, with alcohol gavage during the last 15 days.Middle-dose Se-SP: Mice treated with 200 mg/kg bw of Se-SP via gavage daily for 42 days, with alcohol gavage during the last 15 days. High-dose Se-SP: Mice treated with 400 mg/kg bw of Se-SP via gavage daily for 42 days, with alcohol gavage during the last 15 days.	Control: Cells cultured in normal conditions. Alcohol-only: Cells exposed to 200 mM ethanol for 24 h. SP: Cells co-treated with 200 mM ethanol and 200 μg/ml of SP for 24 h. Se-SP: Cells co-treated with 200 mM ethanol and varying concentrations of Se-SP (50, 100, and 200 μg/ml) for 24 h. Positive control: Cells treated with an antioxidant or apoptosis inhibitor.	Se-SP exhibits strong protective effects against chronic alcohol-induced liver injury both in vitro and *in vivo*. It outperforms native SP by reducing apoptosis, autophagy, and pyroptosis, while enhancing antioxidant enzyme activity. Its optimal effectiveness is observed at 200 mg/kg, offering a promising dietary supplement for oxidative liver damage	(19)
Liu, 2018	Aim: Evaluate the therapeutic potential of Se-PC in enhancing the efficacy of photodynamic therapy (PDT) for cancer treatment. Animal model: BALB/c mice. Cell line: HepG2 and the HL7702.	Control: Mice received no treatment. Laser-only: Mice exposed to laser irradiation 632.8 nm, (150 J/cm^2) without any photosensitizer. PC: Mice injected with 0.2 ml PC 10 mg/ml for 10 days without laser irradiation Se-PC: Mice injected with 0.2 ml	Control: Cells cultured without treatments. PC: Cells treated with 50-400 μg/ml of PC for 4 h. Se-PC: Cells treated with 50-200 μg/ml of Se-PC for 4 h.Laser: Cells exposed to laser irradiation (632.8 nm, 45 mW/cm^2, 26 J/cm^2) for 9 min without photosensitizer.	Se-PC combined with PDT induces potent anticancer activity through mitochondria-mediated apoptosis, partial inhibition of autophagy, and enhanced anti-oxidant enzyme modulation. It demonstrates stronger efficacy and higher tumour selectivity than PC alone, offering a promising and safer strategy for	(29)

Table I. Continued.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
		Se-PC 10 mg/ml for 10 days without laser irradiation. PC-PDT: Mice injected with 0.2 ml of PC 10 mg/ml for 10 days and exposed to laser irradiation (150 J/cm^2). Se-PC-PDT: Mice injected with 0.2 ml of Se-PC 10 mg/ml for 10 days and exposed to laser irradiation (150 J/cm^2).	PC-PDT: Cells treated with PC (50-400 μg/ml) for 4 h, followed by laser irradiation. Se-PC-PDT: Cells treated with Se-PC (50-200 μg/ml) for 4 h followed by laser irradiation.	liver tumour therapy.	
Zhang, 2011	Aim: Evaluate Se-PC protective effects against oxidative stress induced by AAPH (2,2'-azobis (2-amidinopropane) dihydrochloride). Specifically, the study explored Se-APC's ability to inhibit reactive oxygen species (ROS) generation, prevent lipid peroxidation, and protect antioxidant defense systems in human erythrocytes. Cell line: human erythrocytes	NA	Control group: No oxidative agent, no treatment (baseline erythrocyte/plasma conditions) AAPH group (oxidative stress control): Erythrocytes or plasma treated with 100 mM AAPH only (oxidative stress inducer) Se-APC pretreated groups: Erythrocytes or plasma pretreated with Se-APC at concentrations ranging from 0.3 to 1.5 μM, then exposed to 100 mM AAPH; Also used in plasma oxidation assay at 0.06 to 0.3 μM APC pretreated groups: Erythrocytes or plasma pretreated with APC at matching concentrations to Se-APC (e.g., 0.3 μM), followed by AAPH exposure Positive control for antioxidant comparison: Included Trolox as a known antioxidant for reference in the ABTS assay	Se-APC shows clearly superior antioxidant and cytoprotective properties compared to native APC *in vitro*. It effectively scavenges radicals, protects erythrocytes from oxidative hemolysis, and preserves cellular antioxidant defenses, making it a promising candidate for functional food or therapeutic applications targeting oxidative stress-related damage.	(28)

Table I. Continued.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
Chen, 2008	Aim: Evaluate the antioxidant and antiproliferative activities of Se-PC. Cell line: A375, MCF-7, erythrocytes, Hs68	NA	A375 and MCF-7: Control: Cells no treated. Se-PC: Cells treated with Se-PC at varying concentrations (5, 10, 20 and 40 μM) and incubated for 72 h to evaluate antiproliferative effects and for 24 h for apoptosis assays.PCs: Cells treated with phycocyanin (PC) at the same concentrations as Se-PC for comparison and incubated for 72 h to evaluate antiproliferative effects and for 24 h for apoptosis assays. Erythrocytes from Sprague-Dawley rats: Control: Cells exposed to phosphate-buffered saline (PBS). AAPH: Cells treated with 200 mM AAPH for 3 h. AAPH + Se-PC: Cells pre-treated with Se-PC for 30 min at concentrations of 0.1 to 1.25 μM, followed by 200 mM AAPH Se-PC: Cells treated with Se-PC alone for 30 min to confirm its non-toxic effects.	Selenium incorporation into phycocyanin enhances both antioxidant and antiproliferative activities *in vitro*. Se-PC outperformed native PC across all assays, confirming its potential as a selenium-based chemopreventive agent.	(27)
Riss, 2007	Aim: Evaluate the cardiovascular and oxidative stress protective effects of Se-PC derived from Se-SP in the context of atherogenesis. Animal model: Male Golden Syrian hamsters.	Control: Hamsters received tap water. PC: Hamsters received native phycocyanin at a dose of 3.63 mg/day per 100 g bw in water for 12 weeks. Se-PC: Hamsters received Se-PC	NA	Se-PC demonstrated the most potent antioxidant and anti-atherogenic effects *in vivo*, significantly reducing oxidative stress markers and improving lipid profiles. Although PC and Se-SP showed beneficial effects,	(26)

Table I. Continued.

First author, year of publication	Highlights	*In vivo* experimental groups	*In vitro* experimental groups	Se-SP and Se-PC vs. SP and PC	(Refs.)
		at a dose of 3.63 mg/day per 100 g bw for 12 weeks, providing 0.4 μg selenium per 100 g bw. SP: Hamsters received crude SP at a dose of 2.66 mg/day per 100 g bw in water for 12 weeks. Se-SP: Hamsters received Se-SP at a dose of 2.66 mg/day per 100 g bw for 12 weeks, providing 0.4 μg selenium per 100 g bw.		Se-PC was the most effective in modulating NADPH oxidase expression and plasma antioxidant capacity.	

Se-SP, selenium-enriched Spirulina; Se-PC, selenium-containing phycocyanin derived from Se-SP; SS, sodium selenite; PC, phycocyanin; NA, not available.

The protective effects and underlying mechanisms of Se-SP against high glucose-induced calcification in mouse aortic vascular smooth muscle cells was also examined in a previous study (21). Exposure to elevated glucose concentrations led to significant oxidative stress, increased ROS production and DNA damage, all contributing to pathological calcification in vascular tissues. Pre-treatment with Se-SP significantly mitigated these effects by reducing ROS accumulation and limiting oxidative DNA injury (21). In addition, Se-SP modulated key intracellular signaling cascades involved in the calcification process. Specifically, it suppressed the overactivation of the mitogen-activated protein kinase (MAPK) pathway and prevented the inhibition of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, thereby preserving cell homeostasis and inhibiting pro-calcific responses. When compared to native SP, Se-SP exhibited markedly greater efficacy. SP alone exhibited only modest antioxidant activity and did not significantly affect either MAPK or PI3K/AKT signaling under high-glucose conditions (21). Conversely, Se-SP not only reduced oxidative stress more effectively, but also provided broader cytoprotective effects by interfering with multiple calcification-related molecular pathways. Overall, Se-SP demonstrated superior protective effects against glucose-induced vascular damage compared to SP, emphasizing the added value of selenium enrichment in enhancing the bioactivity of SP. These findings support the potential application of Se-SP in the prevention of vascular complications associated with diabetes and metabolic disorders (21).

The neuroprotective potential of Se-SP was further evaluated in a study examining its effects against damage induced by oxygen and glucose deprivation (OGD) in hippocampal neurons harvested from neonatal rats (22). Se-SP treatment significantly improved neuronal viability under OGD conditions. Neurons treated with 10 μg/ml Se-SP exhibited a marked increase in viability, which increased from 57.2 to 94.5%, whereas treatment with SP alone did not provide significant protection (22). Se-SP also substantially reduced OGD-induced neuronal apoptosis, as evidenced by a decrease in the number of TUNEL-positive cells from 45.6 to 6.3%. Furthermore, Se-SP inhibited the accumulation of ROS induced by OGD, improved MMP and modulated the expression of Bcl-2 family proteins, effectively maintaining a balance between pro-apoptotic and anti-apoptotic factors (22). These findings suggest that Se-SP exerts superior antioxidant and cytoprotective effects compared to SP alone, effectively reducing ROS production, preserving mitochondrial function, and preventing neuronal apoptosis under OGD conditions. Thus, Se-SP has promising neuroprotective effects, suggesting its potential as an intervention to support neuronal survival and prevent damage associated with ischemic events (22).

The potential of Se-SP to enhance health outcomes has been investigated vs. its role in managing severe conditions such as sepsis. Notably, its efficacy was assessed in an *in vivo* study involving selenium-deficient female rats (23). That study found that rats treated with Se-SP or sodium selenite (SS) exhibited significantly longer survival times compared to those that received standard SP. Specifically, rats supplemented with Se-SP demonstrated increased plasma selenium levels and longer survival post-sepsis induction, highlighting

the beneficial role of selenium-enriched supplementation. Se-SP treatment led to a significant increase in the levels of the anti-inflammatory cytokine, IL-10, whereas other treatment groups exhibited lower levels. Elevated levels of the pro-inflammatory cytokines, IL-6 and TNF-α, were observed in most groups following sepsis induction; however, the Se-SP group maintained a more balanced cytokine response (23). Although Se-SP improved metabolic stability and acid-base balance, the treatment did not fully prevent sepsis-related mortality. These results suggest that while Se-SP exhibits potential in enhancing survival and modulating inflammatory responses during sepsis, its effectiveness in fully combating severe sepsis remains limited (23). Overall, SS remains the most effective option in correcting selenium deficiency and mitigating sepsis-induced oxidative and metabolic disturbances. Although Se-SP exhibits promise in upregulating antioxidant genes, it fails to deliver functional protection in the acute setting, likely due to lower bioavailability of organic Se forms (e.g., SeMet) or matrix interactions. Spirulina, while theoretically antioxidant, offered no protective effect and may even exacerbate early stress responses in sepsis (23).

The effects of SP, Se-SP and SS on restoring selenium levels and antioxidant defenses were also investigated in another study involving 32 female Wistar rats fed a selenium-deficient diet over a 12-week period (24). Se-SP supplementation effectively restored selenium concentrations in the majority of tissues, such as the liver and kidneys, outperforming SS. While Se-SP increased GPx activity in some tissues, SS was more effective in enhancing SOD activity, particularly in the heart. Additionally, Se-SP restored the expression levels of certain selenoproteins in a tissue-dependent manner, whereas SS had a more pronounced impact on GPx1 expression in the heart. Se-SP ensured better selenium distribution and tissue bioavailability, while SS more effectively enhanced antioxidant enzyme activity and certain selenoprotein expressions. Spirulina alone exhibited only marginal antioxidant benefits without selenium repletion (24).

The anti-osteoporotic efficacy of selenium-containing protein extracted from Se-SP, using both *in vitro* and *in vivo* models was also previously investigated (25). *In vitro*, MC3T3-E1 osteoblast-like cells were treated with 5 and 10 μg/ml of either Se-SP or non-enriched SP for 14 days. *In vivo*, ovariectomized female mice were divided into four groups as follows: The sham-operated, untreated ovariectomized SP-treated (10 mg/kg) and Se-SP-treated (10 mg/kg) mice, with treatment administered intraperitoneally every other day for 2 months (25). That study found that Se-SP enhanced calcium deposition, alkaline phosphatase activity and the expression of osteoblastic markers (BMP2, RUNX2, COL-I and OCN), while also reducing osteoclastogenesis (TRAcP and RANKL) and promoting anti-inflammatory cytokine production (IL-4 and IL-10). Compared to SP alone, Se-SP demonstrated superior efficacy in reversing bone loss and restoring bone microarchitecture in ovariectomized mice (25).

Se-PC. Se-PC, a compound derived from Se-SP, has attracted marked interest for its potent antioxidant and anticancer properties. This bioactive molecule combines the well-known benefits of phycocyanin with the enhanced activity provided by selenium, an essential trace element known for its antioxidant capabilities. The studies identified in the literature collectively highlight the diverse and significant biological activities of Se-PC and its potential applications in various health and therapeutic contexts. The cardiovascular and oxidative stress protective effects of Se-PC derived from SP was first studied in the context of atherogenesis (26). In that study conducted *in vivo* on male Golden Syrian hamsters, Se-PC demonstrated significant lipid-lowering and antioxidant effects. Se-PC reduced plasma TC levels by 10%, outperforming native phycocyanin (PC), which achieved a 7.5% reduction. Additionally, Se-PC significantly decreased non-HDL cholesterol levels by 34%, a more pronounced effect compared to PC. As regards oxidative stress markers, Se-PC restored plasma antioxidant capacity to near-normal levels, showing a 42% improvement over the control group, while PC, SP and Se-SP were effective to a lesser extent (26). In cardiac tissue, Se-PC reduced superoxide anion production by 76%, significantly exceeding the reductions achieved by PC (54%) and spirulina variants (46-56%). In liver tissues, GSH-Px and SOD activities were lower in all treatment groups compared to the controls, suggesting a potential 'sparing effect' of the exogenous antioxidants provided by Se-PC and PC. These results highlight the superior efficacy of Se-PC in modulating lipid metabolism and reducing oxidative stress (26). Se-PC demonstrated the most potent antioxidant and anti-atherogenic effects *in vivo*, significantly reducing oxidative stress markers and improving lipid profiles. Although PC and Se-SP exerted beneficial effects, Se-PC was the most effective in modulating NADPH oxidase expression and plasma antioxidant capacity (26).

The *in vitro* antioxidant and antiproliferative activities of Se-PC were investigated in another study with the aim of examining its role in inducing the apoptosis of human melanoma cells (A375), human breast adenocarcinoma cells (MCF-7) and human fibroblasts (Hs68) (27). The findings of that study revealed that Se-PC significantly increased the percentage of depolarized mitochondria in A375 cells from 11.6% in the control group to 39.0 and 54.7% at the 10 and 20 μM concentrations, respectively. A similar trend was observed in MCF-7 cells, where the percentage of depolarized mitochondria increased from 1.3% in the control to 13.2 and 20.9% at the same concentrations (27). These results suggest that Se-PC induces apoptosis via a mitochondria-mediated pathway. Furthermore, Se-PC demonstrated potent antioxidant properties, inhibiting 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonate) (ABTS) oxidation by 18.8% at 0.5 μM and 46.0% at 1.0 μM. This performance surpassed that of regular PC, which exhibited inhibition rates of 11.7 and 31.1% at the same concentrations. Furthermore, both Se-PC and PC led to a significantly greater inhibition of ABTS oxidation compared to ascorbic acid and Trolox (27). Another significant finding was the scavenging activity of Se-PC against superoxide anions, which are biologically crucial due to their potential to decompose into more reactive oxidative species, such as singlet oxygen and hydroxyl radicals. That study found that Se-PC and PC inhibited superoxide anions in a concentration-dependent manner over a range of 1-16 μM. Additionally, Se-PC demonstrated protective effects against H_2O_2-induced DNA damage. While the control group treated with H_2O_2 alone exhibited DNA damage, no significant DNA damage was observed in groups treated with Se-PC at concentrations

of 10 or 50 μM. Notably, Se-PC was found to be a non-genotoxic compound (27). In summary, Se-PC exhibited superior antioxidant activities compared to PC by effectively neutralizing ABTS, superoxide anion, 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azobis(2-methylpropionamidine) dihydrochloride (AAPH) free radicals. It also exerted protective effects against H_2O_2-induced DNA damage in blood cells. The most noteworthy effect of Se-PC was its ability to inhibit cell growth in A375 melanoma and MCF-7 breast adenocarcinoma cells, primarily by inducing mitochondria-mediated apoptosis. Overall, Se-PC outperformed native PC across all assays, confirming its potential as a selenium-based chemopreventive agent (27).

In another study *in vitro*, the protective effects of Se-PC were evaluated against oxidative stress induced by AAPH (28). Specifically, that study explored the ability of selenium-enriched allophycocyanin (Se-APC) to inhibit ROS generation, prevent lipid peroxidation and protect antioxidant defense systems in human erythrocytes. Se-APC demonstrated superior antioxidant activity compared to regular APC, as evidenced by its significantly higher inhibition of ABTS radicals. It also exhibited protective effects against hemolysis, reducing AAPH-induced hemolysis in erythrocytes in a dose-dependent manner. Additionally, Se-APC effectively inhibited lipid peroxidation, significantly decreasing MDA formation and restoring levels to near control values at a concentration of 1.5 μM. Furthermore, Se-APC protected against ROS generation, reducing ROS levels to 195% at 0.3 μM and returning them to near control levels at 1.5 μM (28). Finally, Se-APC preserved the antioxidant defense system by significantly restoring GSH levels in a concentration-dependent manner. It also prevented the increase in GPx and GSH reductase activities, maintaining their levels comparable to controls when used at 1.5 μM. Se-APC exhibited clearly superior antioxidant and cytoprotective properties compared to native APC *in vitro*. It effectively scavenged radicals, protected erythrocytes from oxidative hemolysis and preserved cellular antioxidant defenses, rendering it a promising candidate for functional food or therapeutic applications targeting oxidative stress-related damage (28).

The therapeutic potential of Se-PC in enhancing the efficacy of photodynamic therapy (PDT) for cancer treatment was evaluated both *in vitro* and *in vivo* (29,30). *In vitro* experiments conducted on Lewis Lung Carcinoma (LLC) cells demonstrated that Se-PC PDT resulted in significantly higher levels of ROS compared to PC PDT or PC-SS PDT, indicating an enhanced induction of oxidative stress within the cancer cells (30). Furthermore, Se-PC PDT treatment led to significantly reduced cell survival rates compared to PC PDT alone, highlighting its superior efficacy in targeting LLC cells. Se-PC represented the most effective and balanced treatment, providing potent cytotoxicity against tumor cells, while preserving antioxidant defenses in normal tissues and minimizing systemic toxicity. Its dual action on tumor inhibition and immune activation rendered it the most promising strategy among the three approaches evaluated (30). In a study conducted on HepG2 cells (human liver cancer cells) and HL7702 cells (normal human liver cells), Se-PC photodynamic therapy (Se-PC PDT) demonstrated selective cytotoxicity, significantly reducing cell viability in HepG2 cells while sparing HL7702 cells (29). The treatment markedly increased intracellular ROS levels in HepG2 cells, leading to oxidative damage and apoptosis, which was significantly more pronounced in the Se-PC PDT group compared to the PC PDT group. This selective induction of apoptosis highlights the potential of Se-PC PDT as a targeted therapeutic approach against liver cancer cells, while minimizing damage to normal liver cells (29).

In vivo, using lung carcinoma-bearing male C57BL/6 mice, Se-PC PDT demonstrated notable efficacy with a tumor inhibition rate of 90.1%, significantly higher than the PC PDT group (53.1%) and the PC-SS PDT group (68.3%) (30). Se-PC PDT also inhibited metastasis, as evidenced by reduced luminescence in major organs, such as the liver and lungs. The treatment enhanced antioxidant defense mechanisms, increasing the activities of SOD and GSH-Px in liver and lung tissues, while maintaining lower levels of MDA, an oxidative stress marker, compared to the PC-SS PDT group, indicating reduced damage to normal tissues. Additionally, Se-PC PDT significantly elevated serum levels of IL-6 and TNF-α, suggesting an enhanced immune response. Mechanistically, Se-PC PDT induced both apoptosis and pyroptosis in tumor cells, with gene expression analysis revealing the upregulation of caspase-1, caspase-3 and caspase-9, alongside the reduced expression of the anti-apoptotic marker, Bcl-2. Furthermore, Se-PC PDT modulated critical signaling pathways, including NF-κB, IL-17 and HIF-1, involved in inflammation, tumor metabolism and immune responses. The treatment also downregulated genes associated with angiogenesis and tumor progression, such as Vegfa, Mmp13, and Serpine1, highlighting its multifaceted anti-tumor effects (30). In a study conducted on BALB/c mice, the Se-PC PDT group exhibited the most significant reduction in tumor volume and weight compared to all other groups (29). This treatment also effectively decreased oxidative stress markers, such as MDA, while enhancing the activity of antioxidant enzymes, including SOD and GSH-Px, in tumor tissues. Additionally, the Se-PC PDT group exhibited a marked increase in apoptosis within tumor cells, highlighting its potent antitumor and antioxidative effects (30). These findings collectively emphasize Se-PC combined with PDT induces potent anticancer activity through mitochondria-mediated apoptosis, partial inhibition of autophagy, and enhanced antioxidant enzyme modulation. It demonstrates stronger efficacy and higher tumor selectivity than PC alone, offering a promising and safer strategy for liver tumor therapy (30).

In conclusion, the present systematic review provides robust evidence that selenium enrichment significantly enhances the biological efficacy of both SP and its key pigment-protein complex, phycocyanin extracted from Se-SP, across a wide range of experimental settings. Compared to their native counterparts, both Se-SP and Se-PC consistently show superior antioxidant, cytoprotective, anti-inflammatory, and in some cases, anticancer activities.

Specifically, Se-SP exhibits markedly more potent protective effects than SP alone, as demonstrated in models of alcohol-induced liver damage, cisplatin-induced cytotoxicity, high glucose-induced vascular calcification, and oxygen-glucose deprivation in neurons. Se-SP improves mitochondrial function, reduces oxidative markers (e.g., ROS and MDA), enhances

antioxidant enzyme activity (e.g., SOD and GPx), and modulates apoptosis-related pathways more effectively than non-enriched Spirulina. Notably, the superiority of Se-SP emerges most clearly in models of hepatic injury, neuroprotection and bone loss, where its selenium-mediated modulation of signaling pathways plays a decisive role. However, Se-SP appears less bioavailable and less effective than inorganic selenium (e.g., SS) in acute systemic conditions such as sepsis, limiting its applicability in urgent or high-burden clinical contexts.

Likewise, Se-PC significantly outperforms native PC in antioxidant capacity, radical scavenging activity, mitochondrial protection and selective cytotoxicity in cancer models. In particular, Se-PC demonstrates enhanced efficacy in PDT for cancer, exerting dual effects of tumor apoptosis and immune activation while maintaining low systemic toxicity. Compared to PC, Se-PC more potently modulates oxidative stress, preserves redox homeostasis, and activates apoptosis-related gene pathways, making it a promising candidate for targeted therapeutic strategies, particularly in oncology.

Despite the compelling results, the available literature presents several limitations, including the scarcity of direct comparative studies between Se-SP and Se-PC, and between these selenium-enriched compounds and conventional selenium forms or combinatorial strategies. Variability in enrichment protocols, dosage regimens, and biological models further complicates comparative interpretation.

Future research is required to prioritize direct head-to-head comparisons of Se-SP vs. Se-PC under standardized conditions, both to elucidate their mechanistic divergences and to optimize their use in specific pathological contexts. Long-term *in vivo* studies and clinical trials will be crucial for validating safety profiles, bioavailability, and dose-response relationships. Exploring combinatorial therapies and synergistic interactions with other bioactive may further expand their application in preventive and functional nutrition, as well as in integrative medicine.

Acknowledgements

The present study was supported by the Ministry of University and Research (MUR) as part of the FSE REACT-EU-PON 2014-2020 'Research and Innovation' resources-Green/Innovation Action-DM MUR 1062/2021-Title of the Research 'GrEEnoncoprev'. The present study was also supported by the Department of Medical, Surgical and Advanced Technologies 'G.F. Ingrassia', University of Catania, Italy.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CS conceptualized the study. CS, CF and CC were involved in the study methodology. CS, CF, CC, PR carried out the search and screening of the articles for inclusion in the systematic review. For the records whose inclusion was in doubt, a focus group was carried out with MF, GOC and MC. The focus group approved the final eligibility of records. PR validated the methodological approach. CC, GOC, and MC were involved in assessing the risk of bias for the articles screening. CF, PR, MC, MF, and GOC were involved in data curation, writing and preparation of the original draft of the manuscript. CC, GOC, MF and MC reviewed and edited the final draft of manuscript. MF and GOC, supervised, and edited the final draft. GOC and MF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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