Molecular Science

AIMS Molecular Science, 13(2): 119–142.
DOI: 10.3934/molsci.2026007
Received: 13 October 2025
Revised: 10 February 2026
Accepted: 24 February 2026
Published: 19 March 2026

http://www.aimspress.com/journal/Molecular

Review

Structural properties and biotechnological applications of cyanobacterial phycobiliproteins

Sapana Jha, Varsha K. Singh, Payel Rana, Ashish P. Singh, Amit Gupta, Palak Rana, Riya Tripathi and Rajeshwar P. Sinha*

Laboratory of Photobiology and Molecular Microbiology, Department of Botany, Institute of Science, Banaras Hindu University, Varanasi-221005, India

* **Correspondence:** Email: rpsinhabhu@gmail.com; Tel: +91-542-2307147; Fax: +91-542-2366402.

Abstract: Cyanobacteria are a promising and sustainable source of numerous bioactive compounds, including phycobiliproteins (PBPs). PBPs are a group of water-soluble pigments that serve as a critical component in the accessory light-harvesting system in cyanobacteria. PBPs are composed of chromophore-binding proteins such as phycocyanin, phycoerythrin, and allophycocyanin, which exhibit distinctive structural and functional properties. PBPs aggregate into larger structures called phycobilisomes, located on the thylakoid membrane of cyanobacteria, consisting of rod and core subunits. PBPs scavenge free radicals and reduce oxidative stress, which plays a pivotal role in the pathogenesis of numerous chronic diseases such as cancer, diabetes, cardiovascular disorders, and neurodegenerative conditions. Due to their pharmacological properties, outstanding therapeutic value, and ecological significance, they have garnered considerable scientific interest in recent years. In this review, we provide an in-depth examination of the structural attributes of PBPs and explore their promising biotechnological applications, offering insights into current developments, challenges, and future directions for utilizing PBPs in scientific and industrial fields.

Keywords: bioactive compounds; cyanobacteria; microalgae; phycocyanin; phycoerythrin

1. Introduction

Cyanobacteria, unique photosynthetic organisms, inhabit almost all kinds of environments, natural and artificial [1]. Although they can be unicellular, filamentous, or colonial, they occasionally

grow large enough to be visible to the naked eye, especially during blooms. Cyanobacteria have been studied extensively for their morphology, certain aspects of their structure, nitrogen fixation, and their mechanism of photosynthesis. Most secondary metabolites can be beneficial to people, whereas some may be harmful to organisms, including people [2,3].

Three principal light-harvesting systems, which comprise two major photosystems and a phycobilisome (PBS), make up the cyanobacterial photosynthetic apparatus. The PBS is characteristic of cyanobacteria and is mainly composed of phycobiliproteins (PBPs). The composition of PBS, being inconsistent, differs from species to species. PBPs are a class of disk-shaped, colored, and water-soluble macromolecular proteins composed of proteins and chromophores, called phycobilins. These phycobilins have open-chain tetrapyrroles that remain covalently bound to PBPs via the amino acid cysteine. Since their discovery, the structure, function, and applications of PBPs have been the subject of extensive research [4]. Single-particle cryo-electron microscopy was used to determine the structure of a PBS that was extracted from the red algae *Griffithsia pacifica*. The PBS had a molecular mass of 16.8 MDa [5]. PBS vary widely in size, ranging from approximately 4.6 to 18 MDa, and may contain nearly 900 polypeptide subunits while accommodating over 2000 chromophores [6].

PBPs are mostly classified into four types: phycocyanin (PC), allophycocyanin (APC), phycoerythrin (PE), and phycoerythrocyanin (PEC). These PBPs classes are distinguished by their absorption maxima: PC (λ_{max} = 610–625), PE (λ_{max} = 490–570), PEC (λ_{max} = 560–600), and APC (λ_{max} = 650–660 nm) [7]. PBPs are ubiquitous in cyanobacteria. While all cyanobacteria contain PC, only a subset possesses PE. In recent decades, the pursuit of bioactive compounds has led to increased interest in the study of microorganisms such as cyanobacteria. These organisms are of commercial interest due to their wide-ranging applications in nutrition, healthcare, wastewater management, energy generation, and the chemical and pharmaceutical sectors [8]. PBPs are of significant biotechnological interest due to their pronounced biological and pharmaceutical activities. In particular, PC is commercially important due to its nutraceutical and therapeutic properties, notable antioxidant, anti-inflammatory, and anticarcinogenic activities, superior fluorescent features, and its use as a natural colorant [9]. Upon exposure to external stimuli like temperature, pH, or ionic composition, PBPs can maximize their absorption. This signifies the structural stability of PBPs. In terms of energy distribution and transfer, PE and PEC are the first PBPs to absorb light and then radiate energy to PC and APC, respectively [10]. The two distinct polypeptides, denoted by α and β, that make up each PBP have a similar sequence and are the result of ancient gene duplication events. Each α- or β-subunit carries at least one phycobilin. PBPs are typically shown as hexamers $(\alpha\beta)_6$ or trimers $(\alpha\beta)_3$ that are connected by certain proteins [11].

Due to the potential for commercial use in a variety of fields, including nutrition, human and animal health, wastewater treatment, energy production, and the chemical and pharmaceutical industries, the hunt for bioactive compounds has intensified in recent decades, sparking an increased interest in the study of microorganisms like cyanobacteria. More precisely, research on PBPs and phycobilins has demonstrated their capabilities as anti-inflammatory, anti-cancer, antibacterial, and antioxidant substances. Cyanobacteria produce high-value natural compounds called PBPs, which have drawn interest due to their potential applications in a variety of sectors, including pharmaceuticals, food, feed, cosmetics, and nutraceuticals [12]. The mechanism of PBS assembly is poorly understood, and the energy transfer routes within PBSs are not well defined.

In this review, we aim to examine the types of cyanobacterial PBPs and highlight the key biotechnological properties of PBPs, with special emphasis on their bioactivities. Particularly for PBPs, emphasis is placed on optimizing their manufacturing, extraction, and purification processes.

Additionally, a brief discussion of economic factors and prospects for the field is given.

2. Structural properties of PBPs

Cyanobacterial PBPs possess a unique ability to capture light, thereby expanding the range of photosynthetically active radiation (PAR) and enabling these organisms to survive in extreme environments where higher plants are unable to grow [13]. Unlike plants, cyanobacteria cannot rely solely on chlorophyll-based light-harvesting antennae to sustain photosynthesis in highly variable environments such as hot springs, glaciers, deep-sea regions, and deserts [14]. Cyanobacteria use an additional light-harvesting complex, the PBS, to enhance their light absorption. This large, multi-protein complex is located on the thylakoid membrane and enables the cells to absorb solar radiation in the 450–660 nm range.

The PBS consists of two major protein types: PBPs and linker proteins (LPs). With the help of LPs, PBPs are organized into two structural components: The core, which attaches to the thylakoid membrane, and the rods, which extend outward from the core [6]. Each PBP typically consists of two polypeptide chains, the α and β subunits. These subunits are colorless apoproteins that contain covalently attached linear tetrapyrrole chromophores, which are responsible for light absorption. Chromophores are attached to cysteine residues through thioether linkages [15]. The number of chromophores present can differ among PBPs. According to their structural features, these chromophores are classified into four major types: phycocyanobilin (PCB), phycoerythrobilin (PEB), phycoviolobilin (PVB), and phycourobilin (PUB) (Figure 1).

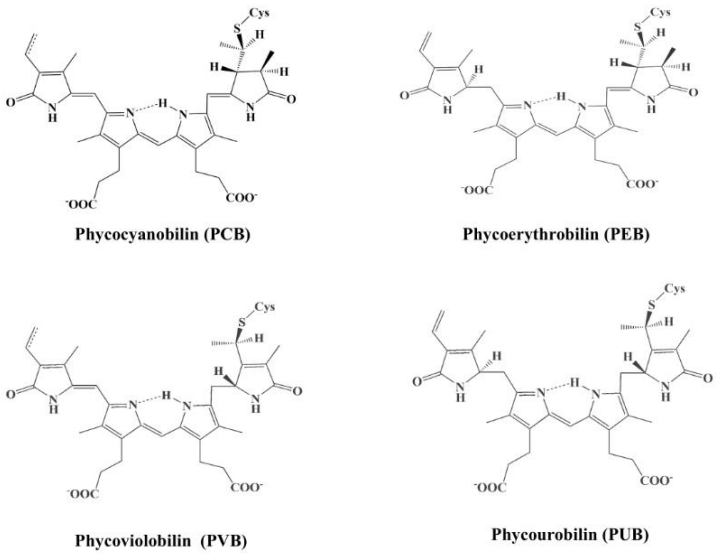

Figure 1. Molecular structure of cysteine-linked chromophores in PBP complexes.

The assembly of PBP trimers and hexamers into the core and rod structures is stabilized by LPs. These LPs not only provide structural integrity to the PBS but also ensure its proper organization on the thylakoid membrane, thereby enabling efficient energy transfer. According to their position and function, LPs are categorized into four types: Group I- rod linkers (L_R) located in the rods; Group II-

rod-core linkers (L_{RC}) connecting rods to the core; Group III- core linkers (L_C) found within the core; and Group IV- membrane linkers (L_{CM}) that anchor the PBS core to the thylakoid membrane [7].

Cryo-EM study on *Thermosynechococcus vulcanus* showed that its phycobilisome features a pentacylindrical APC core with PC rods. The analysis also revealed key linker-chromophore interactions and the pathways guiding energy transfer to PSII (Figure 2) [16]. Cryo-EM was further used to analyze the PBS associated with ferredoxin-$NADP^+$ oxidoreductase (FNR), a vital enzyme for cyclic electron transfer in *Synechocystis* sp. PCC 6803 [17].

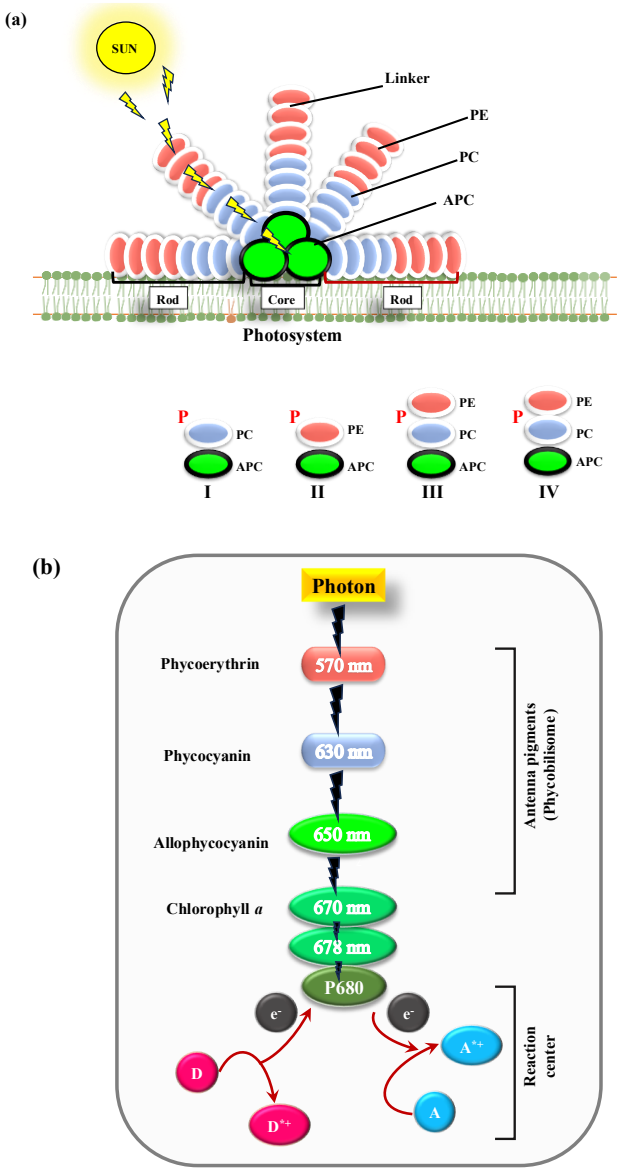

Figure 2. Schematic representation of the PBS structure on the thylakoid membrane showing rod subunits PC and PE and core subunits APC connected by linker polypeptides and basic-PBP composition found in cyanobacteria **(a)**. Schematic illustration of energy transfer steps, including charge separation (photochemical reaction) at the photosystem II reaction center (PSII RC) for the cyanobacteria **(b),** modified from Aryee et al. [18].

2.1. Allophycocyanin

APC resides in the core of the PBS and is universally present in organisms that contain PBPs. It occurs in three subtypes: APC, APC-B, and the APC-Lcm, among which APC is the predominant PBP within the core. While APC assembles into core cylinders, APC-B and APC-Lcm contribute to the formation of the two basal cylinders. Each α and β subunit binds a PCB chromophore via conserved cysteine residues located at positions α-84 and β-84. APC is typically purified in its trimeric form, $(\alpha\beta)_3$, exhibiting a primary absorption peak at 650 nm and a secondary shoulder at 620 nm. At low concentrations, however, the trimer dissociates into αβ monomers, resulting in a shift of the absorption maximum from 650 nm to 618 nm [19].

In certain cyanobacteria, the photosynthetic machinery can undergo remodeling under far-red light (FRL), enabling more efficient utilization of FRL for photosynthesis [20]. Li et al. [21] reported a novel PBS-derived complex composed exclusively of APC core subunits, characterized by red-shifted absorption peaks at 653 and 712 nm. These red-shifted PBP complexes were obtained from the chlorophyll f-containing cyanobacterium *Halomicronema hongdechloris*. Studies revealed that the protein environment around the pyrrole ring A of PCB in the APC α-subunit plays the primary role in FRL absorption.

2.2. Phycocyanin

PCs are present in nearly all PBP-containing organisms, such as cyanobacteria, red algae, glaucophytes, and certain cryptophytes. Based on spectral characteristics, PCs are classified into three subtypes: (1) C-PC (λ_{max} = 610–625 nm), found exclusively in cyanobacteria; (2) PEC (λ_{max} = 560–600 nm), restricted to certain cyanobacteria; and (3) R-PC (λ_{max} = ~615 nm), predominantly occurring in red algae [7]. PCs absorb light in the range of 580-630 nm and typically emit fluorescence with a peak between 635 and 645 nm. A PC molecule generally binds one PCB at α-84 and two PCBs at β-84 and β-155. Studies on chromophore energy transfer have shown that the α-84 PCB and β-155 PCB function as excitation energy donors, while the β-84 PCB serves as the terminal energy acceptor [11]. When separated from the PBS, PC occurs as a hexameric complex $(\alpha\beta)_6$ at pH 5.0-6.0 and as a trimeric complex $(\alpha\beta)_3$ at pH 7.0. Among the PBPs, PC is one of the most extensively studied due to its diverse biological and pharmacological activities [22].

2.3. Phycoerythrin

PEs are the most abundant PBPs in many red algae and some unicellular cyanobacteria. Compared to APC and PC, they contain more phycobilins, enabling them to absorb more light per mole. The chromophores attached to apo-PBPs can be PEB or PUB. The phycobilin composition varies depending on whether cyanobacteria live in freshwater, soil, or marine environments. PEs from freshwater and soil cyanobacteria usually only have PEB chromophores and show absorption maxima near 565 nm [19]. PEs from marine unicellular strains of *Synechococcus* and *Synechocystis* attach PUB chromophores at specific cysteine residues. Generally, a PE molecule carries five chromophores, with additional phycobilins linked to α-143 and a PEB doubly attached to β-50 and β-61. The α and β subunits of PE assemble into trimers, which then aggregate face-to-face to form disk-shaped hexamers, facilitated by a specialized linker peptide called the γ subunit. In some cyanobacteria, the chromophore

composition of PE can change based on light quality, a process known as complementary chromatic adaptation, thought to play a key role in global primary productivity [23].

3. Biotechnological applications

PBPs exhibit a highly organized structure that is directly linked to their biological functions. Structural variations among PBPs determine their absorption maxima, enabling efficient light harvesting and thus enabling cyanobacteria to adapt to diverse light environments. Beyond their primary role in photosynthesis, the presence of specific functional groups and well-defined tertiary structure of PBPs contributes to their diverse bioactive potential. These structural features facilitate interactions with reactive oxygen species (ROS) and cellular biomolecules, thereby underpinning their antioxidant activity and associated protective effects. Furthermore, PBPs can modulate key cellular signaling pathways involved in inflammation, apoptosis, and oxidative stress, which explains their reported anticancer, anti-inflammatory, anti-aging, and neuroprotective activities [24,12,25–29]. In addition, the intrinsic fluorescence and stability of native PBPs support their long-standing applications as food additives, natural colorants, and fluorescent probes (Figure 3).

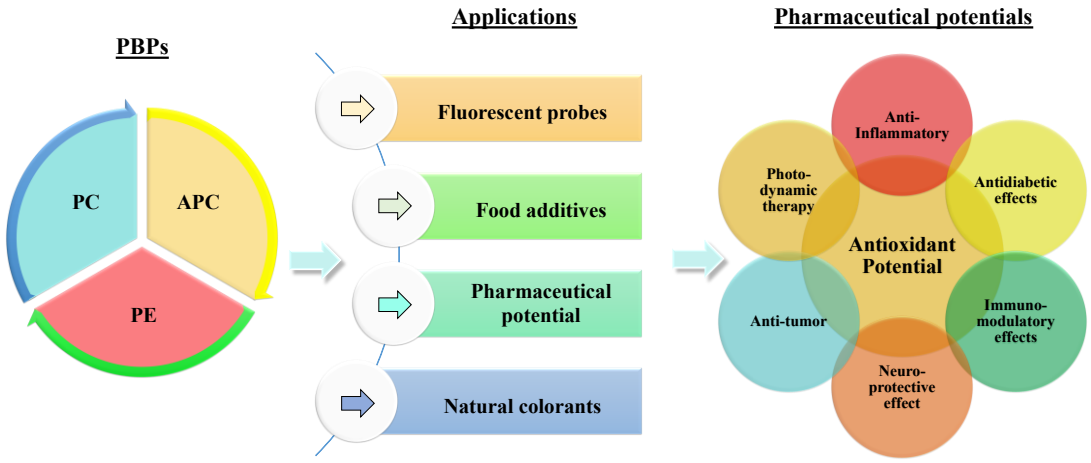

Figure 3. PBPs (APC, PC, and PE) are used as food additives, natural pigments, and fluorescent markers, and have pharmaceutical applications.

3.1. Anti-diabetic effects

These bioactive substances, widely distributed in cyanobacteria such as *Spirulina platensis* and *Anabaena*, have garnered significant interest due to their potential medical applications, particularly in the treatment of metabolic diseases like diabetes mellitus [30]. The anti-diabetic effects of PBPs are mostly ascribed to their capacity to protect pancreatic β-cells, control glucose metabolism, and reduce oxidative stress [31]. PC, as a diabetic-resistant candidate, inhibits α-amylase and β-glucosidase in *in vitro* conditions, reducing the amount of starch that is absorbed, and promotes the uptake of glucose in the insulin-resistant cell line [32]. It was also found that PC enhances insulin sensitivity and the cellular

utilization of glucose, particularly in insulin-resistant cells and mice with type 2 diabetes mellitus (T2DM) treated orally with 200 $mg \cdot kg^{-1}$. This is achieved by activating serine/threonine kinase 1 (AKT), which is a component of the phosphatidylinositol-3 kinase (PI3K) pathway and is essential in the regulation of glyco-metabolism, and AMP-activated protein kinase (AMPK), which, once active, promotes autophagy [33]. PC improves the glucose tolerance and fasting serum insulin levels of diabetic mice while lowering fasting blood glucose and serum biochemical markers such as triglycerides (TG), total cholesterol (TC), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in mice with high-glucose, high-fat diet-induced diabetes mellitus. Furthermore, a molecular investigation showed that PC prevents diabetes mellitus by triggering the AKT and AMPK signaling pathways in the insulin-resistant SMMC-7721 cell model and the animal model produced by a high-glucose, high-fat diet [33]. PBPs have been shown in numerous *in vivo* experiments employing diabetic mouse models to effectively lower fasting blood glucose levels, enhance glucose tolerance, and maintain the structure of the pancreatic islets. Wistar rats with diabetes produced by streptozotocin (STZ) were used to test PC's capacity to block glycation and prevent diabetes. PC was given orally to STZ-induced diabetic rats. After receiving 100–200 $mg \cdot kg^{-1}$ of PC daily, the high levels of glycated haemoglobin (HbA1c) in STZ-induced diabetic rats dropped. The levels of serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), aspartate aminotransferase (SGPT), TC, TG, LDL-C, and total bilirubin were also decreased, indicating that PC may have a hepatoprotective role as a potential defense against complications from diabetes [34]. In insulin-resistant hepatocytes, PC controls glucose homeostasis through the SIRT1/LKB1/AMPK and IRS-2/PI3K/Akt pathways [35]. A decrease in β-cell apoptosis, an improvement in their function, and a control of the hepatic glucose metabolism are the major processes implicated in PC activity, according to the molecular mechanisms underlying the anti-diabetic actions of PC [36]. Moreover, 100 $mg \cdot kg^{-1}$ of PC increased the levels of GK and glucokinase regulatory protein (GKRP) in the pancreas and liver of mice with alloxan-induced diabetes. These findings imply that PC may stimulate the insulin signaling pathway and the expression of GK in the liver and pancreas of diabetic mice [37]. *In vitro*, PC also produced a protective effect through the activation of nuclear erythroid-related factor (Nrf2), which raised the production of the antioxidant enzymes glyoxalase (Glo) and heme-oxygenase (HO). These enzymes regulate inflammation and oxidative stress, two factors that contribute to the development of diabetes [38]. PBPs have been shown to decrease the enzymatic activity of dipeptyl-peptidase (DPP)-IV in two recent *in vitro* experiments. Moreover, inhibiting DPP-IV, an enzyme involved in the metabolism of incretins (metabolic hormones that promote a drop in blood glucose levels), is one of the cutting-edge methods being used to prevent the onset of diabetes. On human enterocyte cells, the inhibitory effects of PC and APC hydrolysates were noted [39,40]. PBPs can also help peripheral tissues take up more glucose by increasing the expression of glucose transporters (like GLUT-4). They may also have insulin-mimetic effects in tissues that are resistant to insulin. Because they come from nature and are not very toxic, PBPs are good candidates for use as supplements to diabetes treatments, potentially revolutionizing the field of diabetes management.

3.2. Neuroprotective and hepatoprotective effects

The neuroprotective effect of PC was shown in rats with kainate-induced brain damage. Oral delivery of PC suppressed the activation of microglia and astroglia caused by kainic acid, suggesting that certain metabolites of this protein were could cross the hemato-encephalic barrier and provide

antioxidant protection in the hippocampus. Furthermore, PC is proposed as a potential therapeutic agent for oxidative stress-related neuronal damage in neurodegenerative disorders like Alzheimer's and Parkinson's diseases. In rat cerebellar granule cell cultures, PC demonstrated neuroprotective activity by counteracting 24-hour potassium and serum deprivation and inhibiting apoptosis triggered by this condition [41].

According to Pentón-Rol et al. [42], administration of PC, whether before or after the onset of injury, led to a significant decrease in infarct size. Beyond reducing tissue damage, PC also provided neuroprotection by limiting neuronal loss in the hippocampus. Additionally, it suppressed lipid peroxidation, thereby reducing oxidative stress, and enhanced the antioxidant capacity, as reflected by the increased ferric reducing ability of plasma in serum and brain tissue homogenates. These results indicate that PC holds promise as a preventive and acute disease-modifying drug candidate for stroke treatment. In SH-SY5Y neuronal cells, exposure to tert-butylhydroperoxide caused a marked decline in cell viability; however, this effect was effectively counteracted by PC treatment at low micromolar concentrations. PC showed a pronounced inhibitory action on the electrochemically induced Fenton reaction. Thus, it is suggested that PC could serve as a neuroprotective agent in ischemic stroke by limiting neuronal oxidative damage and preserving mitochondrial function [43]. The neuroprotective action of PC appears to be largely associated with its antioxidant capacity, though its anti-inflammatory and immunomodulatory effects may also play a significant role in contributing to this protection (Figure 4) [42].

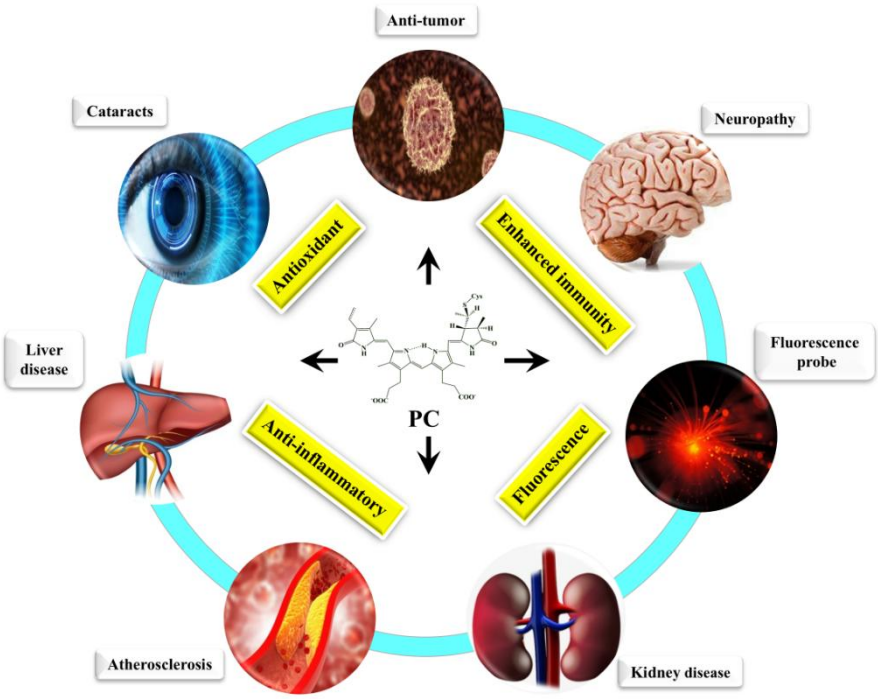

Figure 4. Biomedical potentials of PBPs, modified from Jha et al. [7].

Studies have shown that oral administration of PE produced beneficial effects on hepatocellular, hepatobiliary, renal, and redox biomarkers in rats exposed to CCl_4-induced toxicity [19]. It was concluded that orally administered PE may undergo degradation in the gastrointestinal tract by

proteolytic enzymes, generating low-molecular-weight proteins and bilirubin, which in turn mediate its pharmacological effects. Ou et al. [44] demonstrated that PC protected against CCl_4-induced hepatocyte injury *in vitro* and *in vivo*. The protective effect is thought to involve shielding hepatocytes from free radical damage generated by CCl_4 (Table 1). Additionally, through its anti-inflammatory properties, PC may reduce inflammatory infiltration by suppressing the expression of TGF-1 and HGF during CCl_4-induced liver injury.

Table 1. Therapeutic effects of PBPs and their proposed applications.

PBP	Biological activity	Source of PBP	Applications	Reference
PC	Neuroprotective	*Arthrospira platensis*	EAE indued male Lewis rats and femaleC57BL/6mice: MDA assay. PP assay. FRA assay. ELISA (IL-17, IL-6, IFN-γ).	[45]
	Synapse protection	*Nostoc sphaeroides*	DOX+CP-induced C57BL/6 male mice (MWM, TNF-α, IL-1β, IL-6, MDA, GSH and SOD levels).	[46]
	Neuroprotective	-	C-PC acts as an antioxidant in the CNS, targeting the myelin and axonal damage associated with EAE in Lewis rats.	[42]
	Neuroprotective	-	C-PC enhances the expression of antioxidant enzymes like SOD and catalase, boosts neurotrophic factors including BDNF and NGF, and simultaneously reduces inflammatory mediators such as IL-6, IL-1β, and glial scar formation.	[47]
	Hepatoprotective effect	*Spirulina platensis*	PC minimized the loss of microsomal cytochrome P450, glucose-6-phosphatase, and aminopyrine-N-demethylase, demonstrating its protective effect on hepatic enzyme systems.	[48]
	Hepatoprotective effect	*Arthrospira maxima* SAG 25780	Hepatoprotective against CCl_4-induced toxicity in Wistar rats.	[49]
PE	Hepatoprotective effect	*Phormidium tenue*	Protective effect against CCl_4-induced hepatic and renal toxicity in rats.	[50]
APC	Hepatoprotective effect	*Spirulina platensis*	Hepatoprotective effect on $HepG_2$ human hepatocarcinoma cell line.	[51]

3.3. Immunomodulatory effects

It is well recognized that immune regulation plays a crucial role in protecting the body against diseases. The disease-fighting effects of PBPs are mainly linked to their immunomodulatory activities. Researchers reported that tumor-bearing mice receiving dietary supplementation with PC showed a markedly higher survival rate compared to untreated groups. This aligned with the observed variations in lymphocyte activity across the groups, suggesting that PC exerted stimulatory and enhancing effects on the immune system [19]. Nemoto-Kawamura et al. [52] proposed that PC strengthens biological defense mechanisms against infectious diseases by maintaining mucosal immune functions while alleviating allergic inflammation through the inhibition of antigen-specific IgE antibodies. Pentón-Rol et al. [42] showed that PC could prevent or reduce the severity of experimental autoimmune encephalitis and promote a regulatory T cell response in peripheral blood mononuclear cells of multiple sclerosis patients.

The immunomodulatory effects of PBPs may be linked to their antioxidant potential. Ivanova et al. [53] reported that PC enhanced the lymphocyte antioxidant defense system in individuals with occupational exposure. Similarly, Lee et al. [54] demonstrated that PBPs might safeguard cells against oxidative damage by modulating immune function and promoting cellular repair capacity. Moreover, studies have revealed that the immune mechanisms of PBPs are closely linked to their anti-inflammatory actions at cellular and genetic levels. Chen et al. [55] demonstrated that PC could trigger the secretion of inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Moreover, PC treatment elevated proIL-1β and COX-2 protein expression in a dose-dependent fashion and promptly activated the phosphorylation of key inflammation-related signaling molecules, including ERK, JNK, p38, and IκB. Grover et al. [56] reported that PC displayed immunomodulatory effects by dose-dependently inhibiting the production of pro-inflammatory cytokines, including interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), in Balb/c mice.

When human mononuclear cells are exposed to PC, Treg cell generation is induced, resembling the effect triggered by HO1 induction. Biliverdin, the product of HO1, shares structural similarity with phycobilins and is quickly converted to bilirubin by biliverdin reductase in animal cells. Notably, bilirubin injection in mice stimulates Treg cell formation. Based on these findings, it has been suggested that phycobilins may mimic the action of biliverdin in promoting Treg induction [57].

3.4. Anti-tumor effects

PBPs have a strong antitumor effect because of their significant antioxidant activity, which scavenges reactive species such as hydroxyl, superoxide, and peroxyl radicals [19]. Cancer, a major cause of death globally, arises when cells proliferate uncontrollably, evade normal cell death, and invade areas where they are not supposed to spread. For this reason, treating cancer often involves either preventing the cancer cells from spreading, stopping their growth, or forcing them to die (a process known as apoptosis). Studies have demonstrated that PBPs possess anticancer properties against multiple types of cancer, including breast, liver, lung, colon, leukemia, and bone marrow malignancies (Table 2) [26,58]. Crucially, even at high doses, no serious side effects or mortality have been observed with PBP in animal studies [59]. As an illustration, Jiang et al. [60] discovered that a form of PBP known as PC, extracted from the algae *Arthrospira platensis,* might inhibit the proliferation of certain leukemia cells (known as K562 cells). Because they were unable to continue

their cycle, these cells became trapped in the early G_1 phase. In other experiments, the number of cells in a later phase (G_2/M) decreased when PC from a different species of algae (*Oscillatoria tenuis*) was applied to lung cancer cells (A549) and colon cancer cells (HT-29). The fact that more cells were discovered in the G_0/G_1 and S phases at the same time indicated that the cells had ceased to go through the cycle normally [60]. For example, leukemia K562 cells showed signs of programmed cell death after PC treatment, including cytochrome c release and PARP cleavage. The balance shifted in favor of cell death as a result of the treatment's reduction of Bcl-2, a protein that typically prevents cell death [61]. Another study revealed that the inhibitory effect of PC on HeLa cervical cancer cells was dose-dependent: The higher the concentration, the stronger the suppression. Treated cells showed DNA condensation, membrane changes, and shrinkage (hallmarks of apoptosis) under microscopy, while DNA assays confirmed fragmentation, a sign of programmed cell death [62]. Moreover, the activation of several caspase enzymes, key mediators of cell death, confirmed that the cells were undergoing apoptosis [63]. By altering the growth and behavior of cancer cell types, PC has demonstrated potent anti-cancer actions. It functions by reducing or halting the growth of cancer cells, halting their spread, and causing them to perish naturally through processes like necrosis or cell death (apoptosis) [26,64]. Gantar and colleagues [65], for instance, discovered that when used in conjunction with the chemotherapeutic drug topotecan (TPT), PC from a kind of cyanobacteria (*Limnothrix* sp. 37-2-1) was more effective than TPT alone in treating prostate cancer cells (LNCaP). The combination destroyed more cancer cells, even at a lower dose. It reduced the negative effects of TPT, increased ROS, and activated the cell-death proteins caspase-9 and caspase-3 [65]. Moreover, scientists discovered that MDA-MB-231 breast cancer cells were also affected by PC. It produced apoptosis and caused the cells to stop in the early stage (G_0/G_1) of their cycle, in addition to stopping the cells from developing. This result was brought about by activating the JNK and p38 MAPK pathways, which aid in cell death, and deactivating the ERK pathway, which promotes cell growth [60].

Table 2. Anticancer effects of PBPs and their applications (adopted and modified from Singh et al. [66]).

PBP	Biological activity	Source of PBP	Application	Reference
PC	Anticancer	*Limnothrix* sp.	Regulates anti- and pro-apoptotic genes by increasing levels of Bax and Apaf-1 and activates caspase-8, caspase-9, and caspase-3. Decreasing expression of Bcl-2, Mcl-1, and survivin. In combination with Topotecan, increased expression of the death receptor FAS and cleaved PARP.	[64]
PC	Anticancer	*Spirulina sp*.	Induce apoptosis and suppressed the growth of NSCLC cells by downregulation of TIRAP/NF-jB activity.	[58]
PC	Anticancer	*Spirulina platensis*	Anti-proliferative effect against HepG-2 cell lines.	[67]
PC	Anticancer	*Limnothrix* sp. NS01	Anti-cancer effect on human breast cancer (MCF-7) cells	[68]

Continued on next page

PBP	Biological activity	Source of PBP	Application	Reference
PC	Anticancer	*Spirulina platensis*	Anti-proliferative and anti-migratory function by the reduction of RIPK1/NF-jB activity in the NSCLC cells.	[58]
PC	Anticancer	*Galdieria sulphuraria*	Aqueous extract containing C-PC has antioxidant activity and exerts cytotoxic activity in the human adenocarcinoma A549 cells.	[69]
PE	Anticancer	*Gracilaria lemaneiformis*	Inhibits growth and induces apoptosis of SKOV-3 cells. The ROS/JNK/Bcl-2 signaling pathway, upregulation of JNK, GADD45A, and RAD23, and downregulation of XBP1 and OS9 are critical in PE-induced apoptosis in this cell.	[70]

3.5. Bioluminescent marker effects

The breakdown or synthesis of tetrapyrrole macrocycles leads to the formation of open-chain tetrapyrroles, commonly referred to as bilins. Today, it is well understood that bilins participate in a wide range of biological functions, such as cellular signaling, photomorphogenesis, redox reactions, and light capture within PBSs. Their absorption characteristics, which depend on the extent of conjugation, span the visible, ultraviolet, and near-infrared (NIR) regions, resulting in diverse colors ranging from red to orange to blue/green. Since bilins generally exhibit very weak fluorescence, the number of available spectral data sets is limited. Interestingly, when their structures are made more rigid, their fluorescence can be markedly enhanced. This property underpins the extensive use of biliproteins as fluorescence probes. As a result, substantial research efforts have been dedicated to optimizing biliproteins as fluorescent fusion tags, especially because they can absorb wavelengths that extend into the infrared region [71].

Consequently, open-chain tetrapyrroles are utilized across domains. Their applications range from serving as chromophores in engineered fluorescent proteins [72], natural food colorants [73], and cosmetic formulations [74], to functioning as photosensitizer in photodynamic therapy (PDT) [75], fluorescent probes [76], and light-absorbing components in dye-sensitized and genetically modified solar cells [77], among several other technological areas. PDT is an emerging modality for tumor treatment that involves laser irradiation of photosensitizers. Upon excitation, photosensitizers transition from the ground state to an excited state, generating energy and reactive oxygen species (ROS) [78]. In comparison to conventional chemotherapy, PDT selectively targets and eradicates tumor cells while sparing normal tissues. It has demonstrated favorable therapeutic outcomes in the treatment of skin tumors [79], lung tumors [80], oral and gastric tumors [81], as well as condyloma acuminatum, acne [82], and other diseases. APCs serve as fundamental components of PBPs, the large light-harvesting antenna complexes present in cyanobacteria and red algae [83]. The α- and β-subunits of APC, known as ApcA and ApcB, pair together to create heterodimers, which then spontaneously assemble into disk-like $(\alpha\beta)_3$ trimers. These ApcA/ApcB trimers occupy the central region of the PBS core. The core structure also incorporates linker proteins such as ApcE (or LCM), ApcD, and ApcF. Owing to the natural fluorescence of APC trimers, they are widely employed as markers in immunofluorescence techniques [84]. In APCs, the conserved cysteine residue forms a thioether

linkage with the C31 atom of pyrrole ring A of the PCB chromophore. ApcE attaches PCB through an autocatalytic thioether bond involving Cys196. In contrast, ApcA, ApcB, ApcD, and ApcF depend on bilin lyases to correctly attach PCBs by forming a thioether bond with the conserved Cys81 residues [85]. All APCs share a similar structural organization: They contain an APC-like domain composed of seven α-helices arranged in a globin-like fold, along with an N-terminal extension primarily involved in oligomer formation [86,87]. In *E. coli*, APCs can be produced as red fluorescent proteins through the co-expression of PCB-producing enzymes along with the necessary bilin lyases [88]. Importantly, the spectral properties of APCs can vary depending on their source. For example, "ApcD from *Nostoc* sp. shows a fluorescence peak at 663 nm, whereas recombinant ApcD from *Synechocystis* sp. emits a fluorescence with a peak at 642 nm" [85]. ApcE is a large, membrane-associated protein featuring an APC-like domain at its N-terminus. When expressed as a fluorescent protein in *E. coli*, this domain exhibits a quantum yield of 15% and a fluorescence maximum at 672 nm. By removing the hydrophobic loop and specific N-terminal residues, researchers have generated monomeric, soluble ApcE-based fluorescent proteins with a quantum yield of 6% and an emission peak at 663 nm [89]. The ApcA protein from *Trichodesmium erythraeum* was engineered to develop the far-red fluorescent protein smURFP. Through targeted mutagenesis, specific amino acid substitutions enabled TeApcA to bind the tetrapyrrole biliverdin (BV) without requiring bilin lyases. Although smURFP can fluoresce in mammalian cells supplied with high levels of external BV, its brightness is lower than that of BphP-derived near-infrared fluorescent proteins, such as the miRFP family [72]. APCs exhibit strong natural fluorescence and have evolved to optimize fluorescence resonance energy transfer. Taken together, their properties make APCs valuable molecular frameworks for designing further red-shifted NIR fluorescent proteins.

3.6. Cosmeceutical effects

PC has gained considerable attention in the cosmetic industry due to its bright pigment and rich natural bioactive properties. Among cosmetic formulations, PC-based lip balms have achieved notable popularity, with multiple companies producing them and a growing number of consumers adopting these products [90]. When combined with an appropriate developer and mordant, PC exhibited strong potential as a hair-dye ingredient, retaining nearly 50% of its coloration even after five shampoo washes. In stability assessments involving repeated heating and cooling cycles, it also showed a gradual and consistent fading pattern. PC is suitable for incorporation into anti-aging creams because its strong antioxidant activity helps neutralize ROS, a key contributor to skin aging. Feng et al. [91] investigated the anti-aging potential of PC using *in vivo* (*Drosophila melanogaster*) and *in vitro* (H_2O_2-induced HUVEC cells) experimental models. Wu et al. [92] demonstrated the anti-melanogenic effect of PC, showing that it downregulates tyrosinase gene expression and consequently reduces melanin production. This characteristics positions PC as a promising cosmetic ingredient, particularly for use in sunscreen formulations. Nihal et al. [93] also documented the anti-acne potential of PC, reporting its inhibitory activity against two acne-causing bacterial strains *Propionibacterium acnes* and *Staphylococcus epidermidis*. Several commercial brands have begun incorporating PC into their formulations. For instance, Beauty Relay London offers face creams, facial kits, and hair masks featuring PC as a key ingredient (https://www.beautyrelay.com/), while the Lip Balm Company has introduced PC-enriched lip balms (https://thelipbalmco.in/) [94].

3.7. Nutraceutical applications

Food colorants, or coloring additives, are compounds used to enhance the color of foods and beverages. In the food industry, appearance, especially color, is a critical quality attribute, as it strongly influences consumer perception and acceptance [95]. Food colorants are typically classified into two groups: natural and synthetic. Commonly used synthetic dyes include Sunset Yellow FCF (E110), Tartrazine (E102), Allura Red AC (E129), Carmoisine (E122), and Brilliant Blue [96]. Microorganisms, particularly microalgae, serve as an excellent alternative source of natural food colorants, as they overcome many limitations associated with pigments obtained from plants or animals. They can be produced year-round, offer low cultivation costs, and are well-suited for large-scale production [97]. PC has been tested in a variety of food formulations, including jelly candies [98], and dairy-based products, such as yoghurt [99] and skim milk [100], as well as ice creams and beverages [101].

PC was incorporated as a coloring agent into three beverage types, including wine, isotonic drinks, and tonic beverages, and its color stability was monitored over a 15-day period. The findings indicated that the pigment remained stable, demonstrating its potential as a natural substitute for conventional synthetic colorants [101]. Galetović et al. [100] developed a skim milk product enriched with PBPs, demonstrating notable functional attributes, remaining intact at 138°C for 4 seconds. PC was further incorporated into ice cream, and assessments of color retention and antioxidant capacity were conducted. Results indicated that the pigment remained stable for up to 182 days, with only minimal color degradation afterward, while the antioxidant activity was approximately thirteen times higher than that of the control.

4. Challenges and future prospects

PBPs are water-soluble but extremely sensitive to pH, light, and temperature. Maintaining structural integrity during extraction, purification, and storage is challenging and requires costly chromatographic techniques to achieve high purity [102]. Moreover, PBPs are important biological resources used in the food, cosmetic, and biomedical sectors. Although PBPs represent a valuable resource for biomedical applications, their large-scale commercial production remains a significant challenge. While laboratory-scale extraction and purification are achievable, several limitations such as low selectivity, high energy requirements, and substantial capital investment in equipment like chromatographic systems hinder the commercialization of cyanobacterial PBP production [103]. These limitations can be addressed through stronger collaboration between laboratory scientists and industrial technologists. Although cyanobacteria require only minimal inputs such as light, water, CO_2, and basic nutrients, the main challenge lies in designing industrial-scale bioreactors that provide appropriate light exposure and intensity. Bioreactors must ensure uniform light distribution, as sufficient illumination is essential for cyanobacterial growth, and excessive light intensity may result in photoinhibition or overheating [104]. PBPs consequently must be produced on a large scale, and the choice of high-yield algae strains determines the PBP output. Several challenges need to be addressed and resolved to enable a wider application of PBPs as natural colorants and alternative dietary proteins, particularly if the full biomass or raw extracts are to be utilized. These may be categorized according to the quantity and purity of PBPs, biomass cultivation, safety concerns, and bioavailability. The economic factors that contribute to PBPs' high pricing are linked to these. It is also necessary to take into account several factors related to the hazards of cyanobacteria and algae production. These include negative impacts on

biodiversity and pollution hazards [105]. Numerous pollutants, such as heavy metals, high iodine concentration, radioactive isotopes, ammonium, pesticides, dioxins, and anti-nutritional factors, can be found in edible seaweed, whereas the cultivation climate has a significant impact on seaweed safety [106,107]. Contamination with heavy metals is the greatest threat factor. It is also necessary to select a reactor that takes into consideration the circumstances required for the reactor to attain high efficiency while taking into account the production scale needs and development habits of the strains of algae. The mixotrophic approach is, without a doubt, the best culture technique for promoting PBP accumulation. An eco-friendly method of achieving economical multifunctional resource usage is to use saltwater and industrial effluent as sources of fertilizers.

However, wastewater's high levels of pollutants and salt may have an effect on cyanobacterial growth. Physical equipment for recovering biomass is expensive, even though using chemical flocculation to gather biomass has shown significant advantages [108]. It is feasible to extract and purify cyanobacterial PBPs on a laboratory scale, but commercializing their production is challenging due to a number of obstacles, such as low selectivity, high energy costs, and a significant investment in equipment like chromatographic methods [109]. These limitations can be addressed by establishing connections between industry technicians and laboratory researchers. The difficulty is in designing the industrial bioreactor according to the necessary light exposure and intensity, even though cyanobacteria just need light, water, CO_2, and other nutrients to survive. It is important to construct a bioreactor with evenly distributed light intensity [110].

Moreover, cryo-EM has made it possible to compare the structural organization of PBPs across cyanobacterial species, revealing how environmental conditions shape their assembly patterns, chromophore arrangement, and efficiency of energy transfer. These structural insights create new opportunities for designing PBPs with greater stability, altered light-absorption properties, or customized photophysical features for biotechnological uses [111]. With ongoing improvements in cryo-EM such as higher resolution, better sample handling, and more advanced data analysis, the techniques are expected to become essential for linking detailed structural information with the functional and applied potential of phycobiliproteins.

Furthermore, the advancement of synthetic biology techniques opens new avenues for PBP biosynthesis optimization [112]. Recombinant strains with improved productivity, more chromophores, or altered protein component composition can be created using genetic engineering. An alternative to traditional algae culture is the rerouting of metabolic fluxes toward PBP pathways through the application of metabolic engineering techniques in model organisms like *Synechocystis* or *E. coli*. Furthermore, genome-scale metabolic models and CRISPR-Cas technologies can be used to further optimize these strains and accelerate their growth. To satisfy worldwide demands, it is crucial from an industrial standpoint to incorporate these modified strains into bioreactor systems that are designed for the economical and scalable production of PBPs. For the transfer from bench to market, it will be crucial to address issues with manufacturing costs, downstream processing, regulatory acceptability, and scaling-up. Furthermore, researchers ultimately to establish automated, continuous, and industrial production of PBPs by combining process engineering, biotechnology, and sustainability concepts.

5. Conclusions

PBPs are distinctive pigment-protein complexes that play a vital role in photosynthetic light-harvesting while possessing bioactive properties. Their unique structural arrangements, such as

trimeric and hexameric forms, provide stability and functional versatility, supporting a wide array of biotechnological applications. PBPs exhibit notable therapeutic potentials, including anti-diabetic, antitumor, neuroprotective, hepatoprotective, and immunomodulatory effects, mostly through their antioxidant, anti-inflammatory, and cytoprotective mechanisms. These multifunctional characteristics make PBPs highly promising for use in pharmaceutical, nutraceutical, and biomedical fields. In summary, the combination of their structural distinctiveness and bioactive properties establishes PBPs as valuable natural biomolecules with extensive biotechnological significance. Despite extensive research, the contributions of amino acids and the structural stability of PBPs to energy storage and transfer remain unclear. With the growing global energy demand causing a rapid depletion of fossil fuels, identifying renewable energy alternatives has become essential to prevent future energy crises. Understanding the energy-harvesting mechanisms in cyanobacteria is particularly important for advancing sustainable energy production. Therefore, challenges lie in exploring PBP-chlorophyll integrated systems to develop efficient green energy devices.

Author contributions

Study concept and design, S.J. and R.P.S.; manuscript writing, S.J., V.K.S., P.R., A.P.S., A.G., P.R. and R.T.; manuscript editing, S.J. and V.K.S.; manuscript review, S.J. and R.P.S. All authors have read and agreed to the published version of the manuscript.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

Sapana Jha (No. R/Dev. /Sch./ UGC Non-NET Fello./2022-23/52561) is thankful to BHU for providing institutional fellowship. Varsha K. Singh (09/0013(12862)/2021- EMR-1), Amit Gupta (09/0013(0912)/2019-EMR-I), and Palak Rana (09/0013 (16603)/2023-EMR-I) are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for the Senior Research Fellowship (SRF). Payel Rana (09/0013(21806)/2025-EMR-I) is thankful to the CSIR, New Delhi, India, for financial assistance in the form of Junior Research Fellowship (JRF). Ashish P. Singh (NTA Ref. No. 191620014505) and Riya Tripathi (NTA Ref. No. 231620041285) are thankful to the University Grants Commission (UGC), New Delhi, India, for the financial assistance in the form of a Senior Research Fellowship (SRF) and Junior Research Fellowship (JRF), respectively. The incentive grant received from IoE (Scheme no. 6031), Banaras Hindu University, Varanasi, India, to Rajeshwar Sinha is highly acknowledged.

Conflict of interest

The authors declare no conflicts of interest in this paper.

References

1. Li W, Su HN, Pu Y, et al. (2019) Phycobiliproteins: Molecular structure, production, applications, and prospects. *Biotechnol Adv* 37: 340–353. https://doi.org/10.1016/j.biotechadv.2019.01.008
2. Costa ML, Rodrigues JA, Azevedo J, et al. (2018) Hepatotoxicity induced by paclitaxel interaction with turmeric in association with a microcystin from a contaminated dietary supplement. *Toxicon* 150: 207–211. https://doi.org/10.1016/j.toxicon.2018.05.022
3. Regueiras A, Pereira S, Costa MS, et al. (2018) Differential toxicity of cyanobacteria isolated from marine sponges towards echinoderms and crustaceans. *Toxins* 10: 297. https://doi.org/10.3390/toxins10070297
4. Guan X, Wang J, Zhu J, et al. (2013) Photosystem II photochemistry and phycobiliprotein of the red algae *Kappaphycus alvarezii* and their implications for light adaptation. *BioMed Res Int* 2013: 256549. https://doi.org/10.1155/2013/256549
5. Zhang J, Ma J, Liu D, et al. (2017) Structure of phycobilisome from the red alga *Griffithsia pacifica*. *Nature* 551: 57–63. https://doi.org/10.1038/nature24278
6. Bryant DA, Gisriel CJ (2024) The structural basis for light harvesting in organisms producing phycobiliproteins. *Plant Cell* 36: 4036–4064. https://doi.org/10.1093/plcell/koae126
7. Jha S, Singh VK, Singh AP, et al. (2024) The radiant world of cyanobacterial phycobiliproteins: Examining their structure, functions, and biomedical potentials. *Targets* 2: 32–51. https://doi.org/10.3390/targets2010002
8. Singh VK, Jha S, Rana P, et al. (2023) Resilience and mitigation strategies of cyanobacteria under ultraviolet radiation stress. *Int J Mol Sci* 24: 12381. https://doi.org/10.3390/ijms241512381
9. Manirafasha E, Guo L, Jing K (2020) Nutraceutical and pharmaceutical applications of phycobiliproteins. In: *Pigments from microalgae handbook.* Springer, Cham. 575–584. https://doi.org/10.1007/978-3-030-50971-2_23
10. Bryant DA, Guglielmi G, de Marsac NT, et al. (1979) The structure of cyanobacterial phycobilisomes: A model. *Arch Microbiol* 123: 113–127. https://doi.org/10.1007/BF00446810
11. Pagels F, Guedes AC, Amaro HM, et al. (2019) Phycobiliproteins from cyanobacteria: Chemistry and biotechnological applications. *Biotechnol Adv* 37: 422–443. https://doi.org/10.1016/j.biotechadv.2019.02.010
12. Manirafasha E, Ndikubwimana T, Zeng X, et al. (2016) Phycobiliprotein: Potential microalgae derived pharmaceutical and biological reagent. *Biochem Eng J* 109: 282–296. https://doi.org/10.1016/j.bej.2016.01.025
13. Judson OP (2017) The energy expansions of evolution. *Nat Ecol Evol* 1: 0138. https://doi.org/10.1038/s41559-017-0138
14. McKay CP (2016) Water sources for cyanobacteria below desert rocks in the Negev Desert determined by conductivity. *Glob Ecol Conserv* 6: 145–151. https://doi.org/10.1016/j.gecco.2016.02.010
15. Zheng L, Zheng Z, Li X, et al. (2021) Structural insight into the mechanism of energy transfer in cyanobacterial phycobilisomes. *Nat Commun* 12: 5497. https://doi.org/10.1038/s41467-021-25813-y
16. Kawakami K, Hamaguchi T, Hirose Y, et al. (2022) Core and rod structures of a thermophilic cyanobacterial light-harvesting phycobilisome. *Nat Commun* 13: 3389. https://doi.org/10.1038/s41467-022-30962-9

17. Zhang W, Zhou J, Zhang Y, et al. (2025) Metabolic engineering of a high-light tolerant cyanobacterium *Synechocystis* sp. PCC 6803 for efficient biosynthesis of β-farnesene from CO_2. *Syst Microbiol Biomanufact* 5: 1464–1474. https://doi.org/10.1007/s43393-025-00391-y
18. Aryee AN, Agyei D, Akanbi TO (2018) Recovery and utilization of seaweed pigments in food processing. *Curr Opin Food Sci* 19: 113–119. https://doi.org/10.1016/j.cofs.2018.03.013
19. Chen H, Qi H, Xiong P (2022) Phycobiliproteins—A family of algae-derived biliproteins: productions, characterization and pharmaceutical potentials. *Mar Drugs* 20: 450. https://doi.org/10.3390/md20070450
20. Gan F, Bryant DA (2015) Adaptive and acclimative responses of cyanobacteria to far-red light. *Environ Microbiol* 17: 3450–3465. https://doi.org/10.1111/1462-2920.12992
21. Li Y, Lin Y, Garvey CJ, et al. (2016) Characterization of red-shifted phycobilisomes isolated from the chlorophyll f-containing cyanobacterium *Halomicronema hongdechloris*. *BBA-Bioenergetics* 1857: 107–114. https://doi.org/10.1016/j.bbabio.2015.10.009
22. Ashaolu TJ, Samborska K, Lee CC, et al. (2021) Phycocyanin, a super functional ingredient from algae; properties, purification characterization, and applications. *Int J Biol Macromol* 193: 2320–2331. https://doi.org/10.1016/j.ijbiomac.2021.11.064
23. Kehoe DM (2010) Chromatic adaptation and the evolution of light color sensing in cyanobacteria. *Proc Natl Acad Sci USA* 107: 9029–9030. https://doi.org/10.1073/pnas.1004510107
24. Sonani RR, Patel S, Bhastana B, et al. (2017) Purification and antioxidant activity of phycocyanin from *Synechococcus* sp. R42DM isolated from industrially polluted site. *Bioresource Technol* 245: 325–331. https://doi.org/10.1016/j.biortech.2017.08.129
25. Chaubey MG, Patel SN, Rastogi RP, et al. (2020) Cyanobacterial pigment protein allophycocyanin exhibits longevity and reduces Aβ-mediated paralysis in *C. elegans*: Complicity of FOXO and NRF2 ortholog DAF-16 and SKN-1. *3 Biotech* 10: 332. https://doi.org/10.1007/s13205-020-02314-1
26. Braune S, Krüger-Genge A, Kammerer S, et al. (2021) Phycocyanin from *Arthrospira platensis* as potential anti-cancer drug: Review of *in vitro* and *in vivo* studies. *Life* 11: 91. https://doi.org/10.3390/life11020091
27. Dagnino-Leone J, Figueroa CP, Castañeda ML, et al. (2022) Phycobiliproteins: Structural aspects, functional characteristics, and biotechnological perspectives. *Comput Struct Biotec J* 20: 1506–1527. https://doi.org/10.1016/j.csbj.2022.02.016
28. Zheng J, Inoguchi T, Sasaki S, et al. (2012) Phycocyanin and phycocyanobilin from *Spirulina platensis* protect against diabetic nephropathy by inhibiting oxidative stress. *Am J Physiol-Reg I* 304: R110–R120. https://doi.org/10.1152/ajpregu.00648.2011
29. Minic SL, Stanic-Vucinic D, Mihailovic J, et al (2016) Digestion by pepsin releases biologically active chromopeptides from C-phycocyanin, a blue-colored biliprotein of microalga *Spirulina*. *J Proteomics* 147: 132–139. https://doi.org/10.1016/j.jprot.2016.03.043
30. Liu J, Bai X, Fu P (2022) In silico and *in vitro* assessment of bioactive peptides from *Arthrospira platensis* phycobiliproteins for DPP-IV inhibitory activity, ACE inhibitory activity, and antioxidant activity. *J Appl Phycol* 34: 1497–1511. https://doi.org/10.1007/s10811-022-02732-z
31. Tounsi L, Ben Hlima H, Hentati F, et al. (2023) Microalgae: A promising source of bioactive phycobiliproteins. *Mar Drugs* 21: 440. https://doi.org/10.3390/md21080440

32. Munawaroh HSH, Gumilar GG, Nurjanah F, et al. (2020) *In-vitro* molecular docking analysis of microalgae extracted phycocyanin as an anti-diabetic candidate. *Biochem Eng J* 161: 107666. https://doi.org/10.1016/j.bej.2020.107666
33. Hao S, Li F, Li Q, et al. (2022) Phycocyanin protects against high glucose high fat diet induced diabetes in mice and participates in AKT and AMPK signaling. *Foods* 11: 3183. https://doi.org/10.3390/foods11203183
34. Husain A, Alouffi S, Khanam A, et al. (2022) Therapeutic efficacy of natural product 'C-phycocyanin'in alleviating streptozotocin-induced diabetes via the inhibition of glycation reaction in rats. *Int J Mol Sci* 23: 14235. https://doi.org/10.3390/ijms232214235
35. Ren Z, Xie Z, Cao D, et al. (2018) C-phycocyanin inhibits hepatic gluconeogenesis and increases glycogen synthesis via activating Akt and AMPK in insulin resistance hepatocytes. *Food Funct* 9: 2829–2839. https://doi.org/10.1039/C8FO00257F
36. Ziyaei K, Abdi F, Mokhtari M, et al. (2023) Phycocyanin as a nature-inspired antidiabetic agent: A systematic review. *Phytomedicine* 119: 154964. https://doi.org/10.1016/j.phymed.2023.154964
37. Ou Y, Ren Z, Wang J, et al. (2016) Phycocyanin ameliorates alloxan-induced diabetes mellitus in mice: Involved in insulin signaling pathway and GK expression. *Chem Biol Interact* 247: 49–54. https://doi.org/10.1016/j.cbi.2016.01.018
38. Gao Y, Liu C, Wan G, et al. (2016) Phycocyanin prevents methylglyoxal-induced mitochondrial-dependent apoptosis in INS-1 cells by Nrf2. *Food Funct* 7: 1129–1137. https://doi.org/10.1039/C5FO01548K
39. Li Y, Aiello G, Bollati C, et al. (2020) Phycobiliproteins from *Arthrospira platensis* (*Spirulina*): A new source of peptides with dipeptidyl peptidase-IV inhibitory activity. *Nutrients* 12: 794. https://doi.org/10.3390/nu12030794
40. Villaró S, Jiménez-Márquez S, Musari E, et al. (2023) Production of enzymatic hydrolysates with *in vitro* antioxidant, antihypertensive, and antidiabetic properties from proteins derived from *Arthrospira platensis*. *Food Res Int* 163: 112270. https://doi.org/10.1016/j.foodres.2022.112270
41. Rimbau V, Camins A, Pubill D, et al. (2001) C-phycocyanin protects cerebellar granule cells from low potassium/serum deprivation-induced apoptosis. *Naunyn-Schmied Arch Pharmacol* 364: 96–104. https://doi.org/10.1007/s002100100437
42. Pentón-Rol G, Martínez-Sánchez G, Cervantes-Llanos M, et al. (2011) C-phycocyanin ameliorates experimental autoimmune encephalomyelitis and induces regulatory T cells. *Int Immunopharmacol* 11: 29–38. https://doi.org/10.1016/j.intimp.2010.10.001
43. Marín-Prida J, Pentón-Rol G, Rodrigues FP, et al. (2012) C-phycocyanin protects SH-SY5Y cells from oxidative injury, rat retina from transient ischemia and rat brain mitochondria from Ca^{2+}/phosphate-induced impairment. *Brain Res Bull* 89: 159–167. https://doi.org/10.1016/j.brainresbull.2012.08.011
44. Ou Y, Zheng S, Lin L, et al. (2010) Protective effect of C-phycocyanin against carbon tetrachloride-induced hepatocyte damage *in vitro* and *in vivo*. *Chem Biol Int* 185: 94–100. https://doi.org/10.1016/j.cbi.2010.03.013
45. Cervantes-Llanos M, Lagumersindez-Denis N, Marín-Prida J, et al. (2018) Beneficial effects of oral administration of c-phycocyanin and phycocyanobilin in rodent models of experimental autoimmune encephalomyelitis. *Life Sci* 194: 130–138. https://doi.org/10.1016/j.lfs.2017.12.032

46. Wang C, Zhao Y, Wang L, et al. (2021) C-phycocyanin mitigates cognitive impairment in doxorubicin-induced chemobrain: impact on neuroinflammation, oxidative stress, and brain mitochondrial and synaptic alterations. *Neurochem Res* 46: 149–158. https://doi.org/10.1007/s11064-020-03164-2
47. Min SK, Park JS, Luo L, et al. (2015) Assessment of C-phycocyanin effect on astrocytes-mediated neuroprotection against oxidative brain injury using 2D and 3D astrocyte tissue model. *Sci Rep* 5: 14418. https://doi.org/10.1038/srep14418
48. Vadiraja BB, Gaikwad NW, Madyastha KM (1998) Hepatoprotective effect of C-phycocyanin: Protection for carbon tetrachloride and R-(+)-pulegone-mediated hepatotoxicty in rats. *Biochem Bioph Res Co* 249: 428–431. https://doi.org/10.1006/bbrc.1998.9149
49. Nagaraj S, Arulmurugan P, Rajaram MG, et al. (2012) Hepatoprotective and antioxidative effects of C-phycocyanin from *Arthrospira maxima* SAG 25780 in CCl4-induced hepatic damage rats. *Biomed Prev Nutr* 2: 81–85. https://doi.org/10.1016/j.bionut.2011.12.001
50. Soni B, Visavadiya NP, Madamwar D (2008) Ameliorative action of cyanobacterial phycoerythrin on CCl_4-induced toxicity in rats. *Toxicology* 248: 59–65. https://doi.org/10.1016/j.tox.2008.03.008
51. Fan C, Jiang J, Yin X, et al. (2012) Purification of selenium-containing allophycocyanin from selenium-enriched *Spirulina platensis* and its hepatoprotective effect against t-BOOH-induced apoptosis. *Food Chem* 134: 253–261. https://doi.org/10.1016/j.foodchem.2012.02.130
52. Nemoto-Kawamura C, Hirahashi T, Nagai T, et al. (2004) Phycocyanin enhances secretary IgA antibody response and suppresses allergic IgE antibody response in mice immunized with antigen-entrapped biodegradable microparticles. *J Nutr Sci Vitaminol* 50: 129–136. https://doi.org/10.3177/jnsv.50.129
53. Ivanova KG, Stankova KG, Nikolov VN, et al. (2010) The biliprotein C-phycocyanin modulates the early radiation response: A pilot study. *Mutat Res-Gen Toxi En* 695: 40–45. https://doi.org/10.1016/j.mrgentox.2009.11.002
54. Lee D, Nishizawa M, Shimizu Y, et al. (2017) Anti-inflammatory effects of dulse (*Palmaria palmata*) resulting from the simultaneous water-extraction of phycobiliproteins and chlorophyll *a*. *Food Res Int* 100: 514–521. https://doi.org/10.1016/j.foodres.2017.06.040
55. Chen HW, Yang TS, Chen MJ, et al. (2014) Purification and immunomodulating activity of C-phycocyanin from *Spirulina platensis* cultured using power plant flue gas. *Process Biochem* 49: 1337–1344. https://doi.org/10.1016/j.procbio.2014.05.006
56. Grover P, Bhatnagar A, Kumari N, et al. (2021) C-phycocyanin-a novel protein from *Spirulina platensis-in vivo* toxicity, antioxidant and immunomodulatory studies. *Saudi J Biol Sci* 28: 1853–1859. https://doi.org/10.1016/j.sjbs.2020.12.037
57. McCarty MF (2011) Clinical potential of phycocyanobilin for induction of T regulatory cells in the management of inflammatory disorders. *Med Hypotheses* 77: 1031–1033. https://doi.org/10.1016/j.mehy.2011.08.041
58. Hao S, Li S, Wang J, et al. (2019) Phycocyanin exerts anti-proliferative effects through down-regulating TIRAP/NF-κB activity in human non-small cell lung cancer cells. *Cells* 8: 588. https://doi.org/10.3390/cells8060588
59. Liao G, Gao B, Gao Y, et al. (2016) Phycocyanin inhibits tumorigenic potential of pancreatic cancer cells: Role of apoptosis and autophagy. *Sci Rep* 6: 34564. https://doi.org/10.1038/srep34564

60. Jiang L, Wang Y, Zhu F, et al. (2019) Molecular mechanism of anti-cancer activity of the nano-drug C-PC/CMC-CD59sp NPs in cervical cancer. *J Cancer* 10: 92–104. https://doi.org/10.7150/jca.27462
61. Subhashini J, Mahipal SV, Reddy MC, et al. (2004) Molecular mechanisms in C-phycocyanin induced apoptosis in human chronic myeloid leukemia cell line-K562. *Biochem Pharmacol* 68: 453–462. https://doi.org/10.1016/j.bcp.2004.02.025
62. Li B, Gao MH, Zhang XC, et al. (2006) Molecular immune mechanism of C-phycocyanin from *Spirulina platensis* induces apoptosis in HeLa cells *in vitro*. *Biotechnol Appl Biochem* 43: 155–164. https://doi.org/10.1042/BA20050142
63. Jiang L, Wang Y, Liu G, et al. (2018) C-Phycocyanin exerts anti-cancer effects via the MAPK signaling pathway in MDA-MB-231 cells. *Cancer Cell Int* 18: 12. https://doi.org/10.1186/s12935-018-0511-5
64. Kaur P, Dhandayuthapani S, Venkatesan T, et al. (2020) Molecular mechanism of C-phycocyanin induced apoptosis in LNCaP cells. *Bioorg Med Chem* 28: 115272. https://doi.org/10.1016/j.bmc.2019.115272
65. Gantar M, Dhandayuthapani S, Rathinavelu A (2012) Phycocyanin induces apoptosis and enhances the effect of topotecan on prostate cell line LNCaP. *J Med Food* 15: 1091–1095. https://doi.org/10.1089/jmf.2012.0123
66. Singh AP, Gupta A, Jaiswal J, et al. (2025) Phycobiliproteins: Phycocyanin, allophycocyanin, and phycoerythrin. In: *Microalgae and one health.* Academic Press. 171–186. https://doi.org/10.1016/B978-0-443-22080-7.00033-8
67. Akbarizare M, Ofoghi H, Hadizadeh M, et al. (2020) *In vitro* assessment of the cytotoxic effects of secondary metabolites from *Spirulina platensis* on hepatocellular carcinoma. *Egypt Liver J* 10: 11. https://doi.org/10.1186/s43066-020-0018-3
68. Safaei M, Maleki H, Soleimanpour H, et al. (2019) Development of a novel method for the purification of C-phycocyanin pigment from a local cyanobacterial strain *Limnothrix* sp. NS01 and evaluation of its anticancer properties. *Sci Rep* 9: 9474. https://doi.org/10.1038/s41598-019-45905-6
69. Bottone C, Camerlingo R, Miceli R, et al. (2019) Antioxidant and anti-proliferative properties of extracts from heterotrophic cultures of *Galdieria sulphuraria*. *Nat Prod Res* 33: 1659–1663. https://doi.org/10.1080/14786419.2018.1425853
70. Ying J, Tang Z, Zhao G, et al. (2021) Transcriptionomic study on apoptosis of SKOV-3 cells induced by phycoerythrin from *Gracilaria lemaneiformis*. *Anti-Cancer Agent Me* 21: 1240–1249. https://doi.org/10.2174/1871520620666200908102621
71. Sanattalab E (2024) Insights into marine bioluminescence: Unravelling the intricacies of natural fluorescence probes. *Hacettepe J Biol Chem* 52: 285–296. https://doi.org/10.15671/hjbc.1465113
72. Rodriguez EA, Tran GN, Gross LA, et al. (2016) A far-red fluorescent protein evolved from a cyanobacterial phycobiliprotein. *Nat Methods* 13: 763–769. https://doi.org/10.1038/nmeth.3935
73. Jespersen L, Strømdahl LD, Olsen K, et al. (2005) Heat and light stability of three natural blue colorants for use in confectionery and beverages. *Eur Food Res Technol* 220: 261–266. https://doi.org/10.1007/s00217-004-1062-7
74. Adli SA, Ali F, Azmi AS, et al. (2020) Development of biodegradable cosmetic patch using a polylactic acid/phycocyanin–alginate composite. *Polymer* 12: 1669. https://doi.org/10.3390/polym12081669

75. Zhang Y, Liu H, Dai X, et al. (2021) Cyanobacteria-based near-infrared light-excited self-supplying oxygen system for enhanced photodynamic therapy of hypoxic tumors. *Nano Res* 14: 667–673. https://doi.org/10.1007/s12274-020-3094-0
76. Sekar S, Chandramohan M (2008) Phycobiliproteins as a commodity: Trends in applied research, patents and commercialization. *J Appl Phycol* 20: 113–136. https://doi.org/10.1007/s10811-007-9188-1
77. Xing FL, Zhang ZH, Yang CL, et al. (2022) Phycoerythrobilin/phycourobilin as efficient sensitizers of dye-sensitized solar cell. *Soil Energy* 243: 494–499. https://doi.org/10.1016/j.solener.2022.08.028
78. Qiang X, Wang L, Niu J, et al. (2021) Phycobiliprotein as fluorescent probe and photosensitizer: A systematic review. *Int J Biol Macromol* 193: 1910–1917. https://doi.org/10.1016/j.ijbiomac.2021.11.022
79. Bazylińska U, Kulbacka J, Schmidt J, et al. (2018) Polymer-free cubosomes for simultaneous bioimaging and photodynamic action of photosensitizers in melanoma skin cancer cells. *J Colloid Interface Sci* 522: 163–173. https://doi.org/10.1016/j.jcis.2018.03.063
80. Mokwena MG, Kruger CA, Ivan MT, et al. (2018) A review of nanoparticle photosensitizer drug delivery uptake systems for photodynamic treatment of lung cancer. *Photodiagn Photodyn* 22: 147–154. https://doi.org/10.1016/j.pdpdt.2018.03.006
81. Loshchenov MV, Levkin VV, Chernousov AF, et al. (2018) Laser video fluorescence diagnosis of stomach diseases. *Sovrem Tehnol Med* 10: 42. https://doi.org/10.17691/stm2018.10.4.05
82. Theresia C, Zheng J, Chen XY (2017) Topical ALA-PDT as alternative therapeutic option in treatment-recalcitrant dermatosis: report of 4 cases. *Photodiagn Photodyn* 20: 189–192. https://doi.org/10.1016/j.pdpdt.2017.10.010
83. Grossman AR, Schaefer MR, Chiang GG, et al. (1993) The phycobilisome, a light-harvesting complex responsive to environ mental conditions. *Microbiol Rev* 57: 725–749. https://doi.org/10.1128/mr.57.3.725-749.1993
84. Loos D, Cotlet M, De Schryver F, et al. (2004) Single-molecule spectroscopy selectively probes donor and acceptor chromophores in the phycobiliprotein allophycocyanin. *Biophys J* 87: 2598–2608. https://doi.org/10.1529/biophysj.104.046219
85. Peng PP, Dong LL, Sun YF, et al. (2014) The structure of allophycocyanin B from *Synechocystis* PCC 6803 reveals the structural basis for the extreme redshift of the terminal emitter in phycobilisomes. *Acta Cryst* 70: 2558–2569. https://doi.org/10.1107/S1399004714015776
86. Scheer H, Zhao KH (2008) Biliprotein maturation: The chromophore attachment. *Mol Microbiol* 68: 263–276. https://doi.org/10.1111/j.1365-2958.2008.06160.x
87. Sonani RR, Gupta GD, Madamwar D, et al. (2015) Crystal structure of allophycocyanin from marine cyanobacterium *Phormidium* sp. A09DM. *PLoS ONE* 10: e0124580. https://doi.org/10.1371/journal.pone.0124580
88. Biswas A, Vasquez YM, Dragomani TM, et al. (2010) Biosynthesis of cyanobacterial phycobiliproteins in *Escherichia coli*: chromophorylation efficiency and specificity of all bilin lyases from *Synechococcus* sp. strain PCC 7002. *Appl Environ Microbiol* 76: 2729–2739. https://doi.org/10.1128/AEM.03100-09
89. Tang K, Ding WL, Höppner A, et al. (2015) The terminal phycobilisome emitter, LCM: A light-harvesting pigment with a phytochrome chromophore. *Proc Natl Acad Sci USA* 112: 15880–15885. https://doi.org/10.1073/pnas.1519177113

90. Sowndarya DS (2021) Extraction and purification of C-phycocyanin from *Arthrospira* species and its application in LIP-BALM formulation. *Int J Creat Res Thoughts* 9: b492–b502.
91. Feng Y, Lu H, Hu J, et al. (2022) Anti-aging effects of R-phycocyanin from *Porphyra haitanensis* on HUVEC cells and *Drosophila melanogaster*. *Mar Drugs* 20: 468. https://doi.org/10.3390/md20080468
92. Wu LC, Lin YY, Yang SY, et al. (2011) Antimelanogenic effect of c-phycocyanin through modulation of tyrosinase expression by upregulation of ERK and downregulation of p38 MAPK signaling pathways. *J Biomed Sci* 18: 74. https://doi.org/10.1186/1423-0127-18-74
93. Nihal B, Gupta NV, Gowda DV, et al. (2018) Formulation and development of topical anti acne formulation of *spirulina* extract. *Int J Appl Pharm* 10: 229–233. https://doi.org/10.22159/IJAP.2018V10I6.26334
94. Athiyappan KD, Routray W, Paramasivan B (2024) Phycocyanin from *Spirulina*: A comprehensive review on cultivation, extraction, purification, and its application in food and allied industries. *Food Humanity* 2: 100235. https://doi.org/10.1016/j.foohum.2024.100235
95. Luzardo-Ocampo I, Ramírez-Jiménez AK, Yañez J, et al. (2021) Technological applications of natural colorants in food systems: A review. *Foods* 10: 634. https://doi.org/10.3390/foods10030634
96. Li Y, Li X, Liang ZP, et al. (2022) Progress of microencapsulated phycocyanin in food and pharma industries: A review. *Molecules* 27: 5854. https://doi.org/10.3390/molecules27185854
97. Alam MA, Xu JL, Wang Z (2020) *Microalgae biotechnology for food, health and high value products*. Springer Singapore. https://doi.org/10.1007/978-981-15-0169-2
98. Dewi EN, Kurniasih RA, Purnamayati L (2018) The application of microencapsulated phycocyanin as a blue natural colorant to the quality of jelly candy. In: *IOP Conference Series: Earth Environ Sci* 116: 012047. https://doi.org/10.1088/1755-1315/116/1/012047
99. de O Moreira I, Passos TS, Chiapinni C, et al. (2012) Colour evaluation of a phycobiliprotein-rich extract obtained from *Nostoc* PCC9205 in acidic solutions and yogurt. *J Sci Food Agric* 92: 598–605. https://doi.org/10.1002/jsfa.4614
100. Galetovic A, Seura F, Gallardo V, et al. (2020) Use of phycobiliproteins from atacama cyanobacteria as food colorants in a dairy beverage prototype. *Foods* 9: 244. https://doi.org/10.3390/foods9020244
101. García AB, Longo E, Bermejo R (2021) The application of a phycocyanin extract obtained from *Arthrospira platensis* as a blue natural colorant in beverages. *J Appl Phycol* 33: 3059–3070. https://doi.org/10.1007/s10811-021-02522-z
102. Madji S, Antih J, Tabib M, et al. (2025) Extraction, purification, bioactivity and pharmacological effects of phycobiliproteins (PBPs): A review. *Analytica* 6: 44. https://doi.org/10.3390/analytica6040044
103. Kovaleski G, Kholany M, Dias LMS, et al. (2022) Extraction and purification of phycobiliproteins from algae and their applications. *Front Chem* 10: 1065355. https://doi.org/10.3389/fchem.2022.1065355
104. Zahra Z, Choo DH, Lee H, et al. (2020) Cyanobacteria: Review of current potentials and applications. *Environments* 7: 13. https://doi.org/10.3390/environments7020013
105. Minić S, Gligorijević N, Veličković L, et al. (2024) Narrative review of the current and future perspectives of phycobiliproteins' applications in the food industry: From natural colors to alternative proteins. *Int J Mol Sci* 25: 7187. https://doi.org/10.3390/ijms25137187

106. Rawiwan P, Peng Y, Paramayuda IGPB, et al. (2022) Red seaweed: A promising alternative protein source for global food sustainability. *Trends Food Sci Technol* 123: 37–56. https://doi.org/10.1016/j.tifs.2022.03.003
107. Van der Spiegel M, Noordam MY, Van der Fels-Klerx HJ (2013) Safety of novel protein sources (insects, microalgae, seaweed, duckweed, and rapeseed) and legislative aspects for their application in food and feed production. *Compr Rev Food Sci F* 12: 662–678. https://doi.org/10.1111/1541-4337.12032
108. Liang Y, Deng L, Feng Z, et al. (2023) A chitosan-based flocculation method for efficient recovery of high-purity B-phycoerythrin from a low concentration of phycobilin in wastewater. *Molecules* 28: 3600. https://doi.org/10.3390/molecules28083600
109. Kovaleski G, Kholany M, Dias LMS, et al. (2022) Extraction and purification of phycobiliproteins from algae and their applications. *Front Chem* 10: 1065355. https://doi.org/10.3389/fchem.2022.1065355
110. Zahra Z, Choo DH, Lee H, et al. (2020) Cyanobacteria: Review of current potentials and applications. *Environments* 7: 13. https://doi.org/10.3390/environments7020013
111. Gisriel CJ, Shen G, Brudvig GW, et al. (2024) Structure of the antenna complex expressed during far-red light photoacclimation in *Synechococcus* sp. PCC 7335. *J Biol Chem* 300: 105590. https://doi.org/10.1016/j.jbc.2023.105590
112. Ko YJ, Lee ME, Cho BH, et al. (2024) Bioproduction of porphyrins, phycobilins, and their proteins using microbial cell factories: engineering, metabolic regulations, challenges, and perspectives. *Crit Rev Biotechnol* 44: 373–387. https://doi.org/10.1080/07388551.2023.2168512

AIMS Press