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Review

Chemical Analysis and Biological Activity of Phycocyanin: An Overview

Vittoria Giraud Baldi, Attilio Anzano, Bruna de Falco, Laura Grauso and Virginia Lanzotti *

Department of Agricultural Sciences, University of Naples Federico II, piazza Carlo di Borbone 1, 80055 Portici, Italy
* Correspondence: lanzotti@unina.it

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Abstract: Phycocyanin, a water-soluble phycobiliprotein primarily found in cyanobacteria such as *Arthrospira platensis* (Spirulina), currently represents one of the most commercially valuable bioproducts in the sustainable biotechnology sector. Thanks to its characteristic linear tetrapyrrole chromophore, phycocyanobilin, this molecule not only plays a crucial role in photosynthesis but also exhibits unique physicochemical properties, including distinct fluorescence and an intense blue color. This review provides a comprehensive and up-to-date overview of recent advances regarding the chemical analysis and biological activities of phycocyanin. In the first section, the focus is placed on analytical methodologies, detailing extraction strategies (such as freeze-thaw and ultrasonication) and purification techniques (including ion-exchange chromatography and ultrafiltration) necessary to preserve its structural integrity, which is sensitive to pH and temperature fluctuations. Furthermore, the use of advanced techniques such as HPLC-DAD, FT-IR, and mass spectrometry for its characterization and quantification is examined. The second part of the work explores the broad spectrum of documented bioactivities, with particular emphasis on its potent antioxidant and anti-inflammatory properties, mediated by the modulation of enzymes such as COX-2. The potential anticancer, immunomodulatory, and antimicrobial effects of the molecule are also discussed. Finally, the review addresses current challenges related to the stability and bioavailability of phycocyanin, outlining future perspectives for its use as a functional ingredient in the food, cosmetic, and pharmaceutical sectors, highlighting its role as a key compound for human health and the green industry.

Keywords: cyanobacteria; Spirulina; *Arthrospira platensis*; pigments; phycobiliprotein; analytical methods; pharmacological activity

1. Introduction

Phycocyanin is a blue, water-soluble phycobiliprotein predominantly found in cyanobacteria, such as *Arthrospira platensis* (Gomont) Geitler, commonly known as *Spirulina platensis* or Spirulina (Figure 1), and in certain red algae. It is a key component of the phycobilisome, the supramolecular light-harvesting complex responsible for capturing solar energy and transferring it to the photosynthetic reaction centers [1]. Structurally, phycocyanin consists of α- and β-polypeptide subunits to which linear tetrapyrrole chromophores, known as phycocyanobilins, are covalently attached [2]. These chromophores are responsible for the intense blue color and the characteristic fluorescence of phycocyanin, properties that have also contributed to its increasing use as a natural colorant and fluorescent probe in biomedical and analytical applications [3].

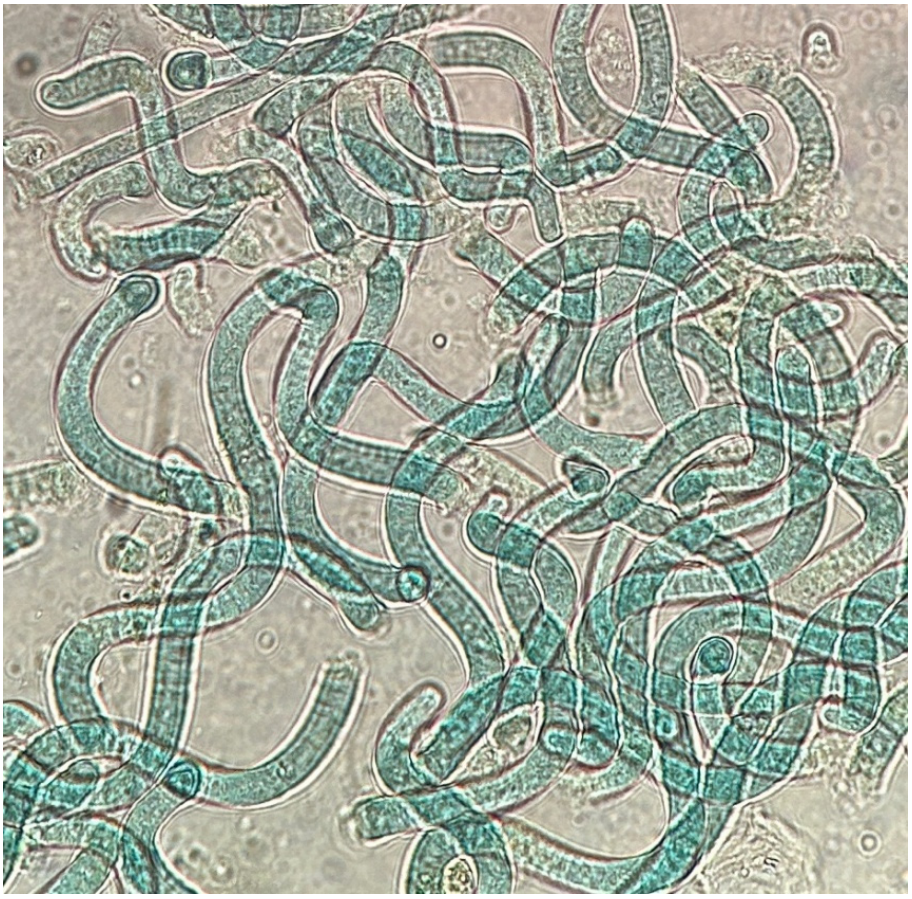

Figure 1. Spirulina image caught on optic microscope.

In recent years, phycocyanin has attracted growing attention due to its dual relevance as both a functional biomolecule and a high value bioproduct. The rising interest in microalgae- and cyanobacteria-derived compounds is largely driven by the need for sustainable and renewable sources of bioactive molecules, coupled with increasing consumer demand for natural additives in food and cosmetic formulations. In this context, phycocyanin represents one of the most commercially valuable pigments, particularly due to its non-toxic nature and its Generally Recognized As Safe (GRAS) status in several regulatory frameworks [4].

The chemical characterization of phycocyanin has become a central focus of research, as its functional properties are closely related to its molecular structure, purity, and stability. Various analytical approaches have been developed and refined to isolate, purify, and quantify phycocyanin from different biological sources [5]. Traditional spectrophotometric methods remain widely used for routine quantification; however, more advanced techniques such as high-performance liquid chromatography (HPLC), capillary electrophoresis, and mass spectrometry have enabled detailed structural analysis and improved detection of degradation products and impurities. Furthermore, recent studies have emphasized the importance of optimizing extraction conditions, including pH, temperature, and solvent systems, to preserve the integrity of the protein and its chromophores [6].

Beyond its chemical and analytical characterization, phycocyanin has been extensively investigated for its broad spectrum of biological activities. A substantial body of evidence highlights its potent antioxidant capacity, primarily attributed to its ability to scavenge reactive oxygen species and inhibit lipid peroxidation [7]. In addition, phycocyanin has demonstrated significant anti-inflammatory effects through the modulation of key signaling pathways, including the downregulation of pro-inflammatory cytokines and enzymes such as cyclooxygenase-2 (COX-2) [8]. Emerging research also supports its antimicrobial, immunomodulatory, and anticancer properties, suggesting its potential role as a therapeutic agent or as a functional ingredient in disease prevention strategies [9].

Despite these promising attributes, several challenges remain regarding the large-scale production, stability, and bioavailability of phycocyanin. The protein is known to be sensitive to environmental factors such as light, temperature, and pH, which can lead to structural degradation and loss of functionality. Consequently, considerable effort has been devoted to developing stabilization strategies, including encapsulation techniques and the use of protective additives, to enhance its shelf life and applicability in various industrial sectors [10,11].

In light of these considerations, this review aims to provide a comprehensive and up-to-date overview of the chemical analysis and biological activity of phycocyanin. The scientific literature search was primarily conducted

on the Scopus database offering extensive coverage of peer-reviewed journals and indexing of multidisciplinary fields of research thus providing a comprehensive overview of the literature. To ensure the robustness of the search and minimize potential bias, the results obtained from Scopus were cross-referenced and validated through complementary searches in Web of Science, PubMed and Google Scholar. This integrated approach confirmed that no landmark studies or significant recent findings were omitted.

In the data discussion, particular emphasis is placed on recent advances in extraction, purification, and analytical methodologies, as well as on the elucidation of the molecular mechanisms underlying its biological effects. Additionally, current limitations and future perspectives are discussed, with the goal of highlighting the potential of phycocyanin as a key bioactive compound in the context of sustainable biotechnology and health-related applications.

2. Chemical Analysis

Phycocyanin is one of the few blue pigments that can be found in nature. Chemically speaking, phycocyanin is organized in a structure composed by more α and β subunits. These two units together form a monomeric unit, which further associate to build two forms of phycocyanin: trimers, made by three monomeric units, or hexamers, made by six monomeric units. Each α subunit carries one chromophore, while each β subunit binds three chromophores. The chromophore found in phycocyanin is called phycocyanobilin, and it's composed of 4 pyrrole groups, responsible of the blue color (Figure 2).

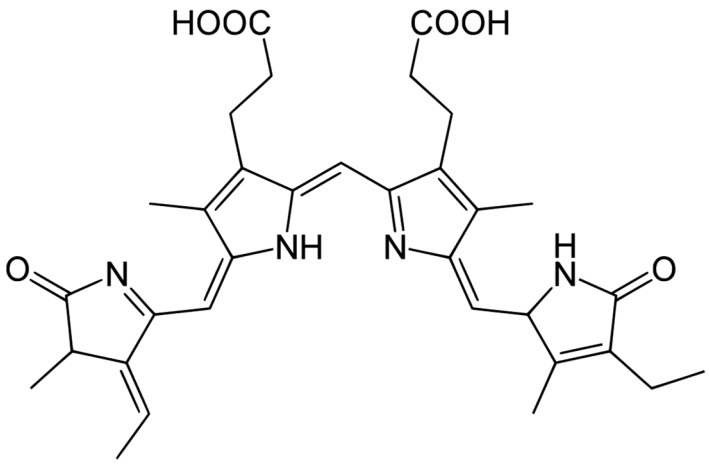

Figure 2. Structure of phycocyanobilin.

The extraction, isolation, and quantification of phycocyanin are strongly influenced by its structural and physicochemical properties. It is a water-soluble phycobiliprotein, and it contains covalently bound chromophores, which are responsible for its characteristic absorption in the visible region. Being a protein, phycocyanin is sensitive to environmental conditions such as pH, temperature, and ionic strength. These characteristics are the key to the development of extraction and isolation strategies of phycocyanin, starting from *Arthrospira platensis* dry biomass, or other cyanobacteria species, and typically consisting in aqueous extraction and cell disruption techniques. In addition, phycocyanobilin spectroscopical characteristic enable its quantification, as it absorbs light around 620 nm thanks to the π→π transitions of its conjugated tetrapyrrole structure. Table 1 summarizes the main methodologies reported in the literature.

The extraction procedures that involve cyanobacteria metabolite extraction usually include a first step to break the cell walls. Freeze-thaw is by far the most used technique, which consists of one or more freezing and thawing cycles, with the thawing occurring at room temperature or higher. This causes the formation of irregular ice crystals that damage cell walls, allowing the release of cytoplasmic material, which will then be extracted with solvents.

Other methods to break cells include sonication, bead milling, enzymatic digestion (using enzymes able to break phospholipids and other membrane constituents), or the French pressure cell method (involving the passage of the extract through a tiny capillary under elevated pressure).

The solvents used for the subsequent extraction are mostly Phosphate-Buffered Saline (PBS) buffer, preferred because of its ability to maintain a neutral pH and protect proteins, and thus phycocyanin, from sudden pH shifts, which would cause its precipitation. Another buffer choice could be TRIS-HCl.

Table 1. Analytical methods used for extraction, isolation, identification and quantification of phycocyanin.

Raw Material	Extraction	Isolation	Identification	Quantification	Ref.
Synechococcus and *Anabaena* pure cultures	Freeze-thaw or enzymatic digestion	UHPLC	DAD (620 nm)	DAD (580, 620, 640 nm)	[12]
Spirulina platensis	Ultrasonication/Homogenization-Centrifugation with $CaCl_2$ as solvent	Active Carbon, LBF, ASP	UV-Vis (620 nm), FT-IR, Fluorescence Spectral Analysis (350–650 nm), Raman Spectral Analysis	UV-Vis (280, 620, 652 nm)	[13]
Calothrix sp., *Westiellopsis* sp., *Calothrix* sp.	Soxhlet extraction and freeze-thaw	ASP, dialysis, IEC	SDS-PAGE	UV-Vis (562, 615, 652 nm)	[14]
Spirulina subsalsa	Sonication and freeze-thaw	Sucrose density gradient ultracentrifugation, dialysis	UV-Vis (615 nm), Fluorescence Analysis (615 nm), FT-IR, ^{1}H-NMR, XRD.	UV-Vis (615, 652 nm)	[15]
Limnospira platensis biomass	Biphasic solid-liquid extraction	FCPC	DAD, UV-Vis (620 nm)	UV-Vis (620 nm)	[16]
Spirulina powder	PBS extraction	Dialysis and ultrafiltration	UV-Vis (620 nm), Fluorescence Spectral Analysis, FT-IR, SDS-PAGE	UV-Vis (280, 620, 652 nm)	[17]
S. platensis dry biomass	Freeze-thaw in PBS	ASP and dialysis	-	UV-Vis (562, 620, 652 nm)	[18]
Cyanobacterium aponinum wet biomass	High pressure homogenization with citrate buffer, Tris-HCL buffer or PBS buffer	-	SDS-PAGE	UV-Vis (620, 652 nm)	[19]
Spirulina aquatilis biomass powder	PBS extraction	Dialysis, EBC, ASP, IEC	UV-Vis (615 nm), steady-state fluorescence, SDS-PAGE, HPLC-DAD	Gravimetric	[20]
Leptolyngbya spp. biomass	PBS, $CaCl_2$ or water extraction, using freeze thawing, bead milling or sonication	-	-	UV-Vis	[21]
S. platensis powder	Freeze-thaw in PBS extraction	ASP, Dialysis and HAC	UV-Vis, SDS-PAGE	-	[22]
Galdieria sulphuraria powder	PBS extraction through bead milling	Osmotic Membrane Distillation	-	UV-Vis (620, 652 nm)	[23]
Arthrospira platensis powder	Freeze-thaw in water or freeze-thaw and sonication in acetone	ASP	HPLC-DAD (620 nm)	Gravimetric	[24]
Phormidium luridum and *Synechococcus lividus*	Water extraction	ASP	^{1}H-NMR (phycocyanobilin)	-	[2]
Mastigocladus laminosus cell culture	French pressure cell, extracted in K_2PO_4	Sucrose density gradient, IEC, preparative isoelectric focusing (separation of α and β subunits)	^{1}H- and ^{15}N-NMR (phycocyanobilin), SDS-PAGE, Native-MS, UV-Vis (α-C-Phycocyanin)	Gravimetric	[25]

Table 1. *Cont.*

Raw Material	Extraction	Isolation	Identification	Quantification	Ref.
Cyanobacterium AP24 cell culture	Homogenization in TRIS-HCl buffer, sonication, freeze-thaw.	ASP, dialysis, IEC	UV-Vis, SDS-PAGE	UV-Vis (620, 652 nm)	[26]
A. platensis dried powder	Freeze-thawing or ezyme digestion in PBS	ASP, dialysis, IEC	HPLC-DAD (620 nm)	Gravimetric	[27]
Phormidium, *Lyngbya* and *Spirulina* spp. culture	Sonication and freeze-thawing in PBS	ASP, dialysis, IEC	UV/VIS Spectroscopy (620 nm), FT-IR, SEC, SDS-PAGE	UV/vis (620, 652 nm)	[28]
A. platensis dry biomass	$CaCl_2$ extraction	ASP, dialysis, IEC	UV/VIS Spectroscopy (620 nm), SDS-PAGE, FT-IR,	Gravimetric	[29]
Arthrospira maxima cell pellet	Sonication and freeze-thaw in PBS	ASP, SEC, IEC	UV-Vis (652 nm), Native-MS	-	[30]
Limnospira maxima, Gloeocapsopsis crepidinum, Nostoc muscorum, Kamptonema sp., Phormidesmis priestleyi, Spirulina major, Dolichospermum circinale, Gloeomargarita lithophora, Synechococcus sp. cell pellets	Sonication and freeze-thaw in water	ASP, IEC	UV-Vis (280, 620, 650 nm), Native-MS, SDS-PAGE	-	[31]

Abbreviations: ASP = Ammonium Sulfate Precipitation; DAD = Diode Array Detector; EBC = Expanded Bed Chromatography; FCBC = Fast Centrifugal Partition Chromatography; FT-IR = Fourier Transform InfraRed; HAC = HydroxyApatite Chromatography; IEC = Ion Exchange Chromatography; LBF = Liquid Biomass Flotation; MS = Mass Spectrometry; NMR = Nuclear Magnetic Resonance; PBS = Phosphate-Buffered Saline, SEC = Size Exclusion Chromatography; UHPLC = Ultra High Performance Liquid Chromatography; UV-Vis = Ultraviolet-Visible Spectroscopy; XRD = X-ray Diffraction.

$CaCl_2$ is used by some research groups because of its ability both to destabilize cell walls for better disruption and to precipitate undesired components of the extract [13,21,29]. Proteins like phycocyanin have their solubility increased by the neutralization of part of their negative charges. If used at the correct concentration, it can cause the precipitation of undesired proteins. However, PBS is preferred because if the $CaCl_2$ concentration is too high, there is a risk of protein precipitation.

The main method used to isolate phycocyanin is ammonium sulfate precipitation. Ammonium sulfate competes with water molecules and decreases the solubility of phycocyanin, causing its precipitation together with the rest of the proteins. The excess salt resulting from the addition of ammonium sulfate is often removed by dialysis, which separates molecules depending on their size using a semi-permeable membrane, as salts could interfere with subsequent analyses. After removal of salt, the components of the protein isolate are either separated by ion exchange chromatography (IEC) or other chromatographic techniques.

IEC for phycocyanin separation is usually conducted using diethylaminoethyl resin (DEAE), a positively charged resin that helps to retain phycocyanin, which is negatively charged. Tris(hydroxymethyl)aminomethane hydrochloride (TRIS-HCl) is used as a washing buffer to keep the pH stable, maintaining phycocyanin charge state; then NaCl is added to promote elution of the protein thanks to the competition between Cl- ions and the negatively charged phycocyanin groups [14,26–29]. Often, Size Exclusion Chromatography (SEC) is coupled with IEC for a first purification step [28–30]. Phycocyanin is a large polymer, therefore the size-based separation of SEC helps to enrich the fraction before performing a finer separation with IEC, that can separate different types of phycobiliproteins based on their different charges.

Other studies separated the different subunits of the phycocyanin to characterize the whole protein [25]. First, sucrose density gradient separation was used to remove uninteresting components from the extract, then total proteins were separated via IEC, using K_2PO_4 as eluent. Phycocyanin was denatured using urea and separated by preparative isoelectric focusing to isolate the different subunits. The subunits were then characterized by Sodium Dodecyl Sulphate-PolyAcrylamide Gel Electrophoresis (SDS-PAGE), UltraViolet-Visible (UV-Vis) spectroscopy and mass spectrometry.

High Performance Liquid Chromatography (HPLC) was used too with the aim of purifying phycocyanin from crude cyanobacteria extract. A study conducted by Canuti used C_4 and C_5 columns to set up a Ultra-High Performance Liquid Chromatography (UHPLC) method, using water and acetonitrile as eluents, both added with 0.1% trifluoroacetic acid (TFA) [12]. TFA in this case is used as an ion-pairing agent to neutralize the negative charges of phycocyanin and improve its hydrophobicity, increasing retention and obtaining a better peak shape. C_8 columns were tested too but resulted in peak tailing and were discarded. Moreover, Kissoudi et al. used a C_4 column to isolate and identify phycocyanin from purified *A. platensis* extracts [27].

Due to the complex nature of phycocyanin, it is not possible to visualize the whole protein by mass spectrometry. More commonly the single subunits are the ones that are visualized, as shown by Hahn et al. [25]. A technique that allows visualization of a whole protein is native mass spectrometry, which uses milder ionization such as Electrospray Ionization (ESI), nano-ESI, Matrix-Assisted Laser Desorption/Ionization (MALDI), to preserve non-covalent interactions that make up the high-order structures of proteins. It also uses solvents that do not compromise the protein three-dimensional structure and keep the pH around physiological value. A nano-ESI approach was used by Bellamy-Carter et al., who studied phycocyanin and other phycobiliproteins in their native state to gather information about the ability of these pigments to bind heavy metals, and the toxic effect they exert on cyanobacteria growth [30]. Another group used nano-ESI native MS to study the high-order structure of phycobiliproteins in different cyanobacterial species, to investigate how these pigments evolved by comparing their conformations across species, an approach known as evolutionary proteomics [31].

Fast Centrifugal Partition Chromatography (FCPC) is an advanced liquid-liquid chromatographic technique used by Pereira et al. to purify phycocyanin from *Limnospira platensis* (Gomont) Santos and Hentschke biphasic extract. In this case, the separation occurs by the partition of the analyte between a mobile phase and a stationary phase (represented by another liquid solvent), that is held still thanks to the centrifugation force [16]. The analyte separates gradually while passing through multiple interconnected columns that contain the same stationary phase. This is a mild technique that avoids protein denaturation and is highly suitable for the analysis of biomolecules.

Expanded Bed Chromatography (EBC) is a technique developed for the purification of molecules from complex extracts, often used to purify biomolecules from lysates or cellular extracts. It is another technique that preserves the integrity of biomolecules, allowing their characterization as whole molecules, and it is suitable for industrial scale-up and large-scale purification, reducing overall purification time of the whole process. It was employed by Ramos et al. to purify phycocyanin from *Spirulina aquatilis* extracts [20].

Hydroxyapatite chromatography is a non-conventional chromatographic technique that is mostly used for protein purification. The hydroxyapatite stationary phase contains both positive (Ca^{2+}) and negative (PO_4^{3-})

groups, making proteins interact strongly as they pass through it. Proteins are then eluted using increasing concentrations of a phosphate salt that competes with the Ca^{2+} groups and releases the proteins one by one in subsequent fractions, based on their affinity with hydroxyapatite. This technique was used by Li et al., who separated phycocyanin after ammonium sulfate precipitation and used a UV-Vis detector to monitor the absorbance and confirm its presence [22].

The identification of phycocyanin is mainly obtained by using two of its important physical properties: the ability of its chromophores to absorb visible light at 620 nm, and its high molecular weight, which makes it suitable for SDS-PAGE separation.

UV-Visible spectroscopy is the main technique used to confirm the presence of phycocyanin in the fractions coming from previous purification steps. To assess the phycocyanin content of the fractions, the absorbance at 620 nm and at 280 nm is measured using a UV-Vis spectrophotometer, together with the absorbance at 652 nm, corresponding to allophycocyanin. To calculate the purity of phycocyanin in fractions containing mostly proteins, the formula commonly used is: Purity Ratio = A620/A280.

Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) is also used to confirm the presence of phycocyanin, as it separates proteins based on their molecular weight. By using SDS and β-mercaptoethanol, the proteins are denatured, and SDS binds along the polypeptide chain, giving a uniform negative charge proportional to the protein length. The proteins are then loaded onto a polyacrylamide gel, and when an electric current is applied, they migrate according to their size and negative charge. If proteins other than phycocyanin are present, they will appear as additional bands in the gel where no bands would be expected.

Nuclear Magnetic Resonance (NMR) is not indicated to study whole proteins, as they result in very rich spectra hard to interpret. It can help in the study of parts of proteins that have been separated through other techniques. Few studies used ^{1}H-NMR to analyze the structure of phycocyanobilin and identified the diagnostic signals of the chromophore [2,15,25]. One of them also employed ^{15}N-NMR to study ^{15}N-labeled phycocyanin, allowing the analysis of the chromophore structure while attached to the protein. They also used Nuclear Overhauser Effect Spectroscopy (NOESY) technique to understand the spatial disposition of the chemical environment around the four nitrogen atoms [25].

Fourier Transform-Infrared (FT-IR) and Raman spectral analysis are two techniques used to study the functional groups of organic molecules. In this matter, FT-IR was used to study the secondary structure of the protein, and to compare extracts before and after the purification process to verify if phycocyanin had been denatured or degraded [13,17,28,29]. Raman spectral analysis was used with a similar purpose [13].

X-ray Diffraction (XRD) and fluorescence spectral analysis were used to study some specific characteristics of the phycocyanin molecule. XRD studies the diffraction of x-rays when they hit the crystals of a pure molecule. In this way, important information about the structure of the molecule is gathered. However, phycocyanin usually forms amorphous crystals, and thus XRD can provide limited structural information [15]. Yue et al. also employed fluorescent spectral analysis, a technique that irradiates a compound with a certain wavelength and measures the emission, to measure the purity of phycocyanin throughout the purification process [13]. Steady-state fluorescence, a particular type of fluorescent spectroscopy was used by Ramos et al. to collect information about the quaternary structure of phycocyanin and its aggregation state [20].

UV-Vis spectroscopy is often used to quantify the phycocyanin content in the extract. Once the absorbance at 620 nm has been measured, a formula to estimate the concentration of phycocyanin is applied, derived from Lambert-Beer equation: Concentration = $[(Abs620 - 0.474Abs652) \times \text{Solvent Volume}]/(\varepsilon \times \text{cyanobacteria mass})$ where ε is the molar extinction coefficient. It is usually assumed to be 5.34 for phycocyanin. Alternatively, the concentration can be estimated from the peak detected by a Diode Array Detector (DAD) after an HPLC-DAD run. The quantity of phycocyanin present in the sample can be determined by using external standard to build a calibration curve [12].

Many research groups have quantified phycocyanin by first isolating the pure compound through chromatographic techniques. Once purification was completed, they determined its weight gravimetrically [20,24,25,27,29].

3. Biological Activity

The biological activities of phycocyanin are summarized in Table 2. The active compound used in the cited studies originates from different sources and has been administered in various forms, either as a purified extract or incorporated into specific pharmaceutical formulations.

Table 2. Pharmacological activities of phycocyanin.

Activity	Origin	Administration Forms	Model Used	Observed Effect	Quantity	Ref.
Antioxidant	*Spirulina subsalsa* HKAR-19	Purified C-PC extract	DPPH, ABTS and SRSA *in vitro* assays	Scavenging activities against free radicals	IC_{50} 64.55 ± 0.21 µg/mL (DPPH assay); IC_{50} 56.81 ± 1.21 µg/mL (ABTS assay); IC_{50} 70.51 ± 1.01 µg/mL (SRSA assay)	[15]
	Geitlerinema sp.	Lyophilized C-PC extract	DPPH *in vitro* assay	Scavenging activities against free radicals	IC_{50} 0.57 ± 0.01 mg/mL	[32]
	Spirulina	PRG Hydrogel	DPPH, ABTS *in vitro* assays and Fe^{2+} chelating activity	Reduction of local oxidative stress response of wounds; Chelating and scavenging activities	20 mg/mL (2% *w*/*v* C-PC within PRG-3 hydrogel matrix)	[33]
	Spirulina platensis	Purified C-PC extract; Functional yogurt (free and nanophytosomal C-PC)	DPPH, ABTS *in vitro* assays	Scavenging activities against free radicals; Improved antioxidant stability during storage in functional yogurt	500 µL (DPPH assay) and 0.1 mL (ABTS assay); 150 and 300 mg/portion (as nanophytosomes, in functional yogurt)	[34]
	Geitlerinema sp. TRV57	Purified C-PC extract	Phosphomolybdenum, FRAP, DPPH, H_2O_2 and Anti-lipid peroxidation *in vitro* assays	Scavenging activities against free radicals; Ferric reducing ability; Lipid peroxidation inhibition property	200 µg/mL; IC_{50} 185 µg/mL (Anti-lipid peroxidation assay)	[35]
	Arthrospira sp.	Crude PC-E extract	β-carotene bleaching, FRAP, DPPH *in vitro* assays and Fe^{2+} chelating activity	Inhibition of β-carotene oxidation; Ferric reducing ability; Chelating and scavenging activities	5 mg/mL	[36]
	Limnothrix sp.	Purified C-PC extract	DPPH *in vitro* assay	Scavenging activities against free radicals	100% activity at the concentration of 0.15 mg/mL; EC_{50} 0.08 mg/mL	[37]
	S. platensis	Purified apo-c-PC (b) and native C-PC extracts	Human erythrocytes	Decreased AAPH-induced erythrocyte haemolysis; Increased erythrocyte tolerance to oxidative stress; Reduced H_2O_2-induced morphological alterations	1 µM (haemolysis assay); 10 µM (erythrocyte morphology analysis)	[38]
	Synechococcus sp. R42DM	Purified C-PC extract	DPPH and FRAP *in vitro* assays; *Caenorhabditis elegans* *in vivo* experiment	Scavenging activities against free radicals; Ferric reducing ability; Lifespan extension in *C. elegans*	80 µg (DPPH assay); 100 µ/mL (*C. elegans in vivo* test)	[39]
Antioxidant-anti-aging	*L. platensis*	C-PC Peptides	*C. elegans*	Increase in antioxidant capacity under oxidative stress, resulting in a delay in the aging process	5 mg/mL (CPCAH-F3)	[40]
Antioxidant-wound healing	Spirulina	PRG Hydrogel	Rats (*Rattus norvegicus)*	Increased rate of re-epithelialization, promoting epidermal remodeling and wound healing; Enhanced wound tissues regeneration through reduced inflammatory factors (TNF-α and IL-6), increased antioxidant enzymes (SOD, CAT and GPx) and increased collagen deposition and angiogenesis (CD31)	20 mg/mL (2% *w*/*v* C-PC within PRG-3 hydrogel matrix)	[33]

Table 2. *Cont*.

Activity	Origin	Administration Forms	Model Used	Observed Effect	Quantity	Ref.
Antibacterial	Spirulina	PRG Hydrogel	*Staphylococcus aureus*, *Pseudomonas aeruginosa*	Growth inhibition of the bacteria cells and damaged integrity of bacterial membrane	20 mg/mL (2% *w*/*v* C-PC within PRG-3 hydrogel matrix)	[33]
	Arthrospira sp.	Crude PC-E extract	Gram-negative (*Escherichia coli*, *Salmonella typhimurium* and *Pseudomonas* sp.) and gram-positive (*S. aureus*—ATCC 25923, *Micrococcus luteus*—ATCC 4698 and *Listeria monocytogenes*)	Growth inhibition of the bacteria cells	10 mg/mL	[36]
Antifungal	*Arthrospira platensis*	Silver nanoparticles	*Aspergillus fumigatus*, *Fusarium oxysporum*	Growth inhibition of the fungal cells caused by the oxidative stress and activation of the cellular antioxidant system	150–300 ppm (of which 50% C-PC)	[41]
Antimicrobial	*Geitlerinema* sp.	Lyophilized C-PC extract	*Bacillus cereus* ATCC 10876, *E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 51299, *Enterobacter aerogenes* NRRL B-3567, *Klebsiella pneumoniae* ATCC 700603, *L. monocytogenes* ATCC 19111, *M. luteus* NRRL B-4375, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 6538, *Salmonella typhimurium* ATCC 14028, and *Yersinia enterocolitica* Y53) and yeast species (*Candida albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida parapsilosis* ATCC 22019, and *Candida krusei* ATCC 6258)	Growth inhibition of the bacteria/yeast cells	250 and 500 µg	[32]
Antiviral	*S. platensis*	Purified C-PC extract	Vero-E6 cells *in vitro* test	Significant decrease in viral infection	IC_{50} 0.515 µg/mL	[34]
Anti-inflammatory	*S. platensis*	Purified C-PC extract	HRBC using membrane stabilization method	Anti-inflammatory activity comparable to the reference standards	100 µL	[34]
	S. platensis	Purified C-PC extract	LPS-induced murine macrophages (RAW 264.7) cell line	Inhibition of nitrite accumulation and iNOS expression; Attenuated secretion of TNF-α and IL-6; Decreased mRNA expressions of IL-1β, CCL2 and CCL5; Pro-apoptosis effect of inflammatory cells; Down-regulation of PDCD5-NF-κB signaling	60, 120 and 240 µg/mL	[42]
Anti-inflammatory-anti-colitis	*Arthrospira maxima*	C-PC extract	Rats with acetic acid-induced colitis	Inhibition of MPO activity leading to reduced neutrophil infiltration and partial recovery of microvilli in epithelial cells	200 and 300 mg/kg	[43]
Anti-inflammatory-dermal biostimulation	*Nostoc* sp., *Spirulina* sp.	Purified C-PC extract	Human skin fibroblast cell line (CCD-966SK) stimulated with LPS	Complete inhibition of inflammation (zero IL-6 and TNF-α release); Significant increase in Collagen Type I and II synthesis; Enhancement of antioxidant enzyme activities (SOD and GPx)	31.25–62.5 ppm (anti-inflammatory activity); 3.91–125 ppm (biostimulation); 1000 ppm (antioxidant activity)	[44]

Table 2. *Cont.*

Activity	Origin	Administration Forms	Model Used	Observed Effect	Quantity	Ref.
Anti-inflammatory-immunomodulatory	*S. platensis*	Purified C-PC extract	Murine macrophage cell line J774A.1	Increase in the expression of TNF-α, IL-1, IL-6, proIL-1 and COX-2 in macrophage cells; Phosphorylation of ERK, JNK, p38 and IkB	100–400 µg/mL	[45]
Anticancer	*S. platensis*	Purified C-PC extract	Human colorectal carcinoma (HCT-116), human liver carcinoma (HepG-2), MCF-7 (human breast adenocarcinoma), and the normal human skin fibroblast (BJ-1) cell lines	Inhibition of cancer cells; Antiproliferative and cytotoxic activities	6.25 and 50 µg/well	[34]
	Geitlerinema sp.	Lyophilized C-PC extract	Human lung fibroblast cells (CCD-19Lu, ATCC CCL-210), human adenocarcinoma alveolar basal epithelial cells (A549, ATCC CCL-185), human non-cancerous pancreatic ductal hTERT immortalized cells (hTERT-HPNE, ATCC CRL-4023, epithelial cell), human pancreatic carcinoma epithelial cells (PANC-1, ATCC CRL-1469)	Disruption of the tumor cell cycle; Induction of tumor cell apoptosis/necrosis and autophagy	IC_{50} from 83.5 µg/mL at 24 h to 53 µg/mL at 72 h (PANC-1 cells); IC_{50} from 74.9 µg/mL at 24 h to 40 µg/mL at 72 h (A549 lung cancer cells)	[32]
	S. platensis	Purified C-PC extract	HeLa cell line (wild-type and CD59-transfected) and normal CHO cells	Upregulation of CD59 protein in tumor cells, inducing Fas expression and subsequent tumor cell apoptosis	160 µg/mL	[22]
	S. platensis	Purified C-PC extract	Mice (*Mus musculus*) with induced melanoma	Increase in the population of immune system cells (T, B and myeloid cells) resulting in positive immune system modulation associated with a reduction in tumor growth	560 mg/kg	[46]
	Oscillatoria tenius	Purified C-PC extract	HT-29 and A549 cell lines	Induced apoptosis in selected human cancer cells; Apoptotic morphological changes (cell shrinkage, membrane blebbing, apoptotic nuclei); G_0/G_1 phase arrest; DNA fragmentation	IC_{50} 30 µg/mL (HT-29); IC_{50} 55 µg/mL (A549)	[47]
	Ulva lactuca	Albumin nanoparticles (ULANP)	HepG2 and MCF-7 cell lines	Increased level of caspase-8 and 9 in both the cell lines; Decrease in the cell viability	20 µg	[48]
Anti-allergic	*Porphyra haitanensis*	Purified R-PC extract	Antigen-sensitized mice (*Mus musculus) in vivo* experiment and IgE-sensitized RBL-2H3 rat mast cell lines *in vitro* assay	Suppression of Th2-mediated immune responses and promotion of Th1 cell polarization; Decreased expression of IL-4 and IL-13; Promotion of IFN-γ through JAK2 and JNK signaling pathways; Inhibition of the release and production of pro-inflammatory mediators (β-hexosaminidase, histamine, ROS) and cytokines (IL-4, TNF-α) in activated mast cells	0.1 and 5 mg/mouse (*in vivo* experiment); 20–200 µg/mL (proliferative activity); 80–150 µg/mL (measurement of β-hexosaminidase and histamine release)	[49]

Table 2. *Cont.*

Activity	Origin	Administration Forms	Model Used	Observed Effect	Quantity	Ref.
Anti-diabetic	*S. platensis*	Purified C-PC extract	Alloxan-induced diabetic rats (*R. norvegicus*)	Promotion of pancreatic b-cell regeneration and increased insulin levels; Inhibition of pro-inflammatory enzymes (5-LO, HAase, MPO, and NOX2) and reduction of pancreatic lymphocyte infiltration; Enhancement of TAS and NO with concomitant reduction of H_2O_2, TOS, and TBARS; Modulation of hepatic glucose metabolism via regulation of key enzymes (HK, PK, G6PD, LDH, G6P, and FBP); Suppression of postprandial hyperglycemia through potent inhibition of intestinal α-amylase, maltase and sucrase; Reduction of serum, pancreatic and intestinal lipase activities leading to improved glycemic control (reduced blood glucose and HbA1c)	200 mg/kg	[50]
Antiglycation	*Pseudanabaena* sp. ABRG5-3	Purified abPC extract	Collagen anti-glycation assay kit	Inhibition of glycation process and formation of glycation-derived products, associated with lower risk of diabetes, renal diseases and malignant tumors	-	[51]
Hepatoprotective	*Spirulina maxima*	Purified C-PC extract	Zebrafish (*Danio rerio*)	Modulation of oxidative stress markers (CAT, SOD, GST, GPx, GSH) and their gene expression; Reduction of LPO; Normalization of hepatic enzymes (AST, ALT); Histopathological improvement of liver tissue (reduced necrosis and inflammation) without inducing toxicity	100 and 200 µg	[52]
Nephroprotective	*A. maxima*	Purified C-PC extract	5/6 nephrectomized (5/6 NFx) rats	Prevention of CKD progression and cardiorenal complications; Reduction of hypertension and left ventricular hypertrophy; Improvement of renal markers (proteinuria, hyperuricemia, creatinine clearance); Antioxidant protection in kidney and heart (ROS and lipid peroxidation reduction); Preservation of GSH/GSSG balance and potential modulation of the renin-angiotensin system	100 mg/kg	[53]

Table 2. *Cont.*

Activity	Origin	Administration Forms	Model Used	Observed Effect	Quantity	Ref.
Neuroprotective	Spirulina	Purified C-PC	Rats (*R. norvegicus*)	BBB Protection: restoration of claudin-5 and PGP levels; inhibition of calpain and MMP proteolytic activities; Redox Modulation: significant reduction in ROS generation and lipid peroxidation; restoration of the GSH pathway (in co-treatment); Glial Modulation: Suppression of astrogliosis (GFAP downregulation); restoration of microglial activation (Iba1 and CD11b expression); Anti-inflammatory: downregulation of NF-kB p65 signaling; reduction in nitrite accumulation and caspase-12 activation; Stress response: strong upregulation of neuroprotective MT and modulation of Nrf2; Anti-apoptotic: reduction of Bax/Bcl-2 ratio and inhibition of Caspase-3; decrease in TUNEL-positive cells; Tissue preservation: reversal of damage to MBP and attenuation of DNA damage (H2A.X phosphorylation)	50 mg/kg	[54]

Abbreviations: AAPH = 2,2′-azobis(2-amidinopropane dihydrochloride; ABTS = 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid); ALT = alanine aminotransferase; Bax = Bcl-2-associated X protein; BBB = blood-brain barrier; C-PC = C-phycocyanin; CAT = catalase; CCL = C-C motif chemokine ligand; CD = cluster of differentiation; CDK = Chronic Kidney Disease; CHO = Chinese Hamster Ovary; COX-2 = cyclooxygenase-2; DPPH = 2,2-diphenyl-1-picrylhydrazyl; EC_{50} = half-maximal effective concentration; ERK = extracellular signal-regulated kinase; Fas = first apoptosis signal; FBP = fructose-1,6-bisphosphatase; FRAP = Ferric Reducing Antioxidant Power; G6P = glucose-6-phosphate; G6PD = glucose-6-phosphate dehydrogenase; GFAP = glial fibrillary acidic protein; GPx = glutathione peroxidase; GSH = reduced glutathione; GSSG = oxidized glutathione; GST = glutathione S-transferase; H2A.X = H2A histone family member X; H_2O_2 = hydrogen peroxide; Haase = hyaluronidase; HbA1c = glycated hemoglobin; HK = hexokinase; HRBC = human red blood cell; Iba1 = ionized calcium-binding adapter molecule 1; IC_{50} = half-maximal inhibitory concentration; IFN-γ = interferon-gamma; IL= interleukin; iNOS = inducible nitric oxide synthase; IκB = inhibitor of kappa B; JAK2 = janus kinase 2; JNK = c-Jun N-terminal kinase; LDH = lactate dehydrogenase; LO = lipoxygenase; LPO = lipid peroxidation; AST=aminotransferase; LPS = lipopolysaccharide; MBP = myelin basic protein; MMPs = matrix metalloproteinases; MPO = myeloperoxidase; MT = metallothionein; NK- κB = nuclear factor-kappa B; NO = nitric oxide; NOX2 = NADPH oxidase 2; Nrf2 = nuclear factor erythroid 2-related factor 2; p38 = p38 mitogen-activated protein kinase; PC-E = E-phycocyanin; PDCD5 = programmed cell death protein 5; PGP = p-glycoprotein; PK = pyruvate kinase; ROS = Reactive Oxygen Species; R-PC = R-phycocyanin; SOD = superoxide dismutase; SRSA = Superoxide Radical Scavenging Activity; TAS = total antioxidant status; TBARS = thiobarbituric acid reactive substances; TNF- α = tumor necrosis factor-α; TOS = total oxidant status; TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labeling.

3.1. Antioxidant Activity

The most extensively studied activity of phycocyanin is undoubtedly its antioxidant capacity. This property is particularly important because it serves as the fundamental mechanism underlying almost all the other biological and pharmacological activities evaluated in this review. Phycocyanin is increasingly recognized as a potent therapeutic agent against oxidative stress, which is considered its most significant biological role.

This antioxidant action can be attributed to several key properties, most notably the chelation of free radicals and metal ions, as well as the inhibition of lipid peroxidation. Specifically, phycocyanin is able to neutralize Reactive Oxygen Species (ROS). These are unstable and highly reactive molecules produced during cellular metabolism that possess an unpaired electron. To achieve stability, ROS "steal" electrons from surrounding cellular structures, causing widespread damage known as oxidative stress. When present in excess, these molecules (such as superoxide anions, hydroxyl radicals, and hydrogen peroxide) accelerate skin aging and contribute to the development of various chronic diseases.

In this context, antioxidants like phycocyanin act as cellular scavengers. They neutralize free radicals by donating the missing electron, effectively stopping the "chain reaction" of oxidative damage without becoming unstable themselves. This process is part of what we call oxidation-reduction (redox) balance.

To evaluate this scavenging efficiency, researchers typically use specific *in vitro* assays. The most common ones include 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), Reducing Power (RP), Superoxide Radical Scavenging Activity (SRSA) and Ferric Reducing Antioxidant Power (FRAP).

For instance, Jaiswal et al. [15] examined phycocyanin extracted from *Spirulina subsalsa* Oerstedt ex Gomont HKAR-19. The study showed that phycocyanin exhibits dose-dependent antioxidant properties. To provide a benchmark, the researchers used ascorbic acid (Vitamin C) as a control, which is known to be one of the most potent natural antioxidants. The DPPH assay is a primary method used to test an antioxidant's ability to inhibit the DPPH• radical. In an alcoholic solution (ethanol or methanol), this radical produces a deep purple color with a maximum absorbance peak between 515 and 517 nm. When an antioxidant donates a hydrogen atom or an electron to the DPPH• radical, the radical is reduced (forming DPPH-H) and the solution turns yellow. This decrease in purple intensity is proportional to the concentration of antioxidants present. In scientific literature, the most common parameter used to express this is the half-maximal inhibitory concentration (IC_{50}), which represents the concentration of antioxidant required to reduce the initial DPPH• concentration by 50%. Therefore, a lower value indicates higher antioxidant potency. The reported IC_{50} for phycocyanin was 64.55 ± 0.21 μg/mL, which was slightly higher than that of ascorbic acid (IC_{50} 55.75 ± 1.02 μg/mL). Similarly, the ABTS assay works by generating a blue-green cationic radical (ABTS•+) that gets decolorized in the presence of antioxidants. The loss of color, measured at 734 nm, directly reflects the antioxidant concentration. In the same study, the IC_{50} values for phycocyanin and ascorbic acid were 56.81 ± 1.21 μg/mL and 42.04 ± 0.01 μg/mL respectively. Finally, the SRSA assay focuses specifically on the ability to scavenge the superoxide radical, one of the first ROS to form in biological systems. Jaiswal et al. [15] found that phycocyanin had an IC_{50} of 70.51 ± 1.01 μg/mL compared to 55.87 ± 0.21 μg/mL for vitamin C. Although ascorbic acid generally showed higher potency (lower IC_{50}), these results demonstrate that phycocyanin possesses a very high and effective antioxidant activity, particularly towards ABTS•+ and DPPH• radicals.

Similarly, Hajiyeva et al. [32] evaluated the antioxidant activity of phycocyanin using the DPPH assay. In this case, lyophilized phycocyanin extracted from *Geitlerinema* sp. (Anagnostidis & Komárek) Anagnostidis was tested and compared with ascorbic acid as a reference standard. The results showed an IC_{50} value of 0.57 ± 0.01 mg/mL for phycocyanin, which was comparable to that of ascorbic acid (0.49 ± 0.08 mg/mL), further confirming its strong free radical scavenging capacity.

In contrast, Meng et al. [33] investigated the antioxidant potential of a phycocyanin-based multifunctional hydrogel (PRG hydrogel), designed by combining phycocyanin with other bioactive components, including gelatin, silk fibroin, rhein, and tetracaine, crosslinked using glutaraldehyde. Among the different formulations obtained (PRG-1 to PRG-5), PRG-3 (gelatin 20% (*w*/*v*), C-PC 2% (*w*/*v*), silk fibroin 1.2% (*w*/*v*), rhein 0.1% (*w*/*v*), tetracaine 0.2% (*w*/*v*) and glutaraldehyde 0.6% (*w*/*v*)) exhibited the most promising results in terms of biological activity. The antioxidant capacity of these hydrogels was evaluated using both DPPH and ABTS assays. Notably, increasing the phycocyanin content led to a marked enhancement in radical scavenging activity, with DPPH inhibition rising from 78.94% to 93.27% and ABTS•+ scavenging from 91.04% to 93.90%. In addition to radical scavenging, the study also assessed the Fe^{2+} chelating activity, a key mechanism underlying antioxidant effects, as it prevents metal-catalyzed formation of ROS. The PRG hydrogels showed a concentration-dependent increase in metal chelation, reaching 50.54% at 20 mg/mL (PRG-3), further supporting their antioxidant potential. Overall,

these findings highlight how the incorporation of phycocyanin into a multifunctional hydrogel system can enhance and extend its antioxidant properties through both radical scavenging and metal-chelating mechanisms.

This potent antioxidant activity directly contributes to the hydrogel's efficacy in wound healing, as demonstrated in a Sprague-Dawley rat model with full-thickness skin defects employed by Meng et al. [33]. By regulating the redox balance and increasing the levels of endogenous enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) at the injury site, the PRG-3 hydrogel effectively reduced oxidative stress, facilitating rapid tissue repair with a healing rate exceeding 95% by day 10. This antioxidant-driven environment not only suppressed pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)) but also promoted superior re-epithelialization and organized collagen deposition. Furthermore, the treatment stimulated angiogenesis, evidenced by increased cluster of differentiation 31 (CD31) gene expression, proving that the phycocyanin-mediated reduction of ROS is a key driver in accelerating the transition from the inflammatory phase to successful tissue remodeling.

In line with these findings, the antioxidant activity of phycocyanin has also been confirmed both in purified systems and in functional food matrices. According to Soliman et al. [34], a purified extract of phycocyanin from *Spirulina platensis* demonstrated a strong radical scavenging capacity, reaching 99.12 ± 0.027% inhibition in the DPPH assay when 500 μL of sample were used, while high antioxidant activity was also observed in the ABTS assay using 0.1 mL of extract. To overcome the stability limits of the pure extract, phycocyanin was encapsulated into nanophytosomes prepared using a thin-film hydration method with soy lecithin as the lipid carrier. The study identified an optimal phycocyanin to lecithin molar ratio of 1:2, which ensured a high encapsulation efficiency (94.65%) and a stable nanostructure. Comparable results were reported in stirred yoghurt systems enriched with these nanophytosomes. The antioxidant capacity was rigorously tested over a 21-day storage period at 4 °C using DPPH and ABTS assays to evaluate the shelf-life stability of the bioactive compounds. In particular, yoghurt samples fortified with encapsulated phycocyanin at concentrations of 150 and 300 mg showed the highest total phenolic content and radical scavenging activity compared to plain yoghurt and samples containing non-encapsulated phycocyanin. This improved performance was attributed to the protective effect of phytosomal encapsulation, which shielded the phycocyanin from the acidic environment of the yoghurt and prevented its premature degradation. Furthermore, the antioxidant capacity in these systems was observed to increase during the 21 days of storage; this trend was likely due to the synergistic effect between the protected phycocyanin, and the gradual release of bioactive peptides generated by the proteolytic activity of *Lactobacillus rhamnosus* KU985435 during milk fermentation. Overall, these findings highlight that while phycocyanin possesses strong intrinsic antioxidant potential, its integration into nanophytosomes is a crucial delivery strategy to maintain functional properties and bioactivity within complex and acidic food matrices.

In another study, Renugadevi et al. [35] examined the antioxidant activity of phycocyanin extracted from the isolated *Geitlerinema* sp. TRV57. The antioxidant properties were assessed using several methodologies, including phosphomolybdenum, FRAP and DPPH radical scavenging assays, as well as hydrogen peroxide (H_2O_2) scavenging and anti-lipid peroxidation assays. In the phosphomolybdenum assay, antioxidants reduce molybdenum (VI) to molybdenum (V), forming a green phosphomolybdate complex. The intensity of this color directly correlates with the sample's antioxidant capacity. In this study, phycocyanin exhibited a concentration-dependent reducing ability, reaching a maximum absorbance of 0.49 at 200 μg/mL. Similarly, the FRAP assay, which measures the reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) ions, showed clear antioxidant activity, with an absorbance of 0.85 at 200 μg/mL. Regarding radical scavenging, phycocyanin achieved its maximum effect at 200 μg/mL for both DPPH (78.75%) and H_2O_2 (95.27%). Finally, anti-lipid peroxidation was evaluated using an egg yolk model induced by $FeSO_4$. In this process, malondialdehyde (MDA) reacts with thiobarbituric acid (TBA) to form a pink-red chromogen; antioxidants inhibit this reaction by reducing MDA formation. Phycocyanin showed a maximum inhibition of 53.65% at 200 μg/mL. Notably, the IC_{50} values were 185 μg/mL for phycocyanin and 68.5 μg/mL for ascorbic acid, indicating that while phycocyanin possesses significant potential, its potency remains lower than that of the standard ascorbic acid in this specific model.

Chentir et al. [36] utilized a crude phycocyanin extract (PC-E) from *Arthrospira* sp. Stizenberger ex Gomont, evaluating its antioxidant potential through DPPH, FRAP, Fe^{2+} chelating, and β-carotene bleaching assays. The latter method measures a sample's ability to prevent the oxidative degradation of β-carotene; in this system, the oxidation of a lipid source (typically linoleic acid) generates free radicals that bleach the orange pigment of β-carotene. Antioxidants neutralize these radicals, thereby slowing color loss. Consequently, higher color retention reflects stronger antioxidant capacity. The crude phycocyanin was tested at concentrations ranging from 1 to 5 mg/mL, exhibiting a moderate, dose-dependent ability to inhibit β-carotene oxidation, reaching 63.28 ± 3.71% at the highest concentration. Regarding the FRAP assay, the reducing power was also dose-dependent, yielding an absorbance value of 1.46 (OD_{700}) at 5 mg/mL. This was notably lower than the butylated hydroxyanisole (BHA)

control, which reached an OD_{700} of 3 at the same concentration. Furthermore, at 5 mg/mL, the extract demonstrated a DPPH radical scavenging activity of 80% and a metal chelating power of 78%.

In a similar way, Gantar et al. [37] evaluated the antioxidant capacity of phycocyanin derived from *Limnothrix* sp. Meffert using the DPPH assay. Within a concentration range of 0.05–0.3 mg/mL, the pigment achieved a full radical scavenging effect (100%) at 0.15 mg/mL, with a reported half-maximal effective concentration (EC_{50}) value of approximately 0.08 mg/mL.

Expanding the evaluation of phycocyanin to biological systems, Pleonsil et al. [38] investigated the antioxidant potential of both native C-phycocyanin (c-PC) and a recombinant apo-beta-subunit (apo-c-PC(β)) from *S. platensis* using human erythrocytes as a model. Red blood cells are particularly susceptible to ROS due to the high concentration of polyunsaturated fatty acids in their membranes and the presence of iron, a known catalyst for oxidation. In this study, protective effects were assessed through a hemolysis assay induced by 2,2′-azobis(2-amidinopropane dihydrochloride (AAPH), a peroxyl radical generator. Both native and recombinant phycocyanin demonstrated a significant, dose-dependent inhibition of hemolysis in normal erythrocytes and those from homozygous hemoglobin E (EE) volunteers. Specifically, at a concentration of 1 μM, native c-PC inhibited hemolysis by 95% in normal cells and 98% in EE cells, outperforming the standard antioxidant trolox (83% and 86%, respectively). Although the recombinant apo-c-PC(β) also showed protective activity, its maximum inhibition was slightly lower, reaching 77% and 75% for the two cell types. Furthermore, scanning electron microscopy (SEM) was employed to observe morphological changes induced by H_2O_2. While exposure to H_2O_2 led to severe cellular distortion and the formation of echinocytes in approximately 80% of the EE erythrocyte population, the addition of 10 μM native c-PC and apo-c-PC(β) significantly preserved cell morphology, reducing the percentage of abnormal cells to 22% and 37%, respectively. These results indicate that phycocyanin not only scavenges radicals but also effectively protects cell membrane integrity and morphology against oxidative stress in a biological environment.

Finally, Sonani et al. [39] explored the antioxidant potential of phycocyanin from *Synechococcus* sp. Nägeli R42DM, bridging the gap between *in vitro* assays and *in vivo* biological effects using the eukaryotic model *Caenorhabditis elegans*. Preliminary *in vitro* tests confirmed the pigment's radical scavenging ability, with a 70% reduction of DPPH at a dose of 80 μg, and a significant reducing power demonstrated through FRAP assay. The study then focused on the protective role of phycocyanin within *C. elegans*, an organism that shares key aging-related signaling pathways with humans. When exposed to oxidative stress induced by 10 mM H_2O_2, worms pre-treated with 100 μg/mL of phycocyanin showed a survival rate of 80%, a significant increase compared to the 43% observed in the control group. This *in vivo* efficacy was further confirmed by measuring intracellular ROS levels; phycocyanin-treated worms showed a marked reduction in oxidative stress induced by paraquat, as visualized through 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) fluorescent staining. Most notably, the antioxidant properties of phycocyanin have a measurable impact on lifespan and healthspan. Treatment with 100 μg/mL of phycocyanin extended the mean lifespan of the worms by approximately 22% (from 14.15 to 18.27 days). Additionally, phycocyanin effectively preserved the pharyngeal pumping rate, a standard hallmark of aging in this model, which declined by only 10–15% in treated groups compared to a 50% decrease in the control. These findings suggest that the antioxidant activity of phycocyanin from *Synechococcus* sp. not only neutralizes free radicals but also actively promotes longevity and delays physiological decline in a living system.

In a study by Zhao et al. [40], the phycocyanin-derived peptides CPCAH-F3 and CPCPH-F3 (extracted from *Limnospira platensis*), were evaluated in an *in vivo* model of induced oxidative stress using *C. elegans* treated with H_2O_2. The results showed that both peptides improved worm survival, likely due to their antioxidant activity. In addition, CPCAH-F3, at a concentration of 5 mg/mL, significantly extended the lifespan of *C. elegans*, suggesting a potential anti-aging effect.

3.2. Antimicrobial Activity

Beyond its well-established antioxidant capacity, phycocyanin exhibits a versatile range of biological activities, with its antimicrobial potential standing out as a particularly promising field of study. As reported in recent research by Hajiyeva et al. [32] the molecule's efficacy was tested against a broad spectrum of microorganisms, specifically including bacterial strains such as *Bacillus cereus* ATCC 10876, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 51299, *Enterobacter aerogenes* NRRL B-3567, *Klebsiella pneumoniae* ATCC 700603, *Listeria monocytogenes* ATCC 19111, *Micrococcus luteus* NRRL B-4375, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 6538, *Salmonella typhimurium* ATCC 14028, and *Yersinia enterocolitica* Y53. Furthermore, the study extended its scope to yeast species, including *Candida albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida parapsilosis* ATCC 22019 and

Candida krusei ATCC 6258. In these experiments, phycocyanin from *Geitlerinema* sp. was utilized in a lyophilized dry form dissolved in acetone, focusing the evaluation on the disc diffusion method to measure the resulting zones of inhibition. The study highlights that the antimicrobial efficacy of phycocyanin is strictly dose-dependent, with significant inhibitory effects appearing at a minimum concentration of 250 μg/disc, while the most robust results were consistently observed at the 500 μg dose. Among the models tested, the Gram-positive bacterium *M. luteus* NRRL B-4375 proved to be highly sensitive, yielding an inhibition zone of 15 ± 0.71 mm, followed by *S. aureus* ATCC 6538 with a zone of 11 ± 0.0 mm. The molecule also maintained effectiveness against Gram-negative pathogens; for instance, *E. coli* ATCC 25922 and *S. typhimurium* ATCC 14028 demonstrated inhibition zones of 9 ± 2.12 mm and 12 ± 0.35 mm, respectively. Notably, the antifungal activity against yeast species was even more pronounced at the 500 μg concentration, where phycocyanin induced a substantial inhibition zone of 18 ± 3.54 mm against *C. krusei* ATCC 90028 and 12 ± 0.35 mm against *C. glabrata* ATCC 90030. Overall, these findings underscore that phycocyanin represents a viable natural alternative to traditional antibiotics, offering a broad-spectrum inhibitory action across diverse microbial classes.

The antibacterial efficacy of phycocyanin was further confirmed when incorporated into the PRG hydrogel system employed by Meng et al. [33]. Testing against *S. aureus* and *P. aeruginosa* revealed that the PRG-3 formulation (20 mg/mL of phycocyanin) yielded the most significant results, achieving impressive antibacterial rates of 95.96% and 87.47%, respectively. The mechanism behind this activity involves the disruption of bacterial membrane integrity. This was evidenced by an increase in electrical conductivity, indicating the leakage of intracellular ions such as K^+, Ca^{2+} and Na^+, and further confirmed by o-nitrophenyl-β-D-galactopyranoside (ONPG) permeability assays. By effectively destroying the inner membranes of both Gram-positive and Gram-negative bacteria, the PRG-3 hydrogel demonstrates robust *in vitro* killing power and high potential for future *in vivo* antimicrobial applications.

Finally, Chentir et al. [36] explored the antibacterial capacity of a crude extract of phycocyanin derived from *Arthrospira* sp. The extract was tested against a panel of Gram-negative strains (*E. coli*, *S. typhimurium*, and *Pseudomonas* sp.) and Gram-positive strains (*S. aureus* ATCC 25923, *M. luteus* ATCC 4698, and *L. monocytogenes*). Using the agar diffusion method, phycocyanin at a concentration of 10 mg/mL proved effective against nearly all tested pathogens. The most significant inhibitory effect was observed against *M. luteus*, which exhibited a substantial inhibition zone of 41 ± 0.6 mm, followed by *E. coli* (22.75 ± 0.7 mm) and *S. aureus* (15.75 ± 0.4 mm). In contrast, the extract showed lower activity against *L. monocytogenes* and *S. typhimurium*, with zones of approximately 8.75 ± 0.7 mm and 9.75 ± 0.4 mm, respectively. These findings further consolidate the role of phycocyanin as a potent natural antimicrobial agent, capable of exerting significant inhibitory pressure on a wide range of clinically relevant bacteria even in its crude extract form.

A recent study by Defaei et al. [41] also evaluated the antifungal activity of phycocyanin from *Arthrospira platensis* against *Aspergillus fumigatus* and *Fusarium oxysporum*, two saprophytic fungi widely distributed in the environment and recognized as opportunistic pathogens affecting both humans and plants. In particular, phycocyanin was incorporated into silver nanoparticles, and the treatment resulted in the highest inhibition of fungal colony growth at concentrations ranging from 150 to 300 ppm. This effect may be attributed to the activation of cellular oxidative stress, more specifically to the generation of ROS.

The therapeutic potential of phycocyanin also extends to its antiviral activity, specifically against the *Coronaviridae* family. Soliman et al. [34] employed human coronavirus 229E (HCoV-229E) as a model for COVID-19, demonstrating that purified phycocyanin extracted from *S. platensis* significantly inhibits viral replication in Vero-E6 cells. The purified compound exhibited a maximum non-cytotoxic concentration of 14.389 g/mL and an IC_{50} of 0.515 g/mL, resulting in a selective index (SI) of 27.9. Time-of-addition assays revealed that this phycocyanin is most effective as a pretreatment for host cells, reducing infectivity by 56% with an SI of up to 36.76. While it also showed moderate efficacy during the replication phase after infection, no significant virucidal effect was observed. These findings suggest that phycocyanin primarily acts by either blocking viral receptor sites on the host cell or interfering with early adsorption and reproduction processes, rather than through direct viral inactivation.

3.3. Anti-Inflammatory Activity

One of the most important pharmacological activities of phycocyanin is its anti-inflammatory potential, which has been extensively documented in several studies. Inflammation is essentially a complex and immediate defensive response of the innate immune system to tissue damage, pathogens, or irritants. This process involves the release of chemical mediators that increase blood flow and vascular permeability, allowing immune cells to reach the site of injury. While this “acute” phase is vital for healing and tissue repair, an uncontrolled or excessive inflammatory response can lead to further tissue destruction and chronic diseases.

In this context, Soliman et al. [34] investigated the anti-inflammatory properties of an extract of phycocyanin from *S. platensis*. Specifically, the study employed the human red blood cell (HRBC) membrane stabilization method. This technique is based on the principle that the RBC membrane is structurally similar to the lysosomal membrane. Since the rupture of lysosomes and the subsequent release of their enzymes are key events in triggering and sustaining the inflammatory cascade, a compound that stabilizes these membranes can effectively inhibit the inflammatory process.

For this assay, 100 μL of phycocyanin solution was tested. The results revealed a potent anti-inflammatory activity, with a membrane protection percentage of 98.76 ± 0.065%. This performance was compared to standard reference drugs, namely aspirin and diclofenac. The study concluded that phycocyanin exhibits high efficacy even at relatively low concentrations, demonstrating its potential as a natural therapeutic agent capable of preventing lysosomal lysis during inflammation.

Another significant area of research involves the potential of phycocyanin to promote dermal biostimulation and protect the skin from inflammatory damage. Nowruzi, B. & Zakerfirouzabad, M. [44] evaluated the effects of purified *Nostoc* sp. Vaucher ex Bornet & Flahault and *Spirulina* sp. Turpin ex Gomont extracts on lipopolysaccharide (LPS)-stimulated human skin fibroblasts (CCD-966SK) to investigate their anti-inflammatory potential. The primary objective of this research was to determine how the pigment influenced tissue regeneration and cellular resistance to exogenous stress. Phycocyanin demonstrated a remarkable capacity to modulate inflammatory mediators. The fibroblasts exhibited a "total resistance" to inflammation at specific concentrations, with no detectable release of IL-6 at 62.5 ppm and a complete suppression of TNF- α secretion at 31.25 ppm. Beyond immune protection, the pigment acted as a potent biostimulant for the extracellular matrix by enhancing the synthesis of Collagen Type I (peaking at 125 ppm) and Collagen Type II, which showed activity even at the very low dose of 3.91 ppm. Finally, the research analyzed the enzymatic antioxidant response, finding that the maximum activity of protective enzymes, such as SOD and GPx, occurred at 1000 ppm. Conversely, at these elevated concentrations, an increase in MDA levels was also noted. This suggests that while phycocyanin is a powerful ally against skin aging and inflammation, its dosage must be carefully calibrated to maximize regenerative benefits without inducing secondary oxidative stress.

The anti-inflammatory potential of phycocyanin has been further elucidated through advanced proteomic analysis, focusing on its ability to modulate complex intracellular signaling pathways. In a study by Hao et al. [42], phycocyanin purified from *S. platensis* was evaluated using LPS-induced murine macrophages (RAW 264.7) as an experimental model. The results demonstrated that phycocyanin exerts a potent inhibitory effect on the inflammatory response by significantly reducing the accumulation of nitrites and the expression of the inducible nitric oxide synthase (iNOS) enzyme in a dose-dependent manner at concentrations of 60, 120, and 240 μg/mL. At a dosage of 120 μg/mL, phycocyanin not only attenuated the secretion of major pro-inflammatory cytokines, such as TNF-α and IL-6, but also significantly decreased the mRNA expressions of interleukin-1β (IL-1β) and key chemokines, specifically C-C motif chemokine ligand 2 and 5 (CCL2 and CCL5). The underlying molecular mechanism was identified as the down-regulation of the programmed cell death protein 5 (PDCD5)—nuclear factor-kappa B (NF-κB) signaling pathway. By inhibiting the synthesis of the PDCD5, phycocyanin effectively suppresses NF-κB activity, thereby halting the inflammatory cascade. Furthermore, the study highlighted a significant pro-apoptotic effect specifically targeted at inflammatory cells, while maintaining a high safety profile; indeed, phycocyanin exhibited no cytotoxicity toward healthy wild-type macrophages even at the maximum tested concentration of 240 μg/mL. These findings confirm that phycocyanin acts as a highly selective therapeutic agent, capable of reprogramming the immune response through precise molecular targeting.

The anti-inflammatory potential of a phycocyanin extract from *Arthrospira maxima* was also evaluated in a model of acute colitis induced by acetic acid in Sprague-Dawley rats as noted by González et al. [43]. In this study, phycocyanin was administered orally at doses of 150, 200, and 300 mg/kg and its efficacy was compared to 5-aminosalicylic acid (5-ASA), a standard drug used in the treatment of inflammatory bowel disease. The results demonstrated that phycocyanin exerted a significant protective effect on the colonic mucosa, as evidenced by a substantial reduction in myeloperoxidase (MPO) activity. Specifically, the doses of 200 and 300 mg/kg achieved the highest inhibition of MPO (approximately 66%), indicating a marked decrease in neutrophil infiltration into the inflamed tissue. Histopathological and ultrastructural examinations showed that phycocyanin mitigated colonic damage, reducing edema, hemorrhage, and inflammatory cell infiltration. Notably, electron microscopy revealed a partial recovery of microvilli in epithelial cells and the near-total absence of inflammatory cells in the basal area of the mucosa. These findings, confirmed by the overall reduction in damage scores, clearly demonstrated that phycocyanin exerted a potent and dose-dependent anti-colitis effect.

The anti-inflammatory profile of phycocyanin is characterized by a complex interaction with the immune system, where it often acts as a sophisticated immunomodulator rather than a simple inhibitory agent. A relevant investigation

by Chen et al. [45], using the murine macrophage cell line J774A.1 provided a detailed molecular perspective on this activity. When treated with purified phycocyanin from *S. platensis* (doses of 100 to 400 μg/mL), macrophages showed an increased expression of key inflammatory mediators, including TNF-α, IL-1β, IL-6, and COX-2. Although these molecules are typically associated with inflammation, their controlled induction by phycocyanin suggests a 'boosting' of the immune surveillance system. This effect is mediated by the rapid phosphorylation of essential signaling pathways, specifically the mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38) as well as inhibitor of kappa B (IκB), which facilitate the activation of the NF-κB pathway. Interestingly, while phycocyanin promoted this moderate immunostimulatory response, it simultaneously exhibited potent antioxidant activity by significantly reducing the production of ROS induced by LPS. This dual behavior indicates that phycocyanin can prime macrophages to enhance their defensive capability, such as the destruction of tumor cells and pathogens, while protecting the cellular environment from oxidative stress. This unique combination of immunomodulation and antioxidant protection reinforces the role of phycocyanin as a bioactive compound capable of maintaining immune homeostasis without triggering uncontrolled inflammatory damage.

3.4. Anticancer Activity

One of the most compelling and extensively researched biological properties of phycocyanin is its potent anticancer activity. In the ongoing search for novel antineoplastic agents, a primary challenge is the identification of molecules that can effectively arrest the uncontrolled proliferation of malignant cells without compromising the integrity of healthy tissues. Unlike many conventional chemotherapeutic agents that lack specificity, an ideal candidate should demonstrate a high degree of selectivity, exerting cytotoxic effects exclusively on tumor cells.

In this context, Soliman et al. [34] investigated the therapeutic potential of a purified extract of phycocyanin derived from *S. platensis*. The researchers evaluated its efficacy against a panel of human cancer cell lines, including HepG-2 (liver carcinoma), HCT-116 (colorectal carcinoma), and MCF-7 (breast adenocarcinoma), using the BJ-1 normal human skin fibroblast line as a control for healthy tissue. By employing the Thiazolyl Blue Tetrazolium Bromide (MTT) assay, a colorimetric method that assesses cell viability through mitochondrial metabolic activity, it was observed that phycocyanin inhibits cancer cell growth in a clear dose-dependent manner. The results regarding liver and colon cancer were particularly striking. At doses as low as 6.25 μg/well, phycocyanin inhibited HepG-2 cells by 70%, a result that notably surpassed the performance of doxorubicin, a standard chemotherapy drug, which achieved only 55% inhibition at the same dose and about 65% using 50 μg/well. A similar trend was observed in HCT-116 cells, where the maximum dose of 50 μg/well resulted in a 74% reduction in cell viability and 63% using the smallest dose (6.25 μg/well). While the activity against breast cancer (MCF-7) was slightly lower than that of doxorubicin at high doses, it remained significant, reaching a 62% inhibition rate (at 50 μg/well) and 56% using the smallest dose. Perhaps the most promising aspect of this research is the high selectivity demonstrated by phycocyanin. While it was lethal to the various cancer cell lines, it showed almost no toxicity toward healthy human BJ-1 fibroblasts. This favorable pharmacological profile, characterized by lower IC_{50} values than doxorubicin in liver and colon models combined with an excellent safety margin, highlights phycocyanin as a candidate of great interest for targeted cancer therapies with reduced side effects.

Building on the evidence of phycocyanin's selectivity, Hajiyeva et al. [32] explored the effects of a lyophilized extract obtained from *Geitlerinema* sp. This research expanded the investigation to a broader range of human cancer cell lines, specifically testing the extract against human lung fibroblast cells (CCD-19Lu) and human adenocarcinoma alveolar basal epithelial cells (A549), as well as human non-cancerous pancreatic ductal hTERT immortalized cells (hTERT-HPNE) and human pancreatic carcinoma epithelial cells (PANC-1). By employing a wide range of concentrations, from 3.125 to 200 μg/mL**,** the study provided a detailed map of how phycocyanin interacts with different tissue types. A key finding of this research was the time-dependent nature of phycocyanin's efficacy, particularly in the pancreatic model. In PANC-1 cells, the inhibitory effect became progressively more pronounced as the incubation period increased, with IC_{50} values decreasing from 83.5 μg/mL at 24 h to 53 μg/mL at 72 h. From a mechanistic standpoint, the antitumor action was attributed to the disruption of the tumor cell cycle and the induction of multiple death pathways, including apoptosis, necrosis, and autophagy. Microscopic observations confirmed these effects, revealing significant morphological alterations such as cell shrinkage, vacuolization, and the formation of apoptotic bodies and blebs, which were absent in the control group. The study also offered a nuanced perspective on selectivity by comparing tumor lines with their healthy counterparts. While phycocyanin demonstrated a promising profile in the pancreatic model, showing lower toxicity toward the normal hTERT-HPNE epithelial cells, the results for lung tissue were more complex. In this case, phycocyanin was highly effective against A549 lung cancer cells (reaching an IC_{50} of 40 μg/mL at 72 h), but it also showed a significant

pro-apoptotic impact on the healthy CCD-19Lu fibroblasts. In conclusion, these findings reinforce the potential of phycocyanin as a potent anticancer agent while highlighting that its biological activity may be influenced by species specificity and tissue-type responses. The study underlines that the purity of the extract, the duration of exposure, and the specific cell type are crucial variables. This complexity suggests that while phycocyanin remains a promising candidate for targeting tumor cells at low concentrations, further research is essential to fully clarify the underlying mechanisms and ensure its safe application across different cancer types.

Addressing the importance of extract purity and mechanistic clarity, Li et al. [22] utilized phycocyanin purified from *S. platensis* to investigate its impact on Cluster of Differentiation 59 (CD59) gene expression in HeLa cells. To clarify the role of this protein, the researchers constructed a recombinant eukaryotic expression vector, pALTER-MAX-CD59, which was transfected into HeLa cells and normal Chinese Hamster Ovary (CHO) cells via liposome-mediated transfection. The results demonstrated that phycocyanin selectively promoted the expression of CD59 and the pro-apoptotic protein Fas (first apoptosis signal) in a dose-dependent manner. Interestingly, HeLa cells transfected with the CD59-insert plasmid showed a significantly higher sensitivity to phycocyanin compared to those transfected with the empty vector (pALTER-MAX), exhibiting a marked decline in multiplication activity. At a concentration of 160 μg/mL, phycocyanin effectively restored Fas expression to levels comparable to normal control cells, thereby activating the death domain and the conduction of pro-apoptotic signals. Notably, phycocyanin treatment had no significant impact on the proliferation or protein expression of normal CHO cells, suggesting that the CD59/Fas pathway serves as a specific mediated target for the anti-tumor activity of phycocyanin.

Beyond its direct cellular effects, phycocyanin has demonstrated a potent ability to modulate the tumor microenvironment by recruiting immune cells. A recent study by Salgado et al. [46], involving a murine melanoma model induced with B16F10 cells, showed that phycocyanin, administered subcutaneously at a dose of 560 mg/kg, effectively reduced tumor mass and dimensions. The anti-tumor action was closely linked to a significant immunomodulatory effect within the tumor-draining inguinal lymph nodes. Flow cytometry and cell count analyses revealed that phycocyanin treatment significantly increased the absolute numbers of B lymphocytes (B220+IgM+), T lymphocytes (both CD4+ and CD8+), and CD11b+ myeloid cells. While the percentage of myeloid cells remained stable, their total count in the inguinal lymph nodes rose significantly, contributing to the overall expansion of the immune cell pool. Interestingly, this immune recruitment was more pronounced in tumor-bearing mice than in healthy controls, suggesting that phycocyanin acts synergistically with tumor antigens to enhance the immune response. Specifically, the expansion of B cells is thought to promote humoral responses and antigen presentation, while the increase in T cells facilitates direct tumor cell killing. Furthermore, histopathological analysis of the brain, heart, and lungs confirmed that this high dose of phycocyanin did not induce systemic toxicity or organ damage, highlighting its safety profile and potential as a targeted immunotherapy for melanoma.

While the immunomodulatory role of phycocyanin highlights its systemic potential, its direct impact on cancer cell viability and replication is equally significant. Thangam et al. [47] explored the antiproliferative effects of highly purified phycocyanin obtained from *Oscillatoria tenuis* C. Agardh ex Gomont. The extract was tested against two different human cancer cell lines: HT-29 (colon adenocarcinoma) and A549 (lung carcinoma). The results demonstrated dose-dependent cytotoxicity, with IC_{50} values of 30 μg/mL for HT-29 and 55 μg/mL for A549 cells after 48 h of exposure. Beyond simple growth inhibition, flow cytometry analysis revealed that phycocyanin acts as a cell cycle modulator, inducing a significant arrest in the G_0/G_1 phase. This arrest prevents DNA replication and effectively halts tumor progression. Mechanistically, the antiproliferative action culminated in programmed cell death (apoptosis), as evidenced by characteristic morphological hallmarks including cell shrinkage, membrane blebbing, and nuclear condensation. Furthermore, the induction of apoptosis was confirmed by the presence of DNA fragmentation and increased lactate dehydrogenase (LDH) leakage, indicating membrane compromise in treated cells. These findings suggest that phycocyanin from *O. tenuis* not only restricts cancer cell multiplication but also triggers a cascade of biochemical events leading to the selective elimination of malignant cells.

Despite the significant results obtained with purified extracts, one of the primary challenges in the therapeutic use of phycocyanin remains its bioavailability and stability in the physiological environment. To address these limitations, a novel approach involves the use of nanotechnology to enhance targeted delivery. Al-Malki [48] investigated the cytotoxic potential of phycocyanin extracted from *Ulva lactuca* Linnaeus encapsulated within albumin nanoparticles (ULANP). These nanoparticles are spherical carriers where the phycocyanin extract is encapsulated within a serum albumin matrix, stabilized through a cross-linking process using glutaraldehyde. This structure protects the bioactive pigment from degradation and facilitates its targeted uptake by malignant cells. When tested against human liver cancer (HepG2) and breast cancer (MCF-7) cell lines, ULANP demonstrated a potent dose-dependent reduction in cell viability. The cytotoxic mechanism was characterized by a significant

elevation in the levels of both caspase-8 and caspase-9 at a concentration of 20 μg of ULANP. The simultaneous activation of these enzymes indicates that the nano-encapsulated phycocyanin triggers apoptosis through both the extrinsic (death receptor) and intrinsic (mitochondrial) pathways. With growth inhibition rates reaching 93.17% in HepG2 and 91.3% in MCF-7 cells, this study highlights that nanoparticle-mediated delivery significantly amplifies the phycocyanin's chemotherapeutic potential while maintaining high selectivity.

In conclusion, the evidence shows that phycocyanin is a very versatile molecule in the fight against cancer. Its strength lies in the fact that it does not act in just one way but attacks the tumor on multiple fronts: it can stop the growth of malignant cells, trigger the biological signals for cell death (apoptosis), and at the same time, help the immune system react more effectively. A very important aspect emerging from these studies is its selectivity: phycocyanin is effective against various types of cancer, such as breast, liver, or melanoma, but it does not harm healthy cells. Furthermore, the use of new technologies like nanoparticles is opening interesting ways to make this pigment even more effective and easier to deliver within the body. All of this suggests that phycocyanin is not just a powerful antioxidant but could become a valuable and safe support for future cancer therapies.

3.5. Anti-Allergic Activity

Regarding the anti-allergic potential, R-phycocyanin (R-PC) purified from the red algae *Porphyra haitanensis* T.J. Chang & B.F. Zheng has demonstrated significant inhibitory effects on type I hypersensitivity reactions. A dual experimental design was employed by Liu et al. [49], who tested phycocyanin in antigen-sensitized mice (*in vivo*) and the RBL-2H3 rat mast cell line (*in vitro*). In the *in vivo* murine model, mice were initially immunized with a combination of tropomyosin (TM) (0.1 mg/mouse) and R-PC (0.1 mg/mouse). During the subsequent oral challenge phase, therapeutic administration of R-PC (5 mg/mouse) via gavage (1 h before each challenge) significantly reduced fecal and serum histamine levels and mitigated allergic symptoms, such as lymphocytic infiltration in the jejunum. These effects were associated with a modulation of the immune response, where R-PC promoted a shift from a Th2 to a Th1 profile by decreasing the production of interleukin-4 (IL-4) and interleukin-13 (IL-13) while increasing interferon-gamma (IFN-γ) levels via the janus kinase 2 (JAK2) and JNK signaling pathways. Furthermore, *in vitro* assays on IgE-sensitized RBL-2H3 mast cells showed that pre-treatment with R-PC at concentrations of 80–150 μg/mL effectively inhibited cellular degranulation, significantly reducing the release of β-hexosaminidase and histamine. Additionally, R-PC was found to suppress the production of pro-inflammatory cytokines such as TNF-α and IL-4 in activated mast cells. Preliminary assays for proliferative activity confirmed the safety of the extract, as R-PC showed no cytotoxicity within a range of 20–200 μg/mL.

3.6. Anti-diabetic Activity

Bahrini et al. [50] examinated for the first time the anti-diabetic activity of a purified phycocyanin extracted from *S. platensis* on alloxan-induced diabetic rats. The investigation evaluated the impact on digestive enzymes, glycogen metabolism, and liver metabolic enzymes associated with hyperglycemia and hyperlipidemia. At a specific dosage of 200 mg/kg, phycocyanin showed several effects; its administration promoted the regeneration of pancreatic β-cells and increased circulating insulin levels, thereby improving glycemic control. It also exhibited potent anti-inflammatory and antioxidant activities, as highlighted by enhanced total antioxidant status (TAS) and nitric oxide (NO) levels, along with concomitant ROS species such as H_2O_2, total oxidant status (TOS), and thiobarbituric acid reactive substances (TBARS). These effects protect β-cells from oxidative damage and create a favorable environment for their long-term regeneration. At the hepatic level, phycocyanin modulated key enzymes involved in glucose metabolism, including hexokinase (HK), pyruvate kinase (PK), glucose-6-phosphate dehydrogenase (G6PD), glycogen phosphorylase (GP), glycogen synthase (GS), LDH, glucose-6-phosphate (G6P), and fructose-1,6-bisphosphatase (FBP), resulting in increased glycogen synthesis, enhanced glycolysis, and decreased hepatic glucose output. Furthermore, phycocyanin suppressed postprandial hyperglycemia by inhibiting intestinal α-amylase, maltase, and sucrase, while also reducing pancreatic, intestinal, and serum lipase activities, which contributed to improved lipid and carbohydrate homeostasis. Collectively, these multifaceted actions of phycocyanin including antioxidant, anti-inflammatory, and enzyme-modulating effects contributed to lowered blood glucose, reduced glycated hemoglobin (HbA1c) levels, and overall amelioration of metabolic disturbances associated with diabetes.

3.7. Antiglycation Activity

According to Aoki et al. [51], a purified extract of phycocyanin from *Pseudanabaena* sp. Lauterborn ABRG5-3 (abPC extract) also exhibits notable antiglycation activity. Non-enzymatic glycation, also known as the Maillard reaction, is a process in which reducing sugars modify proteins and amino acids, leading to the formation of

Amadori intermediates and advanced glycation end products (AGEs), whose accumulation is associated with diabetes, renal diseases, cancer, and other chronic conditions. In this context, phycocyanin was evaluated using a collagen-based antiglycation assay and was found to inhibit the formation of glycation-derived products, thereby preventing the progression of the glycation process and the development of chronic diseases.

3.8. Hepatoprotective Activity

Priyanka et al. [52] provides a comprehensive evaluation of the hepatoprotective and antioxidant potential of high-purity phycocyanin extracted from *Spirulina maxima* (Setchell & N.L. Gardner) Geitler. Using an adult zebrafish (*Danio rerio*) model, researchers induced acute oxidative stress and liver injury through exposure to H_2O_2. The protective efficacy of phycocyanin was tested at various dosages, with the most significant results observed at 100 μg and 200 μg. The treatment led to a marked restoration of both enzymatic and non-enzymatic markers, effectively maintaining the activities of CAT, SOD, glutathione S-transferase (GST) and GPx, alongside the levels of reduced glutathione (GSH), at values comparable to the control group. These biochemical improvements were corroborated by quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis, which confirmed that phycocyanin upregulates the gene expression of these key antioxidant enzymes. Furthermore, phycocyanin administration significantly reduced lipid peroxidation (LPO), as evidenced by decreased MDA levels, thereby protecting cellular membranes from oxidative damage. In terms of hepatoprotection, phycocyanin promoted the normalization of hepatic enzymes, significantly lowering levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are critical indicators of hepatocyte integrity. Histopathological examinations supported these findings, revealing improved liver tissue architecture with reduced necrosis and inflammation. Notably, the study emphasizes the biocompatibility of phycocyanin, as it effectively mitigated-induced damage without inducing inherent toxicity or adverse effects in the zebrafish model.

3.9. Nephroprotective Activity

Phycocyanin also exhibits specific protective roles in complex systemic pathologies, such as Chronic Kidney Disease (CKD). This condition often triggers cardiorenal syndrome, where renal failure leads to severe cardiovascular complications. The nephroprotective activity of phycocyanin was demonstrated by Memije-Lazaro et al. [53] in a 5/6 nephrectomy (5/6 NFx) rat model, which replicates this pathological progression. In particular, the administration of purified phycocyanin (100 mg/kg) demonstrated superior efficacy compared to whole *A. maxima* biomass (1 g/kg). Purified phycocyanin was particularly effective in restoring systemic and renal parameters. It significantly improved renal function by partially normalizing proteinuria, serum uric acid levels, and creatinine clearance, which are typically altered in CKD. Furthermore, it almost entirely prevented systemic hypertension, restricting the systolic blood pressure increase to just 8%, compared to the 80% observed in untreated groups, and blocked left ventricular hypertrophy. At the molecular level, phycocyanin's protection is twofold. Firstly, it preserves the reduced glutathione to oxidized glutathione (GSH/GSSG) redox balance, preventing protein S-glutathionylation and reducing ROS-driven damage in both cardiac and renal tissues. Secondly, the literature suggests that these effects may be linked to the modulation of the renin-angiotensin-aldosterone system (RAAS). As discussed by the authors, bioactive peptides and phycocyanin could promote a shift toward the angiotensin-converting enzyme 2 (ACE2)/angiotensin-(1-7) axis, inducing vasodilation and antiproliferative responses that effectively slow the progression of renal damage and protect the heart from pathological remodeling.

3.10. Neuroprotective Activity

The neuroprotective potential of phycocyanin was extensively investigated by Mitra et al. [54] in Wistar rats challenged with tributyltin chloride (TBTC), a potent environmental neurotoxicant. In this experimental framework, the efficacy of 50 mg/kg of purified phycocyanin was evaluated in comparison to N-acetylcysteine (NAC), a well-established neuroprotective drug used as a positive control. The study demonstrated that phycocyanin effectively reached the cortical tissue and exerted a multi-level protective action that, in many parameters, was comparable to that of NAC. A primary aspect of phycocyanin's action was the preservation of the blood-brain barrier (BBB) integrity; specifically, phycocyanin treatment restored the expression levels of the physical and biological barrier proteins claudin-5 and p-glycoprotein (PGP). This effect was further supported by the ability of the phycobiliprotein to mitigate the proteolytic activities of calpain and matrix metalloproteinases (MMPs), which were directly involved in TBTC-induced BBB permeability. Regarding redox homeostasis, phycocyanin served as a powerful antioxidant by significantly reducing ROS generation and alleviating lipid peroxidation in the cortex. While the restoration of the full glutathione metabolism (including glutathione reductase (GR), SOD, CAT, and GPx activities) and the promotion of autophagy, as indicated by the formation of

microtubule-associated protein 1 light chain 3 (LC3-II) were particularly evident during co-treatment with NAC, phycocyanin independently exerted a strong influence on cellular stress responses. This was highlighted by its ability to modulate the NF-kB p65 signaling pathway and induce a robust upregulation of metallothionein (MT), which provided an additional layer of neuroprotection. Furthermore, phycocyanin exhibited a unique capacity to modulate glial cell dynamics, showing an efficacy that sometimes surpassed or complemented that of NAC. It effectively managed astrogliosis by downregulating the expression of glial fibrillary acidic protein (GFAP) and reversing morphological alterations. Crucially, phycocyanin was able to restore microglial activation (measured through the expression of ionized calcium-binding adapter molecule 1 (Iba1) and CD11b), a process that was otherwise severely impaired by TBTC exposure. These glial-regulatory effects were closely linked to a reduction in nitrite accumulation and the restoration of caspase-12 activation, signaling a mitigation of endoplasmic reticulum stress. Finally, the neuroprotective profile of phycocyanin was completed by its potent anti-apoptotic action; the complex countered the upregulation of Bcl-2-associated X protein (Bax), inhibited caspase-3 activation, and significantly reduced the number of terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells. These actions collectively preserved the neuronal and oligodendroglial populations, as evidenced by the complete reversal of damage to myelin basic protein (MBP) expression and the attenuation of DNA damage marked by H2A histone family member X (H2A.X) phosphorylation.

4. Conclusions

In conclusion, phycocyanin stands out as one of the most promising natural pigments in the current biotechnological landscape. Its unique chemical structure, characterized by the presence of phycocyanobilin chromophores, not only gives it a vibrant blue hue, rare in the natural world, but also underpins its remarkable biological activities.

As detailed in this review, phycocyanin has demonstrated potent antioxidant, anti-inflammatory, and immunomodulatory properties, making it a versatile candidate for applications ranging from food additives to advanced biomedical therapies.

5. Future Perspectives

Despite the promising results, bridging the gap to industrial application requires overcoming several critical hurdles. The primary challenge remains its structural stability. Because phycocyanin is highly sensitive to changes in pH, temperature, and light, its integrity can easily be compromised during processing or storage. Future research should focus on the development of innovative stabilization strategies, such as nano-encapsulation or the use of protective natural additives, to ensure that the protein maintains its functionality within diverse commercial formulations.

From an analytical and production standpoint, the transition from laboratory-scale extraction to large-scale industrial output requires further optimization. While traditional methods like ammonium sulfate precipitation (ASP) and dialysis are effective for purification, they are often time-consuming and difficult to scale. Emerging technologies, such as Fast Centrifugal Partition Chromatography (FCPC) and high-pressure homogenization, offer promising paths toward more efficient and sustainable “green” extraction protocols that minimize solvent waste and maximize purity.

Looking ahead, the next frontier for phycocyanin research lies in a deeper understanding of its bioavailability and molecular mechanisms of action. While its effects *in vitro* are well-documented, more comprehensive clinical trials and *in vivo* studies are needed to confirm its therapeutic efficacy in humans. By bridging the gap between chemical characterization and clinical application, phycocyanin could transition from a niche natural dye to a cornerstone of sustainable biotechnology and preventive medicine.

Author Contributions

Conceived and designed the study: V.G.B., A.A. and V.L. Literature search: V.G.B. and A.A. Methodology: A.A. and B.d.F. Software: V.G.B.; Validation: V.L.; Data curation: V.G.B. and A.A. Writing—original draft: V.G.B., A.A. and V.L. Writing—review and editing: L.G. and V.L. All authors have read and agreed to the published version of the manuscript.

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