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Review Article

Cyano-Phycocyanin: A Potential Photoprotective Nutraceutical to Reduce Ultraviolet Radiation-Induced Damage and Skin Cancer Risk

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Purpose

Antioxidant supplementation has been clinically proven to prevent tissue damage and boost repair mechanisms by mitigating oxidative stress. This article aims to achieve an in-depth understanding of Cyano-Phycocyanin's (C-PC)'s mechanism of action and overall benefits after exposure to ultraviolet radiation (UVR) from the sun. C-PC, a phycobiliprotein extracted from nutrient-dense, safe-to-consume blue-green algae known as Spirulina or Arthrospira platensis (AP), is considered a "superfood" due to its exceptional nutritional profile and bioactive properties. C-PC's potent antioxidant and anti-inflammatory benefits are well-known to promote tissue repair and overall health. UVR accounts for approximately 80-90% of skin environmental aging and is the leading cause of skin cancer (non-melanoma and melanoma). Thus, our hypothesis suggests that C-PC supplementation as an adjunct photoprotective therapy may help prevent or diminish intrinsic and/or environmental aging linked to UVR and the tumorigenicity of UVR.

Method

A PubMed, Clinical Key, and Cochrane Library literature search was conducted using the following search terms: cyano-phycocyanin, spirulina, antioxidant, free-radical damage, ultraviolet radiation, oxidative stress, and skin cancer. Twenty pertinent articles were retrieved as the basis for this clinical review.

Results

Robust in vitro and animal models evidence-based research showed a positive correlation between C-PC supplementation, and cellular protection suggesting a potential role in skin cancer protection.

Conclusion

C-PC in vivo and in vitro research indicates promising results in repairing and reversing cellular damage. However, while preclinical data is compelling, human clinical evidence is still pending to determine the level of benefit linked to oral supplementation with C-PC.

INTRODUCTION

Skin cancer remains one of the most preventable malignancies. Yet its incidence rates continue to rise despite research, policy changes, and decades of public health initiatives focused on behavioral modification, including sunscreen campaigns, tanning bed legislation, and education on UV exposure.[1-4] Despite all these educational efforts in the United States, the number of people diagnosed with skin cancer is higher than the combination of all other cancers diagnosed annually.[3,4] Melanoma affects around 230,000 annually, while non-melanoma skin cancer (NMSC) exceeds 5.4 million cases yearly.[3,4] This trend has significant clinical and economic implications, as treatment costs for melanoma and NMSC were estimated to be around eight billion dollars.[4] Skin cancer has become a significant burden to the health care system.

Ultraviolet radiation (UV) is a known primary environmental driver for developing cutaneous malignancy and is responsible for upwards of 80-90 percent of all skin cancer cases.[2,5-8] While there are three distinct wavelengths of UV radiation categorized into A, B, and C, both UVA and UVB are known to be involved in carcinogenesis, albeit their mechanisms differ. UVA, known to induce indirect oxidative stress and single-strand DNA breaks, whereas UVB causes direct DNA damage, leading to mutations critical in skin

cancer development, highlighting the importance of understanding the distinct effects of UV radiation.[2] Chronic unprotected UV exposure leads to cumulative molecular damage, resulting in promoting tumor development and progression.

While numerous sun-protective strategies are being implemented, they focus on minimizing UV exposure through sunscreen use, protective clothing, and other behavioral modifications. Despite public awareness efforts, the rise in incidence rates suggests that other mechanisms are at play. These efforts directed at UV protection serve as important modifiers but nutraceutical and nutritional interventions may enhance the skin's intrinsic capacity to neutralize UV-induced damage. Currently, this represents a complementary and understudied strategy for photoprotection.

The current literature supports the hypothesis that supplementing with anti-oxidants may bolster the skin's natural defense mechanisms by decreasing reactive oxygen species (ROS), limiting DNA damage, and enhancing the skin's immune defenses and repair. This review explores the potential adjuvant use of Cyano-Phycocyanin (C-PC) to reduce ROS and DNA damage and enhance the skin's natural immune response and repair mechanisms, with the potential to decrease skin cancer prevalence.

CYANO-PHYCOCYANIN ANTI-OXIDANT BENEFITS

There has been a recent surge of interest and research in algal bioactives as potential anti-oxidants that may help mitigate UVR-induced damage. C-PC is a phycobiliprotein extracted from *Arthrospira platensis* (AP) or Spirulina.[9] Spirulina, a nutrient-dense blue-green non-toxic algae, is considered the "best food for the future" or a superfood.[9-11] More specifically, Spirulina has been utilized as a dietary supplement in food due to its high protein value (60-70%).[10,11] The Food and Drug Administration identifies Spirulina as safe for human consumption.[9,10] In addition to its high protein content **(TABLE 1)**, it is also rich in minerals such as iron, magnesium, potassium and trace elements like zinc; vitamins including B1, B2, B3, E and beta-carotene; anti-oxidants such as phycocyanin, chlorophyll, betacarotene, and superoxide dismutase (SOD); fatty acids including gamma-linolenic acid (GLA) and omega6 fatty acid, and polysaccharides like immulina. These confer potential medicinal benefits on Spirulina, including anti-oxidant and anti-inflammatory properties, anti-glycation effects, immune support, cardiovascular health benefits, beneficial effects on insulin sensitivity and blood glucose control, antimicrobial properties, promotion of detoxification, and skin health benefits, including wound healing.[9,10]

C-PC, a pigment-protein complex, has a vibrant blue color due to its bilin chromophores, which make up approximately 10-20% of Spirulina's total biomass.[12] C-PC has been extensively studied for its potential therapeutic benefits, including anti-oxidant, anti-inflammatory, immune-modulatory, anti-cancer, wound-healing, and other health-promoting properties, such as its ability to reduce UVR-induced skin damage.[9,11,13] Specifically, C-PC has been found to play a potential role in preventing skin cancer by either reducing UVR damage or by promoting skin repair.[9] One of the mechanisms involved in UV-protection by C-PC is its ability to directly scavenge free radicals, including $O^{2\bullet-}$, OH-, and H_2O_2, preventing oxidative stress.[9] In addition, C-PC enhances the activity of endogenous anti-oxidant enzymes such as SOD, catalase (CAT), and glutathione peroxidase (GPx),[9-11,14] and downregulates pro-oxidant enzymes such as nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase.[15]

Humans have evolved multiple endogenous anti-oxidant defenses, such as SOD, to protect essential biomolecules against damage caused by ROS generated endogenously (eg, during cellular metabolism, inflammation, aging, and cancer) and exogenously (eg, UVR, pollution, certain foods, and drugs).[16] Anti-oxidants reduce, repair, and even prevent ROS-induced damage to specific biomolecules such as proteins, nucleic acids, and lipids.[16] It has three known modes of action: (i) direct scavengers of already formed ROS; (ii) inhibition of the formation of ROS via their cellular source; and (iii) removing or repairing damages or modifications as a result of ROS.[17] Though ROS generation can be beneficial to signal molecules in metabolism at low lev-

Table 1. Nutrient composition of spirulina[1,2]

Spirulina Component	Percentage (%) by dry weight
Proteins (all essential amino acids, C-PC, and other enzymes)	60-70
Carbohydrates (glycogen, rhamnose-rich polymers, and immulina)	15-25
Phycocyanin (C-PC)	10-20
Lipids (gamma-linolenic acid (GLA), and omega-6 fatty acid)	4-9
Vitamins (B1, B2, B3), Vitamin E, Provitamin A (beta-carotene)	1-2
Pigments (non-phycocyanin)	1-2
Minerals	6-10
Fiber	2-5
Cyanophycin	1-5
Residual water	4-8
Others (superoxide dismutase, phenolic compounds, trace bioactive molecules)	<1

1.Braune S, Kruger-Genge A, Kammerer S, Jung F, Kupper JH. Phycocyanin from *Arthrospira platensis* as Potential Anti-Cancer Drug: Review of *In vitro* and *In* Vivo Studies, *Life (Basel).*2021 Jan27;11(2);91. Doi:10.3390/life11020091. PMID: 33513794:PMCID:PMC7911896. 2.Fernandes R, Campos J, Serra M, Fidalgo J, Almeida H, Casas A, Toubarro D, Barros AIRNA. Exploring the Benefits of Phycocyanin: From Spirulina Cultivation to Its Widespread Applications. *Pharmaceuticals (Basel).* 2023 Apr 14;16(4):592. doi: 10.3390/ph16040592. PMID:

els, the excess stimulation of ROS exogenously and endogenously can overwhelm normal tissue or cellular defenses, leading to oxidative stress and biological damage.[2,18] C-PC, as an anti-oxidant, can potentially target excess oxidative stress and its damaging effects at the cellular level by stabilizing ROS radicals/non-radicals to prevent damage.[17, 18] This review will explore the potential of C-PC, with its strong anti-oxidant and anti-inflammatory properties, to help protect and repair the skin from UVR-induced damage.

METHODS

PubMed, ClinicalKey, and the Cochrane Library were used to conduct a literature search, as they successfully identified C-PC and other terms required for the study. Other databases, such as UpToDate and Clinical Pharmacology, did not include any findings on C-PC and were therefore not used. Initial search terms included Spirulina, phycocyanin, anti-oxidant, and skin cancer prevention. Additional search terms included C-PC, oxidative stress, free-radical damage, anti-inflammatory effects, immunomodulation, anti-cancer effects, and UVR-induced DNA damage. The search was further narrowed to 2019-2025; however, research beyond this period was considered and used for foundational work on the topic. Articles prioritized using refined terms on the anti-cancer properties of C-PC, the impact of oxidative stress, and the proposed cellular mechanisms of action of C-PC were identified, yielding a total of twenty manuscripts. Research on C-PC included both in vivo and in vitro studies conducted in multiple countries, including the US, Switzerland, China, India, Cuba, Brazil, Korea, Taiwan, and Japan. All in vitro and in vivo studies, except the Japanese wound-healing study, used analysis of variance (ANOVA), with $p < 0.05$ considered statistically significant. The Japanese study analyzed the data using Student's t-test, with $p < 0.05$ considered statistically significant. We identified two small human clinical studies (in Japan and the US) focused on the nutraceutical effects of C-PC as an anti-oxidant. The American observational study (n = 4; two females and two males between the ages of 30 and 60 years old) examined the use of C-PC that was patent pending. The Japanese clinical study was a randomized, double-blind, placebo-controlled, parallel-group comparison (n = 96, females between 20 and 65 years old).

RESULTS

IN VITRO AND ANIMAL STUDIES

C-PC has been extensively studied in vivo and in vitro for its anti-oxidant properties. C-PC effectively scavenges ROS, including $O2^{\bullet-}$, H2O2, and $OH^{\bullet}$, thereby reducing oxidative stress. Its strong radical-scavenging capacity is often comparable to or superior to that of standard anti-oxidants such as ascorbic acid or Trolox.[19] C-PC also reduces lipid peroxidation by preventing the formation of lipid hydroperoxides, resulting in membrane protection and increased cell viability.[20] In addition, C-PC decreased mitochondrial ROS, as detected by MitoSOX and DCF-DA probes via confocal microscopy, suggesting that this molecule mitigates mitochondrial oxidative stress, preserving cellular energy production.[19] Animal studies using a Zebrafish model confirmed this observation by showing that purified anti-oxidant peptides from C-PC increased mitochondrial superoxide dismutase (SOD2) expression via activating the Nfr2 signaling pathway and having a protective role on H_2O_2-induced oxidative stress.[10,21] Other animal models showed similar results. For example, C-PC supplementation decreased liver damage and membrane damage measured as malondialdehyde (MDA) while increasing hepatic activity of CAT, SOD, and GPx in Golden Syrian hamsters fed with a cholesterol-rich diet.[22] C-PC supplementation also prevented carbon tetrachloride (CCl_4) hepatotoxicity in a rat model,[23] as well as X-ray-induced liver injury in a murine model.[24] C-PC mechanisms of liver protection are linked to the activation of the Nrf2/HO-1 signaling pathway, resulting in enhanced anti-oxidant enzyme expression. Studies in Balb/c mice showed that various C-PC doses decreased oxidative stress by exhibiting safe immune modulation.[10,25] Additionally, C-PC accelerated dermal wound healing in ICR mice by optimizing mediators and promoting fibroblast proliferation and migration.[10,26]

In vitro data suggest that C-PC also acts as an anti-inflammatory molecule by selectively inhibiting cyclooxygenase-2 (COX-2) in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages.[25] This reduces prostaglandin E2 (PGE2) levels, contributing to its anti-oxidant and anti-inflammatory effects. Different animal models of inflammation (eg, arachidonic acid-induced ear edema and cotton pellet granuloma) showed a reduction in edema, histamine release, MPO activity, and levels of pro-inflammatory mediators (ie, PGE2 and LTB4) by C-PC, suggesting immunomodulatory effects.[26-28] Further reinforcing these findings, Nohiarbatana et al demonstrated that C-PC treatment significantly reduced IL-1β gene expression by 70.24% and nitric oxide secretion by 91.25% in stimulated human cells.[29] Notably, the study observed that C-PC maintained 99.32% cell viability and actively promoted cell proliferation, increasing the number of viable cells by 12.34% over seven days.[29]

Both in vivo and in vitro studies demonstrated the safety of C-PC and its protective anti-oxidant effect against UVR-induced damage. The mechanisms by which C-PC works are diverse, including, but not limited to, free radical scavenging, induction of cellular anti-oxidant defenses (enzymatic and non-enzymatic), and control of inflammation. In vitro studies using HaCaT cells showed that pretreatment with C-PC prevented UVB-induced damage, resulting in a significant increase in cell viability compared with the untreated group,[10,11] linked to a substantial decrease in reactive species production and a reduction in caspase 3/7 activation.[10,11] C-PC has been shown to upregulate anti-oxidant enzymes, thereby minimizing oxidative stress and facilitating cell repair and recovery. Studies using BALB/c-nu mice showed that C-PC supplementation reduced UVB-induced skin erythema and epidermal thickening, decreased cutaneous MDA, and expression of inflammatory factors (interleukin-1α [IL-1α], IL-1β, IL-6, and tumor

necrosis factor-α). It also reduces matrix metalloproteinase [MMP-3 and MMP-9] expression and inhibits the phosphorylation of c-Jun N-terminal kinase, extracellular signal-regulated kinase, and p38 proteins in the mitogen-activated protein kinase family. Similar results were observed in vitro, where C-PC pretreatment also reduced MMPs (1 and 9) expression, suggesting a protective effect over UVB-induced degradation of collagen I and IV.[10,30] Finally, studies using a melanogenesis model (B16F10 murine melanoma cells) showed that UVB-induced oxidative stress was associated with increased melanin synthesis. C-PC reduced ROS production and decreased the expression of tyrosinase and tyrosinase-related protein-1 (TRP-1), leading to a significant decrease in melanin accumulation. C-PC significantly increased (almost doubled) cyclic adenosine monophosphate (cAMP) accumulation during the first 10 minutes, indicating a potential C-PC modulation of alpha-MSH-induced melanogenesis. C-PC also inhibited the activation of microphthalmia-associated transcription factor (MITF), a key regulator of melanogenesis, by suppressing ROS-mediated signaling pathways (eg, MAPK/ERK).[10,18] Moreover, C-PC inhibited the phosphorylation of p38, leading to a decrease in phosphorylated CREB, which is critical for the MIFT function. Wu et al showed that C-PC promotes the degradation of MITF, thereby reinforcing control of melanin production.[31]

Pro-apoptotic effects of C-PC have been reported in several preclinical studies, a finding of interest given the role of apoptosis dysregulation in tumor cell survival. For example, using the macrophage cell line RAW 264.7, Reddy et al confirmed that this molecule induced apoptosis, mediated by the release of mitochondrial cytochrome c, nuclear condensation, and DNA fragmentation.[25] Hao et al showed that C-PC (6 microM) has an antineoplastic role linked to the downregulation of growth factor receptor-bound protein 2 (GRB2)-ERK1/2 pathway.[32] C-PC can also promote Fas cell-surface receptor expression, which is directly involved in apoptosis, while suppressing Bcl-2 protein expression (an anti-apoptotic protein).[33] This is important because a downregulation of Bcl-2 may increase tumor sensitivity to other antineoplastic drugs.[34]

In 2008, Madhyastha et al identified the beneficial effects of C-PC on wound healing.[35] These authors showed that using human fibroblasts, C-PC promoted their proliferation and migration via increased cAMP-mediated mechanisms that depend on the protein kinase A (PKA) pathway. C-PC induced-fibroblast migration is also facilitated by the Rho-family GTPases, including Cdc42 and Rac1, via phosphoinositide-3 kinase (PI-3K) pathway.[35,36] Effects of C-PC on wound healing were also reported in murine models,[36] in which C-PC-treated mice achieved an 80% closure of the wound by the end of the first week. In contrast, untreated mice only showed a 50% wound closure at the same period ($p < 0.05$). Proliferation, healing, and migration were increased in a C-PC dose-dependent manner. Animal studies have shown that 1.25% of C-PC had the best results on day seven after injury.[37] Thus, numerous studies have found that C-PC can promote cell viability and anti-inflammatory, immune-modulating, and anti-cancer properties by increasing anti-oxidant activity and reducing ROS, oxidative stress, melanin synthesis, and levels of MMPs, while increasing fibroblast proliferation, intracellular cAMP, and SOD production.[10,11,18,23,30,38,39] These cellular benefits reduce the harmful effects of UVR and promote the repair of damaged cells (**Figure 1**).[10]

CLINICAL TRIALS: C-PC AND ANTI-CANCER EFFECTS

Healthy skin function depends on protection against external agents, including UVR, microorganisms, pollution, allergens, and other environmental factors, as well as on maintaining internal homeostasis and adequate hydration to sustain an intact epidermal barrier and optimal health.[40,41] Y. Imai et al reported in a randomized, double-blind, placebo-controlled, parallel-group trial that C-PC improved skin barrier function by reducing transepidermal water loss (TEWL).[41] The authors used 410 mg of phycocyanin (C-PC 300 mg, allophycocyanin 110 mg) once daily for 8 weeks, resulting in improved skin moisture and elasticity measured by visual analog scale (VAS).[41] This data may support the hypothesis that C-PC supplementation helps skin to become more resilient and healthier, and therefore may play a role in preventing skin cancer development. A healthy skin barrier is essential for protecting the body from environmental stressors, such as UVR. With chronic exposure, the skin's molecular pathways are adversely affected, leading to photoaging.[42] In addition, C-PC's capacity to suppress specific cell-cycle phases, modulate the cellular redox state, regulate proliferation, and induce apoptosis and necrosis may play a significant role in its anti-tumor activity. In a murine model, the authors showed that topical application of C-PC downregulated TPA (12-0-tetradecanyol-phorbol-13-acetate)-induced ODC (ornithine decarboxylase). ODC plays a role in epidermal tumorigenesis and is induced by UVB and hormones, and is strongly expressed in SCC and BCC.[43]

A patent filed by L. Lerer in the US for the purification of C-PC and its applications reported the use of a 250 mg lyophilized powder administered daily to an undisclosed number of fair-skinned subjects, who reported reduced sunburn potential via self-reported observation.[44] A case study (n = 4, Fitzpatrick phototypes I and II) showed a protective effect of C-PC supplementation (250 mg qd for five days) to targeted narrow-band UVB skin damage (forearm).[44] Participants served as their own controls and experienced decreased skin peeling, pain, and sensitivity, and rapid skin recovery after consuming lyophilized C-PC supplementation.[44]

C-PC in vitro and animal study data have shown anti-oxidant, anti-inflammatory, photoprotective, and antitumorigenic effects. However, clinical trials in humans are lacking, whereas preclinical studies provide a foundation for C-PC's potential protective role against UVB-induced skin damage. Addressing this gap, a 2025 systematic review and meta-analysis of 22 randomized clinical trials (n = 5,385) supported the systemic efficacy of spirulina supplementation. The study demonstrated reductions in key inflamma-

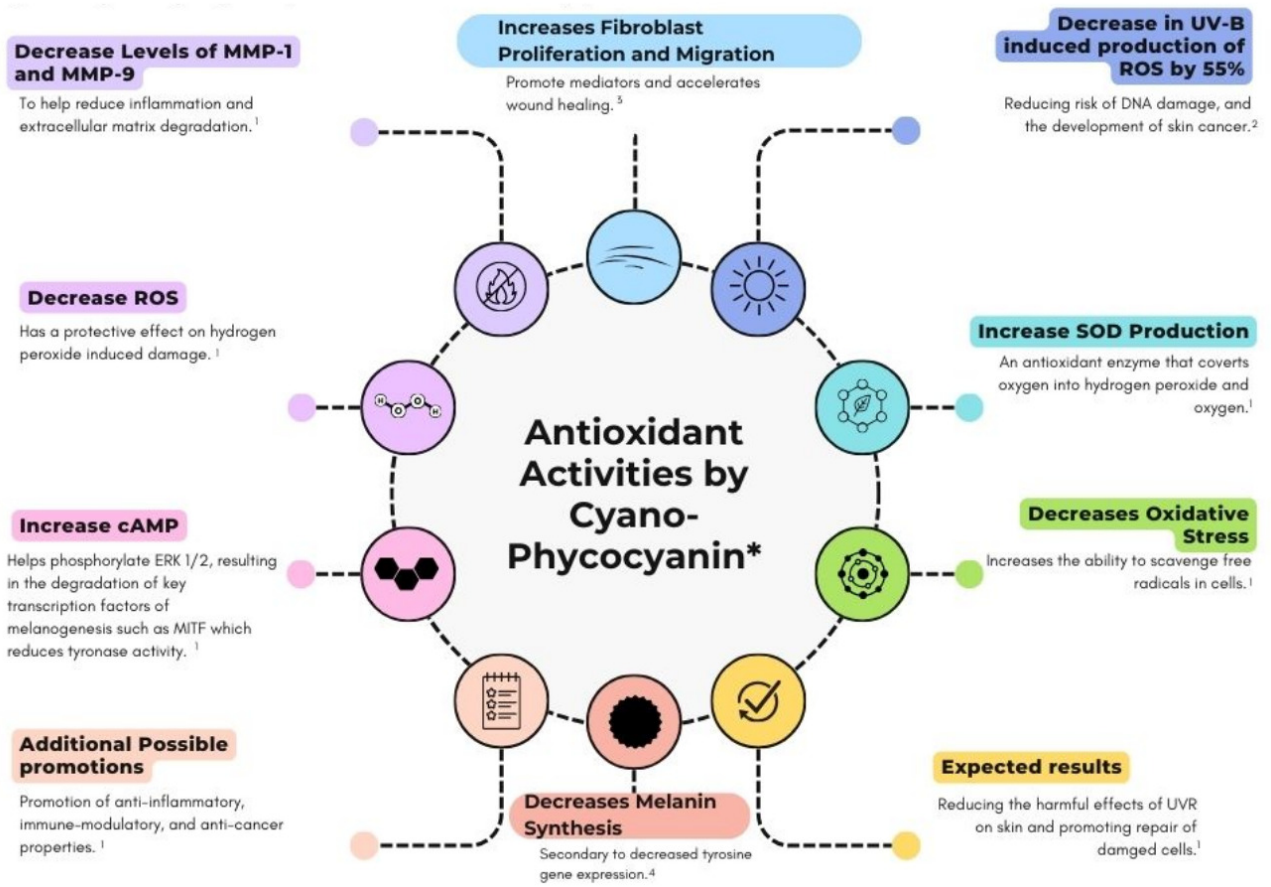


Figure 1. Cyano-Phycocyanin is a powerful anti-oxidant with many potential benefits, as exhibited in in vitro and in vivo studies.

**In vivo* and *in vitro* studies. UV-B: ultraviolet B; UVR: ultraviolet radiation; ROS: reactive oxygen species; MMP: matrix metalloproteinase; SOD: superoxide dismutase; cAMP: intracellular cyclic adenosine monophosphate; ERK: extracellular signal-regulated kinase; MITF: microphthalmia transcription factor. References: 1. Fernandes R, Campos J, Serra M, Fidalgo J, Almeida H, Casas A, et al. AIRNA. Exploring the Beneftis of Phycocyanin: From Spirulina Cultivation to Its Widespread Applications.*Pharmaceuticals.* 2023 Apr 14;16(4):592.doi:10.3390/ph16040592.PMID:37111349. 2. Heck DE, Vetrano AM, Mariano TM, Laskin JD, UVB Light Stimulates Production of Reactive Oxygen Species: UNEXPECTED ROLE FOR CATALASE*,JBC,Volume 278, Issue 25,2003,Pages 22432-22436,ISSN 0021-9258, https://doi.org/10.1074/jbc.C300048200.3.Madhyastha, H.K., Radha, K.S., Nakajima, Y., Omura, S. and Maruyama, M. (2008), uPA dependent and independent mechanisms of wound healing by C-phycocyanin. Journal of Cellular and Molecular Medicine, 12: 2691-2703. https://doi.org/10.1111/j.1582-4934.2008.00272.x 4.Kerthika Devi Athiyappan, Winny Routray, Balasubramanian Paramasivan, Phycocyanin from Spirulina: A comprehensive review on cultivation, extraction, purification, and its application in food and allied industries, Food and Humanity, Volume 2, 2024, 100235, ISSN 2949-8244, https://doi.org/10.1016/j.foohum.2024.100235

tory markers, including CRP, IL-6, and TNF-α, alongside a marked decrease in oxidative stress markers like MDA and an increase in total antioxidant capacity (TAC) in humans.[45] The absence of clinical trials evaluating C-PC for UVB-induced skin damage in humans can be attributed to several key factors. Primarily, C-PC's high molecular weight poses significant bioavailability challenges, limiting its skin penetration and systemic absorption and complicating the development of effective topical or oral formulations for clinical use. While preclinical studies have demonstrated C-PC's potent anti-oxidant and anti-inflammatory effects, the transition to human trials is hindered by the need for advanced delivery systems, such as solid-in-oil nanodispersions, which remain in early development. However, recent advances in C-PC delivery, reported by D. Galinyte et al have demonstrated delivery systems with enriched transfersomes that enable epidermal delivery of C-PC while maintaining stability for up to eight months, providing a viable alternative to solid-in-oil nanodispersions.[46] Additionally, research on C-PC has largely focused on its systemic benefits (eg, anti-cancer and anti-inflammatory properties) and preclinical photoprotection models, with less emphasis on dermatological applications in humans. Regulatory and funding barriers further delay clinical trials, as natural compounds like C-PC require substantial investment and rigorous safety validation to meet cosmeceutical or therapeutic standards. Limited awareness of C-PC's photoprotective potential in dermatology may contribute to its underexploitation in clinical settings, despite promising preclinical data. Lastly, standardization of the C-PC dose used topically for anti-aging, photoprotective, wound-healing, or anti-inflammatory benefits requires further investigation. Currently available data provide only in vitro and animal studies that suggest doses for specific benefits (**Table 2**). C-PC's mechanism of action as a phycobiliprotein and other bioactive molecules contributes to the cellular level's enzymatic and non-enzymatic anti-oxidant defense against UVR, microorganisms, and pollution, keeping skin healthy, as seen in **Figure 2.**

TABLE 2. Various Doses of C-PC have Measurable Cellular Effects.*[1,2,3,4,5]

CELLULAR EFFECT	*IN VIVO*	*IN VITRO*	DOSE
INCREASE IN SOD2	✓		20 ug/mL
DECREASE IN ROS	✓		20 ug/mL
SCAVENGE FREE RADICALS & OXIDATIVE STRESS	✓		2000 mg/kg
DECREASE IN TYROSINE ACTIVITY		✓	0.1 mg/mL
DECREASED MELANIN SYNTHESIS		✓	0.1 mg/mL
ATTENUATION MMP-1 & MMP-9		✓	80 ug/mL
DECREASED UV-B PRODUCED ROS BY 55%		✓	80 ug/mL
PROLIFERATION OF FIBROBLASTS FOR DERMAL WOUND HEALING	✓		75 ug/mL
IMMUNOMODULATORY & ANTITUMOR ACTIVITY	✓		560 mg/kg

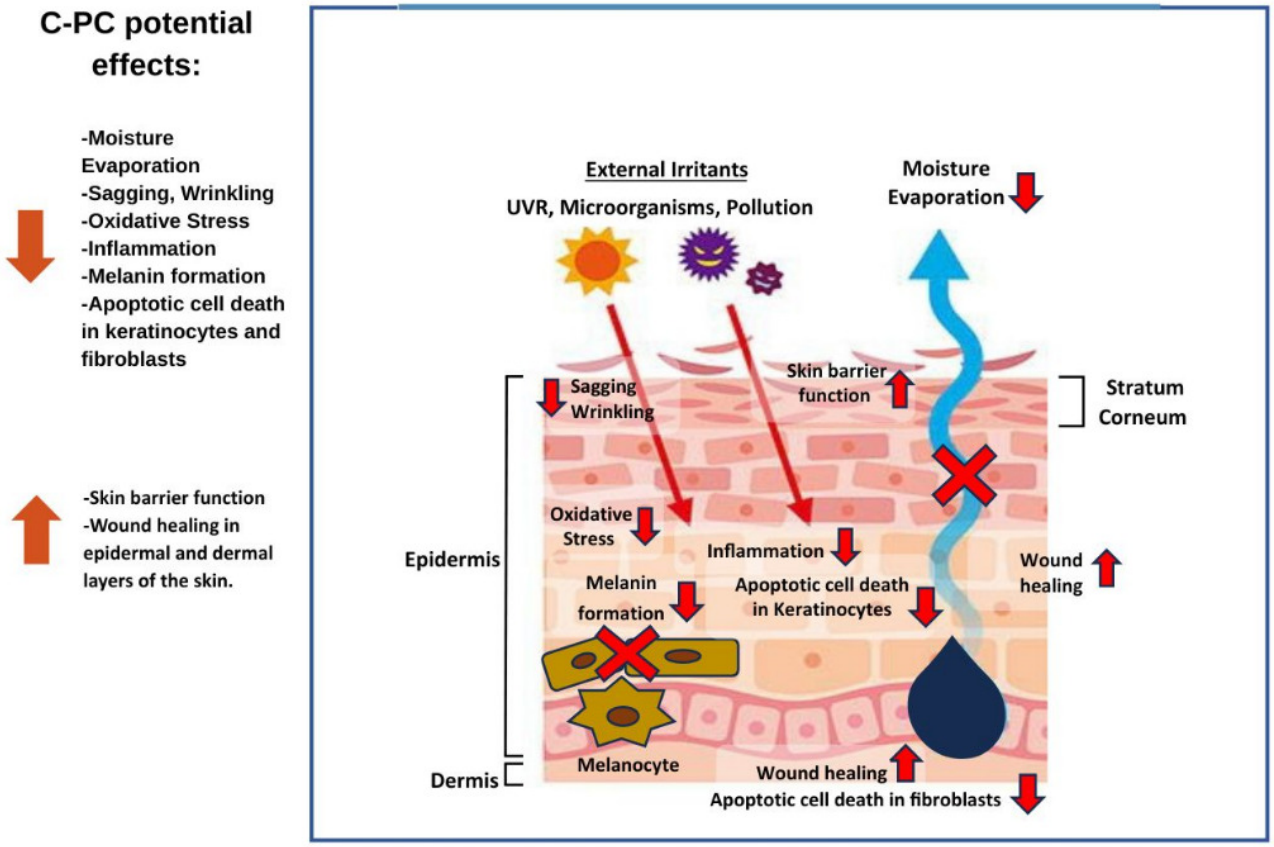
*In vitro and In vivo Studies. Peak activities were measured without compromising cell viability. C-PC: Cyano-Phycocyanin. References: 1. Jang YA, Kim BA. Protective Effect of SpirulinaDerived C-Phycocyanin against Ultraviolet B-Induced Damage in HaCaT Cells. Medicina. 2021; 57(3):273. https://doi.org/10.3390/medicina57030273 2. Wu, LC., Lin, YY., Yang, SY. et al. 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 (2011). https://doi.org/10.1186/1423-0127-18-74. 3. Xu F, Zhang Y, Qiu Y, Yang F, Liu G, Dong X, Chen G, Cao C, Zhang Q, Zhang S and Li B (2022) Three novel antioxidant peptides isolated from Cphycocyanin against H2O2-induced oxidative stress in zebrafish via Nrf2 signaling pathway. Front. Mar. Sci. 9:1098091. doi: 10.3389/fmars.2022.1098091. 4. Priyanka Grover, Aseem Bhatnagar, Neeraj Kumari, Ananth Narayan Bhatt, Dhruv Kumar Nishad, Jubilee Purkayastha, C-Phycocyanin-a novel protein from Spirulina platensis- In vivo toxicity, anti-oxidant and immunomodulatory studies. Saudi Journal of Biological Sciences, Volume 28, Issue 3, 2021, Pages 1853-1859, ISSN 1319-562X,https://doi.org/10.1016/j.sjbs.2020.12.037. 5. Salgado MTSF, Silva MCS, Fratelli C, Braga ARC, Lopes TBG, Ferreira E, da Silva ILD, Paiva LS, Votto APS. Bioactive C-phycocyanin exerts immunomodulatory and anti-tumor activity in mice with induced melanoma. Toxicol Appl Pharmacol. 2024 Mar;484:116874. doi: 10.1016/j.taap.2024.116874. Epub 2024 Feb 28. PMID: 38428464.

DISCUSSION

Annual skin examinations for high-risk patients, education, encouragement of monthly self-exams, and the use of protective measures such as sunscreen, UV-protective clothing, and other tools are often recommended by dermatology providers. Protecting the skin's external surface is necessary, but targeting the underlying cellular mechanisms can further reduce the incidence of skin cancer. While these protective measures are essential, growing evidence indicates that oxidative stress and cellular inflammation contribute to UVR-induced skin damage. This is supported by recent large-scale human evidence, including a 2025 meta-analysis of twenty-two clinical trials (n = 5,385) that confirmed that supplementation with Spirulina significantly reduces systemic inflammatory markers, such as IL-6 and CRP, while enhancing total antioxidant capacity in humans.[45]

Antioxidant properties are primarily found in C-PC, and its functional properties have been studied, including radical scavenging, antioxidant, anti-inflammatory, antimicrobial, anti-cancer, and wound-healing activities.[10,47] Topical applications on human skin, particularly dermal keratinocytes, are promising, as studies have demonstrated that ROS production by UVB induction has been reduced by over 50%.[47] In vitro studies have shown the potential to decrease DNA fragmentation in UVB-irradiated cells treated with C-PC, decrease UVB-induced production of ROS over 50%, decrease levels of MMP-1 and MMP-9, and tyrosinase activity, and show a pro-apoptotic influence on different cancer lines.[10,18,30,48] New quantitative data further validate these mechanisms, demonstrating that C-PC can reduce IL-1β gene expression by over 70% and nitric oxide secretion by 91% in stimulated human cells while maintaining near-perfect cell viability.[29] In vivo studies showing that C-PC increases SOD2 activity through activation of Nrf2 signaling, enhances free-radical scavenging and reduces oxidative stress in cells, and promotes mediators and fibroblast proliferation and migration for tissue regenera-

Figure 2. Mechanisms by which Cyano-Phycocyanin may protect skin cells from External Irritants e.g. Sun Exposure, Microorganisms, Pollution



Adapted From: Clinical Findings on Skin Health Regarding Phycocyanin and the Natural Blue Pigment from Spirulina, and its Possible Mechanisms of Action. Earthrise. Published 2024. Accessed November 14, 2024. https://www.earthrise.com/article-14.

tion collectively suggest a likely contribution to its anti-oxidant potential and dermal wound healing.[10,23,24,38,39]

The clinical utility of these findings is supported by the recent development of enriched transferosomes, which have been shown to deliver C-PC to the epidermis and remain stable for up to eight months.[46] The mechanism of action of C-PC and its potent anti-oxidant capacity are shown to slow skin aging, resulting in fewer wrinkles, making it a potential anti-aging nutraceutical and UVR adjunct protectant.[47,49] Finally, C-PC may serve as a potential adjuvant cancer treatment due to its well-studied effects on cancer cells in vitro using human cell cultures.[10] It shows a pro-apoptotic influence on different cancer lines such as breast, colorectal, lung, squamous cell, melanoma, and leukemia.[10] C-PC has also undergone numerous in vivo and in vitro anti-cancer studies and has shown significant inhibitory effects on growing cancer cells, including inhibition of DNA replication, cell cycle arrest, and apoptosis, along with low toxicity to healthy cells and minimal generation of ROS.[9,50,51] Its promising anti-cancer activity has been studied by showing C-PC inducing tumor cell autophagy and apoptosis by inhibiting the tumor cell cycle by suppressing at specified phases, modifying the redox state, and promoting genes and receptors that promote apoptosis.[51]

At present, clinical use of C-PC should be approached cautiously. Human data remain limited, and available studies rely on surrogate measures of skin health rather than on validated outcomes of photoprotection or skin cancer prevention. However, as patient interest in nutraceuticals and oral photoprotective strategies continues to grow, dermatology providers may benefit from understanding the existing evidence to guide informed clinical discussions, set appropriate expectations, and emphasize evidence-based sun safety practices. Worth noting: C-PC should not be viewed as a replacement for well-established sun protective behaviors, but rather as a possible adjunct to reduce UVR-induced oxidative damage. Further well-designed, placebo-controlled human trials are needed to determine whether the biological effects observed in preclinical models translate into meaningful clinical benefit. Until such data are available, C-PC remains a promising but investigational adjunct within the broader framework of UVR risk reduction.

LIMITATIONS

Several methodological limitations are warranted during the research conducted for this manuscript. First, the data search was restricted to peer-reviewed articles published in English, potentially excluding relevant data from non-Eng-

lish-speaking cohorts. Second, because the field of algal research is rapidly evolving, not all literature may have been captured. Third, although a thorough set of search terms was used across PubMed, ClinicalKey, and the Cochrane Library, the possibility remains that some studies were inadvertently missed due to indexing practices or variations in terminology. Future research on C-PC should broaden its scope and include a diverse array of specialized databases to ensure a more global representation of the subject. This review is primarily limited by the available evidence, as the data supporting C-PC and its clinical use stem from in vitro experiments and animal models. While these studies provide important insights into how C-PC works at the biological level, they do not fully capture human or clinical outcomes. Moreover, current human placebo-controlled studies are limited in number and focus primarily on surrogate measures of skin health rather than on clinically meaningful, validated endpoints. As a result, conclusions regarding the clinical effectiveness of C-PC for UVR-related skin damage or skin cancer prevention remain preliminary. Additionally, the authors note variability across preclinical studies, including differences in dosing, formulation, routes of administration, and outcome measures. This directly limits comparison between studies and, therefore, standardized clinical recommendations cannot be concluded. Larger, placebo-controlled human trials are warranted to better define optimal dosing, long-term safety, and the potential role of C-PC as an adjuvant photoprotection therapy.

CONCLUSION

Ultraviolet radiation protection remains the primary modifiable risk factor for cutaneous malignancies; therefore, there is a need for more effective preventive strategies beyond behavior modification. Current preclinical evidence demonstrates the anti-oxidant and anti-inflammatory benefits of C-PC on UVR-induced skin damage. The current evidence, however, is primarily derived from in vitro and animal models; as a result, human data remain limited, and the clinical effectiveness in humans has not been fully elucidated. Well-designed, placebo-controlled, randomized human trials with validated endpoints are needed to determine whether the biological effects observed in these preclinical studies translate into clinically meaningful benefits. At this time, given the available data, C-PC should be considered a promising, but still investigational, adjuvant to appropriate photoprotection.

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