IJPSR (2015), Vol. 6, Issue 11 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 14 May, 2015; received in revised form, 21 June, 2015; accepted, 30 August, 2015; published 01 November, 2015

REVISITING THE ROLE OF PHYCOCYANIN IN CURRENT CLINICAL PRACTICE

A. Soni *[1], M. Dubey [1], M. Verma [2], R. Dhankhar [1], V. Kaushal [1], R. Atri [1] and R. Sabharwal [3]

Department of Radiotherapy [1], Department of Biochemistry [2], PGIMS, Rohtak, Haryana, India.
Consultant Radiation Oncologist [3], Department of Health, Government of Haryana, Kurukshtra, Haryana India.

Keywords:

Anti-oxidant, apoptosis, cancer, free radicals, Phycocyanin.

Correspondence to Author:
Dr. Abhishek Soni

Senior Resident, Department of Radiotherapy, Post-graduate institute of medical sciences, Rohtak, India – 124001

E-mail: abhisheksoni246@gmail.com

ABSTRACT: C-phycocyanin (C-PC) is a biliprotein found in edible blue-green algae. Its anti-cancer, anti-inflammatory, anti-proliferative and anti-oxidant activities has been evidenced by many *in vitro* and *in vivo* studies. Anti-inflammatory activity of C-PC demonstrated by free radical scavenging, inhibition of DNA damage, and decreased ROS. Here, the effects of C-PC on cytotoxicity and cell signaling through the apoptotic and other pathways were studied. Results indicated that anti-proliferative effects of C-PC are mediated by inactivation of BCR-ABL signaling and the downstream pathway PI3K/AKT. Phycocyanin induces apoptotic death, and Bcl-2 expression inhibits it via generation of free radicals. C-PC exerted antimelanogenic mechanisms by downregulating p38 MAPK-regulated CREB pathway activation and upregulating MAPK/ERK-dependent degradation of MITF protein. C-PC-mediated PDT (photodynamic therapy) is approved as a potential therapy for cancer. Phycocyanin can be consumed as a dietary supplement or a food component to obtain health benefits against CVD (cardiovascular disease) and NAFLD (non-alcoholic fatty liver disease). These results suggest that phycocyanin which had been obtained from blue green algae are potential medicaments in the treatment of various kinds of human ailments and cancers.

INTRODUCTION: Phycocyanin extracted from Spirulina was first marketed in 1980 by Dainippon Ink and Chemicals under the brand name "Lina Blue–A.[1] Phycocyanin is a dietary supplement dedicated to individuals who are undergoing chemotherapy and radiation for cancer and is used to ease negative symptoms during treatment as well as rejuvenate post treatment.

Phycocyanin is an important molecule extracted from Spirulina platensis, a 3.6 billion years old blue green algae and its nutritional values and therapeutic values are well documented.[2, 3]

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(11).4588-00

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(11).4588-00

Spirulina is known to have nutritional advantages of high-quality protein, minerals, vitamins, essential amino acids, cyanocobalamin (B12), tocopherols and essential fatty acids including β-carotene and γ -linolenic acid (GLA).[2, 3] Phycocyanin is a water soluble, natural and non-toxic molecule with anticancer, antioxidant, antiviral and anti-inflammatory activities.[3,4] Phycocyanin is also a powerful agent for the immune system in human and animals, and provides protection from a number of diseases.[3] The deep blue colour of Phycocyanin has been widely used as a colorant in food industry for food additive purposes.[3] Various research studies also support strong hepatoprotective, cytoprotective and neuroprotective profile of phycocyanin.

Most of the studies are based on the laboratory experimental results on mice and cultured cell lines, and, still very less literature is available to conclude any concrete result for Phycocyanin use

in current era of medical practice. Thus, this article reviews the role of phycocyanin in today's clinical practice.

Structure:

Phycocyanin occurs as the major phycobiliprotein in Cyanobacteria and as a secondary phycobiliprotein in some red algae.[2] C-Phycocyanin (C-PC) is a natural compound.[5] The pigment is composed of two subunits, α and β, which occur in equal numbers, but the exact number may vary among the species. Both α and β subunits contain only the PCB chromophore.[2] The structure of C-phycocyanin from the thermophilic blue green algae Mastigocladus laminosus has been determined at 3 Å resolution by X-ray diffraction methods. The protein found to consist of three α-β units arranged around a threefold symmetry axis to form a disc with dimensions of 110 Å × 30 Å with a central channel of 35 Å in diameter. Both subunits, α and β, have a similar structure and are related by a local twofold rotational axis.[6] Its molecular weight is between 70,000 and 110,000 Daltons. Phycocyanin has visible absorption maximum between 615 and 620 nm and maximum fluorescence emission at ~650 nm.[2] Phycocyanin accepts quanta from phycoerythrin by fluorescent energy transfer in organisms in which it is present.[2]

The purity of C-PC is evaluated using the absorbance ratio of A620/A280, and a purity of 0.7 is considered as food grade, 3.9 as reactive grade, and more than 4.0 as analytical grade. Purity is directly related to process costs, and, in general, the more purified a product is, the more expensive to obtain it.[1]

Fig.1 shows chemical structure of the bilin chromophores in phycocyanin, which is very similar to bilirubin, a heme breakdown product.[2]

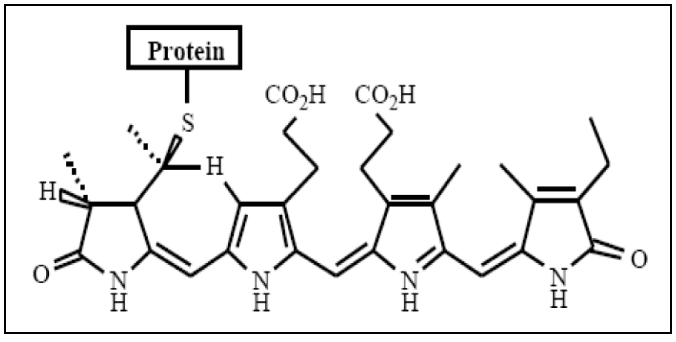

FIG.1: CHEMICAL STRUCTURE OF PHYCOCYANIN BILIN CHROMOPHORE (OPEN-CHAIN TETRAPYRROL) [2]

Sources:

Phycocyanin can be extracted mainly from blue green algae and may be from red algae (rhodophytes) and cryptophytes.[7] Main sources are Spirulina platensis, Arthrospira platensis, Spirulina maxima, Phormedium fragile, Nostoc muscorum, Oscillatoria species, Nostoc humifusum, Anabaena oryzae, Wollea saccata, Anabaena flous aquae, Limnothrix and Porphyra haitanensis, thermophilic cyanobacterium Mastigocladus laminosus, Agmenellum quadruplicatum, Remyella diplosiphon, Phanizomenon flos-aquae, marine cyanobacterium Synechococcus sp. IO9201, Galdieria sulphuraria (rhodophyte), Anabaena sp. PCC 7120, Leptolyngbya species, Scytonema julianum, Thermosynechococcus elongates, Tolypothrix tenuis, Nostoc minutum, Klamath algae, Acaryochloris marina, and Microcystis aeruginosa.[6-17]

Extraction and Purification:

A number of drying methods like spray dried, crossflow dried and oven dried methods, are used for Spirulina processing, and results in approximately 50% loss of phycocyanin. So fresh biomass is suitable for extraction of phycocyanin.[18] Blue green algae are grown in nutrient medium (like Zarrouk's medium) containing different amounts of nitrogen and salt. In Spirulina species, Phycocyanin pigments increase from 12% to 22% on increasing nitrogen levels.[3] Spirulina has a wide variety in composition of Phycocyanin pigments ranging from R-phycocyanin (R-PC) from 5.75 to 12.35%, allophycocyanin (A-PC) from 2.53 to 6.11% and C-phycocyanin (C-PC) from 1.65 to 4.02% as a result of changing nitrogen contents and salt stress.[3, 19]

The concentration of Phycocyanin pigment including C-Phycocyanin (C-PC), allophycocyanin (A-PC), and R-phycocanin (R-PC) are determined spectrophotometrically at 618 and 650 nm, 650 and 618 nm, and 498, 615 and 650 nm respectively as reported by Kursar and Alberte.[20] Cyanobacteria adjusts the contents and relative ratio of its pigments with the light quality, like more production under red or violet light.[21] C-PC is a natural blue pigment accounting for 14% of SP dry weight.[22] The increase in NaCl levels in nutrient

medium led to significant increase in production of Phycocyanin contents and soluble protein in Spirulina cells.[23, 24] Phycocyanin production also depends on iron concentration in the media.[25] Thus, Spirulina species grown under combined stress of high NaCl and nitrogen deficient levels, produce higher amount of Phycocyanin.[3, 21, 26, 27]

Many methods have been used for the separation and purification of C-PC. C-PC is purified from Spirulina platensis by ammonium sulfate precipitation, ion-exchange chromatography, modified flow cytometry and free-flow electrophoresis (FFE).[5, 28, 29] SDS-polyacrylamide gel electrophoresis is performed to assess the molecular weight and purity of C-PC. SDS-PAGE analysis of the purified fraction clearly showed 2 protein bands corresponding to α and β subunits of C-PC. The purity of C-PC, as judged by an A620/A280 purity ratio greater than 4.0, is sufficient for further testing. [5, 30] Femtosecond laser spectroscopies are used to examine the electronic structures of cyanobacteria.[31]

Table 1 shows the purity of C-PC after various stages of purification which can be implied for further analysis of grading the phycocyanin. The table signifies that the purity can be increased and a food grade phycocyanin was isolated.[1]

TABLE 1: PURIFICATION OF PHYCOCYANIN[1]

Sr. No.	Purification process	Extraction purity at 615/280nm	Phycocyanin concentration (mg/ml)
1	Crude Phycocyanin	0.61	1.94
2	Ammonium sulphate precipitation	0.73	2.39
3	Membrane filtration	0.89	2.64
4	Dialysis	0.99	2.90

Cell cytotoxicity was evaluated by the 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxyanilide inner salt (XTT) assay. Western blot analysis is used to study the expression and phosphorylation of proteins in the PI3K/AKT pathway.[5] The oxygen radical absorbance capacity (ORAC) assay is used to assess antioxidant activity of phycocyanin.[32] C-PC concentration from G. sulphuraria is low than cyanobacteria.[33]

Uses:

The spray-drying method is used to load chitosomes with C-phycocyanin for colonic drug delivery.[34] Phycocyanin extracted from Spirulina platensis displayed favorable health benefits such as improving immune function, promoting zooblast regeneration and inhibiting the growth of cancer cells.[35] Since phycocyanin is photosensitive, it has been proposed as a new photosensitizer for photodynamic therapy.[36] C-phycocyanin is endowed with various biological and pharmacological properties.[5] C-phycocyanin possesses significant antioxidant activities and can enhance immunity and inflammatory responses.[5]

Studies have shown that C-phycocyanin can induce apoptosis in cancer cells such as a mouse macrophage cell line (RAW 264.7), prostate cell line (LNCaP), breast cell line (MCF-7), and erythromyeloid leukemia cell line (K562).[5] Phycocyanin is used in treatment of hepatocellular carcinoma, rectal cancer, leukemia, melanoma and used in food industry, biomedicine and cosmetics industry. Subashini et al demonstrated that C-phycocyanin induced apoptosis in K562 cells is mediated by cytochrome *c* release, PARP cleavage, and Bcl-2 down-regulation.[5] C-phycocyanin could be used for treating ischemia-reperfusion injury through the activation of ERK pathway and suppression of p38 MAPK pathway.[37, 38] Phycocyanin is a potent antioxidant as well as herbicidal agent, and possesses significant immune enhancing and antiviral properties.[1, 39, 40] It's enhancing biological defense activity against infections disease reduces allergies inflammation by the suppression of IgE antibody.

The phycocyanin is used as coloring agent in food item like jellies, chewing gums, ice sherbaths, and dairy products, and it enhances antioxidant capacity of food and beverages.[1, 41] In Japan, China, and Thailand, phycocyanin is used in cosmetics like lipstick and eyeliners.[1] It is used in biomedical research and pharmaceutical industries.[1, 42, 43] It is used in immune diagnostic applications.[1] C-PC selectively stimulates the lymphocyte antioxidant defence system of occupationally exposed subjects. The activation of the antioxidant protective mechanisms as part of the early radiation response

is probably related to the chronic low-dose occupational exposure. The modulating capacity of C-PC at the molecular level may be of interest for the protection of occupationally exposed persons.[44]

Antioxidative Properties of Phycocyanin:

Antioxidant activity of Phycocyanin is demonstrated by ascorbate/iron/H2O2 assays, DPPH (2,2 diphenyl-1-picrylhydrazyl) assay and ABTS (2,2'-azino-bis ethylbenzthiazoline-6-sulfonic acid) assay.[8, 45] Oxidative stress, mainly characterized by reactive oxygen species (ROS), damages tissues and therefore is associated with several pathological conditions, such as atherosclerosis, nonalcoholic steatohepatitis (NASH), and aging. [46] Hydroxyl and peroxyl radicals are associated with oxidative damage to lipids and DNA.[46] Human studies have reported the protective effects of BGA against oxidative damage *in vivo* and *in vitro*.

SP supplementation of 8 grams per day for 12 weeks significantly decreased plasma levels of MDA (malondialdehyde), a biomarker of oxidative stress, in diabetic patients. Similarly, healthy elderly Korean subjects who consumed 8 grams per day of SP for 16 weeks showed a decrease in the lipid peroxidation level, whereas the total antioxidant status and levels of antioxidant enzymes, such as SOD and GPx, were elevated in plasma, indicating that SP supplementation was able to improve antioxidant status in the human subjects. C-PC markedly inhibited the production of alkoxyl radicals that are generated by the reaction of tert-butyl hydroperoxide with ferrous ions in the presence of luminol. In addition, C-PC prevented DNA damage and scavenged hydroxyl and peroxyl radicals. Furthermore, C-PC inhibited peroxyl radical-induced oxidative hemolysis and lipid peroxidation in normal human erythrocytes.[46, 47]

C-PC from AFA extract demonstrated protective effects against cupric chloride-induced lipid oxidation in human plasma samples. Cysteine-rich cyanopeptide beta 2 isolated from C-PC of SF demonstrated free radical scavenging, inhibition of DNA damage, and decreased ROS production.[48] Selenium-containing allophycocyanin (Se-APC) extracted from selenium-enriched SP inhibited 2,20-azobis-2-methylpropanimidamide, dihydrochloride (AAPH)-induced oxidative hemolysis, and morphological changes in human erythrocytes.[49] Se-APC, furthermore, inhibited AAPH-induced intracellular ROS production and MDA accumulation.[46] Treatment with C-Pc protects the rats from Tributyltin (TBT) induced thymic atrophy, but not proved in humans for such a role.[50] Phycocyanin may inhibit atherosclerosis by activating heme oxygenase-1.[51] Phycocyanin helps in displacing fluoride, facilitating antioxidant formation, reverses sodium fluoride-induced thyroid changes, improves behaviour and protects Purkinje cells. Phycocyanin supplementation during pregnancy may reduce the risk of fluoride toxicity to offspring.[52]

Lipid-Lowering Effect of Phycocyanin:

In human clinical trials, supplementation with Spirulina Platensis (SP) exhibited lipid-lowering effects. In patients with type 2 diabetes, subjects who consumed 2 grams per day of SP for 2 months showed significantly lower plasma triglyceride (TG) concentrations as well as a significant reduction in ratios of total cholesterol : HDL-C and LDL-C : HDL-C.[46] Eight grams per day of SP supplementation for 12 weeks significantly reduced plasma triglyceride concentrations and blood pressure in type 2 diabetic patients with higher initial triglyceride levels, whereas subjects with high initial total cholesterol and LDL-C showed significant reductions in the plasma lipids. In patients with a hyperlipidemic nephritic syndrome, 1 gram per day of SP supplementation for 2 months significantly decreased plasma total cholesterol, LDL-C, and triglyceride concentrations. Up to now, BGA dosages used in human clinical trials have ranged from 1 to 8 grams per day for up to 24 weeks, whereas 5 gram per day is generally recommended by the manufacturers.[46]

Although individual cases of discomfort or unpleasant condition have been reported with BGA supplementation from time to time, Dietary Supplements Information Expert Committee (DSI-EC) of the United States Pharmacopeial Convention has awarded Spirulina (SM and SP) a grade A safety rating and agreed that Spirulina is generally safe to be consumed.[53] Concern over using BGA during pregnancy and breast feeding is

not clearly defined in humans. However, numerous animal studies indicated that SP consumption during pregnancy and lactation did not induce signs of maternal intoxication.[46]

In contrast, Kapoor and Mehta had demonstrated that SP supplementation could improve iron status during pregnancy, as evidenced by a higher hemoglobin count, serum iron, and serum ferritin.[54] Further study is necessary to evaluate the effect of BGA supplementation in humans during specific nutrition status and pathological conditions.[46] Morcos et al perfused atherosclerotic artery segments obtained within 5 hours postmortem with 0.1 mg/ml phycocyanin in oxygenated Krebs Ringer solution at 30 mmHg for five minutes followed by washout with Phycocyanin free Krebs for ten minutes. Histologically, on light and fluorescence microscopy, artery section revealed fluorescence localization within the plaque particularly at the site of elastic lamina and also at the internal elastic lamina but not in the medial muscle layer.

These properties suggested therapeutic use of Phycocyanin for plaque localization and regression.[55] Both C-PC and CD59 inhibit the process of atherosclerosis, and the anti-atherosclerotic properties of C-PC might be due to promoting CD59 expression, preventing proliferation of smooth muscle cell and the apoptosis of endothelial cells, reducing lipid levels, and finally inhibiting atherosclerosis.[56] Phycocyanin prevents hypertension and endothelial dysfunction related disease like metabolic syndrome.[57]

Effect of C-PC on Lipid Peroxidation:

ROS initiate the peroxidation of membrane lipids, leading to the accumulation of lipid peroxides and leakage of cytosolic enzymes into circulation.[46] Bhat and Madyastha reported C-PC inhibited nearly 95% of peroxyl radical-induced lipid peroxidation. C-PC with a reduced chromophore can efficiently inhibit peroxyl radical-induced lipid peroxidation in a dose-dependent manner.[58]

Anti-Inflammatory Effects of Phycocyanin:

Oxidative stress plays important roles in lung disease, gastrointestinal dysfunction, endothelial dysfunction and atherosclerosis.[45] Anti-oxidative and anti-inflammatory effects can be demonstrated by non-alcoholic steatohepatitis model.[59] C-phycocyanin suppresses inflammation by inhibiting the expressions of inducible cyclooxygeanase-2 (COX-2) and nitric oxide synthase, and by inhibiting the production of pro-inflammatory cytokines. Also, Phycocyanin scavenges free radicals, including alkoxyl, hydroxyl and peroxyl radicals; inhibits liver microsomal lipid peroxidation, decreases prostaglandin E(2) production, reduce myeloperoxidase production, decreases nitrite production, inhibits platelets aggregation, and uppresses the activation of nuclear factor-κB (NF-κB) via preventing degradation of cytosolic IκB-α. These all effects lead to anti-inflammatory activity of Phycocyanin.[60] Upto now, the antinociceptive properties of phycocyanin have been less thoroughly investigated.[45]

Consumption of BGA has been demonstrated to promote immunity and to protect against inflammatory diseases, such as colitis, arthritis, and allergic rhinitis in animal and human studies.[61] SP organic extracts markedly decreased the secretion of proinflammatory cytokines, including the granulocyte-macrophage colony stimulating factor, IL-6, MCP-1, and TNFa. Moreover, translocation of NF-jB from cytoplasm to nucleus was also inhibited. Anti-inflammatory effects of BGA have been shown in cell studies, animal studies, and human studies. Furthermore, understanding of the effect of BGA on acute or chronic inflammatory pathways is necessary because although the two pathways share some of common mediators, protective effects against chronic inflammation at a low degree for a long period of time are more relevant and beneficial to the prevention of metabolic diseases such as CVD and NAFLD.[46] Several components of BGA, including GLA and PC, have been implicated in their anti-inflammatory effects. SP contains 1.3% GLA. An anti-inflammatory effect of SP is also often associated with antioxidant and antiviral properties of C-PC and R-PC.[46] Phycocyanin supplementation significantly reduces the salicylate-induced tinnitus in mice.[62]

Antibacterial Role:

The antibacterial activity of S. maxima extracts were assayed against five bacterial strains (*P. aeruginosa, B. subtilis, S. aureus, E. coli* and *Streptococcus sp.*) by evaluation of the inhibition of zones. Generally, all S. maxima extracts were found to be effective with antibacterial activity and were dose dependant. This phenomenon was in agreement with that found by Ozdemir et al.[63] The data in Table 2 showed that the most susceptible bacteria were Streptococcus sp. and B. subtilis to S. maxima with highest inhibition zones ranged 6–13 mm at concentrations 100–400 µl/disk. It is of interest to note that all S. maxima extracts manifested similar degrees of susceptible towards both Gram-positive and Gram-negative bacteria. The lower inhibition zone ranged from 6 to 9 mm of extracts obtained for *S. maxima*.[1]

TABLE 2: ANTIBACTERIAL ACTIVITY OF PHYCOCYANIN[1]

Sr. No.	Microorganism	Zone of inhibition at various concentrations of C-PC (mm)			
		100µl	200µl	300µl	400µl
1	*Streptococcus*	9	11	12	13
2	*Pseudomonas*	8	10	11	12
3	*Bacillus*	8	10	11	13
4	*Staphylococcus*	6	7	8	9
5	*E. coli*	7	9	10	11

Sarada et al showed that phycocyanin was able to markedly inhibit the growth of drug resistant bacteria *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* while no activity was recorded in *Acinetobacter baumanii* and *Enterococcus durans*.[64]

Phycocyanin as Immune System Modulator:

The regular intakes of phycocyanin boost immune responses.[65-67] When used as an adjuvant to chemotherapy Phycocyanin boost immune system to fight cancer spread, improved cancer response to chemotherapy and decreased risk that chemotherapy may give rise to a new cancer. Phycocyanin affects the stem cells in the bone marrow, which produce white blood cells that make the immune system and red blood cells that oxygenate the body. Phycocyanin emulates the affect of erythropoetin, which regulates red blod cells production. Phycocyanin suppresses allergic IgE antibody response and enhances secretary IgA antibody response in mice. The immune cells involved in cancer control, NK cells and cytotoxic T lymphocytes, function more effectively with intake of Phycocyanin.[65, 68]

Phycocyanin Mediated Apoptosis

COx-2 play a significant role in promoting tumor growth in multiple organ systems and is overexpressed in human lung, breast, colorectal and prostrate tumors. C-phycocyanin from S. platensis is a specific COx-2 inhibitor. Phycocyanin generates free radicals, which induce damage at macromolecular level, leading to apoptotic cell death.[60] Pardhasaradhi et al demonstrated Phycocyanin inability to induce apoptosis in Bcl-2 transfectants which correlated well with significant decrease in production of ROS (reactive oxygen species) in these cells.[60] Z-VAD, a pancaspase inhibitor, inhibits phycocyanin-mediated apoptosis, which indicates some role of caspases in apoptotic death of BC-8 cells (monoclonal cells of rat histiocytic tumor). Phycocyanin downregulates Bcl-2 expression in BC-8 cells, thereby make them vulnerable to apoptotic death. Since many tumors are resistant to apoptosis due to Bcl-2 expression, therefore, Phycocyanin treatment leading to Bcl-2 down-regulation, may make them sensitive to other anticancer agents that kill the tumor cells via apoptosis. Pardhasaradhi et al showed that phycocyanin induce apoptosis in tumor cells via ROS production, which is suppressed by Bcl-2.[60]

Anti-Cancer Effects:

Shanab et al showed that Spirulina Platensis showed higher antioxidant activity and moderate anticancer efficiency among various algal species due to its total phycobiliprotein pigments, and secondary metabolites.[8] Shalaby et al revealed that Spirulina platensis shows highest antioxidant activity under salt stress conditions.[69] Wang et al reported that c-phycocyanin interact with the membrane associated glyceraldehydes-3-phosphate dehydrogenase (GADPH) and B-tubulin, causing polymerization of microtubules and actin filaments leading to arrest the cell cycle at G0/G1 phase, thus exhibiting higher antiproliferative activity.[70]

The anticancer potential of C-PC extracted from Spirulina platensis is very well known.[71] Phycocyanin induces apoptosis in the existing as well as proliferating cancer cells. Various mechanisms of its anticancer activity are clear from **Table 3**.[71]

TABLE 3: VARIOUS MECHANISMS OF ANTITUMOR ACTIVITY OF C-PC ISOLATED FROM SPIRULINA PLATENSIS [71]

Sr. No.	Mechanism	Study	Year
1	Interference of DNA synthesis in the tumor cells	Wang et al	2001
2	Activation of caspase-dependent programmed cell death pathways (apoptosis)	Pardhasaradhi et al Li et al Roy et al Li et al	2003 2006 2007 2010
3	Inhibition of tumor cell growth by membrane destruction, leading to increased leakage of cell constituent	Abd El-Baky	2003
4	Inhibition of tumor cell growth by stimulation of expression level of the proto-oncogene c-myc	Liu et al	2000
5	Improvement of host immune functions	Hayashi et al Li et al	2006 2010

Gantar et al demonstrated that in contrast to the C-PC of Spirulina platensis, the C-PC from the cyanobacterium Limnothrix species exhibited low activity.[72] Previous studies have reported that phycocyanin from Spirulina platensis inhibited the growth of human hepatocellular carcinoma cell line SMMC-7721, human rectal cancer cell line HR8348, and human leukemia HL-60, as well as K562 and U937 cell line. Phycocyanin from Porphyra haitanensis was also reported to inhibit the growth of HL-60 cells. Phycocyanin inhibits the growth of Ehrlich Ascites Carcinoma Cells (EACC) in a dose dependent manner, by a pathway other than the apoptosis, by membrane destruction, which led to increase in the leakage of cell constituent and increase in GST and LDH enzyme activities.[3] Spirulina maxima and its protein extract mainly C-phycocyanin provided moderate genotoxic protection (~30%) against hydroxyurea and some protection against the hydroxyurea induced cytotoxicity in mice.[73]

C-phycocyanin attenuates cisplatin-induced nephrotoxicity in mice.[74] Hence, Phycocyanin have antitumor activity and may be used as a chemopreventive agent.[3]

Effect on Prostate Cancer:

Gantar et al reported that when only 10% of standard dose of topotecan was combined with C-PC, the prostate cancer cells (LNCaP) were killed at a higher rate than when topotecan was used alone at full dose. C-PC induce apoptosis through generation of ROS and activation of caspase-9 and caspase-8.[72]

Melanogenesis Inhibitor:

C-phycocyanin is a potential melanogenesis inhibitor. C-phycocyanin inhibits melanin biosynthesis by dual mechanisms; the promoted MITF protein degradation via MAPK/ERK signaling pathway upregulation, and the suppressed activation of CREB via the p38 MAPK pathway down-regulation as is clear from Table 4.[37, 75]

TABLE 4: PATHWAY INVOLVED FOR C-PHYCOCYANIN AS MELANOGENESIS INHIBITOR[37, 75]

Negative impact	Positive impact
-C-phycocyanin may also exert its negative impact on p38 phosphorylation -to restrict activation of the CREB -resulting in restricted MITF gene expression	-C-phycocyanin elevates the cellular abundance of cAMP -which triggers the activation of down-stream MAPK/ERK pathway -leading to the reduction of MITF proteins -activation of ERK1/2 resulted in the phosphorylation of MITF at S73 -induced the subsequent ubiquitin-dependent proteasomal degradation of MITF

The structure resemblance of C-phycocyanin constituents to MAPK pathway modulators (like SB203580 and bilirubin), account for its antimelanogenic effect.[37] SB203580 [4-(4'-fluorophenyl)-2-(4'- methylsulfinylphenyl)-5-(4'-pyridyl) imidazole] acts as a competitive inhibitor of ATP binding of MAP kinase homologues p38a, p38b and p38b2, and blocks a-MSH induced melanogenesis in B16 cells.[76] The prosthetic group of C-phycocyanin, phycocyanobilin might possess similar pyridinyl imidazole structural features to that of SB203580, so, sharing comparable inhibitory mechanisms.[37] In constrast, a structurally related molecule of phycocyanobilin, bilirubin, have an anticancer activity through the MAPK/ERK pathway activation.[77]

C-phycocyanin was found to be at nucleus at the early stage of entrance and afterwards accumulated

at the cytoplasm.[37] Phycocyaniobilin, could function as either or both an ERK activator and a p38 MAP kinase inhibitor to regulate melanin synthesis.[37]

Hematological Role:

In chronic leukemias, including chronic myeloid leukemia (CML), Philadelphia negative myeloproliferative neoplasms (MPNs), and chronic lymphocytic leukemia (CLL), evidence of defects in the regulation of cellular signaling pathways has been reported. Currently, treatment of a CML patient is usually based on a potent protein-tyrosine kinase inhibitor such as imatinib. Imatinib inhibits the kinase activity of the BCR-ABL oncoprotein, thus hindering cell proliferation. Although imatinib is an effective medication, drug resistance is a problem. Therefore, an alternative medicine is needed.[5] Phycocyanin is an antioxidant protector of human erythrocytes against peroxyl radicals.[78]

The anticancer effects of C-PC appear to mediated by various mechanisms such as an increase in the proapoptotic Fas rotein, down-regulation of Bcl-2, and selective inhibition of COX2. The pathway through which C-PC exerts its activities will enable its application as a therapeutic agent for MPNs.[5] Tantirapan et al found that C-PC at a micromolar level exhibited a cytotoxic effect on human erythromyeloid leukemia cell line (K562 cells).[5]

Subhashini et al demonstrated a decrease to approximately 65% of the control growth of K562 cells treated with C-PC. Decrease in the cell growth is a result of apoptosis via downregulation of anti-apoptotic Bcl-2, release of cytochrome c into the cytosol, and cleavage of poly(ADP) ribose polymerase (PARP). C-PC induce apoptosis and inhibit proliferation of cancer cells by altering signal transduction related to both apoptosis enhancement and terminated proliferation in cancer cells, possibly through the Ras/Raf/Mek/ERK, JAK/STAT, MAPK and PI3K/AKT pathways in K652 cells.[5]

Hepatocellular Carcinoma (HCC):

Roy et al demonstrated a 50% decrease in proliferation of doxorubicin sensitive (S-HepG2) and doxorubicin resistant (R-HepG2) HCC cell lines with phycocyanin. C-PC also enhanced the sensitivity of R-hepG2 HCC cells to doxorubicin. They showed downregulation of the anti-apoptotic protein Bcl-2 and upregulation of the pro-apoptotic Bax protein in the R-HepG2 cells.[79] Nishanth et al reported a significant down regulation of MDR1 (multidrug resistance-1) expression in C-PC treated HepG2 cells through cyclooxygenase-2 (COX-2) and reactive oxygen species mediated pathways. In a concentration dependent manner, C-PC increased the doxorubicin accumulation in HepG2 cells and enhanced cells sensitivity to doxorubicin by 5 folds. Further studies reveal the involvement of AP-1 and NF-κB in the C-PC induced down regulation of MDR1. The inactivation of the signal transduction pathways involving ERK, Akt, p38 and JNK by C-PC was also observed.[80]

Ou et al produced hepatoprotective activity of C-phycocyanin against carbon tetrachloride-induced hepatocyte damage in vivo and in vitro. Mechanisms involved through C-PC's scavenging ability and ability to block inflammatory infiltrate through its anti-inflammatory activities by inhibiting HGF and TGF-β1 expression.[81] Phycocyanin being COX-2 inhibitor, significantly inhibits liver microsomal lipid peroxidation hence protecting the liver by preventing oxidative stress in hepatocytes.[82] Phycocyanin inhibits microsomal lipid peroxidation induced by Fe+2 – ascorbic acid or the free radical initiator 2, 2' azobis (2-amidinopropane) hydrochloride (AAPH).[83] C-PC extracted from Porphyra yezoensis could develop to new photosensitizers for cancer photodynamic therapy.[84]

Colon Carcinoma:

Lu et al reported that the recombinant α-subunit of C-phycocyanin (CpcA) inhibited the growth of human colon carcinoma COLO 205 cells. The apoptotic process was associated with the Bax/Bcl-2 ratio up-regulation, mitochondrial membrane depolarization, cytochrome *c* release, and caspase-9 activation. It was proven that CpcA induced the death of COLO 205 cells through intrinsic apoptotic pathway.[85]

Breast Cancer:

Phycocyanin is an ideal photosensitizer which accumulates in breast cancer tissue and attracts He-Ne laser to target at tumor tissues. Being natural

and non-toxic, phycocyanin is a good substitute to highly toxic photosensitizers or chemotherapeutic drugs. It also causes inhibition of MCF-7 cell proliferation and morphological changes like chromatin condensation, blebs formation and loss of microvilli. C-PC-mediated photodynamic therapy activates immune system, induce pro-apoptotic Fas genes activation, cause apoptotis of cancer cells and down-regulates anti-apoptotic protein expression such as P53, Bcl-2, NF-kB and CD44 mRNA. Hence, Phycocyanin could be the new potential anticancer drug for therapy of Human Breast Cancer.[86]

Cervix Cancer:

Treatment of Human cervical cancer cell line (HeLa) cells with Phycocyanin increases hypodiploid cells population and DNA fragmentation. Phycocyanin reduces antiapoptotic proteins Bcl-2 level and promote death receptor genes expression like Fas/FasL and ICAM. Caspases play a central role in all apoptotic pathways and a higher level of caspases are seen in phycocyanin treated cells. Hence, Phycocyanin might be the new potential anticancer agent for Cervical Cancer therapy.[87]

Phycocyanin and Laser Therapy:

In this photochemical method, Phycocyanin is injected into a patient suffering from atherosclerosis or cancer. After being injected, phycocyanin is taken up selectively into the atherosclerotic plaques or the cancer cells. Destruction of the atherosclerotic plaques or the cancer cells occurs on subsequent irradiation. Phycocyanin has several advantages over prior art chemicals used for similar purposes. First, it is only marginally sensitive to ultraviolet part of the spectrum; consequently the patients can be irradiated without taking concern that they will be sensitized to subsequent sunlight exposure. Second, phycocyanin is taken up selectively into the atherosclerotic plaques, with little or no uptake by the surrounding normal cells. This ensures that upon subsequent irradiation, atherosclerotic plaques are selectively destroyed with little or no damage to surrounding cells or tissue.[88]

Effect on Pancreas:

Li et al demonstrated that cleavage of poly (ADP-ribose) polymerase (PARP) and activation of caspase-3 was blocked by Phycocyanin in hIAPP-treated cells. Also, PC significantly prevented the hIAPP-induced overproduction of malondialdehyde (MDA) and intracellular ROS, as well as changes in activities of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) enzymes. Furthermore, hIAPP triggered mitogen-activated protein kinases (MAPKs) activation, but these effects were effectively suppressed by PC.[89,90] So, the study reported that PC protects INS-1E pancreatic beta cells of rat insulinoma against hIAPP-induced apoptotic cell death through attenuating oxidative stress and modulating c-Jun N-terminal kinase (JNK) and p38 pathways.[89] This is not proved in humans till now. PC may have a potential to treat type-2 diabetes mellitus as it enhances insulin sensitivity, regulates glucolipide metabolism and ameliorates insulin resistance of peripheral target tissues.[91]

Ischemia Reperfusion Injury:

C-phycocyanin could be used for treating ischemia-reperfusion injury through the activation of ERK pathway and suppression of p38 MAPK pathway.[38] Phycocyanin may be used to treat ischemic stroke as phycocyanobilin has an effective influence on major inflammatory mediators of acute cerebral hypoperfusion.[92]

Cardiovascular Disease (CVD) and Non-Alcoholic Fatty Liver Disease (NAFLD):

Chronic diseases, such as CVD and NAFLD, are highly related to impaired lipid metabolism, oxidative stress, and inflammation. Phycocyanin provides multiple health-promoting properties: inhibition of inflammation via decreased nuclear factor kappa B (NF-kB) activity; lowering plasma lipid concentrations by decreasing intestinal cholesterol absorption and hepatic lipogenesis; and prevention of oxidative stress by blocking lipid peroxidation and increasing free radical scavenging.[46,93] In conclusion, Phycocyanin can be consumed as a dietary supplement or a food component to obtain health benefits against CVD and NAFLD.[46]

Neuroprotective Effects:

The anti-inflammatory, antioxidant and immune-modulatory properties contribute to the neuroprotective effects of Phycocyanin. Either the therapeutic or prophylactic application of Phycocyanin is able to significantly reduce the infarct volume, and also protect hippocampal neurons from death, induced by cerebral ischemia or reperfusion injury. Phyocyanin is platelet aggregation inhibitor with a potential to hamper arterial thromboembolism.[94]

Nephroprotective Effects:

Phycocyanin protects the renal cell integrity by stabilizing lipid peroxidation and protecting against oxalate induced nephro injury. Lipid peroxidation produce aldehydes like malondialdehyde (MDA) that are extremely active and can diffuse within or even escape from the cell and attack targets far from the site of the original free radical initiated event, resulting in cell damage and therefore act as 'cytotoxic second messengers'. Phycocyanin pre-treatment decreased the lipid peroxidation and reversed the effects of oxalate on oxidative stress parameters by interacting with hydroxyl radical and by rebalancing the GSH content, catalase and G6PD activity in oxalate treated animals.[95]

Acute Lung Injury:

Acute lung injury (ALI) is characterized by damage to the epithelial and endothelial cells in lungs, mediated by several pro-inflammatory mediators and finally impairs respiratory function. Phycocyanin exhibits its anti-inflammatory activity by inhibiting inducible nitric oxide synthase (iNOS) expression and NO production possibly by suppressing nuclear transcription factor-kB (NF-kB) activation, a key transcription factor promoting proinflammatory gene expression. Leung et al reported that posttreatment of ALI model with C-PC significantly reduces the tissue permeability, and protein concentration in bronchoalveolar lavage fluid (BALF) and improves pulmonary histological alterations.[96]

Wound Healing:

Phycocyanin directly enhances wound repair by its anti-oxidant property and scavenging destructive free radicals mechanism. Secondly, stimulation of keratinocyte is one mechanism by which phycocyanin might enhance wound repair process.[97]

Side Effects: Phycocyanin is usually non-toxic, but may cause liver damage, stomach pain, nausea, vomiting, weakness, thirst, rapid heartbeat, shock, and death. Phycocyanin may cause systemic anaphylaxis, urticaria, labial edema, asthma, diarrhea and diffuse erythema.[98]

CONCLUSION: Phycocyanin is a natural product from cyanobacteria and is a rich source of antioxidants. In view of current practice, antioxidant properties of phycocyanin have been investigated for their anti-inflammatory, anti-proliferative and anti-cancer effects. The results revealed for the first time that the C-phycocyanin activities and its antitumor actions such as in leukemia, colon cancer, pancreatic cancer etc. could be a promising natural antitumor agent with a potential for future pharmacological and medical applications. In the future, these marine algae-derived materials or compounds will be used more often in pre-clinical studies for drug discovery. In our review article, like other anti-cancer agents, phycocyanin being a natural product, should be more acceptable as an anticancer compound.

ACKNOWLEDGEMENTS: The authors are thankful to Pubmed, BioMed Central and Google database for providing the detailed parameters of the articles.

REFERENCES:

1. Muthulakshmi M, Saranya A, Sudha M, Selvakumar G: Extraction, partial purification, and antibact erial activity of phycocyanin from Spirulina isolated from fresh water body against various human pathogens. J Algal Biomass Utln 2012; 3(3):7–11.
2. Romay C, González R, Ledón N, Remirez D, Rimbau V: Phycocyanin - A Biliprotein with Antioxidant, Anti-Inflammatory and Neuroprotective Effects. Current Protein and Peptide Science 2003; 4:207-16.
3. El-Baky HHA: Overproduction of Phycocyanin pigment in Blue Green Alga Spirulina Sp. And it's inhibitory effect on growth of Ehrlich Ascites Carcinoma Cells. J Med Sci 2003; 3(4):314-24.
4. Biswas A, Vasquez YM, Dragomani TM, Kronfel ML, Williams SR, Alvey RM, et al: Biosynthesis of cyanobacterial phycobiliproteins in Escherichia coli: chromophorylation efficiency and specificity of all bilin lyases from Synechococcus sp. strain PCC 7002. Appl Environ Microbiol 2010; 76(9):2729-39.
5. Tantirapan P, Suwanwong Y: Anti-proliferative effects of C-phycocyanin on a human leukemic cell line and induction of

apoptosis via the PI3K/AKT pathway. J Chem Pharm Res 2014; 6(5):1295-1301.

6. Schirmer T, Bode W, Huber R: X-ray crystallographic structure of the light-harvesting biliprotein C-phycocyanin from the thermophilic cyanobacterium *Mastigocladus laminosus* and its resemblance to globin structures. Journal of Molecular Biology 1985; 184(2):257–77.
7. Eriksen NT: Production of Phycocyanin – a pigment with applications in biology, biotechnology, foods and medicine. Applied Microbiology and Biotechnology 2008; 80(1):1-14.
8. Shanab SMM, Mostafa SSM, Shalaby EA, Mahmoud GI: Aqueous extracts of microalgae exhibit antioxidant and anticancer activities. Asian Pac J Trop Biomed 2012; 2(8):608-15.
9. Liu H, Jing H, Wong TH, Chen B: Co-occurrence of phycocyanin- and phycoerythrin-rich Synechococcus in subtropical estuarine and coastal waters of Hong Kong. Environ Microbiol Rep 2014; 6(1):90-9.
10. Singh P, Tiwari A, Singh SP, Asthana RK: Desiccation induced changes in osmolytes production and the antioxidative defence in the cyanobacterium Anabaena sp. PCC 7120. Physiol Mol Biol Plants 2013; 19(1):61-8.
11. Hsieh P, Pedersen JZ, Bruno L: Photoinhibition of cyanobacteria and its application in cultural heritage conservation. Photochem Photobiol 2014; 90(3):533-43.
12. Kronfel CM, Kuzin AP, Forouhar F, Biswas A, Su M, Lew S, et al: Structural and biochemical characterization of the bilin lyase CpcS from Thermosynechococcus elongatus. Biochemistry 2013; 52(48):8663-76.
13. Ferrari SG, Silva PG, González DM, Navoni JA, Silva HJ: Arsenic tolerance of cyanobacterial strains with potential use in biotechnology. Rev Argent Microbiol 2013; 45(3):174-9.
14. Caddeo C, Chessa M, Vassallo A, Pons R, Diez-Sales O, Fadda AM, et al: Extraction, purification and nanoformulation of natural phycocyanin (from Klamath algae) for dermal and deeper soft tissue delivery. J Biomed Nanotechnol 2013; 9(11):1929-38.
15. Nganou C: Low absorption state of phycocyanin from Acaryochloris marina antenna system: on the interplay between ionic strength and excitonic coupling. J Chem Phys 2013; 139(4):045101.
16. Tao Y, Mao X, Hu J, Mok HO, Wang L, Au DW, et al: Mechanisms of photosynthetic inactivation on growth suppression of Microcystis aeruginosa under UV-C stress. Chemosphere 2013; 93(4):637-44.
17. Thangam R, Suresh V, Asenath Princy W, Rajkumar M, Senthilkumar N, Gunasekaran P, et al: C-Phycocyanin from Oscillatoria tenuis exhibited an antioxidant and in vitro antiproliferative activity through induction of apoptosis and G0/G1 cell cycle arrest. Food Chem 2013; 140(1-2):262-72.
18. Sardana R, Pillai MG, Ravishankar GA: Phycocyanin from *Spirulina* sp: influence of processing of biomass on phycocyanin yield, analysis of efficacy of extraction methods and stability studies on Phycocyanin. Process Biochemistry 1999; 34(8):795–801.
19. Liu S, Chen Y, Lu Y, Chen H, Li F, Qin S: Biosynthesis of fluorescent cyanobacterial allophycocyanin trimer in Escherichia coli. Photosynth Res 2010; 105(2):135-42.
20. Kursar AT, Alberte SR: Photosynthetic unit organization in a red algae. Plant Physiol 1983; 72:409-14.
21. Singh SP, Montgomery BL: Salinity impacts photosynthetic pigmentation and cellular morphology changes by distinct mechanisms in Fremyella diplosiphon. Biochem Biophys Res Commun 2013; 433(1):84-9.
22. Deng R, Chow TJ: Hypolipidemic, antioxidant, and anti-inflammatory activities of microalgae Spirulina. Cardiovasc Ther 2010; 28:e33–e45.
23. Srivastava AK: Assessment of Salinity-Induced Antioxidative Defense System of Diazotrophic Cyanobacterium Nostoc muscorum. J Microbiol Biotechnol 2010; 20(11):1506-12.
24. Leema JT, Kirubagaran R, Vinithkumar NV, Dheenan PS, Karthikayulu S: High value pigment production from Arthrospira (Spirulina) platensis cultured in seawater. Bioresour Technol 2010; 101(23):9221-7.
25. Wang C, Kong HN, Wang XZ, Wu HD, Lin Y, He SB: Effects of iron on growth and intracellular chemical contents of Microcystis aeruginosa. Biomed Environ Sci 2010; 23(1):48-52.
26. Chen CY, Kao PC, Tsai CJ, Lee DJ, Chang JS: Engineering strategies for simultaneous enhancement of C-phycocyanin production and CO2 fixation with Spirulina platensis. Bioresour Technol 2013; 145:307-12.
27. Suzuki E, Ohkawa H, Moriya K, Matsubara T, Nagaike Y, Iwasaki I, et al: Carbohydrate metabolism in mutants of the cyanobacterium Synechococcus elongatus PCC 7942 defective in glycogen synthesis. Appl Environ Microbiol 2010; 76(10):3153-9.
28. Jasser I, Karnkowska-Ishikawa A, Kozłowska E, Królicka A, Łukomska-Kowalczyk M: Composition of picocyanobacteria community in the Great Mazurian Lakes: isolation of phycoerythrin-rich andphycocyanin-rich ecotypes from the system--comparison of two methods. Pol J Microbiol 2010; 59(1):21-31.
29. Moraes CC, Mazutti MA, Maugeri F, Kalil SJ: Modeling of ion exchange expanded-bed chromatography for the purification of C-phycocyanin. J Chromatogr A 2013; 15(1281):73-8.
30. Jaiswal P, Prasanna R, Singh PK: Physiological characterization and molecular profiling of toxic and non-toxic isolates of cyanobacterium Microcystis. J Environ Biol 2013; 34(3):555-60.
31. Womick JM, Miller SA, Moran AM: Toward the origin of exciton electronic structure in phycobiliproteins. J Chem Phys 2010; 133(2):024507.
32. Benedetti S, Benvenuti F, Scoglio S, Canestrari F: Oxygen radical absorbance capacity of phycocyanin and phycocyanobilin from the food supplement Aphanizomenon flos-aquae. J Med Food 2010; 13(1):223-7.
33. Sørensen L, Hantke A, Eriksen NT: Purification of the photosynthetic pigment C-phycocyanin from heterotrophic Galdieria sulphuraria. J Sci Food Agric 2013; 93(12):2933-8.
34. Manconi M, Mura S, Manca ML, Fadda AM, Dolz M, Hernandez MJ, et al: Chitosomes as drug delivery systems for C-phycocyanin: preparation and characterization. Int J Pharm 2010; 392(1-2):92-100.
35. de Jesus Raposo MF, de Morais RM, de Morais AM: Health applications of bioactive compounds from marine microalgae. Life Sci 2013; 93(15):479-86.
36. Li B, Chu X, Gao M, Li W: Apoptotic mechanism of MCF-7 breast cells in vivo and in vitro induced by photodynamic therapy with C-phycocyanin. Acta Biochim Biophys Sin 2010; 80–9.
37. Wu L, Lin Y, Yang S, Weng Y, Tsai Y: Antimelanogenic effect of c-phycocyanin through modulation of tyrosinase expression by upregulation of ERK and downregulation of p38 MAPK signaling pathways. Journal of Biomedical Science 2011; 18:74.
38. Khan M, Varadharaj S, Ganesan LP, Shobha JC, Naidu MU, Parinandi NL, et al: C-phycocyanin protects against ischemia-reperfusion injury of heart through involvement of p38 MAPK and ERK signaling. Am J Physiol Heart Circ Physiol 2006; 290:2136-45.
39. Krishnaraj RN, Chandran S, Pal P, Berchmans S: Screening of photosynthetic pigments for herbicidal activity with a new computational molecular approach. Comb Chem High Throughput Screen 2013; 16(10):777-81.

40. Sharaf M, Amara A, Aboul-Enein A, Helmi S, Ballot A, Astani A, et al: Molecular authentication and characterization of the antiherpetic activity of the cyanobacterium Arthrospira fusiformis. Pharmazie 2010; 65(2):132-6.
41. Chu WL, Lim YW, Radhakrishnan AK, Lim PE: Protective effect of aqueous extract from Spirulina platensis against cell death induced by free radicals. BMC Complement Altern Med 2010; 10:53.
42. Kuddus M, Singh P, Thomas G, Al-Hazimi: A Recent developments in production and biotechnological applications of C-phycocyanin. Biomed Res Int 2013; 2013:742859.
43. Tian Y, Pappas D: Investigation of saturation and photobleaching of allophycocyanin by single-molecule recrossing events. Appl Spectrosc 2010; 64(3):324-7.
44. Ivanova KG, Stankova KG, Nikolov VN, Georgieva RT, Minkova KM, Gigova LG, et al: The biliprotein C-phycocyanin modulates the early radiation response: a pilot study. Mutat Res 2010; 695(1-2):40-5.
45. Lee J, Hou M, Huang H, Chang F, Yeh C, Tang J, et al: Marine algal natural products with antioxidative, anti-inflammatory, and anti-cancer properties. Cancer Cell International 2013; 13:55.
46. Ku CS, Yang Y, Park Y, and Lee J: Health Benefits of Blue-Green Algae: Prevention of Cardiovascular Disease and Nonalcoholic Fatty Liver Disease. J Med Food 2013; 16(2):103–11.
47. Pleonsil P, Soogarun S, Suwanwong Y: Anti-oxidant activity of holo- and apo-c-phycocyanin and their protective effects on human erythrocytes. Int J Biol Macromol 2013; 60:393-8.
48. Madhyastha H, Vatsala TM: Cysteine-rich cyanopeptide beta2 from Spirulina fusiformis exhibits plasmid DNA pBR322 scission prevention and cellular antioxidant activity. Indian J Exp Biol 2010; 48:486–93.
49. Zhang H, Chen T, Jiang J, Wong YS, Yang F, Zheng W: Selenium-containing allophycocyanin purified from seleniumenriched Spirulina platensis attenuates AAPH-induced oxidative stress in human erythrocytes through inhibition of ROS generation. J Agric Food Chem 2011; 59:8683–90.
50. Gupta M, Dwivedi UN, Khandelwal S: C-Phycocyanin: An effective protective agent against thymic atrophy by tributyltin. Toxicology Letters 2011; 204(1):2–11.
51. Strasky Z, Zemankova L, Nemeckova I, Rathouska J, Wong RJ, Muchova L, et al: Spirulina platensis and phycocyanobilin activate atheroprotective heme oxygenase-1: a possible implication for atherogenesis. Food Funct 2013; 4(11):1586-94.
52. Banji D, Banji OJ, Pratusha NG, Annamalai AR: Investigation on the role of Spirulina platensis in ameliorating behavioural changes, thyroid dysfunction and oxidative stress in offspring of pregnant rats exposed to fluoride. Food Chem 2013; 140(1-2):321-31.
53. Marles RJ, Barrett ML, Barnes J, Chavez ML, Gardiner P, Ko R, et al: United States pharmacopeia safety evaluation of Spirulina. Crit Rev Food Sci Nutr 2011; 51:593–604.
54. Kapoor R, Mehta U: Supplementary effect of Spirulina on hematological status of rats during pregnancy and lactation. Plant Foods Hum Nutr 1998; 52:315–24.
55. Morcos NC, Berns M, Henry WL: Phycocyanin: Laser activation, Cytotoxic effects, and Uptake in human atherosclerotic plaque. Lasers in Surgery and Medicine 1988; 8:10-17.
56. Li B, Chu XM, Xu YJ, Yang F, Lv CY, Nie SM: CD59 underlines the antiatherosclerotic effects of C-phycocyanin on mice. Biomed Res Int 2013; 2013:729413.
57. Ichimura M, Kato S, Tsuneyama K, Matsutake S, Kamogawa M, Hirao E, et al: Phycocyanin prevents hypertension and low serum adiponectin level in a rat model of metabolic syndrome. Nutr Res 2013; 33(5):397-405.
58. Bhat VB, Madyastha KM: C-phycocyanin: a potent peroxyl radical scavenger in vivo and in vitro. Biochem Biophys Res Commun 2000; 275:20–5.
59. Pak W, Takayama F, Mine M, Nakamoto K, Kodo Y, Mankura M, et al: Anti-oxidative and anti-inflammatory effects of spirulina on rat model of non-alcoholic steatohepatitis. J Clin Biochem Nutr 2012; 51(3):227–34.
60. Pardhasaradhi BVV, Ali AM, Kumari AL, Reddanna P, Khar A: Phycocyanin-mediated apoptosis in AK-5 tumor cells involves down-regulation of Bcl-2 and generation of ROSMol Cancer Ther 2003; 2:1165–70.
61. Selmi C, Leung PS, Fischer L, German B, Yang CY, Kenny TP, et al: The effects of Spirulina on anemia and immune function in senior citizens. Cell Mol Immunol 2011; 8:248–54.
62. Hwang JH, Chen JC, Chan YC: Effects of C-phycocyanin and Spirulina on salicylate-induced tinnitus, expression of NMDA receptor and inflammatory genes. PLoS One 2013; 8(3):e58215.
63. Ozdemir G, Karabay NU, Dalay MC, Pazarbasi B: Antibacterial activity of volatile component and various extracts of Spirulina platensis. Phytother Res 2004; 18:754-7.
64. Sarada DVL, Kumar CS, Rengaswamy R: Purified C-phycocyanin from Spirulina platensis (Nordstedt) Geitler: a novel and potent agent against drug resistant bacteria. World Journal of Microbiology and Biotechnology 2011; 27(4):779-83.
65. Abd-El Baky HH, El-Baroty GS: Healthy Benefit of Microalgal Bioactive Substances. Journal of Aquatic Science 2013; 1(1):11-23.
66. Chang CJ, Yang YH, Liang YC, Chiu CJ, Chu KH, Chou HN, et al: A novel phycobiliprotein alleviates allergic airway inflammation by modulating immune responses. Am J Respir Crit Care Med 2011; 183(1):15-25.
67. El-Sheekh MM, Mahmoud YA, Abo-Shady AM, Hamza W: Efficacy of Rhodotorula glutinis and Spirulina platensis carotenoids in immunopotentiation of mice infected with Candida albicans SC5314 and Pseudomonas aeruginosa 35. Folia Microbiol (Praha) 2010; 55(1):61-7.
68. Fan M, Liao Z, Wang RX, Xu N: Isolation and antibacterial activity of anabaena phycocyanin. African Journal of Biotechnology 2013; 12(15):1869-73.
69. Shalaby EA, Shanab SMM, Singh V: Salt stress enhancement of antioxidant and antiviral efficiency of Spirulina platensis. J Med Plants Res 2010; 4(24):2622-32.
70. Wang H, Liu Y, Gao X, Carter CL, Liu ZR: The recombinant beta subunit of C-phycocyanin inhibits cell proliferation and induces apoptosis. Cancer Letters 2007; 247(1):150-8.
71. Gardeva E, Toshkova R, Yossifova L, Minkova K, Ivanova N, Gigova L: Antitumor Activity of C-phycocyanin from Arthronema africanum (Cyanophyceae). Braz Arch Biol Technol 2013; 1-10.
72. Gantar M, Dhandayuthapani S, Rathinavelu A: Phycocyanin Induces Apoptosis and Enhances the Effect of Topotecan on Prostate Cell Line LNCaP Journal of Medicinal Food 2012; 15(12):1091-95.
73. Álvarez-González I, Vázquez-Sánchez J, Chamorro-Cevallos G, Madrigal-Bujaidar E: Effect of Spirulina maxima and its protein extract on micronuclei induction by hydroxyurea in pregnant mice and their fetuses. J Med Food 2013; 16(11):992-6.
74. Nasri H: C-Phycocyanin attenuates cisplatin-induced nephrotoxicity in mice. Ren Fail 2013; 35(7):1054-5.
75. Wu M, Hemesath TJ, Takemoto CM, Horstmann MA, Wells AG, Price ER, et al: c-Kit triggers dual phosphorylations, which couple activation and degradation of the essential melanocyte factor Mi. Genes Dev 2000; 14:301-12.
76. Singh SK, Sarkar C, Mallick S, Saha B, Bera R, Bhadra R: Human placental lipid induces melanogenesis through p38

MAPK in B16F10 mouse melanoma. Pigment Cell Res 2005; 2:113-21.
77. Ollinger R, Kogler P, Troppmair J, Hermann M, Wurm M, Drasche A, et al: Bilirubin inhibits tumor cell growth via activation of ERK. Cell Cycle 2007; 6:3078-85.
78. Romay C, Gonzalez R: Phycocyanin is an antioxidant protector of human erythrocytes against peroxyl radicals. Journal of Pharmacy and Pharmacology 2000; 52(4):367-68.
79. Roy KR, Arunasree KM, Reddy NP, Dheeraj B, Reddy GV, Reddanna P: Alteration of mitochondrial membrane potential by Spirulina platensis C-phycocyanin induces apoptosis in the doxorubicin-resistant human hepatocellular-carcinoma cell line HepG2. Biotechnol Appl Biochem 2007; 47:159–67.
80. Nishanth RP, Ramakrishna BS, Jyotsna RG, Roy KR, Reddy GV, Reddy PK, et al: C-Phycocyanin inhibits MDR1 through reactive oxygen species and cyclooxygenase-2 mediated pathways in human hepatocellular carcinoma cell line. European Journal of Pharmacology 2010; 649(1–3):74–83.
81. Ou Y, Zheng S, Lin L, Jiang Q, Yang X: Protective effect of C-phycocyanin against carbon tetrachloride-induced hepatocyte damage in vitro and in vivo. Chemico-Biological Interactions 2010; 185(2):94–100.
82. Sathyasaikumar KV, Swapna I, Reddy PV, Murthy CR, Roy KR, Dutta-Gupta A, et al: Co-administration of C-Phycocyanin ameliorates thioacetamide-induced hepatic encephalopathy in Wistar rats. J Neurol Sci 2007; 252:67–75.
83. Bermejo-Bescos P, Pinero-Estrada E, Villar del Fresno AM: Neuroprotection by Spirulina platensis protean extract and phycocyanin against iron-induced toxicity in SH-SY5Y neuroblastoma cells. Toxicology In Vitro 2008; 22:1496–1502.
84. Wang Y, Cai C, Li B, Liu C, He P: Photodynamic effect of two kinds of phycobiliproteins on human liver cancer cell line SMMC-7721 in vitro. Sheng Wu Gong Cheng Xue Bao 2009; 25(9):1417-23.
85. Lu W, Yu P, Li J: Induction of apoptosis in human colon carcinoma COLO 205 cells by the recombinant α subunit of C-phycocyanin. Biotechnology Letters 2011; 33(3):637-44.
86. Cai XH, Zheng S, He LM: "The experimental study of application of phycocyanin in cancer laser therapy". Chinese Journal of Marine Drugs 1995; 53(1):15.
87. Li B, Gao M, Zhang X, Chu X: Molecular immune mechanism of C-phycocyanin from Spirulina platensis induces apoptosis in HeLa cells in vitro. Biotechnology and Applied Biochemistry 2006; 43:155–64.
88. Morcos NC, Henry WL: Medical uses for Phycocyanin. United States Patent 1989; Patent No.4886831.
89. Li XL, Xu G, Chen T, Wong YS, Zhao HL, Fan RR, et al: Phycocyanin protects INS-1E pancreatic beta cells against human islet amyloid polypeptide-induced apoptosis through attenuating oxidative stress and modulating JNK and p38 mitogen-activated protein kinase pathways. Int J Biochem Cell Biol 2009; 41(7):1526–35.
90. Li XL, Chen T, Wong YS, Xu G, Fan RR, Zhao HL, et al: Involvement of mitochondrial dysfunction in human islet amyloid polypeptide-induced apoptosis in INS-1E pancreatic beta cells: An effect attenuated by phycocyanin. Int J Biochem Cell Biol 2011; 43(4):525-34.
91. Ou Y, Lin L, Yang X, Pan Q, Cheng X: Antidiabetic potential of phycocyanin: effects on KKAy mice. Pharm Biol 2013; 51(5):539-44.
92. Marín-Prida J, Pavón-Fuentes N, Llópiz-Arzuaga A, Fernández-Massó JR, Delgado-Roche L, Mendoza-Marí Y, et al: Phycocyanobilin promotes PC12 cell survival and modulates immune and inflammatory genes and oxidative stress markers in acute cerebral hypoperfusion in rats. Toxicol Appl Pharmacol 2013; 272(1):49-60.
93. Ku CS, Yang Y, Park Y, Lee J: Health benefits of blue-green algae: prevention of cardiovascular disease and nonalcoholic fatty liver disease. J Med Food 2013; 16(2):103-11.
94. Pentón-Rol G, Marín-Pridaa J, Pardo-Andreua G, Martínez-Sáncheza G, Acosta-Medinaa EF, Valdivia-Acostaa A, et al: C-Phycocyanin is neuroprotective against global cerebral ischemia/reperfusion injury in gerbils. Brain Research Bulletin 2011; 1-11.
95. Farooq SM, Asokan D, Sakthivel R, Kalaiselvi P, Varalakshmi P: Salubrious effect of C-phycocyanin against oxalate-mediated renal cell injury. Clin Chim Acta 2004; 348(1-2):199-205.
96. Leung PO, Lee HH, Kung YC, Tsai MF, Chou TZ: Therapeutic Effect of C-Phycocyanin Extracted from Blue Green Algae in a Rat Model of Acute Lung Injury Induced by Lipopolysaccharide. Evidence-Based Complementary and Alternative Medicine 2013; 1-11.
97. Gur CS, Erdogan DK, Onbasılar I, Atilla P, Cakar N, Gurhan ID: In vitro and in vivo investigations of the wound healing effect of crude Spirulina extract and C-phycocyanin. Journal of Medicinal Plants Research 2013; 7(8):425-33.
98. Petrus M, Culerrier R, Campistron M, Barre A, Rouge P: First case report of anaphylaxis to spirulin : identification of Phycocyanin as responsible allergen. Allergy 2010; 65:924–32.

How to cite this article:
Soni A, Dubey M, Verma M, Dhankhar R, Kaushal V, Atri R and Sabharwal R: Revisiting the Role of Phycocyanin in Current Clinical Practice. Int J Pharm Sci Res 2015; 6(11): 4588-00.doi: 10.13040/IJPSR.0975-8232.6(11).4588-00.