

PHYCOCYANIN FROM *Spirulina* sp. AND *Galdieria* sp.: A SYSTEMATIC REVIEW OF BIBLIOMETRIC TRENDS, BIOACTIVITIES, AND STRUCTURAL BIOLOGY

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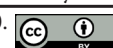
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Abstract

Phycocyanin is a blue pigment-protein complex widely produced by cyanobacteria and red algae, including *Spirulina* and *Galdieria* sp. The complex has attracted considerable attention due to its potential as a natural colorant and bioactive compound with antioxidant, anti-inflammatory, and anti-cancer properties. This review presents a comprehensive analysis of research trends, structural characteristics, and biofunctional applications of phycocyanin based on a bibliometric study using Scopus data (1973–2025) and VOS viewer. We highlight the differences in the molecular composition and thermal stability between phycocyanin derived from *Spirulina* and *Galdieria*, with *Galdieria* demonstrating higher heat tolerance and industrial relevance. Various extraction and purification techniques, including ultrasonication, enzymatic hydrolysis, and chromatography, were compared to assess yield and purity. Despite extensive studies on *Spirulina*, significant knowledge gaps remain regarding the structural biology, production scalability, and application feasibility of phycocyanin from extremophilic algae. This review identifies underexplored study areas and suggests that future studies should focus on improving extraction efficiency, assessing industrial-scale production stability, and expanding its applications in the food, cosmetic, and pharmaceutical sectors. Advancing interdisciplinary research is crucial for unlocking the full potential of phycocyanin as a sustainable and functional biopigment.

Keywords: biopigment, cyanobacteria, extremophile, medical properties, stability



Fikosianin dari *Spirulina* sp. dan *Galdieria* sp.: Kajian Sistematis Tren Bibliometrik, Bioaktivitas, dan Struktur Biologis

Abstrak

Fikosianin adalah kompleks pigmen-protein biru yang diproduksi secara luas oleh sianobakteria dan alga merah, terutama *Spirulina* dan *Galdieria* sp. Senyawa ini telah menarik perhatian yang signifikan karena potensinya sebagai pewarna alami dan senyawa bioaktif dengan sifat antioksidan, antiinflamasi, dan antikanker. Ulasan ini menyajikan analisis komprehensif tentang tren penelitian, karakteristik struktural, dan aplikasi biofungsional fikosianin berdasarkan studi bibliometrik menggunakan data Scopus (1973–2025) dan VOS viewer. Kami menyoroti perbedaan komposisi molekuler dan stabilitas termal antara fikosianin yang berasal dari *Spirulina* dan *Galdieria*, dengan yang terakhir menunjukkan toleransi panas yang lebih tinggi dan relevansi industri yang lebih besar. Berbagai teknik ekstraksi dan pemurnian dibandingkan, seperti ultrasonikasi, hidrolisis enzim, dan kromatografi, untuk menilai hasil dan kemurnian. Meskipun *Spirulina* telah diteliti secara luas, masih terdapat celah pengetahuan yang signifikan mengenai biologi struktur, skalabilitas produksi, dan kelayakan aplikasi fikosianin dari alga ekstremofilik *Galdieria*. Ulasan ini mengidentifikasi bidang penelitian yang belum banyak dieksplorasi dan menyarankan agar studi di masa depan fokus pada peningkatan efisiensi ekstraksi, penilaian stabilitas produksi skala industri, dan perluasan aplikasinya di sektor makanan, kosmetik, dan farmasi. Pengembangan penelitian interdisipliner sangat penting untuk mengoptimalkan potensi penuh fikosianin sebagai biopigmen yang berkelanjutan dan fungsional.

Kata kunci: biopigmen, ekstremofil, sianobakteri, sifat medis, stabilitas

INTRODUCTION

Microalgae, including eukaryotic algae and photosynthetic cyanobacteria, are widely recognized for their ability to produce high-value biomass. Several studies have shown that biomass can serve as a source of food, fuel, pharmaceuticals, and pigments. One of the most promising applications is in the food industry, particularly as a source of natural colorants (Naik *et al.*, 2024). Microalgal pigments, such as chlorophylls and phycobiliproteins, are functional compounds involved in photosynthesis, oxygen transport, and antioxidant defense. Compared with synthetic dyes, natural pigments offer safer, more sustainable, and health-promoting alternatives (Low *et al.*, 2021).

Phycocyanin is one of the most commercially valuable pigments derived from microalgae. It is a blue water-soluble biliprotein containing a linear tetrapyrrole chromophore (bilin) covalently attached to an apoprotein (Hachicha *et al.*, 2022). As a member of the phycobiliprotein family, it absorbs light between 610 and 620 nm and facilitates energy transfer during photosynthesis (Ashaolu *et al.*,

2021). It is commonly found in cyanobacteria and some red algae and can make up to 20% of the total protein content (Patel *et al.*, 2018). *Spirulina* sp. is a widely used blue-green algae that is used as a phycocyanin source. It contains 60–70% protein, along with carbohydrates and lipids, and is known for its functional food applications (Kameshwari *et al.*, 2020). Phycocyanin extracted from *Spirulina* is not only used as a food colorant, but also offers health benefits, including antioxidant, anti-inflammatory, and anticancer activities (Chentir *et al.*, 2018; Fernández-Rojas *et al.*, 2014). Another potential source is *Galdieria sulphuraria*, a unicellular red alga known for its ability to survive in extreme environments, including high temperatures (up to 56°C), low pH (down to 0.2), and high salinity (Abiusi *et al.*, 2021; Schmidt *et al.*, 2005). This extremophilic alga also produces phycocyanin, which has applications in the food, cosmetic, and pharmaceutical industries (Sørensen *et al.*, 2013).

Despite its benefits, the broader industrial use of phycocyanin is limited due to its sensitivity to environmental factors, such as

heat, pH, and oxidation (Chentir *et al.*, 2018). Improving the stability, yield, and application potential of the compound remains a key research focus. To understand global trends and research gaps, bibliometric analysis offers valuable insights. While previous bibliometric studies have broadly addressed microalgae (Rumin *et al.*, 2020; Sahabudin *et al.*, 2024; Tan *et al.*, 2021; Yang *et al.*, 2023), no study has specifically focused on phycocyanin from *Spirulina* and *Galdieria*. Therefore, this review aims to provide a comprehensive bibliometric analysis of the study landscape, benefits, and applications of phycocyanin from *Spirulina* and *Galdieria*. While both serve as primary sources of phycocyanin, the microalgae produce distinct types categorized by their biological origins and physical properties. *Spirulina* sp. primarily produces phycocyanin, which is heat-sensitive (45–50 °C), while the thermo-acidophilic *Galdieria* sp. produces a thermophilic variant capable of maintaining stability at temperatures exceeding 60 °C. These fundamental differences, rooted in their structural biology, dictate their respective industrial applications and extraction requirements.

MATERIALS AND METHODS

Data Collection

This study adopted a bibliometric approach, as adapted from Purba *et al.* (2024) and Kombe (2023). Bibliometric data were retrieved from the Scopus database on July 4, 2025. The search focused specifically

on literature related to phycocyanin from *Spirulina* sp. and *Galdieria* sp. The following query string was used in the Scopus Advanced Search field (Figure 1):

TITLE-ABS-KEY (microalga OR alga) AND TITLE-ABS-KEY (phycocyanin) AND (Spirulina OR Arthrospira OR Galdieria).

This search yielded 923 documents comprising 730 research articles, 125 review papers, 39 book chapters, and 29 conference proceedings. The metadata was downloaded and subjected to further analysis using the built-in Scopus analytics tools.

Refinement of the Search Results

The retrieved publications were manually screened to ensure the accuracy and relevance of the bibliometric analysis. Irrelevant records, particularly those unrelated to phycocyanin extracted from microalgae, were excluded following the refinement approach suggested by Tan *et al.* (2021). Only documents directly addressing *Spirulina* sp., *Galdieria* sp., and their associated phycocyanin studies were retained for the final analysis.

Bibliometric Analysis and Clustering

The refined dataset was analyzed using VOSviewer software version 1.6.20 to visualize bibliometric networks and keyword co-occurrence maps. Clustering was performed based on publication year, document type, interrelated study topics, and keyword co-occurrence patterns. The analysis

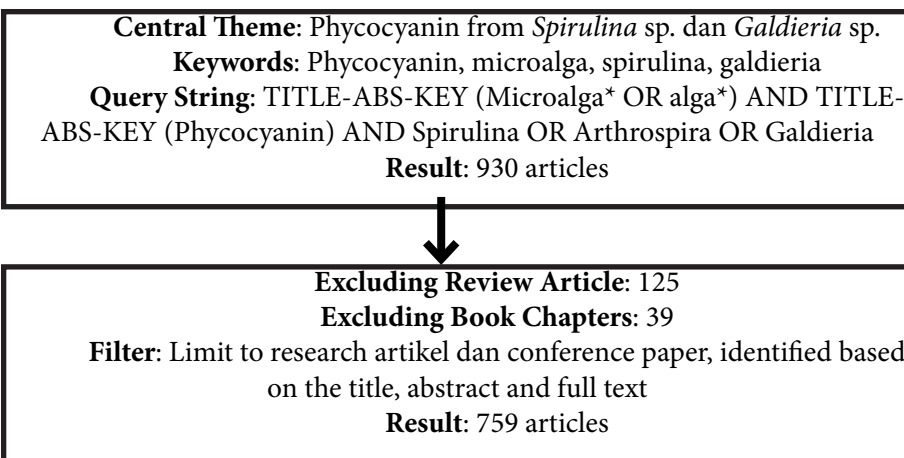


Figure 1 Flowchart of literature screening and selection process



covered publications from 1973 to 2025, showing temporal trends, core themes, and study networks related to phycocyanin from *Spirulina* and *Galdieria*.

Systematic Literature Review

A systematic literature review was conducted to examine the structural characteristics and stability of phycocyanins derived from *Spirulina* sp. and *Galdieria* sp. This review addresses the 3D structure of phycobiliproteins, extraction and purification techniques, and the influence of environmental factors (e.g., temperature and pH) on phycocyanin stability. Literature searches were conducted in Scopus, PubMed, ScienceDirect, and Google Scholar using keywords such as *phycocyanin structure*, *protein thermal stability*, and *extremophile algae*. The inclusion criteria were peer-reviewed journal articles and reviews, publication years between 2015 and 2025, and clear relevance to the study focus.

Relevant studies were critically assessed for methodological rigor and thematic alignment. Extracted data were grouped by the source organism, structural

analysis techniques, and reported stability under stress conditions. Key results, study gaps, and inconsistencies across studies were synthesized to inform the direction of the current investigation. All references were compiled and cited in accordance with academic standards.

RESULTS AND DISCUSSION

Annual Publication Trend

According to the data retrieved from the Scopus database (Figure 2), the earliest publication related to phycocyanin from microalgae was published in 1973. The annual number of publications remained below ten until 1996. Although some fluctuations occurred between 1996 and 2011, a steady increase in publication output was observed from 2012 onward and continued until 2024. By mid-2025, 759 publications related to phycocyanin from *Spirulina* sp. or *Galdieria* sp. were indexed.

The disparity in the depth of discussion between the two microalgae in this review stemmed directly from their respective historical study timelines. Research on phycocyanin has historically been dominated

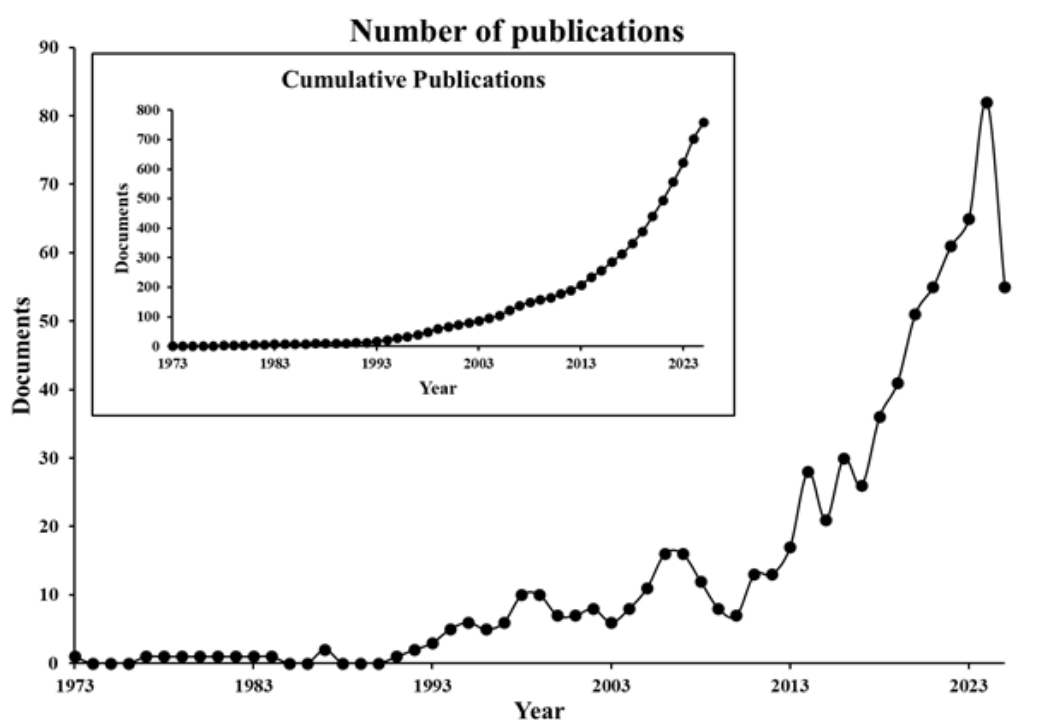


Figure 2 Annual and cumulative publication trends on phycocyanin from *Spirulina* sp. and *Galdieria* sp. (1973–2025). Inset graph shows the cumulative number of publications over time.

by *Spirulina*. The earliest study in 1973, titled Increase aggregation of C-phycocyanin produced by phenol and benzene, investigated the effect of aromatic compounds, such as benzene and phenol, on the aggregation of C-phycocyanin derived from *Spirulina platensis*. It was found that aggregation was also influenced by pH levels (MacColl & Berns, 1973). For decades, *Spirulina* remained the primary focus, experiencing a substantial surge in publications starting around 2012 as global demand for natural food colorants and nutraceuticals intensified. In contrast, the exploration of *Galdieria* sp. as a commercial source of phycocyanin is a relatively recent development.

While its extremophilic biology has been known, significant targeted research into its highly stable phycocyanin only began to gain tangible traction in the mid-to-late 2000s and early 2010s. More recent studies from 2025 further highlight the importance of biomass quality and extraction conditions in optimizing phycocyanin yield (Chaiklahan *et al.*, 2025). Efficient and cost-effective purification methods, such as foam fractionation and ion-exchange chromatography, have also been explored. For instance, Antecka *et al.* (2025) reported that purified phycocyanin is relatively stable, showing resistance to degradation across a temperature range of 4–50 °C and pH values ranging from 3 to 10. Even after incubation

at 60 °C for 5 h, only a 13% reduction in the concentration was observed.

Subject Area Analysis

From 730 Scopus-indexed documents published between 1973 and 2025, research on phycocyanin from microalgae was distributed across 25 subject areas. The three most productive categories were agricultural and biological sciences, biochemistry, genetics and molecular biology and environmental science (Figure 3). Other significant fields include chemical engineering, chemistry, medicine, immunology, microbiology, engineering, energy, and pharmacology.

Less dominant but still relevant subject areas were earth and planetary sciences, physics and astronomy, materials science, multidisciplinary sciences, nursing, computer science, mathematics, social sciences, veterinary science, business and management, health professions, neuroscience, economics and finance, decision sciences, and dentistry. These broad disciplinary spread highlights the interdisciplinary nature of the phycocyanin research.

Keywords Analysis

A co-occurrence analysis of author keywords was conducted to identify key research themes in the phycocyanin field. A total of 1,938 author keywords were extracted from the Scopus database and analyzed using

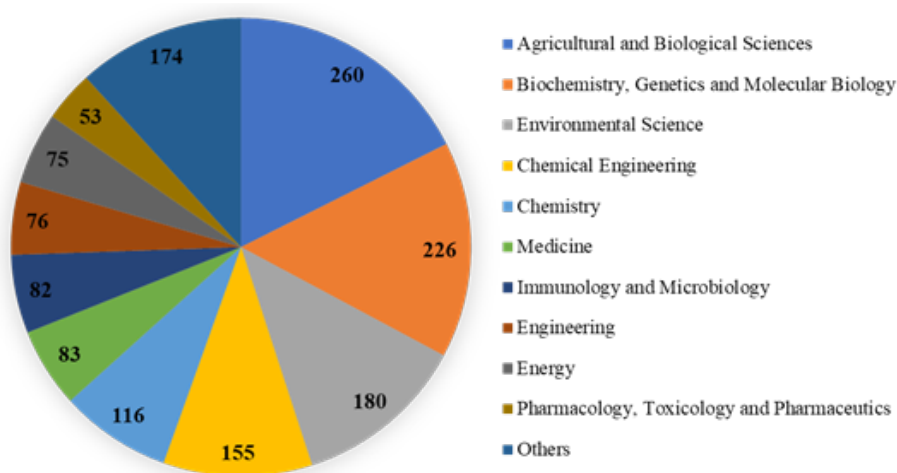


Figure 3 Distribution of publications on phycocyanin from *Spirulina* sp. and *Galdieria* sp. categorized by subject area.



VOSviewer. Keywords that appeared at least five times were included in the visualization. In the VOSviewer map, each keyword is represented by a node, with larger node sizes indicating more frequent appearances. Keywords were clustered by color to represent thematic groupings (Figure 4).

Due to overlapping terminology (such as microalgae vs. algae), similar keywords were merged to avoid redundancy. The analysis also revealed that research novelty could be identified by linking distant or weakly associated keywords, an approach that guided future interdisciplinary investigations (Purba *et al.*, 2022). Keywords located far apart on the network map signified limited co-occurrence, suggesting potential areas for new or underexplored studies. The most frequently occurring keywords were *phycocyanin* (227), *cyanobacteria* (88), *microalgae* (80), and *Spirulina platensis* (79), which were located centrally in the network and showed their prominence in the literature. In addition to *Spirulina platensis*, other phycocyanin-producing species included *Arthrospira maxima* (6) and *Galdieria sulphuraria* (19), which were red algae. Related pigments, such

as *phycoerythrin* (23) and *allophycocyanin* (17), were also notable.

Some studies used the name *Arthrospira platensis*, a synonym for *Spirulina platensis*, such as research on CO₂ decarbonization by Jung *et al.* (2024) and studies on light intensity and inoculum density effects on pigment content by Dianursanti *et al.* (2025). The term *cyanobacteria* appeared 88 times, while *blue-green algae* appeared 13 times, reflecting the diverse terminology. Phycocyanin extraction generally began with microalgae cultivation under optimal light, temperature, and nutrient conditions (Dianursanti *et al.*, 2025). Subsequently, the biomass was harvested and extracted using phosphate buffer (pH 6–7) or Tris-HCl buffer (pH 5–8) (Lin *et al.*, 2022). Extraction methods included freeze-thawing (Taqi *et al.*, 2025) and ultrasonication (Scherhag & Katzberg, 2024). The purification methods varied: activated charcoal at 8% w/v with a 4-minute mixing time at 200 rpm yielded a purity index of 1.77 (Lin *et al.*, 2025a), while fractional ammonium sulfate precipitation followed by dialysis and Sephadex G-50 column chromatography achieved a purity of 3.01 (Taqi *et al.*, 2025).

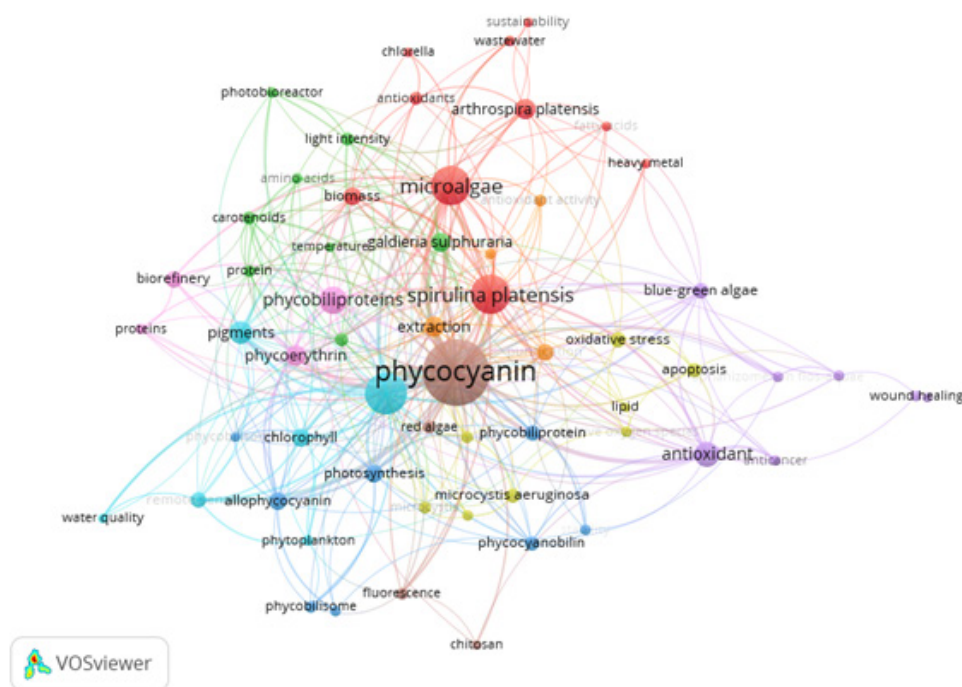


Figure 4 Co-occurrence network map of author keywords generated using VOSviewer. Node sizes represent keyword frequencies, line connections indicate co-occurrence links, and colors correspond to distinct thematic clusters.

The biomedical potential of phycocyanin was also evident in the network map, using keywords such as *antioxidant* (32), *anticancer* (6), *anti-inflammatory*, and *wound healing* (6). Phycocyanin demonstrated 89% DPPH radical scavenging activity and 11% superoxide neutralization capacity (Lin *et al.*, 2022). Purified phycocyanin inhibited 69.64% of MCF-7 breast cancer cells and 71.11% of HRT-18 colon cancer cells by 1,000 µg/mL after 72 h (Taqi *et al.*, 2025). Furthermore, bioactive peptide gels derived from *Spirulina platensis* accelerated periodontal wound healing and reduced inflammation (Jalali *et al.*, 2025).

Molecular and Structural Characteristics of Phycocyanin

Phycobiliproteins are classified into three main types: phycoerythrin (red), phycocyanin (blue), and allophycocyanin (blue). Among these, phycocyanin is the pigment most abundantly synthesized by microalgae, particularly *Spirulina* sp. (Batista de Oliveira *et al.*, 2021; Puzorjov & McCormick, 2020; Susilaningsih *et al.*, 2025). Due to the limited availability of natural blue pigments, phycocyanin has gained attention as an alternative natural colorant in the food industry (Tavanandi & Raghavarao, 2020).

Structurally, phycocyanin is a high-value biliprotein composed of an α (α) polypeptide chain with a molecular weight of approximately 10–19 kDa and a β (β) polypeptide chain ranging from 14 to 21 kDa, forming a functional monomer. The α subunit binds covalently to a single phycocyanobilin chromophore, whereas the β subunit typically binds two phycocyanobilin groups through thioether bonds, which are responsible for the distinct blue coloration of phycocyanin (Yuan *et al.*, 2022). In aqueous solutions, phycocyanin assembled into ($\alpha\beta$) units that further formed multimeric complexes ($\alpha\beta$)_{*n*}, with *n* ranging from 1 to 6, giving rise to molecular weights between approximately 44 and 260 kDa (Ma *et al.*, 2020; S. Zhang *et al.*, 2021). The predominant forms were ($\alpha\beta$)₃ trimers and ($\alpha\beta$)₆ hexamers. The chemical structures of the monomer and hexamer forms of phycocyanin are shown in Figure 5.

Although the primary structure of phycocyanin is relatively conserved, its molecular and thermal properties vary significantly across microalgal species. For instance, *Spirulina*-derived phycocyanin, despite its industrial appeal as a natural blue dye, exhibited notable thermal instability. Its pigment integrity and protein structure degraded significantly at temperatures between 50 and 60 °C. The critical thermal stability point was approximately 47 °C, and irreversible denaturation was observed at 65 °C. Its color stability and solubility were optimized in the pH range of 5.0–8.0 (Chaiklahan *et al.*, 2012; Park *et al.*, 2018). This sensitivity to heat limits its applicability in food processing and other high-temperature applications.

Phycocyanin from *Galdieria sulphuraria*, a thermo-acidophilic unicellular red alga that thrives in extreme environments, demonstrated much greater thermal resilience. Several studies have demonstrated the robustness of this pigment. For instance, Rahman *et al.* (2020) reported the successful extraction of thermally stable phycocyanin from *Galdieria* sp., which was suitable for use as a natural blue dye. Phycocyanin retained 65% of its color intensity after 150 min of heat exposure at 62 °C and showed consistent stability above 60 °C. Optimal extraction conditions were achieved at pH 7, with high pigment purity ($A_{620}/A_{280} > 4$) at pH 5, and a peak absorbance at 620 nm. The pigment recovery efficiency exceeded 80%, yielding 19 mg of pure phycocyanin from 3 g of wet biomass (Moon *et al.*, 2014).

This stark contrast in the thermal stability between *Spirulina* sp. and *Galdieria* sp. phycocyanin showed structural diversity among phycobiliproteins. These differences could arise from species-specific amino acid sequences that influence hydrophobic interactions, hydrogen bonding, and salt bridges. Analytical techniques, such as fluorescence and molecular dynamics simulations, have been widely used in several studies to investigate these stability mechanisms, specifically by monitoring changes in the secondary structure and integrity of ionic bonds (Zhang *et al.*, 2025). In

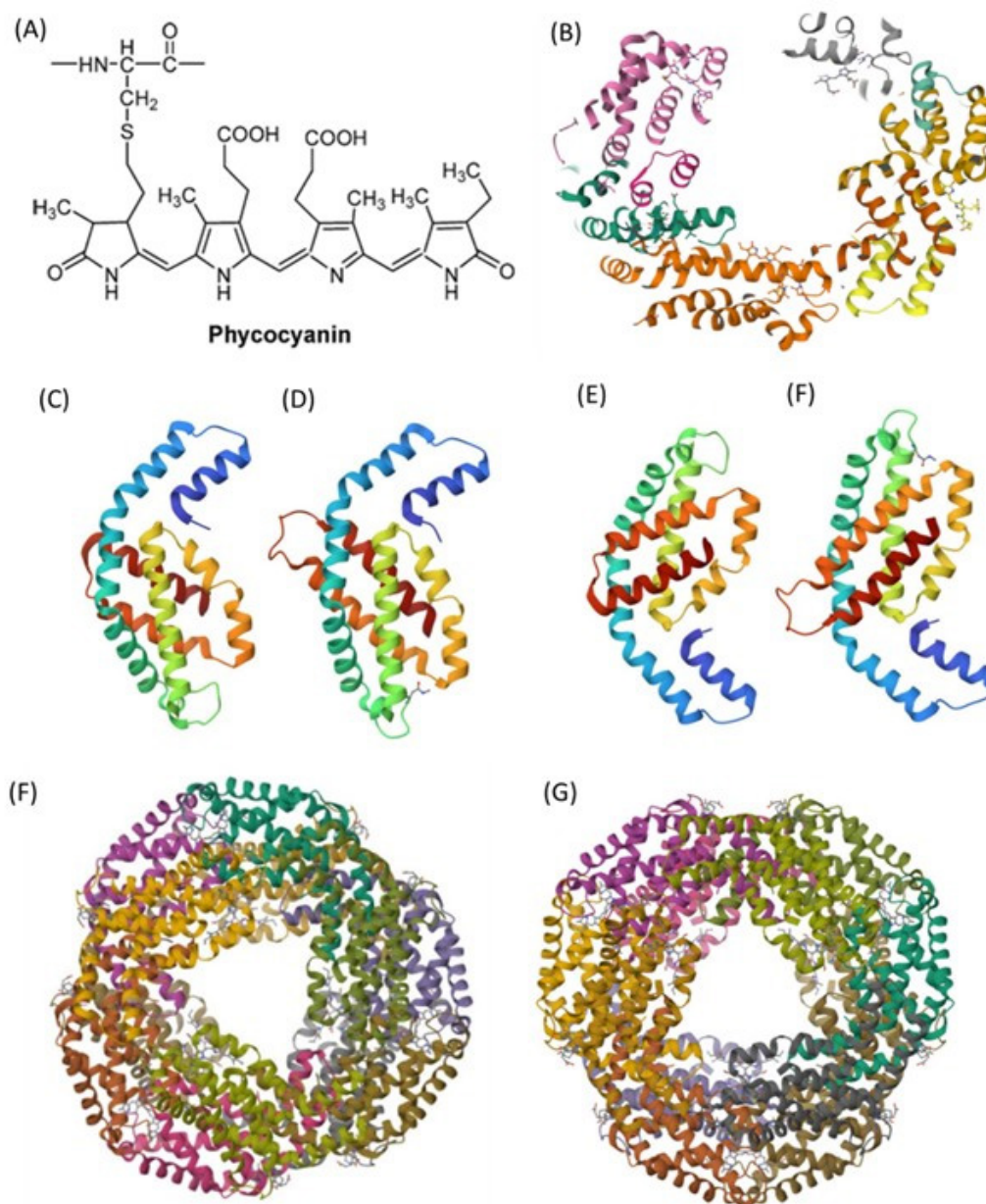


Figure 5 Chemical and three-dimensional structural representations of phycocyanin from *Spirulina platensis* and *Galdieria sulphuraria*. (A) Chemical structure of phycocyanobilin chromophore linked to a cysteine residue. (B) Representative hexameric structure (αβ)₆ displaying the arrangement of α-subunits (green, orange, pink) and β-subunits (grey, yellow, brown). (C, D) 3D ribbon structures of the α-subunit and β-subunit from *S. platensis*, respectively. (E, F) 3D ribbon structures of the α-subunit and β-subunit from *G. sulphuraria*, respectively. (F/G) 3D hexameric assembly of phycocyanin from *S. platensis* (PDB ID: 1HA7). (G/H) 3D hexameric assembly of phycocyanin from *G. sulphuraria* (PDB ID: 3KVS). (Structures retrieved from the RCSB Protein Data Bank [<https://www.rcsb.org/>]).

addition, the arrangement of their quaternary structures, such as tighter packing or stronger inter-subunit bonding, along with more stable chromophore–protein interactions, contributed to the thermal robustness of the protein.

The Chemical and Biochemical Compounds of *Spirulina* sp. and *Galdieria* sp.

Spirulina is a prokaryotic microorganism from the genus of multicellular cyanobacteria, commonly referred to as blue-green algae. It is widely used in the food industry, with *Spirulina maxima* and *Spirulina platensis* being the most studied species (Trotta *et al.*, 2022). These species typically inhabit alkaline salt lakes in subtropical and tropical regions, including Central and South America, Africa, and Asia (AlFadhly *et al.*, 2022). *Spirulina* is one of the most thoroughly studied microalgae because of its high protein content, which offers substantial industrial potential. Cultivating *Spirulina* has several advantages, including low production costs, ease of harvesting, and the ability to thrive in extreme environments, such as high pH and heterotrophic conditions, which reduce the risk of contamination from other microorganisms (Sorrenti *et al.*, 2021).

Spirulina contained a range of bioactive pigments that fall into three main categories, namely chlorophylls, carotenoids and xanthophylls, and phycobiliproteins. Chlorophylls are essential for photosynthesis and are responsible for the green coloration of *Spirulina* (Martins *et al.*, 2021). However, they are currently less favored in food applications because of their visual properties. Carotenoids, which appear yellow to orange and are fat-soluble, protect cells from photooxidative damage. Notable carotenoids in *Spirulina* include β -carotene, canthaxanthin, astaxanthin, lutein, and zeaxanthin, which are widely used as food additives, colorants, and flavoring agents (Park *et al.*, 2018).

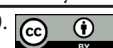
Among *Spirulina* pigments, phycocyanin has received growing interest in recent years as a natural blue dye. Synthetic dyes are linked to adverse health effects, such as behavioral issues in children,

including hyperactivity (Arnold *et al.*, 2012). Currently, natural dyes available in the market are often derived from higher plants, such as pandan, suji, and turmeric; however, their competitiveness is limited compared to synthetic dyes (Sedjati *et al.*, 2016). Phycocyanin is a safer and more sustainable alternative. Beyond its coloring potential, *spirulina* provides diverse pharmacological benefits, including antioxidant (Feng *et al.*, 2022), anti-inflammatory, anticancer (Fernandes *et al.*, 2023), hepatoprotective (İlter *et al.*, 2018), probiotic (Cai *et al.*, 2022), neuroprotective (Cervantes-Llanos *et al.*, 2018), hypoglycemic, and hypolipidemic properties (AlFadhly *et al.*, 2022).

Galdieria sulphuraria is a thermoacidophilic unicellular red alga that can thrive under extreme conditions (Maamoun *et al.*, 2020). It tolerates very low pH (down to 0.2) (Abiusi *et al.*, 2021), high temperatures (up to 56°C) (Barcytė *et al.*, 2018), and high osmotic pressure (up to 400 g/L of sugar or 2–3 M salt) (Schmidt *et al.*, 2005). *G. sulphuraria* produces a variety of bioactive compounds with significant biotechnological potential. One of the most notable groups is phycobiliproteins, which exhibit antioxidant, antibacterial, and anticancer properties (Dagnino-Leone *et al.*, 2022). Phycocyanin derived from *G. sulphuraria* has been applied in industries such as cosmetics, diagnostics, food, and pharmaceuticals (Carbone *et al.*, 2020; Marín Prida *et al.*, 2022; Sørensen *et al.*, 2013).

Bioactivity and Functional Potential

The increasing consumer demand for natural and functional products has accelerated innovation across the food, pharmaceutical, and cosmetic industries (Dewi *et al.*, 2018; Kraseasintra *et al.*, 2022; Lafarga *et al.*, 2020). Among natural biopigments, phycocyanin has emerged as one of the most promising alternatives to synthetic blue dyes. It was approved for use in food products in several countries owing to its broad range of health-promoting bioactivities. These include potent antioxidant, anti-



inflammatory, and neuroprotective effects, and position phycocyanin as a valuable nutraceutical ingredient.

Numerous *in vitro* and *in vivo* studies have investigated the biological functions of phycocyanin, revealing its diverse pharmacological applications. In particular, phycocyanins derived from *Spirulina* sp. and *Galdieria* sp. have demonstrated multifunctional potential across various sectors. Currently, phycocyanin derived specifically from *Spirulina* has been widely approved for use in food products in several countries. However, while *Galdieria*-derived phycocyanin demonstrates superior stability, it is still in the developmental stage regarding widespread regulatory food approval. Phycocyanins from both sources possess a broad range of health-promoting bioactivities. A summary of the key bioactivities reported in the literature is presented in Tables 1 and 2.

Extraction, Purification, and Characterization Techniques

Efficient phycocyanin extraction depends on multiple critical parameters, including temperature, pH, solvent type, biomass form (wet or dry), light intensity, biomass-to-solvent ratio, and cell disruption method (Pez Jaeschke *et al.*, 2021). *Spirulina* sp. is well recognized for its high phycocyanin content, comprising approximately 20%–25% of its total biomass (Li *et al.*, 2020; Vernès *et al.*, 2015), whereas *Galdieria sulphuraria* exhibited a slightly higher phycocyanin yield, ranging from 26% to 32% of the total biomass (Graziani *et al.*, 2013).

Among the various extraction techniques, organic solvents were commonly used. However, these solvents pose health and environmental risks, necessitating the development of safer and more efficient alternatives. Enzymatic hydrolysis has shown promise for phycocyanin extraction, as it breaks down the algal cell wall structure to release intracellular components. However, this method requires precise control over the operating conditions and can be costly because of the price of enzymes (Bae *et al.*, 2020). Heat-assisted extraction is another approach, although it must be carefully

managed. Excessive temperatures can degrade the pigment, making temperature regulation essential for maintaining pigment integrity. Ultrasonication was also adopted to enhance extraction efficiency, as ultrasonic waves facilitate cell wall disruption and promote phycocyanin release (Lin *et al.*, 2025a; Lin *et al.*, 2025b).

The method used to disrupt the cell membrane significantly influenced both the extraction yield and purity of phycocyanin (Tables 3 and 4). Several techniques were explored, including freeze–thaw cycles, homogenization, bead milling, ultrasonication, and enzyme-assisted extraction. Each method operated on distinct principles ranging from mechanical disintegration and chemical lysis to physical disruption through sound waves and enzymatic hydrolysis, offering varying levels of efficiency and purity. For instance, mechanical cell disruption via bead beating in *Spirulina* yielded up to 217.14 mg/g, while applying the same principle to *Galdieria* yielded only 10.80 to 30 mg/g. Similarly, physical extraction using freeze–thaw cycles for *Galdieria* produced 53 mg/g, while *Spirulina* achieved peak yields of 217.18 mg/g. Ultrasonication demanded substantially more energy for *Galdieria* (up to 1000 W) to achieve a mere 8.1 mg/g yield, which was different from *Spirulina*, where lower power intensities easily yielded up to 90.00 mg/g. Consequently, while *Spirulina* is highly amenable to conventional mechanical and physical extraction, *Galdieria* required more severe and energy-intensive conditions to effectively breach its cell membrane.

Optimizing phycocyanin purification is essential not only to enhance product quality and yield but also to increase market value and minimize production costs (Ashaolu *et al.*, 2021). Standard purification methods typically include ammonium sulfate precipitation, followed by dialysis and column chromatography (Prabakaran *et al.*, 2020). Alternative purification techniques include ultrafiltration (Li *et al.*, 2020), microfiltration combined with ultrafiltration (Li *et al.*, 2020), and activated charcoal treatment (Aoki *et al.*, 2021). A summary of these purification strategies is provided in Table 5. Notably, Lauceri *et al.* (2023) developed a single-

Table 1 Bioactivities, dosages, and analytical methods of phycocyanin from *Spirulina* sp.

Bioactivity	Effect	Dose/ Concentration	Analytical method	Reference
Antioxidant	Free radical scavenging	25–150 µg/mL	DPPH	(Katari <i>et al.</i> , 2023)
		40–2,500 µg/mL	DPPH	(Mohamed <i>et al.</i> , 2018)
		0.05–0.5 mg/mL	DPPH, ABTS	(Lin <i>et al.</i> , 2025a)
		62.34 mg/g	DPPH, FRAP, Fe ²⁺ -chelating	(Safari <i>et al.</i> , 2020)
		5–1,000 µg/mL	DPPH, FRAP, HORAC, H ₂ O ₂	(Agrawal <i>et al.</i> , 2021)
		0.05–1 g/L	ABTS, FRAP	(Wan <i>et al.</i> , 2021)
		0.5–10 mg/mL	Superoxide anion, ABTS, reducing power	(Liu <i>et al.</i> , 2022)
	Cytoprotective against UVB MMP-1 and MMP- 9 attenuation ROS attenuation ROS attenuation Serum antioxidant activity	0.05–0.3 mg/mL	DPPH (ESR spectroscopy)	(Nihal <i>et al.</i> , 2018)
		5–80 µg/mL	EZ-Cytox viability assay	(Jang & Kim, 2021)
		20–80 µg/mL	ELISA	(Jang & Kim, 2021)
		40–80 µg/mL	DCFDA fluorescence staining	(Jang & Kim, 2021)
		>1,600 µg/mL	MDA assay	(Liu <i>et al.</i> , 2018)
		100–1,000 mg/kg (oral)	SOD, Catalase	(Grover <i>et al.</i> , 2021)
Anticancer	Proliferation inhibition, apoptosis induction	0–750 µg/mL	MTT assay	(Katari <i>et al.</i> , 2023)
		100–200 µg/mL	MTT assay	(Liu <i>et al.</i> , 2018)
	HeLa cell inhibition	232.2–464.4 µg/mL (IC ₅₀ & 2×IC ₅₀)	Wound healing assay	(Katari <i>et al.</i> , 2023)
	Cell cycle arrest (G1, S, G2)	100–400 µg/mL	Flow cytometry	(Katari <i>et al.</i> , 2023)
	MMP/TIMP regulation	10–25 µg/mL	Western blot, Zymography, qRT-PCR	(Kunte & Desai, 2017)
	H22 cell suppression	10 mg/mL	Histological analysis	(Liu <i>et al.</i> , 2018)
	HepG2 inhibition	100–500 µg/mL	MTT assay	(Prabakaran <i>et al.</i> , 2020)

Table 1 Bioactivities, dosages, and analytical methods of phycocyanin from *Spirulina* sp. (cont.)

Bioactivity	Effect	Dose/ Concentration	Analytical method	Reference
Antidiabetic	α -Amylase & β -Glucosidase inhibition	50–250 μ g/mL	Spectrophotometry	(Prabakaran <i>et al.</i> , 2020)
	In vivo antidiabetic effect	100–200 mg/kg (oral)	T2DM mouse model	(Hao <i>et al.</i> , 2022)
	Glycemic & lipid profile regulation	50 mg/kg (oral)	HOMA- β , HOMA-IR, lipid panel	(El-Sayed <i>et al.</i> , 2018)
Anti-inflammatory	Enzyme & membrane stability inhibition	100–500 μ g/mL	Spectrophotometry	(Prabakaran <i>et al.</i> , 2020)
	Acute lung injury attenuation	100–400 mg/kg (i.p.)	Lung ratio, WB, H&E, IF	(Zhang <i>et al.</i> , 2022)
	NO, TNF- α , IL-6 inhibition	50–200 μ g/mL	Griess, ELISA, CCK-8	(Liu <i>et al.</i> , 2022)
	Fibrosis prevention (EMT markers)	10–50 μ g/mL	IF, WB (EMT markers)	(Pattarayan <i>et al.</i> , 2017)
	Adipose cytokine inhibition	500 mg/kg (oral)	ELISA (adipose tissue)	(Silva-Neto <i>et al.</i> , 2023)
	Cytokine suppression (ILs, TNF- α , GM-CSF, etc.)	100–1,000 mg/kg (oral)	ELISA	(Grover <i>et al.</i> , 2021)
Antimicrobial	<i>E. coli</i> , <i>S. aureus</i> , <i>L. monocytogenes</i> inhibition	2.5–25 μ g/mL	Well-diffusion, MIC/MBC	(Safari <i>et al.</i> , 2020)
	<i>E. coli</i> , <i>S. aureus</i> , <i>A. hydrophila</i> inhibition	0–320 μ g/mL	Well-diffusion, turbidity assay	(Mohamed <i>et al.</i> , 2018)
	<i>P. acnes</i> , <i>S. epidermidis</i> inhibition	10% extract	Disc & well diffusion	(Nihal <i>et al.</i> , 2018)
Anti-obesity	Body fat/adiposity inhibition (in vivo)	500 mg/kg (oral)	WAT & adiposity index	(Silva-Neto <i>et al.</i> , 2023)
	Adipogenesis/lipogenesis inhibition	0–20 μ g/mL	HFD-induced adipocyte model	(Seo <i>et al.</i> , 2018)

Table 2 Bioactivities, dosages, and analytical methods of phycocyanin from *Galdieria* sp.

Bioactivity	Effect	Dose/ Concentration	Analytical method	Reference
Antioxidant	Free radical scavenging activity	0.05, 0.1, 0.25, 0.5, and 1 g/L	ABTS and FRAP assays	(Wan <i>et al.</i> , 2021)
	Attenuation of ROS and oxidative stress	0.1 and 0.2 mg/mL/g of liver	MDA, GPx, and GST assays	(Gdara <i>et al.</i> , 2018)
	Attenuation of UVA-induced ROS	0.4 µM 0.1 or 0.25 mg/mL	DCFDA assay DCFDA assay in HaCaT cells	(Ferraro <i>et al.</i> , 2020) (Imbimbo <i>et al.</i> , 2019)

Table 3 Phycocyanin extraction methods: extraction conditions, yield, purity index, advantages, and disadvantages for *Spirulina* sp.

Method	Condition	Yield mg/g DW	Purity Index*	Advantage	Disadvantage	Reference
Freeze/thaw	4 cycles, -20°C/4 h continued at room temperature/1,5 h pH 6,8 (NaOH) with ratio 1:20 (w/v)	41.90	2.10			(Ferreira-Santos <i>et al.</i> , 2020)
	3 cycles, -20°C/4 h continued at room temperature/1,5 h pH 6,8 (NaOH) with ratio 1:20 (w/v)	217.18	0.77	Easy to perform, plasma membrane is destroyed continuously resulting in high yields	Time-consuming and costly, requires a lot of solvents, not suitable for industrial scale	(Chentir <i>et al.</i> , 2018)
	6 cycles, -40°C/4 h continued at room temperature/1 h pH 6,8 (phosphate buffer 0,1 M) with ratio 1:6, 1:8, and 1:10 (w/v)	73.73–74.51	0.56–0.66			(Tavanandi <i>et al.</i> , 2018)
Mixing or Homogenization	25,200× g/10 min, pH 6,8 (phosphate buffer 0,1 M) with ratio 1:6 (w/v)	52.11	0.6			(Tavanandi <i>et al.</i> , 2018)
	70°C/4 h, extraction at 25°C/24 h (dry biomass) with phosphate buffer 0,01 M with homogenization assistance at a biomass concentration 0,02 g/mL	103.07	0.67	Easy to perform and doesn't require special skills	Time-consuming, not suitable for industrial scale	(Pan-utai & Iamtham, 2019)

Table 3 Phycocyanin extraction methods: extraction conditions, yield, purity index, advantages and disadvantages for *Spirulina* sp. (cont.)

Method	Condition	Yield mg/g DW	Purity Index*	Advantage	Disadvantage	Reference
Bead beating	Low-density beads with 80–85% filling	217.14	0.46			(Ferreira-Santos <i>et al.</i> , 2020)
	Bead with a diameter of 0.25–0.50 mm, 4 cycles with a vibration frequency of 30 Hz for 25 s	94.90	–	Short time, low energy, high biomass yield	Low purity, time dependent on bead type, need additional purification steps	(Jaeschke <i>et al.</i> , 2019)
	Bead for 60 s and 5 cycles	10.1	–			(Abiusi <i>et al.</i> , 2021)
Ultrasonic	Extraction for 10 s at 60 W in an ice bath for 30 cycles	18.20	0.65			(Liao <i>et al.</i> , 2011)
	Soaking for 120 min, 50% ultrasonication amplitude for 2.5 min	51.51	0.62			(Tavanandi <i>et al.</i> , 2018)
	Frequency 20–100 kHz, power intensity >1 W/cm ²	90.00	0.67 – 0.93	High purity, suitable for industrial scale, adjustable temperature, can be combined with other methods	High cost, can damage phycocyanin if exposed to continuous ultraviolet exposure, requires complicated tools and processes	(Pan-utai & Iamtham, 2019)
	Extraction for 2 min with a frequency of 20 kHz, power of 520 W, and a cycle of 2 s on/2 s off	67.86	–			(Lin <i>et al.</i> , 2025a)
	Extraction for 5 min with a power of 520 W and a cycle of 2 s on/2 s off	50.14	0.38			(Lin <i>et al.</i> , 2025b)
Enzyme-assisted extraction	Enzyme concentration 1%, incubation time 16 h with ratio 1:6 (w/v)	82.07	1.19			(Tavanandi & Raghavarao, 2020)

Table 3 Phycocyanin extraction methods: extraction conditions, yield, purity index, advantages and disadvantages for *Spirulina* sp. (cont.)

Method	Condition	Yield mg/g DW	Purity Index*	Advantage	Disadvantage	Reference
Enzyme-assisted extraction	Enzyme concentration 0.6%, incubation time 16 h, ultrasonication amplitude 50% for 2.5 min at a ratio of 1:6 (w/v)	92.73	1.09	Stable, environmentally friendly, efficient	Needs to be combined with other methods to improve efficiency, requires specialized skills, and may affect the stability of phycocyanin	(Tavanandi & Raghavarao, 2020)
	Lysozyme enzyme 1 mg/mL using D-15M high pressure homogenizer (10–12,000 psi) at 4–8°C	20–25	0.80–0.90			(Ruiz-Domínguez <i>et al.</i> , 2019)

*Phycocyanin purity index (A620/A280): ≥ 0.7 for food grade, ≥ 1.5 for cosmetic grade, ≥ 3.9 for reagent grade, ≥ 4.0 for analytical grade (Güroy *et al.*, 2017; Sala *et al.*, 2018).

Table 4 Phycocyanin extraction methods: extraction conditions, yield, purity index, advantages and disadvantages for *Galdieria* sp.

Method	Condition	Yield mg/g DW	Purity Index*	Advantage	Disadvantage	Reference
Freeze/thaw	-80°C/4 min (2×) followed by room temperature 25°C, homogenization pH 7.2 (phosphate buffer) and centrifugation 25,000× g/ 90 min at a ratio of 1:10 (w/v)	53	1.1	Easy to perform, plasma membrane is destroyed continuously	Time-consuming and costly, slightly biomass	(Moon <i>et al.</i> , 2014)
Bead beating	4,000 rpm/90 s (6 replicates) 0.1 g in 0.5 mm glass beads and 0.3 g in 0.1 mm glass beads	30	0.71	Cost-effective, does not require large energy, can be applied on an industrial scale	Requires specialized equipment, needs temperature control	(Avci & Haznedaroglu, 2022)
	3 cycles with a vibration frequency of 30 Hz for 5 min with ice break between each cycle	10.80	–			(Carone <i>et al.</i> , 2024)

Table 4 Phycocyanin extraction methods: extraction conditions, yield, purity index, advantages and disadvantages for *Galdieria* sp. (cont.)

Method	Condition	Yield mg/g DW	Purity Index*	Advantage	Disadvantage	Reference
Ultrasonic	Extraction for 15 min at 1,000 W power in an ice bath at intervals of 0.3 s and on 0.4 s, followed by freeze-thaw (3 replicates)	8.1	–	High purity, suitable for industrial scale, adjustable temperature, can be combined with other methods	High cost, can damage phycocyanin if exposed to continuous ultraviolet exposure, requires complicated tools and processes	(Wan <i>et al.</i> , 2011)

*Phycocyanin purity index (A_{620}/A_{280}): ≥ 0.7 for food grade, ≥ 1.5 for cosmetic grade, ≥ 3.9 for reagent grade, ≥ 4.0 for analytical grade (Güroy *et al.*, 2017; Sala *et al.*, 2018).

Table 5 Summary of phycocyanin purification techniques, conditions, and purity index (A_{620}/A_{280})

Microalgae	Purification method	Purity	Reference
<i>Spirulina</i> sp.	Ammonium sulfate precipitation + Ion-exchange chromatography (IEC)	4.58	(Kumar <i>et al.</i> , 2014)
	Ammonium sulfate precipitation + Size-exclusion chromatography (SEC)	2.90	(Puzorjov & McCormick, 2020)
		4.50	(Chen <i>et al.</i> , 2022)
	Ammonium sulfate precipitation + column chromatography	6.17	(Purohit <i>et al.</i> , 2019)
		5.72	(Sivasankari <i>et al.</i> , 2021)
	Chitosan and activated charcoal	3.14	(Minic <i>et al.</i> , 2016)
		1.77	(Lin <i>et al.</i> , 2025b)
	Activated charcoal	0.67	(Pan-utai & Iamtham, 2019)
		3.10	(Aoki <i>et al.</i> , 2021)
	Ultrafiltration	1.62	(Sala <i>et al.</i> , 2018)
		0.80	(Campos Assumpção de Amarante <i>et al.</i> , 2020)
<i>Galdieria</i> sp.	Ammonium sulfate precipitation (6 cycles)	1.10	(Sørensen <i>et al.</i> , 2013)
	Ammonium sulfate precipitation + ultrafiltration + hydroxyapatite chromatography	3.60	(Wan <i>et al.</i> , 2021)

step extraction–purification process using ammonium sulfate solution, achieving a purity index greater than 2.5. Although precipitation with ammonium sulfate consistently yields high-purity phycocyanin, it remains an expensive option.

Research Gap

Although studies on phycocyanins from *Spirulina* sp. and *Galdieria* sp. have grown steadily over the past two decades, significant knowledge gaps persist, particularly in the fields of structural biology, applied biotechnology, and industrial scalability. Most existing studies emphasized extraction techniques or bioactivities, while the molecular architecture and thermal stability of phycocyanin remain underexplored, specifically through advanced methods such as cryo-EM or molecular dynamics (Lin *et al.*, 2025a; Yuan *et al.*, 2022). In particular, the 3D structural variability of phycocyanin across different extremophilic microalgae species, such as *Galdieria*, were not systematically compared with that of the more commonly studied *Spirulina*-derived phycocyanin. Understanding this structural diversity is critical for optimizing the stability of phycocyanin under industrial conditions (Moon *et al.*, 2014; Rahman *et al.*, 2020).

Although phycocyanin demonstrates strong antioxidant and therapeutic properties, its application as a natural food preservative or dye remains limited because of its poor stability under light, heat, and oxidative stress. Studies have rarely addressed long-term pigment retention in food matrices or the cost-effectiveness of industrial-scale purification, specifically for products sourced from extremophiles (Abiusi *et al.*, 2021; Lauceri *et al.*, 2023). Specifically, there is a distinct lack of studies exploring advanced formulation and processing technologies, such as microencapsulation, to physically protect and stabilize extremophilic phycocyanin during commercial manufacturing and prolonged shelf storage (Prasetyaningrum *et al.*, 2025).

Another overlooked area is the economic and environmental feasibility of using complex purification techniques, such as chromatography and ultrafiltration, on a commercial scale (Pan-utai & Iamtham,

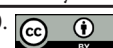
2019). There was also a lack of standardized benchmarks for purity, color intensity, or antioxidant performance that could allow for effective cross-study comparisons. Taken together, these gaps emphasize the need for integrative research that bridges structural characterization, food system integration, and commercial scalability. Deepening our understanding of the structural and functional diversity of phycocyanin, particularly from extremophilic sources, such as *Galdieria* sp., could open pathways for its broader application in sustainable industries.

Future Research

Although various studies have revealed the structural characteristics and stability of phycocyanins derived from *Spirulina* and *Galdieria*, further studies are needed, particularly in the context of industrial applications and advanced structural approaches. Future research should focus on standardizing stability evaluation methods for phycocyanin, including parameters such as temperature, pH, light exposure, and oxidation. Currently, no integrated framework comprehensively evaluates stabilization treatments, specifically for phycocyanin sourced from extremophilic microalgae such as *Galdieria sulfuraria*. A standardized set of structural and functional benchmarks is required to ensure that data across studies can be objectively compared and evaluated.

The integration of experimental and computational approaches was essential. In-depth molecular dynamics simulations were required to model the conformational stability of phycocyanin under various environmental conditions, such as high temperatures or extreme pressures. These simulations can be combined with experimental data from Cryo-Electron Microscopy (Cryo-EM) or X-ray crystallography to generate more accurate and realistic 3D structural models.

Further studies should focus on protein engineering based on 3D structural data, for example, by substituting specific amino acids prone to degradation with more stable residues. This approach enhances the functional durability of phycocyanin in industrial formulations such as food



coloring, cosmetics, and nutraceuticals. Moreover, studies on the energy efficiency and environmental impact of current phycocyanin stabilization technologies are urgently needed, as many commonly used processes, such as refrigeration and encapsulation, consume large amounts of energy. Therefore, the development of energy-efficient and eco-friendly stabilization systems, such as those using natural polymers or biodegradable encapsulation materials, represents a promising and innovative direction for sustainable phycocyanin applications.

CONCLUSION

In conclusion, phycocyanin from *Spirulina* and *Galdieria* exhibits considerable potential as a natural pigment with antioxidant, anti-inflammatory, and anticancer properties. Although *Spirulina* has been widely studied and commercialized, its thermal sensitivity limits its broader industrial application. However, *Galdieria* exhibits promising thermal stability and extraction efficiency; however, it remains underrepresented in scientific literature. This review shows that structural biology is the primary determinant of phycocyanin quality. The molecular architecture comprising amino acid sequences and quaternary packing directly dictates the pigment's resilience to industrial stressors, which in turn preserves its functional bioactivities. This study is limited in exploring the structural biology, stability under industrial-scale cultivation, and economic feasibility of phycocyanin. This review highlights the urgent need for further interdisciplinary studies focusing on the molecular characteristics, biofunctionality, and application scalability of phycocyanin, particularly in extremophilic microalgae, to fully harness its potential in functional foods, cosmetics, and pharmaceuticals.

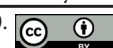
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