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REVIEW ARTICLE

Potential Therapeutic Applications of C-Phycocyanin

Saira M. Bannu[1], Dakshayani Lomada[2], Surendra Gulla[1], Thummala Chandrasekhar[3], Pallu Reddanna[4] and Madhava C. Reddy[1,*]

[1]*Department of Biotechnology and Bioinformatics, Yogi Vemana University, Kadapa, Andhra Pradesh 516 005, India;* [2]*Department of Genetics and Genomics, Yogi Vemana University, Kadapa, Andhra Pradesh 516 005, India;* [3]*Department of Environmental Science, Yogi Vemana University, Kadapa, Andhra Pradesh 516005, India;* [4]*Department of Animal Sciences, University of Hyderabad, Hyderabad, Telangana 500 046, India*

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Abstract: ***Background*:** Cancer and other disorders such as inflammation, autoimmune diseases and diabetes are the major health problems observed all over the world. Therefore, identifying a therapeutic target molecule for the treatment of these diseases is urgently needed to benefit public health. C-Phycocyanin (C-PC) is an important light yielding pigment intermittently systematized in the cyanobacterial species along with other algal species. It has numerous applications in the field of biotechnology and drug industry and also possesses antioxidant, anticancer, anti-inflammatory, enhanced immune function, including liver and kidney protection properties. The molecular mechanism of action of C-PC for its anticancer activity could be the blockage of cell cycle progression, inducing apoptosis and autophagy in cancer cells.

***Objectives*:** The current review summarizes an update on therapeutic applications of C-PC, its mechanism of action and mainly focuses on the recent development in the field of C-PC as a drug that exhibits beneficial effects against various human diseases including cancer and inflammation.

***Conclusion*:** The data from various studies suggest the therapeutic applications of C-PC such as anti-cancer activity, anti-inflammation, anti-angiogenic activity and healing capacity of certain autoimmune disorders. Mechanism of action of C-PC for its anticancer activity is the blockage of cell cycle progression, inducing apoptosis and autophagy in cancer cells. The future perspective of C-PC is to identify and define the molecular mechanism of its anti-cancer, anti-inflammatory and antioxidant activities, which would shed light on our knowledge on therapeutic applications of C-PC and may contribute significant benefits to global public health.

Keywords: C-Phycocyanin, therapeutic agent, cancer, inflammation, cell death, public health.

1. INTRODUCTION

C-Phycocyanin belongs to biliproteins, a group of colored photoreceptors which capture light energy and transfer it to chlorophylls for photosynthesis. Most of the C-PC's are isolated from cyanobacteria or blue-green algae and also from red algae, glaucophyta, cryptophyta, *etc*. [1-3]. Additionally, C-PC is shown to possess anticancer [4], immunity promoting [5], antioxidative [6] and anti-inflammation properties. Furthermore, C-PC also acts as non-toxic photo-sensitizer used in the adjuvant Photodynamic Therapy (PDT) of tumours [7]. *Spirulina platensis* (*Arthospira platensis*), a member of cyanobacteria has an eminent source of C-PC including other proteins (>60%) which hydrolyzed into bioactive peptides [8-10]. Moreover, other species of *Spirulina* such as *Spirulina fusiformis* [11] and *Spirulina maxima* [12, 13] were also considered as potent source of C-PC.

In addition, C-PC was isolated from other cyanobacterial species including *Coccochloris elabens* [14], *Synechococcus lividus* [15], Synechocystis PCC 6803 [16], *Synechococcus vulcanus* [17], *Synechococcus elongate* [18], *Lyngbya* [19, 20], *Oscillatoria quadripunctulata* [20], *Aphanizomenon flos-aquae* [21], *Arthronema africanum* [11], *Phormidium fragile* [22], *Nostoc* [23], *Synechococcus* sps [24], *Anabaena marina* [25], *Oscillatoria tenuis* [26], *Pseudanabaena* sps. LW0831 [27], Limnothrix [28] and *Oscillatoria minima* [29]. Moreover, C-Phycocyanin was isolated from a few red algal species such as *Cyanidium caldarium* [30], *Gracilaria chilensis* [31] and *Centroceras clavulatum* [2]. Furthermore, C-PC was also produced from cryptophyta and glaucophyta species such as *Chroomonas* and *Hemiselmispacifica* [32, 33] and *Cyanophora paradoxa* [34, 35]. In the present review, we emphasized the structure and characterization of C-PC that belongs to *Spirulina platensis* and minor modifications are also possible depending on the algal species. Our laboratory also studied the impact of C-PC on cyclooxygenase-2 (Cox 2) inhibition as well as induction of apoptosis [36-38].

1.1. Phycobilisomes, Phycobiliproteins and Light Harvesting Process

Blue-green algae along with certain primitive plant groups, hold two distinct photosynthetic Reaction Centers (RCs), which include P700 and P680 of Photosystem I (PSI) and Photosystem II (PSII). Each RC is associated with an antenna of LHC (Light-harvesting Complex) [2, 39]. These light harvesting complex of blue-green and red algae including cryptophytes and glaucophytes generally consist of Phycobilisomes (PBSs) which in turn consist of key photosynthetic pigment molecules, the Phycobiliproteins (PBPs) (Fig. **1**).

Phycobiliproteins are water soluble and light intake protein-pigment aggregates found in certain algae and photosynthetic bacteria [29, 40]. As mentioned above, these protein-pigments absorb light and transfer energy to the reaction centers of photoactive compounds confined in the thylakoid membranes. These are majorly found as fluorescent proteins and expressed as natural color-

*Address correspondence to this author at the Department of Biotechnology and Bioinformatics, Yogi Vemana University, Kadapa, Andhra Pradesh 516 005, India; E-mail: cmadhavareddy@gmail.com

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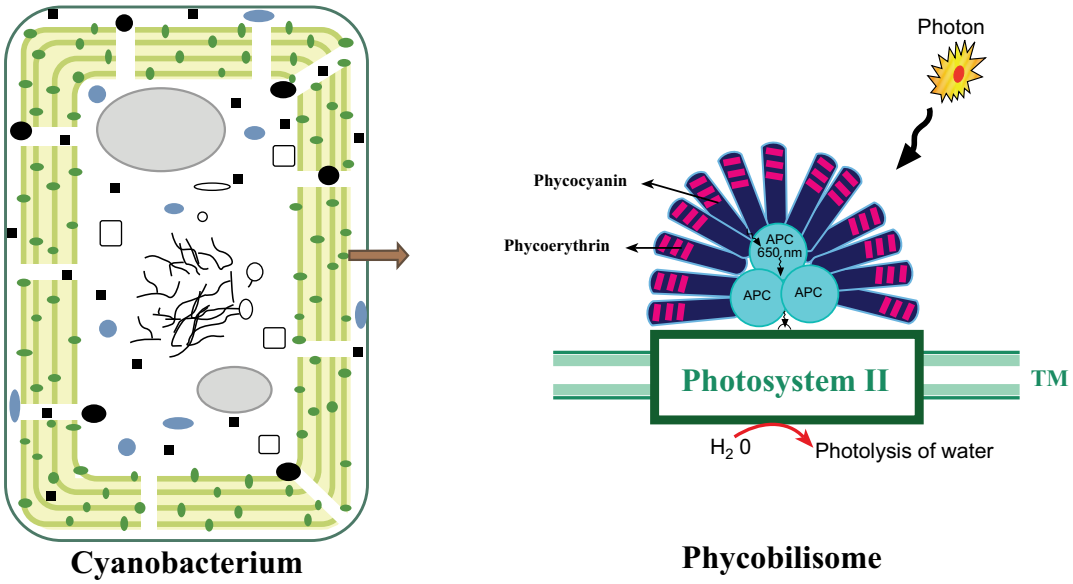

Fig. (1). Typical structure of phycobilisome along with different phycobiliproteins in cyanobacterial cell. APC-Allophycocyanin, TM-Thylakoid membrane. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ants due to their non-toxic and non-carcinogenic nature [41]. Phycobiliproteins are multichain holoproteins consisting of apoproteins and covalently attached phycobilins. Moreover, these are open chain tetrapyrrole chromophores with no metal complexes. Phycobiliproteins are divided mainly into three major groups depending on different chromophores *i.e.* phycoerythrene (PE, bright pink), phycocyanin (PC, cobalt blue) and allophycocyanin (APC, brighter aqua blue) [42]. The major role of phycobiliproteins was photosynthetic light harvesting and their absorption maxima are approximately 570 nm (PE), 630 nm (C-PC) and 650 nm (APC) located at wavelengths where chlorophylls have low extension coefficient [43]. These phycobiliproteins are organized as supramolecular structures that assemble on PSII of superficial layer of thylakoid membrane and form phycobilisome as mentioned above for the purpose of maximizing energy transfer to chlorophyll complex proteins (Fig. **1**). In detail, phycobilisomes contain a central core of APC with C-PC and PE hexamers stacked on top of each other forming rod-shaped extensions [42]. The inner part of the rods is composed of C-PC hexamers and in some blue-green and red algae, the phycobilisome does not contain PE, while the phycobilisomes of *Aphanizomenon fols-aquae* lacks APC [44]. The phycobilisome core-membrane linker protein ApcE may provide a flexible surface, which allows phycobilisomes to attach to reaction centers of photosystems. The energy is transferred from PE to PC within the rod and then APC in the core and finally to photosystem II intermittently to photosystem I, that mediates through linker protein [45].

1.2. Physico-chemical Properties of C-PC

C-PC exhibits spectral property by acting as a light harvesting pigment which is the basis for identification and quality. Several researchers described the spectral properties, vitality, absorption peaks and amino acid composition of C-PC as represented in Table **1** [2, 19, 46, 47]. C-PC of *S. platensis* comprises α and β subunits which in turn consist of 162 and 172 amino acids with 16.3 and 18.9 kDa molecular weights respectively. In microns, molecular weight of α subunit was 14500 μ and for β subunit, it was 15000 μ as shown in Table **2** [48]. Minor variation was noticed in these properties of C-PC which in turn depends on the algal species. For instance, Yu *et al*. (1999) reported differently that molecular weights of both α and β subunits of *S. platensis* were 14900 μ and 17200 μ respectively (Fig. **2**).

Table 1. Spectral property of C-PC.

Pigment	C-PC
Emission maxima	~642 nm
Quantum yield Φ	0.81
Absorption peak m	~621 nm
Extinction coefficient	$1.54x10^6$ M^{-1} cm^{-1}
Fluorescence absorbance	0.15 nm
Fluorescence emission	647 nm
Absorptivity	7.0 (L/g.cm)

Both pH and temperature play an essential role in the stability of C-PC which in turn depends on strain, isolation method and conditions. Generally, C-PC is stable under 40ºC and above this temperature the pigment gets decompose and the optical density decreases [49]. The concentration and half-life of C-PC in solution decrease expeditiously when incubated at temperatures between 47ºC and 64ºC, specifically, it remains at 50% after incubating at 59°C for 30 min [7]. Moreover, C-Phycocyanin has its maximal constancy in the pH range from 5.5 to 6.0 and some reports stated that color and optical density were almost constant between 4.0 to 8.5 pH conditions [49]. Some of the membrane technologies were also discovered to enhance the stability of C-PC extracts obtained from the ultrasonic breakage of *Spirulina platensis* [50]. Apart from light harvesting function, C-PC is also used as a food additive, cosmetic colorant, fluorescence detection probe and plays a secondary role as intercellular nitrogen storage compounds that are mobilized for other purposes during nitrogen shortage period [51, 52]. Majorly, the role of C-PC as a therapeutic agent is discussed in detail in the below paragraphs.

1.3. Regulation of C-PC Synthesis

Cyanobacterial species carry two genes namely *C-PCA* and *C-PCB* encoding α and β chains of C-PC. Both the genes are located in the C-PC operon and translated from the same mRNA transcript

Table 2. α and β subunits of C-PC.

S.No	Properties	α Chain	β Chain
1.	Amino acid sequence	MKTPLTEAVSIADSQGRFLSSTEIQVAFG RFRQAKAGLEAAKALTSKADSLISGAAQA VYNKFPYTTQMQGPNYAADQRGKDKCAR DIGYYLRMVTYCLIAGGTGPMDEYLIAGI DEINRTFELSPSWYIEALKYI KANHGLSGDAATEANSYLDYAINALS	MFDAFTKVVSQADTRGEMLSTAQIDA LSQMVAESNKRLDAVNRITSNASTIVSNAARSLFA EQPQLIAPGGNAYTSRRMAACLRDME IILRYVTYAVFAGDASVLEDRCLNGLRETY LALGTPGSSVAVGVGKMKEAALAIVND PAGITPGDCSALASEIASYFDRACAAVS
2.	Formula	$C_{781}H_{1218}N_{208}O_{243}S_6$	$-C_{780}H_{1267}N_{221}O_{252}S_{10}$
3.	Theoretical isoelectric point	5.83 pI	-4.96 pI
4.	Molecular weight in Microns	14,500 μ	-15,000 μ
5.	kDa	16.3 kDa	-18.9 kDa

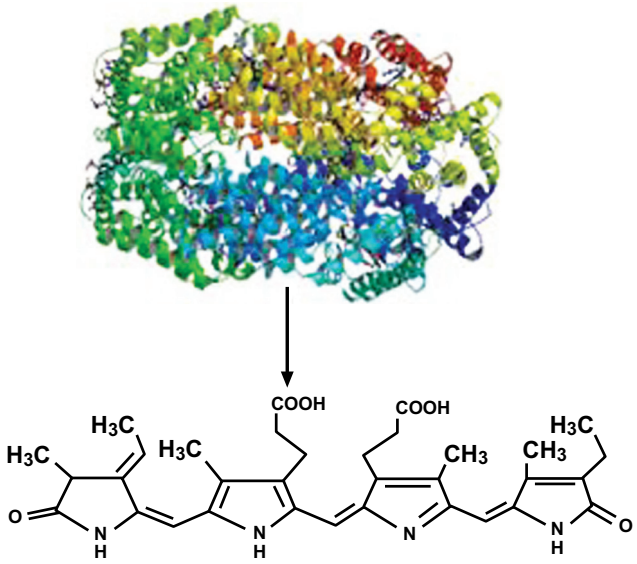

Fig. (2). 3D crystal structure of C-PC retrieved from RCSB PDB format and chemical structure of C-PC.

[53]. Genes that code for linker proteins and enzymes that are involved in phycobilin synthesis and phycobiliproteins are often directly and adjacently forming gene clusters. In red algae, the phycobiliprotein and the linker protein genes are located on the plastid genome [54]. The expression of *C-PCA* and *C-PCB* genes are controlled by light, temperature, nutrients *etc*. [55]. Low light intensities excite the synthesis of C-PC and other pigments, while pigment synthesis is restrained at high light intensities [56]. In *Arthronema africanum* C-PC and APC concentrations were 23% and 12% of dry biomass at 36ºC [41]. C-PC synthesis in *Anabaena* species was stimulated by organic carbon and later it was found that there was almost no effect or negative effect in *A. platensis* [56, 57]. In addition, glucose repressed the C-PC production in red alga, *Galderia sulphuraria* [58]. Several other environmental factors including the habitat of species also influence the C-PC synthesis [2].

2. THERAPEUTIC APPLICATIONS OF C-PC

2.1. C-PC as an Anti-cancer Agent

Several groups have demonstrated the anti-cancer activity of C-PC both *in vitro* and *in vivo*. C-PC inhibited cell proliferation, migration and colony formation, promoted apoptosis, cell cycle arrest in lung cancer cell lines like NCI-H1299, NCI-H460 and LTEP-a2by down regulating NF-kB signalling (Fig. **3**) [59]. C-PC exhibited anti-migratory and anti-proliferative activity in H358, H1650 and LTEP-a2 cancer cells by serine/threonine-protein kinase 1 silencing and inhibiting NF-kB signalling [60]. The combination of selenium with C-PC(Se-PC) exhibits anti-cancer, anti-oxidant and anti-inflammatory properties. Se-PC inhibited HepG2 liver cancer cells growth and influenced cell death through the radical generation. Additionally, *invivo* experiment with Se-PC combination and C-PC alone groups showed 75.4% and 52.6%tumor inhibition respectively indicating more efficacy of the combination group. In liver tumor microenvironment, C-PC enhanced the activity of antioxidant enzymes, the damage of hematocyte and mitochondria-mediated apoptosis during the early stage of tumor development [61]. The conjugation of C-PC and Bovine Serum Albumin (BSA) with stabilized polypyrrole nanoparticles inhibited cancer cells by damaging cellular macromolecules through ROS generation [62]. C-PC combined with Hematoporphyrin Monomethyl Ether (HME) and nanoparticles of magnetic Fe_3O_4 [modified by oleic acid (OA) and 3-triethoxysilyl-1propanamine] inhibited MCF-7 cell growth (breast cancer cells) by releasing ROS both in *in vitro* and *in vivo*. MCF-7 cells injected into BALB/c mice subcutaneously induced STAT3 phosphorylation and Bax mediated apoptosis [63]. The biofabrication of silver nanoparticles with C-PC showed inhibition of tumor growth in Ehrlich ascites carcinoma. C-PC exhibited cytotoxicity effect and inhibitory effect on MCF-7 cells [64]. Photosensitized C-PC at 625 nm illumination produced ROS, generated cytotoxic stress through ROS induction in breast cancer cells and exhibited low-level light therapy [65]. C-PC (96 μg/L) combined with ATRA (0.073 mM) and then treated to HeLa cell line and A549 lung cancer cells reduced ATRA toxicity, downregulated the cell growth, cell cycle progress, promoted cell cycle arrest G0/G1 and apoptosis, downregulated the expression of Cyclin D1, CDK4, Bcl-2, CD59 upregulated Caspase-3 [66] promoted complement mediated cytolysis [67, 68]. C-PC from *A. africanum* showed the antitumor activity at a concentration of 100 μg/ml treated for 24 hrs, suppressed the myeloid Graffi tumor also lead to boost the activities of Cu/ZnSOD, MnSOD and Glutathione reductase. In Graffi tumor cells C-PC elevated SOD (superoxide dismutase)and CAT (catalase) activity which accumulates the H_2O_2 to initiate apoptotic process and adversely impact the development of tumor by a cysteine protease that play a vital responsibility during apoptosis [69].C PC isolated from cynobacterium of *Spirulina platenesis* showed anticancer effect in prostate cell lines (LNCaP). Treatment of human

hepatoma cells (HepG2) with C-PC resulted in a great decrease in the propagation of cells at 7.0 μg/ml and LC 50 is at 1.75 μg/ml [70]. C-PC suppressed the proliferation of K562 cells, the changes occurred in the integrin β1 and intercellular Focal Adhesion Kinase (FAK) expression in K562 cells was evaluated through flow cytometry, MTT assay, and quantitative RT-PCR. Surface expression of integrinβ1on K562 cells was increased compared to normal bone marrow derived mononuclear cells [71]. C-PC with 50μM concentration in 48h proliferate the cell lines up to 49% and also induced apoptosis in K562 cells, nuclear condensation, cell shrinkage, blebbing that release the Cytochrome c into cytosol from mitochondria, down regulated Bcl-2 and cleavage of poly (ADP) ribose polymerase. Cells treated with C-PC in agarose electrophoresis the genomic DNA showed the typical pattern fragmentation for apoptotic cells that down regulates the anti-apoptotic, Bcl-2 genes [38]. C-PC conjugated with the Carboxymethyl Chitosan (CMC) with the leading specific ligand CD59 (CMC-CD59sp) on HeLa cells inhibited cell proliferation in *in vitro* induced cell apoptosis, upregulation of cleaved caspases-3 protein expression, down regulation of cyclinD1 and Bcl-2 proteins [72]. C-PC in Pancreatic adenocarcinoma suppressed the cancer in pancreas both *in vitro* and *in vivo* by upregulating G2/M arrest of cell cycle and apoptosis in PANC-1 cells by energizing p38and JNK signaling pathways and by suppressing Erk pathway [73]. C-PC suppressed esophageal squamous cell carcinoma through cell cycle arrest of G0/G1 phase; by stimulating apoptosis and inhibiting cell proliferation *via* PARP, cleaved protein caspase-3 and Bax, the expression levels of cyclin D1, Bcl-2, MMP-2, MMP-9 and CDK4 were suppressed [74]. C-PC isolated and purified from local cyanobacterial strain *Limnothrix sp*. NS01 showed the anti-cancer effect in MCF-7 cell lines stimulated apoptosis, ROS levels, lipid peroxidation and suppressed MMP, glutathione, ATP levels and expressions levels like Bcl2, Stat3, cyclin D1 and regulatory proteins of cell cycle [75]. C-PC loaded electrospun fiber mat exhibited anti-cancer activity on colon cancer by arresting cell cycle G0/G1 phase and suppressing Bax, Bcl-2, inducing caspases-3 and cytochrome c [76]. C-PC played a crucial role as a COX-2 inhibitor by focusing on the angiogenic pathway in the chemoprevention of experimental colon cancer. Piroxicam-nonsteroidal anti-inflammatory drug conjugated with C-PC used in DMH induced colon cancer of rat. Tumor size was decreased by treating with C-PC combined Piroxicam and elevated levels of MMP-2, MMP-9 (Matrix Metalloproteinase) and VEGF-A were noticed [77]. C-PC had the ability to suppress the melanogenesis by downregulating tyrosinase at transcriptional and post-transcriptional levels, by this antioxidative activity and regulation potential of tyrosinase suppressed the melanogenic activity [78]. A375 melanoma cells treating C-PC by SiLAD (a35 S *in vivo/in vitro* labelling analysis for dynamic proteomics) treatment method suppressed proliferation of melanoma cells by down regulating GRB2-ERK1/2 pathways [79]. C-PC purified from *Spirulina platensis* exhibited G0/G1 cell cycle arrest and DNA fragmentation, antiproliferative and antioxidant activity against breast adenocarcinoma cells and human melanoma cells [80]. C-PC (20 μg/L) derived from *Spirulina platensis* combined with Betaine (4) enhanced anti cancer effect on A549 cell line, inhibited the cell cycle progress, decreased cell viability, NF kB activation, tumor size and increased total p38 MAPK expression [81]. Then C PC (10 μM)combined with Doxorubicin(1μM) and expressed on adult rat ventricular cardiomyocyte inhibited DOX induced Bax expression, caspase-3 activation, cytochrome c release, upregulation of Bcl-2/ Bax expression, prevention of DOX induced DNA fragmentation, downregulation of DOX stimulate apoptotic cells and upregulation of ROS [82]. HepG2 cells incubated with Microcystis-PC (MC-PC) were exposed to He-Ne laser beam, induced apoptosis due to the localization of C-PC in mitochondria and enhanced ROS accumulation, and release of cytochrome c into cytosol, these cellular changes enhanced the Caspase-3 and arrested cell cycle at G2/M position [83]. In MCF-7 cells C-PC inhibited the tumor formation enhanced immune activity, upregulated expression of FAS in tumor tissue, CD44, NF-kB and P53 expression, promoted the restraining effect against proliferation, induced Caspase-9 activity and cytochrome-c release, reduced Bcl-2 protein, induced cell death by apoptosis thereby mediating photodynamic therapy [84].

2.2. C-PC as an Anti-inflammatory Agent

C-PC is a well-known anti-inflammatory compound, showing an anti-inflammatory effect on LPS induced macrophages cell line by downregulating PDCD5 and IL-6. Gonzalez *et al*. induced colitis with 4% acetic acid in rats and observed decreased levels of PDCD5 by suppressing the NF-kB signalling. C-PC administered before colitis induction with acetic acid. After 24 hrs, C-PC decreased myeloperoxidase enzyme activity. However, myeloperoxidase enzyme activity was enhanced in the untreated colitis animal group [85]. Hence, the antioxidative and scavenging role of C-PC against ROS could cause clotic induction. C-PC inhibits allergic reactions by inactivating the mast cells to release histamine [86]. C-PC inhibited inflammation-related genes in LPS-induced BV 2 microglial cells [87]. C-PC also inhibited NO and PGE2 overexpression by downregulating iNOS and COX-2 and decreased TNF-α expression and neutrophils infiltration at the site of inflammation [87]. C-PC significantly decreased the release of histamines from rat mast cells by inhibitingCOX-2 activity and the formation of leukotriene B4 [88]. C- PC downregulated NF-kB signalling, TNF-α, nitrate production, iNOS induction in LPS activated macrophage cell line RAW 264.7 [89]. C-PC has an anti-inflammatory role in the skin during the tropical administration using liposome carrier for the topical administration of proteins that enhances anti-inflammation activity in *in vitro* and *in vivo* experiments. It was observed that drug delivery is strongly dependent on vesicle composition and morphology [90]. C-PC exhibited anti-inflammation activity in ear swelling of mouse due to ova albumin by reducing the edema and activity of myeloperoxidase, which is proportional to a number of neutrophils accumulated at inflammation site, is an evidence for anti-chemoattractant action of biliprotein through LTB4 expression in arachidonic acid mediated ear inflammation in mouse [91]. C-PC conjugated with N-acetylcysteine (NAC) reduces inflammation and oxidative stress. NAC modulated redox pathway associated enzymes and countered the ROS levels in a combination of C-PC. It reduces apoptotic markers, activation of astroglial cells and cell death that helps to modulate the glial cell activity [92].

2.3. C-PC Acts as an Antioxidant by Inhibiting ROS

C-PC contains bilin chromophores, closely related to bilirubin, an antioxidant scavenging peroxy radicals involved in generation ROS C-PC hydrolyzed with trypsin showed the Apo-protein made substantial support to the antioxidant activity [93]. The work on *Drosophila* showed the therapeutic potential of C-PC associated with *Spirulina*on Parkinson's disease that improved locomotor behavior and life span when used as a nutritional supplement [94]. C-PC purified from species of *Oscillators tenuis* showed *in vitro* anti-proliferative activity, antioxidant activity, induction of apoptosis through cell cycle arrest of G0/G1 [95]. Antioxidant activity of C-PC among blue-green algae *Aphanizomenonflos-aquae* protects plasma cells and human erythrocytes from oxidative damage as investigated by spectral changes of C-PC that induced AAPH (2, 2azobis (2-amidinopropane) hydrochloride) and $CuCl_2$. The incubation extract of oxidizing agents decreases the absorption of C-PC at 620 nm by the disappearance of blue color indicates the rapid oxidation of protein, it suppresses the Luminol chemiluminescence in a dose dependent fashion, scavenging free radicals (OH, $H_2O_2$and RO) and peroxides arise during the respiratory burst of phagocyte [96]. C-PC diminished chemiluminescence signals of enzymes participated in ROS production by activated phagocytes, Myeloperoxidase, and NADPH oxidase by interfering stimulant binding or pathway of arachidonic acid metabolism [97]. C-PC inhibited lipid peroxidation in microsomes by binding to Fe^{+2}-

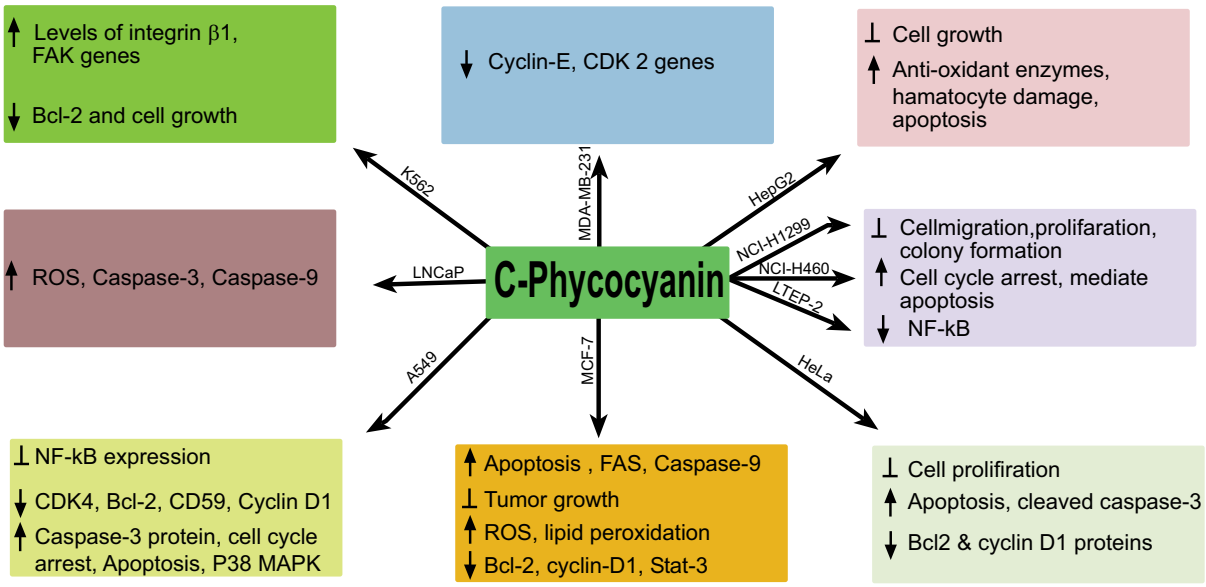

Fig. (3). Probable action mechanism of C-Phycocyanin in various cancer cell lines.

ascorbic acid or 2,2 azobis (2-amidinopropane) hydrochloride (AAPH), a free radical initiator. It reduced carbon tetrachloride induced lipid peroxidation by the *in vivo* method [88]. Antioxidant properties of C-PC arise from metal chelation, radical scavenging through the involvement of free radicals in some of the disorders like cancer, atherosclerosis, and reperfusion injury through oxidative stress. C-PC has good antioxidant and anti-inflammation properties and effectively eliminates the hydroxyl and oxygen free radicals [98]. C-PC functioned as neuroprotector against neurotoxicant tributyltin chloride and highlighted the capacity of modulating the activity of glial cell in Rat brain [92]. C-PC generated cell death by mediating ROS and suppressing BCl-2 over expression in AK5 cells [99]. Phycocyanobilin and Genistein suppressed proliferation and activation of estrogen on hepatic stellate cells by inhibiting NADPH oxidase activity [100]. C-PC functioned as oxalate mediated renal cell injury inhibitor, could prevent chronic, and also acute stone diseases in humans. It suppressed the oxidative stress and Cisplatin instigated renal toxicity in a dose-dependent manner [101], suppressed antioxidant enzymes, CAT activity in the kidney, Glutathione-S-transferase, glutathione reductase, downregulated ROS and lipid peroxidation [102]. C-PC inhibited carbon tetrachloride induced hepatocyte damage *in vitro* and *in vivo* by suppressing serum alanine transaminase, aspartate transaminase and scavenging free radicles in damaged hepatocytes [103]. C-PC suppressed liver toxicity caused by free radicals, liver enzymes activity by downregulating content of ammonia and upregulating prothrombin in the plasma. C-PC enhanced brain CAT and GPx activities and thus reduced lipid peroxidation [104]. C-PC exhibited neuroprotective effect, protected hippocampus cell death of neurons in injury of cerebral ischemia/reperfusion in gerbils by blocking lipid peroxidation and by inducing the Ferric Reducing Ability of Plasma (FRAP) due to its antioxidant activity [105].

2.4. C-PC Induces Cell Cycle Arrest and Apoptosis

Apoptosis is a programmed cell death with a sequence of events leading to eliminate damaged cells without releasing harmful substances in the surrounding area. Newer treatments are being studied that interfere with the cancer cells' ability to avoid apoptosis. Kunte M *et al.,* showed that inhibitory function of C-PC exhibited protein extract treatment for breast cancer (MDA-MB-231) and liver cancer cell line reduced human matrix metalloproteinase (MMP-2, and MMP-9) expression and down regulated cyclin-E and CDK2 expression [106]. Antidiabetic role of C-PC was studied in pancreatic cell INS-1. Methylglyoxal induced apoptosis in INS-1 cells was due to reduced ATP levels and increased levels of intracellular reactive oxygen species. C-PC protected INS-1 cells from methylglyoxal induced apoptosis by activating antioxidant enzymes and nuclear erythroid factor-2(Nrf2) [107]. Gantar *et al.*, worked on the effect of anti-cancer drug topotecan on prostate cell lines which offers the same level of cytotoxicity when combined with C-PC. C-PC combined with a lower amount of topotecan induced apoptosis through generating ROS and activating caspases [108]. C-PC showed good results in inducing apoptosis by measuring the expression of COX-2 levels in the cell lines, several experiments demonstrate correlation between overexpression of COX-2 and apoptosis downregulation [36]. This was proved by Reddy *et al.* by inducing with BLPS on mouse macrophage cell line, that expresses enhanced levels of COX-2. These cell lines were entering into apoptotic pathway after C-PC treatment in a concentration dependent manner, but the controls without treatment entered into the cancer pathway. These results showed that C-PC induced apoptosis in RAW 264.7 cell line by DNA ladder appearance, nuclear condensation, cleavage of poly (ADP ribose) polymerase (PARP), cytochrome c release demonstrated by FACS analysis [37]. Similarly, Subhashini *et al.*, proved the inhibitory effect of C-PC in K562 cells, in a time and concentration dependent manner. Characteristics of apoptosis like formation of membrane blebs, cell shrinkage, and micro nuclei formation were demonstrated using electron and fluorescence microscopy [37, 38]. C-PC protected amyloid polypeptide induced cell death in INS-IE pancreatic beta cells by modulating oxidative stress, c-Jun N-terminal Kinase (JNK) and P38 pathways [109]. In diabetic nephropathy mice C-PC and Phycocyanobilin induced renal and urinary oxidative stress markers expression and normalized expression of NADPH oxidase [110]. In type 2 diabetes, the amyloid deposits constitute of Human islet amyloid polypeptide (hIAPP) fibril conjugation of C-PC with Se induced apoptosis, inhibited the formation of ROS by protecting apoptosis of hIAPP fibrils for the cytotoxicity of Beta cells and acted as a potential therapeutic target for diabetes [111].

2.5. C-PC Function in Downregulating Autoimmune Phenotype

C-PC showed anti-arthritic effects by upregulating the levels of β-glucuronidase in arthritis induced by zymosan [112]. The development of Cyclooxygenase (COX)-2 inhibitors for the management

of inflammation and pain could be comparable with nonselective Nonsteroidal Anti-inflammatory Drugs (NSAIDs) therapeutic efficacy. [112]. C-PC inhibited atherosclerosis by increasing expression of CD59, suppressing muscle cell proliferation, apoptosis of endothelial cell, reducing fat levels in the blood [113]. C-PC linked tetrapyrrole Phycocyanobilin (PC) has a great potential to treat ischemia stroke by effecting PC12 cell survival, oxidative status, and gene expression. This Phycocyanobilin prevents H_2O_2 and glutamate induced PC12 cell injury and modulates several genes related to inflammatory, immunological and proinflammatory response and counteracted oxidative imbalance in bilateral common carotid arteries occlusion [114]. C-PC increased the level of antioxidant enzymes in the body and lowers low-density lipoprotein, serum cholesterol, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase, and triglycerides [115]. C-PC upregulated CAT, SOD, GPx to prevent cardiovascular disease and atherosclerosis [116]. In EAE model, C-PC acts as a neuroreceptor by inducing regulatory T-cells. C-PC as an antioxidant that improved the myelin and axonal damage of EAE by supporting the central and essential mechanism for multiple sclerosis [117]. C-PC and IFN-beta increased the expression of genes related to gliogenesis, remyelination, and axon-glia and could be a potential therapeutic target for multiple sclerosis [118]. In patients with multiple sclerosis and ischemia stroke, C-PC and Phycocyanobilin enhanced remyelination. Whereas, C-PC in rats and mice promoted white matter regeneration in cerebral cortex in EAE analyzed electron microscopy. Recently, it was demonstrated that oxidative stress control, induction of regulatory T cells, and pro inflammatory mediators, gene expression modulation and COX-2 inhibition as probable mechanism involved in the recruitment, differentiation and oligodendrocyte precursor cell maturation in lesions of demyelination [119]. Phycocyanobilin and C-PC administered by oral route in C57BL/6 mice improved the clinical status and reduced IL6 expression in brain IL-6 and proinflammatory cytokines IFN-γ and also improved neuro-inflammation, protected from axonal loss and demyelination [120].

Additionally, C-PC has been demonstrated as a cardioprotective agent. Doxorubicin treated intraperitoneally and orally caused cardiotoxicity with higher mortality, larger ascites volume, congestion of liver, oxidative stress and structural organization change in heart, loss of myofibrils vacuolization and swelling of mitochondrial was observed. However, treatment with Spirulina protected mice from DOX-induced cardiotoxic effect resulting in less mortality, low level of lipid peroxidation, less volume of ascites, normal levels of antioxidant enzymes and minimal damage to heart tissue [121]. C-PC has radical scavenging and antioxidant properties, thus providing protection against oxidative stress. This protection is due to the inhibition of necrosis, apoptosis shown by decreased TUNEL positive staining, Bax expression, caspase 3 activity. Oxidative stress, lipid metabolism, and mitochondrial damage play an essential role in cardiovascular diseases [122].

2.6. C-PC has Wound Healing Capacity

Wound healing is a process that requires the coordinated actions of inflammatory cells releasing cytokines, cell-cell contact and cell-matrix communication. C-PC treatment on wound-induced the cellular migration towards the wounded area by regulating Urokinase-type plasminogen activator (uPA) through cAMP-dependent protein kinase A pathway. RNA study data showed that uPA has importance for the C-PC mediated migration of fibroblasts. Furthermore, C-PC enhanced the G1 phase of cell cycle and increased the cell cycle progression through cyclin dependent kinases 1 and 2 in uPA-independent manner and also elevated expression of chemokines and Rho-GTPases in uPA-dependent manner [123]. C-PC as a scaffold molecule upregulated hydroxyproline, hexamine and protein content and downregulated contents of uronic acid in wounds. C-PC influenced the higher rate of migration on keratinocytes co-cultured with fibroblasts acting as an alternative scaffold material for wound healing [124]. C-PC enhanced the proliferation of human keratinocytes (HS2) and stimulated tissue regeneration in Sprague-Dawley wounded rats [125].

CONCLUSION

Cancer and other diseases such as inflammation, autoimmune diseases and diabetes are major public problems all over the world. There is a desperate need to develop a therapeutic target molecule for the treatment of these diseases. C-Phycocyanin isolated from various algal cells has been shown to exhibit pleiotropic properties with a wide range of therapeutic applications. In the current review, we summarized therapeutic applications of C-PC such as anticancer activity, anti-inflammation, anti-angiogenic activity and healing capacity of certain autoimmune disorders. C-PC showed an enhanced anti-cancer effect when conjugated with drugs or nanoparticles also highlighted. Moreover, C-PC showed antidiabetic property by enhancing insulin sensitivity which has potential clinical utility in type-2 diabetes. Although, several studies have been demonstrated regarding therapeutic applications of C-PC, very little is known about the molecular mechanism of action of C-PC in the disease environment. It has been well studied that C-PC inhibited cancer cell growth by down regulating BCl-2 cyclin D1, cyclin E and CDK 2 genes. Moreover, C-PC showed anti-oxidant properties by enhancing anti-oxidant enzymes, mediating apoptosis and inducing cleaved caspase gene expression. However, the role of C-PC in cancer microenvironment and type of cancer cell line is controversial. Hence, a lot of research is required to clarify the actual action mechanism of C-PC in tumor microenvironment and abovementioned disease conditions. Elucidating the action mechanism of C-PC would shed light on our knowledge of therapeutic applications of C-PC for various diseases in the near future.

LIST OF ABBREVIATIONS

C-PC	=	C-Phycocyanin
APC	=	Allophycocyanin
PE	=	Phycoerythrene
COX-2	=	Cyclooxygenase-2
IL-6	=	Interleukin-6
kDa	=	Kilo Daltons
NF-kB cells	=	Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells
ROS	=	Reactive Oxygen Species
TNF-α	=	Tumor Necrosis Factor Alpha
MMP	=	Matrix Metalloproteinase
MITF	=	Melanocyte Inducing Transcription Factor
MAPKs	=	Mitogen Activated Protein Kinases
PDCD5	=	Programmed Cell Death 5
FAK	=	Focal Adhesion Kinase Genes
DMH	=	Dimethyl Hydantoin
VEGF	=	Vascular Endothelial Growth Factor

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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