Biochemistry & Analytical Biochemistry
ISSN: 2161-1009

Sonani, et al., Biochem Anal Biochem 2015, 4:2
DOI: 10.4172/2161-1009.1000172

Review Article Open Access

Antioxidant Potential of Phycobiliproteins: Role in Anti-Aging Research

Ravi Raghav Sonani*, Rajesh Prasad Rastogi and Datta Madamwar*

BRD School of Biosciences, Vadtal Road, Satellite Campus, Post Box No. 39, Sardar Patel University, Gujarat, India

***Corresponding authors:** Sonani RR, BRD School of Biosciences, Vadtal Road, Satellite Campus, Post Box No. 39, Sardar Patel University, Vallabh Vidyanagar 388 120, Anand, Gujarat, India, Tel: +91 02692 229380; Fax: +91 02692 236475; E-mail: ravi123sonani@gmail.com*

Madamwar D, BRD School of Biosciences, Vadtal Road, Satellite Campus, Post Box No. 39, Sardar Patel University, Vallabh Vidyanagar 388 120, Anand, Gujarat, India, Tel: +91 02692 229380; Fax: +91 02692 236475; E-mail: datta_madamwar@yahoo.com

Rec date: Jan 30, 2015; **Acc date:** Apr 10, 2015; **Pub date:** Apr 14, 2015

Abstract

Aging research has made significant progress over recent years, particularly after the formulation of 'Oxidative stress theory of aging'. According to this theory, aging and its associated abnormalities may be prevented, at least to some extent, by application of certain antioxidants. Cyanobacterial phycobiliproteins (PBPs), the major light harvesting pigment proteins are widely characterized for their *in vivo* and *in vitro* antioxidant activity. Since, reactive oxygen species (ROS) are considered as important factors to cause aging, PBPs can be used as an effective free radical scavengers and be a potent candidate to develop the anti-aging drug. The use of PBPs in preventing the oxidative stress mediated abnormalities or aging is rationally debated. The present review enlightens the recent advances in the field of antioxidant function of PBPs and major challenges in the application of these pigment proteins in anti-aging research. Also included is the possible mechanism behind the anti-aging capacity of these ecologically as well as economically important biomolecules.

Keywords: Phycobiliproteins; Antioxidant; Anti-aging; Free radicals; Proteostasis

Introduction

In contemporary scenario, oxidative stress and its effect on life attracts attention of many researchers due to substantial increase in the occurrence of oxidative stress related diseases such as atherosclerosis, arthritis, diabetes and cancer [1]. Many researchers have studied various oxidative stress mediated health disorders, which led to the invention of various antioxidants. Antioxidant can enhance the life-saving process by reducing the detrimental effects of oxidative stress caused by various means. Numerous natural and synthetic antioxidants are recognized; however, the natural antioxidants have become more popular because of their great advantages with no or little side effects [2].

Marine cyanobacteria are considered as emerging source of several compounds including fatty acids, carotenoids, polysaccharides and pigment proteins showing various biological activities. Specifically, protein and peptides of marine origin are widely studied and found to have potential biomedical applications [3]. Such wide range of application is credited in account of plenty of essential amino acids present in their constitution [4]. Phycobiliproteins (PBPs) are found in very high abundance (around 60% of the total protein content and 20% of the dry cell weight) in cyanobacteria [5]. They have been considered as a potent pharmacological and medicinal agent due to their antioxidant capacity [5,6]. On the other hand, PBPs are widely exploited as natural colorants in various food products including dairy products, chewing gums, jellies and in cosmetic industries due to their unique fluorescent properties [7].

In recent time, various biomolecules having potent antioxidant capacity are being used in anti-aging research. Aging is defined as systematic decline in physiological as well as biochemical functions that affects most living organisms. Isolation of first long-lived Caenorhabditis elegans mutant has raised the curiosity among researchers and ignited the aging research over past 30 years [8]. The 'Oxidative stress theory of aging' postulated the 'free radicals' as major cause of aging. Couple of evidences in favour of this postulation has provided the platform to fight against aging by application of various antioxidants. The present review highlights the recent updates on antioxidant assets of PBPs and its most significant role in anti-aging research.

The phycobiliproteins (PBPs)

PBPs are composed of apoproteins providing scaffold and chromophores giving unique spectral features to them. PBPs apoprotein is consist of two dis-similar peptides namely α- and β-subunits (Figure 1A) [6]. The heterodimer (αβ), made of α- and β-subunits is further associates to form trimmers (α3β3) and hexamers ((α3β3)2). Trimmers and hexamers are stacked sequentially to construct the giant light harvesting complex – phycobilisome (PBS) (Figure 1B) [9]. PBPs α- and β- subunits are uniform in length, with 160 to 180 amino acid residues, respectively [10]. X-ray crystallographic studies have shown that the fold of α- and β- subunit of PBPs are a well-defined helical globin-like domain with seven helices (A, B, E, F', F, G and H) and helical hairpin domains (X and Y) at the N-teminus. Of which, helical hairpin domains are responsible for providing the stability to αβ monomers [11]. Despite of having considerable divergence in amino acid sequences of PBPs apoproteins, the tertiary structure of all PBPs are highly similar [12]. Chromophore, covalently attached to the cysteinyl residue of PBPs apoproteins via thioether linkage, is open-chain tetrapyrrole pigments. Chromophore acts as cofactor in the PBPs with light-harvesting and transferring properties [13]. Conjugated double bond system is the heart of chromophore functioning. Chromophore-chromophore and chromophore-protein interaction and different degree of conjugation

facilitates the diversity in PBPs spectral phenotypes among various cyanobacterial species [14]. Chromophores are classified in various sub-classes on the basis of their spectral characteristic. Phycocyanobilin (PCB), phycoviobilin (PVB), phycoerythrobilin (PEB) and phycourobilin (PUB) are the majorly found chromophores [15]. PBPs are also sub-divided into 3 major families according to the type of their attached chromophore and consequent spectral (absorption and fluorescence) characteristics: allophycocyanin (APC, λA max = 650-655 nm; λF max = 657-660), phycocyanin (PC, λA max = 610-620 nm; λF max = 645-653) and phycoerythrin (PE, λA max = 540-570 nm; λF max = 575-585) (Figure 1C-D) [6]. APC and PC contain PCB and PVB whereas PE contains PEB and PUB as a cofactor with their protein scaffold.

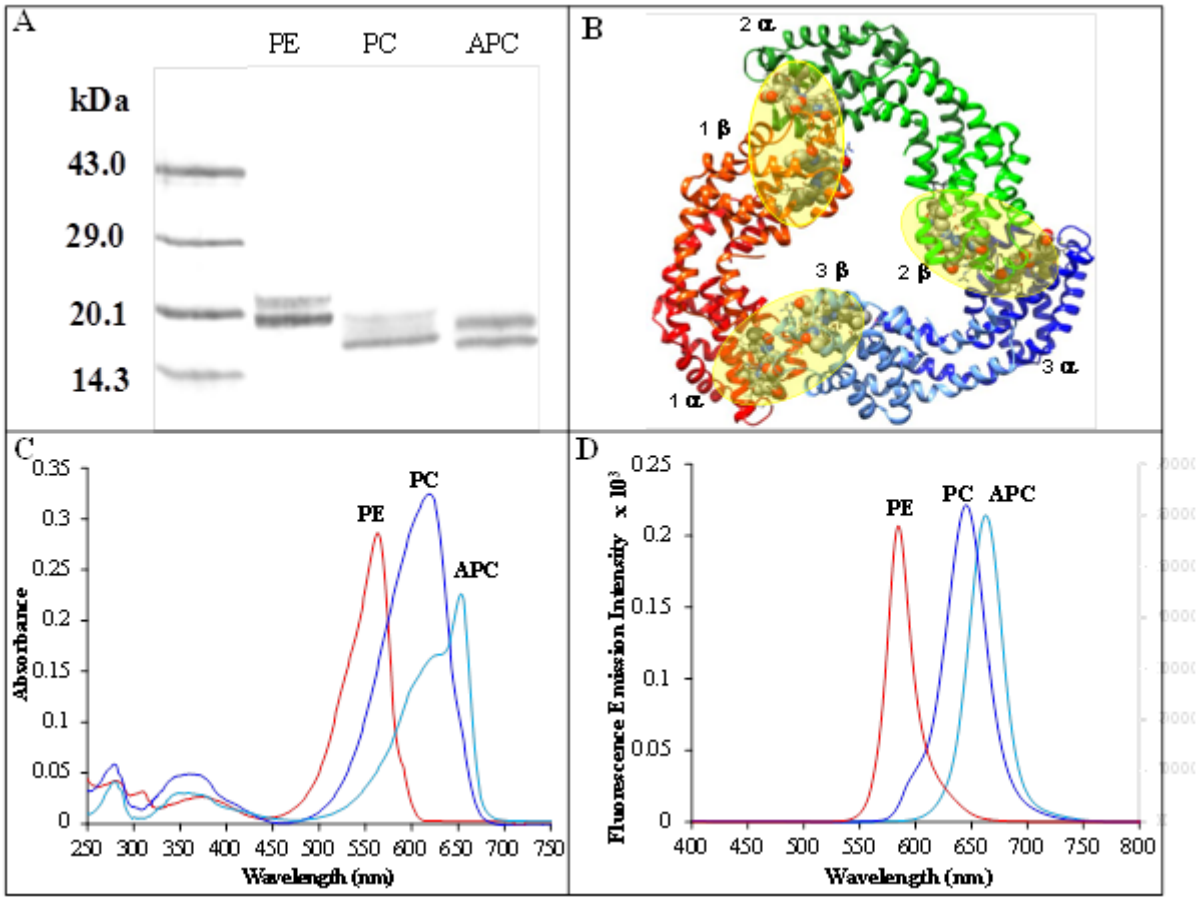


Figure 1: (A) 15% silver stained SDS-PAGE of purified PE, PC and APC purified from Lyngbya sp. A09DM. Presence of two bands in lane of each purified PBP corresponds to their α-(smaller one) and β- subunits (larger one). (B) Ribbon model of APC α- and β- subunits associated in to trimmer. The highlighted region show the presence of PCB chromophores attached with each subunits. Figure was prepared by using software PyMol 1.3. (C-D) UV-visible spectra (C) and Fluorescence emission spectra (D) of PE, PC and APC purified from Lyngbya sp. A09DM. (Figure 1A, 1C and 1D are adapted from Sonani et al. [6].

PBPs are widely studied by many research due to their unique and bright colour, non-toxic and proteineous nature. PBPs have been reported to express pharmacological and health beneficial effects including antioxidant, anticancerous, neuroprotective, anti-inflammatory, hepatoprotective and hypocholesterolemic. Numbers of physiologically abnormalities have been proven to be averted in various experimental animals by PBPs administration [16-20].

Antioxidant activity of PBPs

During last few decades, the PBPs have been exclusively investigated for their antioxidant or free radical scavenging potential by various *in vitro* and *in vivo* experimental systems (Table 1). Recently, Sonani et al. [6] have described the *in vitro* antioxidant and radical scavenging activity of three major PBPs - PE, PC and APC purified from the marine cyanobacterium Lyngbya sp. A09DM. We have established that PE exhibits its antioxidant activity mainly via primary route i.e., by scavenging the already produced reactive oxygen species (ROS) through redox reaction. On the contrary, the PC and APC work via both primary as well as secondary route (by chelating the metal ion which produces ROS) to express their antioxidant activities [21]. Antioxidant action of PBPs is hypothesized to differ due to different mechanisms associated with side chains of various constituting amino acids [6]. Variation in amino acids distribution on outer surface of PBPs may favour one mechanism over other and thus, PBPs express diverse antioxidant activity. For example, amino acid with hydrophobic side chain is good proton donor and metal ion chelator. Similarly, acidic, basic and aromatic amino acids are

supposed to sequesters metal ion [2]. PBPs are reported to chelate as well as reduce the ferrous ion very efficiently [6]. This indicated the combined involvement of both electron donating and metal ion chelating ability of the PBP-constituting amino acids in expressing antioxidant activity. Specifically, PE showed lower chelating ability and higher reducing power in comparison with PC and APC. This indicated the leading role of redox potential of PE in its antioxidant activity. Contrary to PE, the antioxidant activity of PC and APC was contributed equally by both reducing ability and chelating ability [6]. The variation in mode of action might be due to variation in surface distribution of hydrophobic and hydrophilic amino acid. It signified the presence of more amino acids having reduction ability than that having chelating potential on outer surface of PE whereas both are equally distributed on outer surface of PC and APC in their native-folded state [6]. Establishment of antioxidant nature of PBPs will be of great importance in therapeutics of ROS-associated disorders.

Type of study	Experimental system	Experimental details	References
In vivo	Rat	Colitis rat model, Myeloperoxidase (MPO) activity	González et al. [42]
		Sprague - Dawley rat, Equilibrium binding assays for Peripheral benzodiazepine receptors Heat shock protein 27kD expression	Rimbau et al. [16]
		Carbon tetrachloride (CCl4)-induced lipid peroxidation Myeloperoxidase (MPO) activity	Romay et al., [43]
		Male wistar rat Oxalate induced renal calculi formation Microscopic evaluation of urinary crystals Histopathology of rinal tissues Renal tubular damage assessment by urinary marker enzymes (alkaline phosphatase, acid phosphatase and γ-glutamyl transferase	Farooq et al. [44]
		Male wistar rat Thioacetamide induced fulminant hepatic failure Lipid peroxidation and tryptophan measurement in brain tissue Glutathione peroxidase and Catalase activity estimation in brain homogenate Histopathology and electronmicroscopy of brain tissue	Sathyasaikumar et al. [19]
	Hamster	Male golden Syrian hamsters Body weight, food intake and organs weight measurement Measurement total cholesterol (TC) and HDL cholesterol (HDL-C) in plasma Immunoblotting of NADPH oxidase	Riss et al. [45]
		Male golden Syrian hamsters Copper-induced LDL oxidation Measurement of enzymatic activities of SOD, CAT, and GSH-Px in liver	Sheu et al. [46]
	C. elegans	1. N2 wild type *C. elegans* 2. Life span assay 3. Pharyngeal pumping counting assay 4. Paraquat sensitivity assay	Sonani et al. [6]
		1. N2 wild type, CL4176 (Alzheimer's disease model), *mu86, e1370, hx546* mutants. 2. Life span assay 3. Pharyngeal pumping counting assay 4. Stress resistance assay 5. Paralysis assay	Sonani et al. [40]
In vitro	Human Erythrocyte	Normal human erythrocytes and plasma samples Azobis (2-amidinopropane) dihydrochloride (AAPH) induced oxidative stress Cytosolic glutathione measurement Lipid peroxidation assay	Romay and González [47]

		Normal human erythrocytes Azobis (2-amidinopropane) dihydrochloride (AAPH) induced oxidative stress Haemolysis assay	Benedetti et al. [48]
		Normal human erythrocytes Azobis (2-amidinopropane) dihydrochloride (AAPH) induced oxidative stress Haemolysis assay Structural morphological analysis by SEM	Pleonsil et al., [49]
	Rat Cardiomyocyte	Adult rat ventricular cardiomyocytes Cell viability assay Lactate dehydrogenase assay ROS measurement by H2DCF-DA and DHE fluorescence TUNEL assay Caspase-3 assay DNA laddering assay	Khan et al. [50]
	Biochemical assays*	ARSA, HRSA, PRSA	Romay et al., [43]
		FRAP	Soni et al. [5]
		SRSA, HRSA, H2O2-RSA, HOCl-RSA, PRSA, Iron chelating activity.	Bermejo et al. [51]
		DPPH, HRSA,SRSA, NO-RSA, FICA, R Power	Thangam et al. [52]
		DPPH, ABTS, FRAP, HRSA, SRSA, FICA, R Power	Sonani et al. [6]

*Abbreviations

ARSA: Alkoxyl radical scavenging activity assay; HRSA: Hydroxyl radical scavenging activity assay; PRSA: Peroxyl radical scavenging activity assay; NO-RSA – nitrous oxide ion scavenging activity assay; H2O2-RSA: Hydrogen peroxide radical scavenging activity assay; HOCl-RSA: Hypochlorous acid radical scavenging activity assay; FRAP: Ferric ion reducing ability of plasma assay; DPPH: α, α –diphenyl- β -picrylhydrazyl ion scavenging activity assay; ABTS: 2'- azino - bis (3 - ethylbenzothiazoline - 6 - sulphonic acid) ion scavenging activity assay; FICA: Ferrous ion-chelating activity assay; R Power: Reducing power assay

Table 1: *In vitro* and *in vivo* anti-oxidant and radical scavenging activity of PBPs.

Oxidative stress, antioxidants and aging

Oxygen molecule is the final electron acceptor in mitochondrial oxidative phosphorylation. With increasing age, the mitochondria produce various reactive oxygen species (ROS) as by product of oxidative phosphorylation. Generally, in early life, ROS and their effect is abolished by inherent antioxidant defence of the body. But in the later part of life, the imbalance between ROS and antioxidant defence occurs due to the increase in either ROS production rate, decline in antioxidant defence or both [22]. Such imbalance will cause ROS-accumulation leading to damage of the life indispensible macromolecules [22]. Accumulated ROS damages the mitochondrial molecules and thus, also impairs healthy metabolic activity. Accumulation of ROS damages gives rise to systematic dysfunction of almost all organs, which ultimately figures in aging [23]. This 'oxidative stress theory of aging' has been greatly supported on the basis of some solid evidences. First, ROS accumulation is found to accelerate within eukaryotic cells mainly as by-products of mitochondrial respiration. Second, ROS has been proved to damage the life obligatory macromolecules. Third, it has been well established that the long lives animals (worms, flies and mice) are associated with reduced oxidative stress and/or increased antioxidant defence activity. Forth, transgenic animal models, engineered with increased antioxidant defence have been confirmed by longevity phenotype. Fifth, effectiveness of some exogenous antioxidant supplements like ascorbic acid, vitamin E (α-tocopherol) [24], trolox [25] and α -lipoic acid [26,27] in moderating aging and associated abnormalities.

The 'oxidative stress theory for aging' has generated the curiosity among researchers to find the anti-aging dietary supplements. In light of this theory, various natural antioxidants like resveratrol, quercetin, curcumin, mycosporine-like amino acids and green tea extract have been studied in great details by using various model organisms [23].

Aging associated abnormalities

Aging is systematic and progressive decline in physiological as well as biochemical integrity raising the susceptibility to death [28]. Accumulation of such health defects increases the risk for the aging associated disease including arthritis, atherosclerosis, muscular dystrophy, cataracts, pulmonary dysfunctions, cancer, diabetes, cardiovascular and neurodegenerative disorders [29,30]. López-Otín et al. has reviewed nine major molecular and cellular hallmarks of aging includes: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [28]. Due to the oxidative microenvironment in mitochondria and nucleus, occurrence of somatic mutation becomes highly prone in aged individual [31]. Other abnormalities linked with DNA damage, such as chromosomal

aneuploidies and copy number variation, increased clonal mosaicism also found to associate with aging [32-35]. Increasing mutational load with age causes dysfunction of various tissues, majorly by impairing the respiratory functionality.

Loss of proteostasis is established as the chief mediator for oxidative stress caused age associated disease [36]. Generally, oxidative stress caused the denaturation of native folding of proteins, which resulted in unfolded proteins (Figure 2). The unfolded proteins are generally refolded by molecular chaperons or destructed by either the ubiquitin-proteasomal or lysosomal (autophagic) pathways (Figure 2). The unfolded proteins fail to undergo either of these phenomenon lead to protein aggregation, which ultimately resulted in proteo-toxicity (Figure 2). Such disruption in proteostasis causes mismanagement in cellular traffic, premature protein degradation, and formation of toxic folds [37,38]. All of these are recognized as common molecular events for a large number of disorders including Huntington's disease (HD, CAG-repeat/polyglutamine aggregation), Parkinson's disease (nonCAG repeat aggregation disease), Alzheimer's disease (Aβ peptide oligomerization), Kennedy's disease, Spinocerebellar ataxias, Amyotrophic lateral sclerosis (ALS) and Prion disease [39].

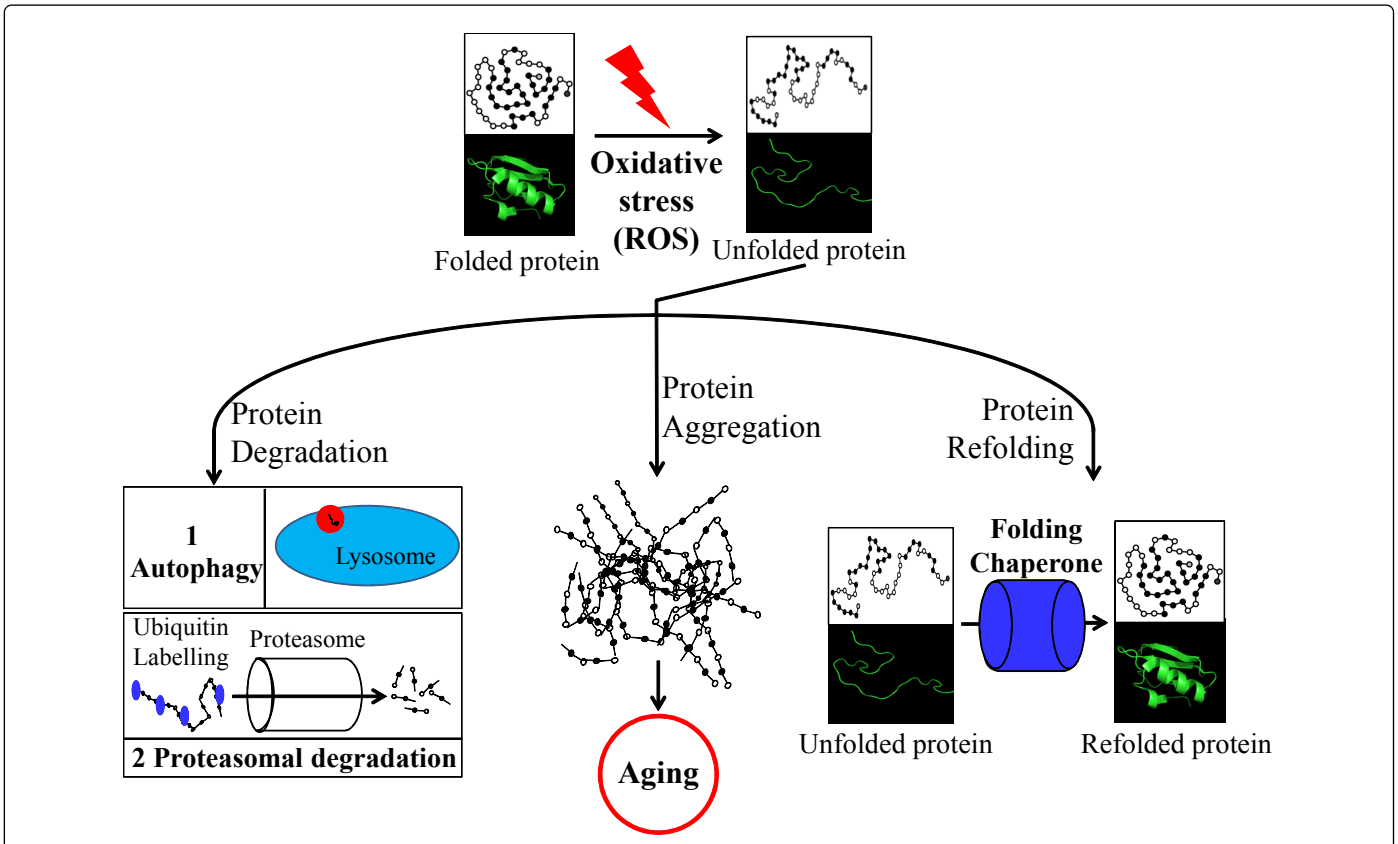
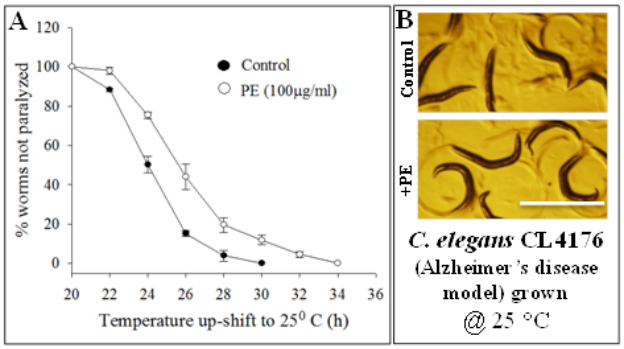


Figure 2: Proteostasis disruption leads to Aging. Oxidative stress impairs the proteins folding post-transnationally or during the translation. Unfolded or misfolded proteins are generally processed by two pathways. In first way, they are either undergoes proteins degradation by various pathways in cluding lysosomal/cheparon –mediated autophagy and ubiquitin – proteosomal degradation. Otherwise, they are refolded by folding chaperons like heat shock proteins. If the protein fails two undergo either of process, it tries to aggregate in haphazard manner, leading to proteotoxicity and thus, aging.

PBPs as anti-aging molecules

Enhancement of endogenous antioxidant system or provision of exogenous antioxidant supplement was believed to alleviate the aging and associated abnormalities. Currently, our research group is working on the topic - 'Is PBP's antioxidant virtue can be explored to alleviate aging and associated abnormalities?' We have reported that the PE, one of the PBPs having antioxidant nature, efficiently moderates the progression in physiological dysfunctions and molecular mechanism associated with aging in Caenorhabditis elegans (C. elegans) [6,40]. PE feeding also confers the better stress tolerance in *C. elegans* under thermo- as well as oxidative stress [40]. Moreover, PE was found to inhibit the development of Aβ plaque and thus, Alzheimer's disease in C. elegan CL4176 (Alzheimer's disease model) (Figure 3) [40]. Nevertheless, PE-mediated life span expansion of *C. elegans* null mutants (e1370, mu86, hx546) for up- and down- stream components of insulin signalling pathways (IIS pathway) suggested that the PE's anti-aging action is independent of IIS pathway [40]. Better survival of *C. elegans* upon PE treatment in paraquat sensitivity assay has confirmed the in vivo potential of PE's antioxidant activity in moderating aging (Figure 4A) [6]. Inefficiency of PE in expanding life span of hsf-1 knockout *C. elegans* has first time evidenced the dependency of PE's life expanding action on heat shock response transcription factor (HSF-1) (Figure 4B) [40].



Figures 3: PE effectively moderates the proteotoxicity by preventing proteins aggregation and delayed proteotoxicity mediated paralysis phenotypes in *C. elegans* CL14176. (A) Effect of PE in suppressing Aβ1-42-associated paralysis phenotype in *C. elegans* CL4176 animals. Survival curves (in term of paralysis) after temperature upshift to 25°C. (B) Representative images of PE treated and control *C. elegans* CL4176 animal after induction of Aβ – peptide expression by temperature upshift to 25 °C. Scale bar represents 1 mm. (Figure 3A and 3B are adapted from Sonani et al. [40].

Moreover, Singh et al. has reported the crystal structure and in silico affinity of PC αβ dimer with β- secretase (Figure 5), the potential drug target for Alzheimer's disease [41]. The same was also evidenced experimentally by using the Alzheimer model *C. elegans* CL4176 [41]. These couple of reports have greatly enlightened the possibility to explore the PBP's antioxidant nature in the invention of the natural drug that can delay the onset of aging process.

Conclusions and Future Perspective

Since the amino acid sequences of PBPs vary among different species/strains of cyanobacteria, an extensive research is needed to explore the various chemical natures of different PBPs from different cyanobacteria. However, the question 'How does exactly the PBPs works against aging?' is still remains elusive. Further research on anti-aging potential of PBPs may reveal the better understanding about their mode of action in averting the aging process. Scarcity in the reports describing the PBP's anti-aging potential also propose to employ various eukaryotic experimental systems including rat, drosophila, hamsters, human cell lines to verify the in vivo antioxidant activity and thus, to establish consistence anti-aging virtue of PBPs. Overall, the present review may attest the opening of new horizons for putative role of PBPs in moderation of aging and associated life threating diseases.

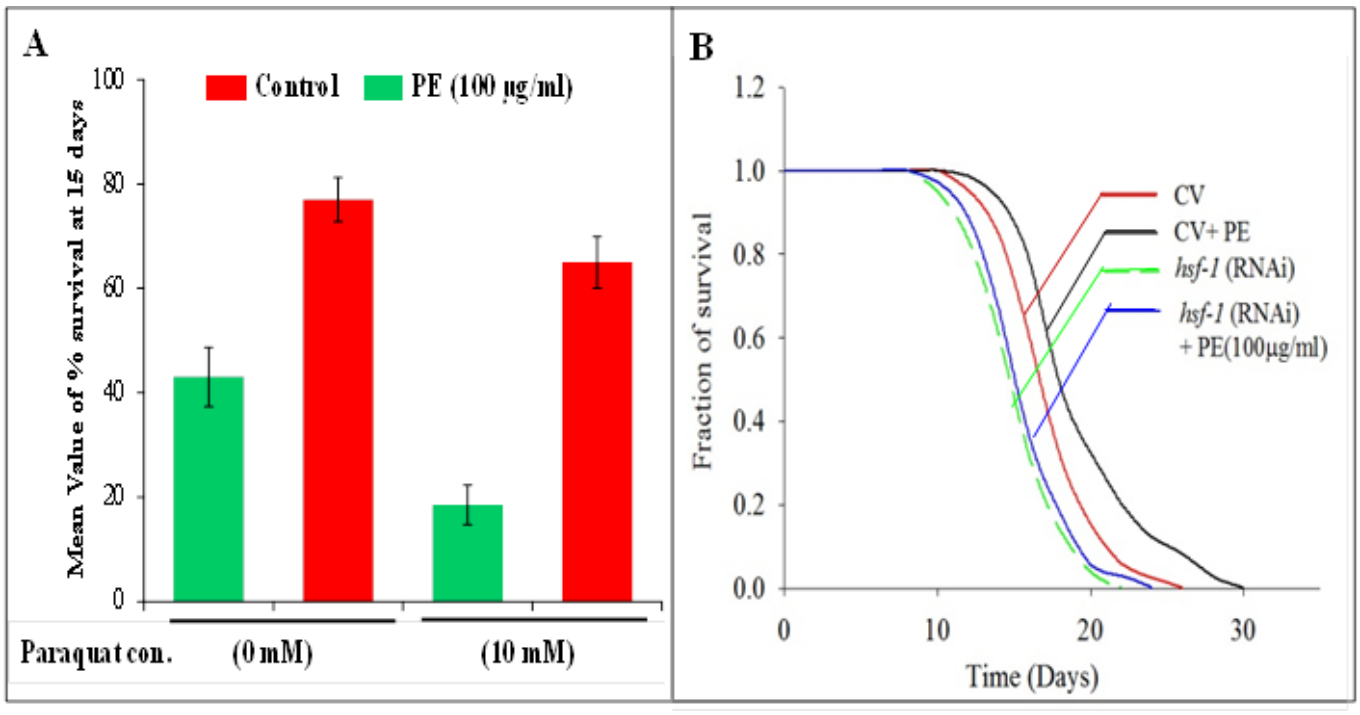


Figure 4: (A) Paraquat sensitivity assay: PE significantly improves the survival of N2 wild type *C. elegans* under normal as well as oxidative stressed (paraquat exposure) environment. (B) Survival curve of N2 wild type and hsf-1 (RNAi knockout) *C. elegans* under control and PE treated conditions. Since PE-exposure does not increase the mean life span of hsf-1 (RNAi knockout), PE's life expanding action in proposed to be dependent on HSF-1 (heat shock factor). (Figure 4A and 4B are adapted from Sonani et al. [6] and Sonani et al. [40], respectively)

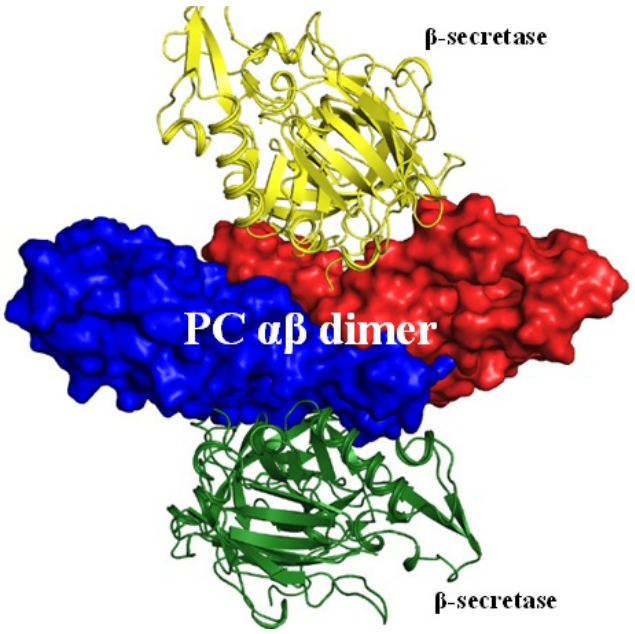


Figure 5: Protein-protein docking between PC αβ-Dimer and β-Secretase. PC αβ-Dimer were docked with two different β-secretase (PDB IDs: 1FKN, yellow, and, 3UQP, green) structures. 1FKN is found to dock in close proximity of the β- subunit while the 3UQP is found to dock in an α-subunit proximal location. (Adapted from Singh et al. [41].

Acknowledgements

Ravi Raghav Sonani gratefully acknowledges the Department of Science and Technology (DST), New Delhi, India for financial help in the form of the INSPIRE (IF120712) fellowship. Rajesh Prasad Rastogi is thankful to the University Grant Commission (UGC), New Delhi, India for Dr. D. S. Kothari Postdoctoral Research Grant.

References

1. Pan M, Jiang TS, Pan JL (2011) Antioxidant activities of rapeseed protein hydrolysates. Food Bioprocess Technol 4: 1144-1152.
2. Sarmadi BH, Ismail A (2010) Antioxidative peptides from food proteins: a review. Peptides 31: 1949-1956.
3. Lordan S, Ross RP, Stanton C (2011) Marine bioactives as functional food ingredients: potential to reduce the incidence of chronic diseases. Mar Drugs 9: 1056-1100.
4. Taboada C, Millán R, Míguez I (2010) Composition, nutritional aspects and effect on serum parameters of marine algae Ulva rigida. J Sci Food Agric 90: 445-449.
5. Soni B, Trivedi U, Madamwar D (2008) A novel method of single step hydrophobic interaction chromatography for the purification of phycocyanin from Phormidium fragile and its characterization for antioxidant property. Bioresour Technol 99: 188-194.
6. Sonani RR, Singh NK, Kumar J, Thakar D, Madamwar D (2014) Concurrent purification and antioxidant activity of phycobiliproteins from Lyngbya sp. A09DM: an antioxidant and anti-aging potential of phycoerythrin in Caenorhabditis elegans. Process Biochem 49: 1757-1766.
7. Rasmussen RS, Morrissey MT (2007) Marine biotechnology for production of food ingredients. Adv Food Nutr Res 52: 237-292.
8. Klass MR (1983) A method for the isolation of longevity mutants in the nematode Caenorhabditis elegans and initial results. Mech Ageing Dev 22: 279-286.
9. MacColl R (2004) Allophycocyanin and energy transfer. Biochim Biophys Acta 1657: 73-81.
10. Sonani RR, Rastogi RP Joshi M Madamwar D (2015) A stable and functional single peptide phycoerythrin (15.45 kDa) from Lyngbya sp. A09DM. Int J Biol Macromol 74: 29-35.
11. Singh NK, Sonani RR, Rastogi RP, Madamwar D (2015) The phycobilisomes: An early requisite for efficient photosynthesis in cyanobacteria. EXCLI J (In press).
12. Anderson LK, Toole CM (1998) A model for early events in the assembly pathway of cyanobacterial phycobilisomes. Mol Microbiol 30: 467-474.
13. Dale RE, Teale FW (1970) Number and distribution of chromophore types in native phycobiliproteins. Photochem Photobiol 12: 99-117.
14. Anwer K Sonani R, Madamwar D, Singh P, Khan F, et al. (2015) Role of N-terminal residues on folding and stability of C-phycoerythrin: simulation and urea-induced denaturation studies. J Biomol Struct Dyn 33: 121-133.
15. Singh NK, Parmar A, Sonani RR, Madamwar D (2012) Isolation, identification and characterization of novel thermotolerant Oscillatoria sp. N9DM: Change in pigmentation profile in response to temperature. Process Biochem 47: 2472-2479.
16. Rimbau V, Camins A, Romay C, González R, Pallàs M (1999) Protective effects of C-phycocyanin against kainic acid-induced neuronal damage in rat hippocampus. Neurosci Lett 276: 75-78.
17. Romay C, Armesto J, Remirez D, González R, Ledon N, et al. (1998) Antioxidant and anti-inflammatory properties of C-phycocyanin from blue-green algae. Inflamm Res 47: 36-41.
18. Riss J, Décordé K, Sutra T, Delage M, Baccou J-C, et al. (2007) Phycobiliprotein C-phycocyanin from Spirulina platensis is powerfully responsible for reducing oxidative stress and NADPH oxidase expression induced by an atherogenic diet in hamsters. J Agric Food Chem 55: 7962-7967.
19. Sathyasaikumar KV, Swapna I, Reddy PV, Murthy ChR, Roy KR, et al. (2007) Co-administration of C-Phycocyanin ameliorates thioacetamide-induced hepatic encephalopathy in Wistar rats. J Neurol Sci 252: 67-75.
20. Liu Y, Xu L, Cheng N, Lin L, Zhang C (2000) Inhibitory effect of phycocyanin from Spirulina platensis on the growth of human leukemia K562 cells. J Appl Phycol 12: 125-130.
21. Khantaphant S, Benjakul S, Ghomi MR (2011) The effects of pretreatments on antioxidative activities of protein hydrolysate from the muscle of brownstripe redsnapper (Lutjanus vitta). LWT Food Sci Technol 44: 1139-1148.
22. Sohal RS, Mockett RJ, Orr WC (2002) Mechanisms of aging: an appraisal of the oxidative stress hypothesis. Free Radic Biol Med 33: 575-586.
23. Si H, Liu D (2014) Dietary antiaging phytochemicals and mechanisms associated with prolonged survival. J Nutr Biochem 25: 581-591.
24. Harrington LA Harley CB (1988) Effect of vitamin E on lifespan and reproduction in Caenorhabditis elegans. Mech Ageing Dev 43: 71-78.
25. Ishii N, Senoo-Matsuda N, Miyake K, Yasuda K, Ishii T, et al. (2004) Coenzyme Q10 can prolong C. elegans lifespan by lowering oxidative stress. Mech Ageing Dev 125: 41-46.
26. Brown MK, Evans JL, Luo Y (2006) Beneficial effects of natural antioxidants EGCG and alpha-lipoic acid on life span and age-dependent behavioral declines in Caenorhabditis elegans. Pharmacol Biochem Behav 85: 620-628.
27. Benedetti MG, Foster AL, Vantipalli MC, White MP, Sampayo JN, et al. (2008) Compounds that confer thermal stress resistance and extended lifespan. Exp Gerontol 43: 882-891.
28. López-Otín C Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153: 1194-1217.
29. Kikis EA, Gidalevitz T, Morimoto RI (2010) Protein homeostasis in models of aging and age-related conformational disease. Adv Exp Med Biol 694: 138-159.

30. Stadtman ER, Oliver CN (1991) Metal-catalyzed oxidation of proteins. Physiological consequences. J Biol Chem 266: 2005-2008.
31. Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, et al. (2013) The role of DNA damage and repair in aging through the prism of Koch-like criteria. Ageing Res Rev 12: 661-684.
32. Faggioli F, Wang T, Vijg J, Montagna C (2012) Chromosome-specific accumulation of aneuploidy in the aging mouse brain. Hum Mol Genet 21: 5246-5253.
33. Forsberg LA, Rasi C, Razzaghian HR, Pakalapati G, Waite L, et al. (2012) Age-related somatic structural changes in the nuclear genome of human blood cells. Am J Hum Genet 90: 217-228.
34. Jacobs KB, Yeager M, Zhou W, Wacholder S, Wang Z, et al. (2012) Detectable clonal mosaicism and its relationship to aging and cancer. Nat Genet 44: 651-658.
35. Laurie CC, Laurie CA, Rice K, Doheny KF, Zelnick LR, et al. (2012) Detectable clonal mosaicism from birth to old age and its relationship to cancer. Nat Genet 44: 642-650.
36. Powers ET, Morimoto RI, Dillin A, Kelly JW, Balch WE (2009) Biological and chemical approaches to diseases of proteostasis deficiency. Annu Rev Biochem 78: 959-991.
37. Kakizuka A (1998) Protein precipitation: a common etiology in neurodegenerative disorders? Trends Genet 14: 396-402.
38. Chiti F Dobson CM (2006) Protein misfolding, functional amyloid, and human disease. Annu Rev Biochem 75: 333-366.
39. Morimoto RI (2008) Proteotoxic stress and inducible chaperone networks in neurodegenerative disease and aging. Genes Dev 22: 1427-1438.
40. Sonani RR Singh NK, Awasthi A, Prasad B, Kumar J, et al. (2014) Phycoerythrin extends life span and health span of Caenorhabditis elegans. Age (Dordr) 36: 9717.
41. Singh NK, Hasan SS, Kumar J, Raj I, Pathan AA, et al. (2014) Crystal structure and interaction of phycocyanin with Î²-secretase: A putative therapy for Alzheimer's disease. CNS Neurol Disord Drug Targets 13: 691-698.
42. González R, Rodríques S, Romay C, Ancheta O, González A, et al. (1999) Anti-inflammatory activity of phycocyanin extract in acetic acid-induced colitis in rats. Pharmacol Res 39: 55-59.
43. Romay CH, González R, Ledón N, Remirez D, Rimbau V (2003) C-phycocyanin: a biliprotein with antioxidant, anti-inflammatory and neuroprotective effects. Curr Protein Pept Sci 4: 207-216.
44. Farooq SM, Asokan D, Kalaiselvi P, Sakthivel R, Varalakshmi P (2004) Prophylactic role of phycocyanin: a study of oxalate mediated renal cell injury. Chem Biol Interact 149: 1-7.
45. Riss J, Décordé K, Sutra T, Delage M, Baccou JC, et al (2007) Phycobiliprotein C-phycocyanin from Spirulina platensis is powerfully responsible for reducing oxidative stress and NADPH oxidase expression induced by an atherogenic diet in hamsters. J Agric Food Chem 55: 7962-7967.
46. Sheu MJ Hsieh YY Lai CH Chang CC, Wu CH (2013) Antihyperlipidemic and Antioxidant Effects of C-phycocyanin in Golden Syrian Hamsters Fed with a Hypercholesterolemic Diet. J Tradit Complement Med 3: 41-47.
47. Romay C, González R (2000) Phycocyanin is an antioxidant protector of human erythrocytes against lysis by peroxyl radicals. J Pharm Pharmacol 52: 367-368.
48. Benedetti S Benvenuti F, Pagliarani S, Francogli S, Scoglio S, et al. (2004) Antioxidant properties of a novel phycocyanin extract from the blue-green alga Aphanizomenon flos-aquae. Life Sci 75: 2353-2362.
49. Pleonsil P Soogarun S, Suwanwong Y (2013) Anti-oxidant activity of holo- and apo-c-phycocyanin and their protective effects on human erythrocytes. Int J Biol Macromol 60: 393-398.
50. Khan M, Varadharaj S, Shobha JC, Naidu MU, Parinandi NL, et al. (2006) C-phycocyanin ameliorates doxorubicin-induced oxidative stress and apoptosis in adult rat cardiomyocytes. J Cardiovasc Pharmcol 47: 9-20.
51. Bermejo P, Piñero E, Villar ÁM (2008) Iron-chelating ability and antioxidant properties of phycocyanin isolated from a protean extract of Spirulina platensis. Food Chem 110: 436-445.
52. Thangam R, Suresh V, Asenath Princy W, Rajkumar M, SenthilKumar N, et al. (2013) 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 140: 262-272.