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Review

Nutraceutical and therapeutic potential of Phycocyanobilin for treating Alzheimer's disease

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Alzheimer's disease (AD) is a devastating neurodegenerative condition provoking the loss of cognitive and memory performances. Despite huge efforts to develop effective AD therapies, there is still no cure for this neurological condition. Here, we review the main biological properties of Phycocyanobilin (PCB), accounting for its potential uses against AD. PCB, given individually or released in vivo from C-Phycocyanin (C-PC), acts as a bioactive-molecule-mediating antioxidant, is anti-inflammatory and has immunomodulatory activities. PCB/C-PC are able to scavenge reactive oxygen and nitrogen species, to counteract lipid peroxidation and to inhibit enzymes such as NADPH oxidase and COX-2. In animal models of multiple sclerosis and ischemic stroke, these compounds induce remyelination as demonstrated by electron microscopy and the expression of genes such as *Mal* up-regulation of and *Lingo-1* down-regulation. These treatments also reduce pro-inflammatory cytokines levels and induce immune suppressive genes. PCB/C-PC protects isolated rat brain mitochondria and inactivate microglia, astrocytes and neuronal apoptosis mediators. Such processes are all involved in the pathogenic cascade of AD, and thus PCB may effectively mitigate the injury in this condition. Furthermore, PCB can be administered safely by oral or parenteral routes and therefore, could be commercially offered as a nutraceutical supplement or as a pharmaceutical drug.

Keywords. Alzheimer's disease; C-Phycocyanin; neuroprotection; nutraceutical; Phycocyanobilin

1. Introduction

Alzheimer's disease (AD) is the most common fatal neurodegenerative disorder that begins as mild short-term memory deficits and culminates in total loss of cognition and executive functions (Pimplikar *et al.* 2010). Learning, reasoning, communication and performance of daily activities are compromised in patients with this disease, accompanied by changes in personality and behavior. These alterations impact progressively and affect the quality of life of both the patient and the family (Querfurth and LaFerla 2010). The major risk factors for developing AD are aging and a family history of the disease. Most cases of AD are late-onset and sporadic, with no proven evidence for a Mendelian pattern of inheritance. About 95% of all cases of AD occur in patients older than 60 years and are called sporadic AD or late-onset AD, while less than 5% is defined as familial AD and occurs in people between 30 to 60 years old (Bertram *et al.* 2010). The Alzheimer's Disease International reported that there are over 9.9 million new cases of dementia each year worldwide, implying one new case every 3.2 seconds. Around 50 million people lived in the world with dementia in 2017, and it has been estimated that this number will almost double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050 (Alzheimer's Disease International 2018). Noteworthy, almost 2/3 of the people affected with dementia are from developing countries, including those in the Latin America and the Caribbean region, in which it is

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expected that there will be a greater increase of dementia incidence in the coming years (Alzheimer's Disease International 2018).

A widely accepted mechanism for explaining the pathogenesis of AD is the amyloid cascade. According to this hypothesis, the deposition of extracellular β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles in diseased brains (Hardy 2017; Takahashi *et al.* 2010) negatively impacts the neuronal physiology, causing the loss of synaptic function, mitochondrial damage, activation of microglia and final neuronal death (Arbor *et al.* 2016; Farooqui 2010). Recent investigations have also revealed the existence of pathways that connect Aβ with Tau protein hyperphosphorylation in the pathogenesis of AD (Bloom 2014). Despite the years that AD has been studied, it has not yet been possible to identify therapeutic agents capable of blocking the synthesis and aggregation of Aβ (Coman and Nemeş 2017). For this reason, new treatment options must be explored in order to intercept the Aβ plaque formation and to stop its consequences in the biochemical and behavioral progression of AD.

Our group has studied for several years novel pharmacological strategies for ameliorating the injury either caused by acute or chronic neurodegenerative diseases, such as ischemic stroke (IS) and Multiple Sclerosis (MS), respectively. Among the common processes involved in the pathogenesis of neurodegenerative diseases are the collapse of the blood–brain barrier (BBB), the excitotoxicity, the mitochondrial damage, the oxidative stress and the neuroinflammation (Sweeney *et al.* 2018; Reddy and Oliver 2019). In these regards, Tseveleki *et al.* (2010), by using animals models of IS, MS and AD, observed that several genes and pathways are commonly regulated in these three brain disorders, thus suggesting that a drug candidate able to modulate either of these pathways can be a potential treatment for these diseases. In this article we review the properties of Phycocyanobilin (PCB), the chromophore attached to C-Phycocyanin (C-PC) and its main bioactive metabolite, supporting its nutraceutical and therapeutic applications against AD. This work emphasizes relevant biological actions of C-PC/PCB such as antioxidant, anti-inflammatory, immunomodulatory and neuroprotectant.

2. C-Phycocyanin and Phycocyanobilin for neurodegenerative disorders

PCB (figure 1), a linear tetrapyrrolic chromophore covalently bound to C-PC, plays an essential light-harvesting role in blue–green algae such as *Spirulina platensis* (McCarty *et al.* 2010). Spirulin extract has well-known biological attributes, in particular as a nutritional supplement in humans, and a plethora of health benefits has been described in diseases models involving dysfunctional immunity, cardiac failure, arterial hypertension, oxidative stress, muscle-skeletal damage and neurological disorders (Wu *et al.* 2016). Interestingly, the oral administration of Spirulin extract during 4 weeks to rats with L-methionine-induced vascular dementia attenuated the animal´s cognitive deficits, along with the normal stabilization of glutathione (GSH), acetylcholinesterase (AChE) and thiobarbituric acid-reactive substances (TBARS, a lipid peroxidation biomarker) levels in their brains (Wang *et al.* 2020). The spry dried extract coming from the culture of *Spirulina platensis* fermented with *Lactobacillus plantarum*, a gut microbiome enhancing bacteria, also improved the memory performance, activated ERK and CREB proteins, and induced the expression of BDNF in mice with scopolamine-induced impairment (Choi *et al.* 2018). As the main protein component of Spirulin-derived preparations, C-PC has a relevant biological role on the health applications described for this cyanobacteria. The study of the C-PC individual activities has opened a very attractive field as a nutraceutical for many human diseases (Fernández-Rojas *et al.* 2014). It is recognized that its pharmacological actions rely on PCB (4.7% of the molar mass of C-PC), released from this biliprotein after its enzymatic degradation when administered *in vivo*, either as a purified protein or as component of Spirulin extracts, by oral or parenteral routes (Minic *et al.* 2018). Similarly, the versatile properties demonstrated for orally administered Spirulin extracts in different animal species strongly suggest that ingested PCB, which represents the 0.66% of the dry weight of Spirulin biomass, can be absorbed in sufficient amounts for achieving positive biological actions (McCarty 2007).

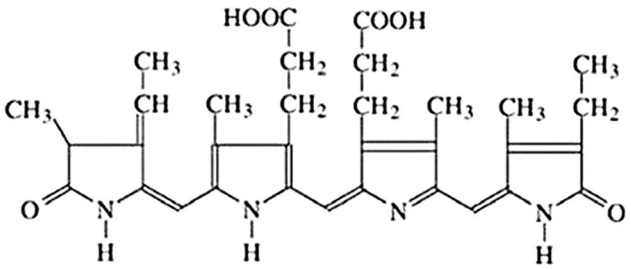

Figure 1. Chemical structure of Phycocyanobilin.

Based on this, our group has studied if purified preparations of C-PC and PCB were able to counteract

the injury in some important neurological disorders, and we have observed beneficial effects of these natural molecules in models of MS (Pentón-Rol *et al.* 2011b, 2016; Cervantes-Llanos *et al.* 2018) and IS (Pentón-Rol *et al.* 2011a; Marín-Prida *et al.* 2013; Pavón-Fuentes *et al.* 2020). C-PC was able to decrease the clinical severity of the disease by regulating multiple processes in the central nervous system (CNS), including neurodegeneration, inflammation and the redox state in a mice model of experimental autoimmune encephalomyelitis (EAE) (Pentón-Rol *et al.* 2016). The C-PC treatment in gerbils with cerebral ischemia, either prophylactically or therapeutically, reduced the infarct volume and also improved the recovery of locomotor behavior and restored the normal redox balance in serum and brain (Pentón-Rol *et al.* 2011a). In this line, the antioxidant properties of C-PC include a potent scavenging activity against peroxyl radicals, an important reactive oxygen species (ROS) involved in deleterious oxidative damage to lipids and proteins (Lissi *et al.* 2000). PCB has also shown strong protective actions against oxidative stress in PC12 neuronal cells against hydrogen peroxide and glutamate injuries, and in rats with acute cerebral hypoperfusion, an effect associated with its modulation of gene expression (Marín-Prida *et al.* 2013). PCB treatment regulated the brain expression of genes related to neuroinflammation, energy metabolism, remyelination, synaptic plasticity, angiogenesis and antiapoptosis, offering important mechanisms of brain protection in brain hypoperfusion (Marín-Prida *et al.* 2013). These results encourage the potential uses of PCB in AD.

3. Pathogenesis of Alzheimer's disease

As mentioned above, the amyloid cascade hypothesis is among the main theories for explaining the pathogenesis of AD, which states that neurodegeneration occurs as a result of the formation of soluble Aβ oligomers, leading to extracellular Aβ aggregates (plaques and fibrils), along with the accumulation of intracellular neurofibrillary tangles (Bloom 2014). The Aβ peptide is a fragment of a type I transmembrane protein called amyloid precursor protein (APP), composed of approximately 40–43 amino acids in the region within the ectodomain and the transmembrane parts of this protein (Takahashi *et al.* 2017). APP may undergo a sequential cleavage by specific enzymes at different locations, producing distinct products (Madav *et al.* 2019). Interestingly, the pathogenic variant of these fragments (i.e. $A\beta_{1–42}$) accounts only for ∼5–10% of all APP-derived peptides in the human brain (Gouras *et al.* 2000). Under physiological conditions, the so-called non-pathogenic or non-amyloidogenic pathway for APP processing is initiated by the α-secretase enzyme cleavage. This produces a soluble N-terminal fragment from α site of APP (named sAPPα) and the αC-terminal membrane-bound fragment (αCTF/C83). Subsequently, γ-secretase cleaves the remaining fragment to P3 and APP intracellular domain (AICD) (van der Kant and Goldstein, 2015). In this processing, the α-secretase acts on the APP domain containing the $A\beta_{1–42}$ fragment, and thus, it precludes the production of pathogenic Aβ peptides. In the amyloidogenic pathway, APP is cleaved by β-secretase (β-site APP-cleaving enzyme, BACE1) leading to a soluble N-terminal fragment (named sAPPβ) and the βC-terminal membrane-bound fragment (βCTF/C99), which then is cleaved by γ-secretase and releases Aβ peptides and the AICD (van der Kant and Goldstein, 2015). As γ-secretase cuts may occur at different places, diverse Aβ peptides are formed, among which soluble $A\beta_{40–42}$ are highly toxic and creates oligomeric structures that arrange themselves into β-sheets forming ordered fibrils and eventually, the amyloid plaques (Ahmed *et al.* 2010).

Aβ oligomers interfere in synaptic neurotransmission by acting at both the pre- and the post-synaptic compartments. This is evidenced by altering neurotransmitter uptake and release, preventing synaptic plasticity, disrupting long-term potentiation and favoring long-term depression, promoting cytoskeletal damage at the level of synapses and altering the levels and functioning of post-synaptic receptors (Majdi *et al.* 2020). Furthermore, Aβ oligomers cause oxidative damage and disruption of neuronal ion homeostasis and kinase/phosphatase activities (Hardy 2006). They also induce intracellular metabolic alterations that lead to accumulation of hyperphosphorylated Tau protein, whose aggregation creates the neurofibrillary tangles that disrupt intracellular metabolism at a level sufficient to cause neuronal death (Glabe 2005). Amyloid plaques and neurofibrillary tangles cause a massive release of glutamate in certain cortical and subcortical structures that can cause widespread neuronal death and cell death through excitotoxicity mediated by the N-methyl-D-aspartate (NMDA) receptor, causing dementia (Nunomura *et al.* 2001).

Several mechanisms are proposed to explain the pathway through which Aβ induces the death of neuronal cells (table 1) (Kadowaki *et al.* 2005), including the induction of oxidative stress (Tönnies and Trushina 2017), excitotoxicity, mitochondrial damage (Ong *et al.*

Table 1. Effects of Aβ on neuronal cells death

Study	Effects	Summary of results
Varadarajan *et al.* 2000; Avdulov *et al.* 1997; Aksenov *et al.* 2001	Oxidative stress	Aβ(1–42) causes elevation of the protein carbonyls and decreases cell survival in neurons, promotes lipid peroxidation in brain membranes and generates hydrogen peroxide and other ROS.
Gu *et al.* 2012	Disturbed energy metabolism	Aβ generates potential neurotoxic effects that cause cellular metabolic deficiency.
Stricker *et al.* 2009	Demyelination	In brains of the patients and animals with Aβ plaques shows focal demyelination associated with AD.
Lee *et al.* 2010	Inflammatory mediators	Aβ induces the expression of proinflammatory cytokines in glial cells, the activation of the complement cascade and the stimulation of inflammatory enzyme systems, factors that can contribute to neuronal dysfunction and cell death.
Serrano-Pozo *et al.* 2011	Activated brain microglia	β-amyloid peptide activates the microglial cells and contributes to the progression of chronic neurodegenerative diseases, such as AD.
Gu *et al.* 2012	Mitochondrial damage	Aβ induces programmed cell death related to the mitochondria due to depolarization of the mitochondrial membrane potential.
Gu *et al.* 2012 Folch *et al.* 2018	Apoptotic death	Aβ triggers mitochondrial apoptosis signaling. Aβ induces expression of genes that promote neuronal death by apoptosis.

2013; Zhao *et al.* 2018), the accumulation of intracellular calcium (Wilkaniec *et al.* 2016), the ROS and the nitric oxide production (Lamoke *et al.* 2015), axonal transport dysfunction (Salminen *et al.* 2015), cerebral hypoperfusion (Wang *et al.* 2016), inflammatory processes (Heppner *et al.* 2015), increased sensitivity to apoptosis (Cheng *et al.* 2016) and alterations in myelin (Mitew *et al.* 2010).

4. Safety of C-Phycocyanin and Phycocyanobilin

C-PC/PCB from *Spirulina platensis* extracts has the GRAS status (generally recognized as safe) granted by the United States Food and Drug Administration (FDA) (Eriksen 2008). A toxicity evaluation carried out in albino rats for 14 weeks with concentrations ranging from 0.25 to 5.0 g of C-PC per kg of body weight, revealed that this molecule did not induce any symptoms of toxicity neither of mortality (Naidu *et al.* 1999). In addition, the body weight of the rats was not affected, nor the values in absolute and relative weights of vital organs as well as their histological examination, while the hematology and serum enzymes did not reveal differences with respect to the control group. Similarly, in a chronic toxicity study, the oral administration of C-PC at 0.12, 0.4 and 4 g/kg in Sprague-Dawley rats for 12 weeks, did not significantly influenced the blood and serum indicators as well as the organs/body weight and no pathological signs were found in the brain, heart, liver, spleen, lung and kidney (Lufei *et al.* 2012). Furthermore, the consumption of a C-PC-enriched Spirulin extract (2.3 g/day, equivalent of approximately 1 g/day C-PC, accounting for ∼ 40% of the extract) daily for 2 weeks in 24 human adults was safe and effective against joints pain (Jensen *et al.* 2016a). This extract did not alter the platelet activation (P-selectin expression), the partial thromboplastin time, the thrombin clotting time, or the fibrinogen activity, but it reduced the levels of aspartate transaminase and alanine transaminase as well as chronic pain associated with joints (Jensen *et al.* 2016a). The anti-pain effect of Spirulin extract has also been documented in previous two human clinical pilot studies (Jensen *et al.* 2016b). Although no toxicity study has been reported with PCB so far, pharmacological reports have indirectly described its safe applications in animals and human cells. Peripheral blood mononuclear cells (PBMC) isolated from healthy donors and treated with 100 μM PCB for 6 h before stimulation with anti-CD3 for 72 h did not shown differences in their viability (95.5%) in comparison with vehicle control (95.6%) (Basdeo *et al.* 2016). C57BL/6 mice treated with either 30 mg/kg PCB or vehicle (PBS 1X) on days 0, 3, and 5 by oral gavage and sacrificed on day 7, did not evidence any significant weight change or macroscopic signs of their colons between both groups (Basdeo *et al.* 2016). Our group demonstrated the benefits of C-PC and PCB given by oral administration in rodent models of EAE. In this sense, we recently reported that both compounds

ameliorated the clinical signs, improved the motor performance, reduced the oxidative damage, protected myelin integrity and modulated proinflammatory cytokine levels in mice or rats with EAE (Cervantes-Llanos *et al.* 2018). Therefore, these studies indicate that C-PC/PCB at the evaluated doses did not cause adverse effects in experimental animals and humans. This evidence suggests the safe use of C-PC and PCB in a chronic disease such as AD, given their non-toxic actions in a chronic model of neurodegenerative disease such as MS.

4.1 *C-Phycocyanin and amyloid precursor protein*

As above-mentioned, APP sequential cleavage by the enzymes β and γ-secretase produces $A\beta_{40–42}$ toxic peptides (Mueller *et al.* 2018). In cases of familial AD there are specific mutations in the genes that encode APP and as a consequence the excessive accumulation of the Aβ peptide and the deposition in the brain occurs (Mueller *et al.* 2018). Therefore, pathogenic pathways for AD are focused on cell traffic, maturation and processing of APP, and the generation, aggregation and subsequent deposition of Aβ (Tanzi 2005). In this sense, when C-PC was administered to mice with EAE, it was able to significantly reduce the density of APP in spinal cords, as measured by quantitative immunohistochemistry (Pentón-Rol *et al.* 2016). Given that APP processing is crucially involved in the AD pathogenesis, the reduction of its expression levels in the CNS as shown in EAE mice treated with C-PC, could be the preliminary evidence for motivating the study of C-PC/PCB in AD.

Recent studies have also reported direct activities of C-PC on Aβ generation pathway. By using thioflavin-T fluorescence assay, Liu *et al.* (2019) observed that C-PC effectively inhibits the fibril formation of Aβ peptides at stoichiometric molar ratio of 5:1 (Aβ:C-PC). This was confirmed by transmission electron microscopy in *in vitro* assays, showing abundant long and mature fibrils in the absence of C-PC, while this biliprotein substantially reduced the amount of fibrils, forming small fibril clusters (Liu *et al.* 2019). On the other hand, a crystallographic and *in silico* study has shown promising results, evidenced by the interaction between C-PC and β-secretase with a free binding energy (−644.4 and −731.7 kJ/mol for β-secretase structures PDB ID 1FKN and PDB ID 3UQP, respectively) comparable to that of experimental peptide inhibitors of this enzyme (−446.2 and −532.1 kJ/mol, respectively) (Singh *et al.* 2014). However, these *in silico* results remain to be proved by appropriate experimental assays. Moreover, C-PC at 100 μg/mL significantly delayed the onset of temperature-induced paralysis in worms *C. elegans* strain CL4176, which serves as a transgenic model of AD (Singh *et al.* 2014). suggesting that C-PC is a potent inhibitor of the disease progression through limiting the accumulation of $A\beta_{1–42}$.

4.2 *C-Phycocyanin and Phycocyanobilin and oxidative stress*

It is known that oxidative stress plays an important role in the pathogenesis of AD. This imbalance between antioxidants and pro-oxidants can occur as a result of the increase in the levels of free radicals and/or a decrease in antioxidant defenses, a situation that favors the ROS attack on lipids, proteins, nucleic acids, carbohydrates, and other molecules, altering its structures and functions. Especially, the brain is of high risk for this oxidant damage, due to its composition in large part of lipids and its high rate of oxygen consumption (Huang *et al.* 2016). Protein oxidation, lipid peroxidation, DNA oxidation and the formation of 3-nitrotyrosine, H_2O_2, reactive nitrogen species (RNS) and ROS are the manifestations of the extensive oxidative stress observed in AD (Butterfield and Halliwell 2019). It is considered that both the soluble and the aggregate forms of Aβ when inserted into neuronal membranes can provoke oxidative stress and therefore neurotoxicity (Butterfield *et al.* 2001). Malondialdehyde (MDA) appears to be increased in the frontal lobe, temporal and hippocampus and is slightly increased in the occipital lobe in subjects with AD compared to controls of the same age (Zabel *et al.* 2018). The activity of superoxide dismutase (SOD) in AD is increased in the parietal lobe which is involved in the metabolic control of the oxidation and reduction reactions within the cells (Sultana *et al.* 2008). On the other hand, it has been shown that Aβ peptides can activate the microglia which then generates peroxynitrite (ONOO-) that acts as a damaging species to neurons. The ONOO- is known for its harmful effects, causing irreversible damage to a variety of biological targets such as DNA, lipids and proteins (Pacher *et al.* 2007). Very high levels of nitrated proteins are represented in the neurons of patients with AD (Sedgwick *et al.* 2018). All these changes induced by Aβ could be inhibited by the C-PC and PCB that has had such good results in the field of oxidative stress. In this sense, we have described an ameliorating effect

of oral C-PC in rats with EAE on serum levels of MDA and the peroxidation potential (Cervantes-Llanos *et al.* 2018). Interestingly, in a study using SH-SY5Y neuronal cell line, C-PC protected cells viability from t-BOOH-induced oxidative death, and it was also able to inhibit the electrochemically generated Fenton reaction (Marín-Prida *et al.* 2012). When administering PCB intraperitoneally in rats as a treatment in this case against cerebral ischemia, this drug decreased the levels of MDA, PP and SOD activities in ischemic brain and serum (Marín-Prida *et al.* 2013). Our results demonstrated that the PCB protects PC12 cells in the presence of H_2O_2 and glutamate, making evident its potential to preserve neuronal integrity and its excitotoxicity capacity (Marín-Prida *et al.* 2012). Given that peroxyl radicals are crucial mediators of lipid peroxidation, it is relevant to mention that C-PC and PCB have potent quenching effects on this ROS, with activities higher than well-known standard antioxidants such as Trolox, ascorbic acid, and reduced glutathione (Tsikas 2017; Benedetti *et al.* 2010; Pleonsil *et al.* 2013). Therefore, the antioxidant actions of PCB observed in different experimental settings, could justify its potential beneficial impact on counteracting the oxidative stress involved in AD (Simunkova *et al.* 2019).

4.3 *C-Phycocyanin and Phycocyanobilin and activated brain microglia*

The proliferation and activation of microglia in the brain, concentrated around the amyloid plaques, is a prominent feature of AD (Hansen *et al.* 2018). It has been observed that these brain cells contribute to the mechanisms of neuronal damage and cognitive loss in AD (Stansley *et al.* 2012). The constant formation and deposition of amyloid aggregates causes chronic microglial activation and the alteration of its functions, such as the defective phagocytic clearance of Aβ (Heneka *et al.* 2015). Microglia can even be activated by Aβ oligomers at low nanomolar concentrations before they form aggregates (Maezawa *et al.* 2011), suggesting that these cells are involved in early stages of AD pathogenesis, long before clinical symptoms become evident. Once activated, microglia can mediate synapse loss by losing its capacity of monitoring and remodeling neuronal circuits (Paolicelli *et al.* 2011). Moreover, activated microglia promotes the phosphorylation of Tau protein in primary neurons, suggesting its role in the exacerbation of neurofibrillary tangles-induced neuronal injury (Gorlovoy *et al.* 2009; Spangenberg and Green 2017). Microglia exposed to Aβ may also mediate neuronal damage by the NADPH oxidase overproduction of H_2O_2 (Shimohama *et al.* 2000), the increased formation of nitric oxide by iNOS activity thereby mediating the Aβ nitration that enhances its propensity to aggregate (Youm *et al.* 2013), and the expression of neurotoxic cytokines such as TNF-α and IL-1β, both of which suppress long-term potentiation in the hippocampus (Yirmiya and Goshen 2011; Pickering *et al.* 2005). Several studies have suggested that newly generated microglia sustaining chronic AD neuroinflammation could be from peripheral monocytes that cross the BBB, and then undergo differentiation into microglial cells in the brain parenchyma (Fiala *et al.* 1998; Mandrekar and Landreth 2010). Interestingly, Giri *et al.* (2003) observed that both soluble and fibrillar amyloid peptides ($Aβ_{1–40}$ and $Aβ_{1–42}$) at nanomolar concentrations increase mRNA expression of cytokines (TNF-α, and IL-1β) and chemokines (MCP-1, MIP-1β) in THP-1 monocyte cell line. Thus, this evidence suggest that peripheral monocytes may also contribute to Aβ-mediated inflammatory response, once gained access into the brain.

Several studies have shown that C-PC and PCB may counteract the deleterious actions of microglia in pathological conditions, relevant to AD. In BV-2 murine microglial cell line stimulated with LPS, both Spirulin extract (500, 750, and 900 μg/mL) and C-PC (85, 125, and 150 μg/mL) reduced the expression of iNOS, COX-2, TNF-α, and IL-6 mRNAs (Chen *et al.* 2012). In rats with chemically induced colon cancer, the oral administration of C-PC was able to inhibit the rise in the levels of MCP-1 chemokine and to reduce the number and size of tumors (Saini and Sanyal 2014). In a model of diabetic nephropathy in *db/db* mice, it was shown that PCB inhibits the expression of NADPH oxidase components, as well as the production of NADPH-induced superoxide in cultured human mesangial cells (Zheng *et al.* 2012). In a recent work, we reported that C-PC given at a dose of 8 mg/kg in mice with EAE, significantly reduced the expression of Mac-3 (microglia marker) in spinal cords (Pentón-Rol *et al.* 2016), which suggest that this treatment can effectively control the activation of microglia in chronic disease states. Furthermore, C-PC administered orally also reduced the activation of microglia induced by kainic acid in rats (Rimbau *et al.* 1999). Such evidence suggests that PCB, when released from C-PC *in vivo*, can be absorbed and pass through the BBB and by this way it could suppress the ROS production from activated microglia.

4.4 *C-Phycocyanin and Phycocyanobilin and mitochondrial damage and apoptotic death*

The metabolic insufficiency in the brain, particularly the energy production, is critical to the development of AD pathology, because it contributes to neuronal loss and cognitive impairment (Kapogiannis and Mattson 2011). Overexpression of Aβ leads to mitochondrial dysfunction, characterized by alterations of the electron transport chain and the opening of the mitochondrial permeability transition pore (MPT) (Moreira *et al.* 2010). As a consequence of MPT, several deleterious events occurs, which include the external mitochondrial membrane rupture, the oxidative phosphorylation disruption, the increase in adenosine 5′-triphosphate (Shariatpanahi *et al.* 2016), the hydrolase activity (reverse mode) of F0F1-ATP synthase, the inhibition of complex I due to the decrease in NADH, the release of mitochondrial Ca^{2+} and mediators of cell death such as cytochrome c, AIF factor and Smac/Diablo protein to cytosol (Morganti *et al.* 2018). Aβ peptides, in the presence of Ca^{2+}, exacerbate the MPT, thus clearly suggesting an association between Aβ, mitochondrial dysfunction and alteration of Ca^{2+} homeostasis (Moreira *et al.* 2010). In this regard, our group studied cerebral mitochondria as a pharmacological target of C-PC, inducing MPT by an overload of Ca^{2+}/phosphate (Pi) in rat cerebral mitochondria. Interestingly, the C-PC treatment significantly prevented MPT and mitochondrial swelling, indicating the mitoprotective capacity of C-PC (Marín-Prida *et al.* 2012). We also measure the ability of C-PC to inhibit the release of cytochrome c, after an overload of Ca^{2+}/Pi in rat brain mitochondria by western blot. The results demonstrated that C-PC has an inhibitory action on the release of cytochrome c. These C-PC results could be mediated by its antioxidant properties, since the effect was significantly greater than the effect of the antioxidant Trolox (Marín-Prida *et al.* 2012). Moreover, an inhibition in the mitochondrial levels of ROS was observed when treated with C-PC, indicating that its antioxidant capacity is part of the mechanism of protection against mitochondrial damage by Ca^{2+}/Pi (Marín-Prida *et al.* 2012). In a different study, it was observed that the treatment of PCB restored the cerebral expression levels of Bcl-2 in rats with brain hypoperfusion, which was diminished in vehicle-treated diseased animals (Marín-Prida *et al.* 2013). Overexpression of the Bcl-2 protein promotes axonal regeneration in the CNS and in patients with AD, suggesting its role against neuroinflammation, present in the surviving glial that surrounds the amyloid plaques (Chang *et al.* 2018; Gu *et al.* 2012). These results suggest that PCB has an anti-apoptotic effect, which is mediated by the positive regulation of Bcl-2, a gene that, however, is down-regulated by Aβ in human neurons (Paradis *et al.* 1996).

The brain uses 20% of the body's daily energy in the form of ATP in order to supply the energy requirements of neurons and glia as it does not have an energy reserve (Kuzawa and Blair 2019: Zhang *et al.* 2015a). For this reason, brain cells must continuously produce ATP, as the only source of maintenance of their energy homeostasis (Khatri and Man 2013). However, if the mitochondria are damaged as occurs in pathologies such as AD, then they produce free radicals which leads to a decrease in the supply of ATP, decreases energy and reduces energy consumed by neuronal axons (Zhang *et al.* 2015a). In this sense, both C-PC and PCB can be drug candidates for AD endorsed by their mitoprotective and antioxidant properties, being the cerebral mitochondria one of its therapeutic targets.

4.5 *C-Phycocyanin and Phycocyanobilin and inflammatory mediators*

It has been reported that peripheral inflammation can contribute to neurodegeneration in AD (Walker *et al.* 2019). Aβ interferes with neuronal function and triggers an inflammatory response in brains with AD (Bolós *et al.* 2017), and thus it has been recognized that inflammation is one of the important feature of this disease (Sinyor *et al.* 2020). In addition to the neuritic plaques and neurofibrillary tangles, the neuropathological features of AD are accompanied by activated microglia and astrocytes that overexpress proinflammatory cytokines such as IL-1β, IL-6 and TNF-α (Giri *et al.* 2003; Kinney *et al.* 2018). Aβ oligomers from senile plaques potentiate the secretion of IL-6 by astrocytes, which are also found in increased levels in brain tissue with AD (Serpente *et al.* 2014). IFN-γ, acting in synergy with Aβ, causes the release of TNF-α and reactive nitrogen species that are toxic to neurons (Lee *et al.* 2010).

Several reports have documented the activities of C-PC/PCB on the inflammatory component of a variety of CNS diseases models. C-PC protected astrocytes from H_2O_2-induced oxidative damage by decreasing ROS levels and promoting the expression and activity of SOD and catalase (Min *et al.* 2015). C-PC also downregulated IL-6 and IL-1β and induced the expression of neurotrophic factors (BDNF and NGF) in

astrocytes under toxic H_2O_2 (Min *et al.* 2015). In mice intoxicated with tributyltin chloride, an organo-metallic pesticide compound and a potent neurotoxicant, the i.p. application of 50 mg/kg C-PC effectively reduced cortical astrocyte activation and apoptosis, along with a decrease in ROS and NF-kB levels (Mitra *et al.* 2015). C-PC given orally was also effective against salicylate-induced tinnitus, a common symptom of different hearing impairments, in mice by down-regulating the mRNAs expression of TNF-α, IL-1b and COX-2 genes in the cochlea and inferior colliculus (Hwang *et al.* 2013).

Our group has studied the anti-inflammatory properties of PCB (Boraschi and Penton-Rol 2014). In mice with EAE, the oral administration of PCB significantly reduced the concentrations of proinflammatory cytokines such as IL-6 and IFN-γ in the brain, as compared with diseased animals treated with vehicle (Cervantes-Llanos *et al.* 2018). In a model of acute cerebral hypoperfusion in rats, we carried out a gene expression assessment by quantitative real time PCR (qRT-PCR) for evaluating the PCB effects on different brain areas. PCB treatment reduced the mRNA levels of IFN-γ, IL-6, CD74, CCL12 and IL-17A in olfactory bulb and anterior cerebral cortex, in comparison to the vehicle-treated group (Marín-Prida *et al.* 2013). In addition, we studied the levels of IL-4, showing that PCB significantly up-regulates the expression of this anti-inflammatory cytokine in the three cerebral areas evaluated (Marín-Prida *et al.* 2013). IL-4 induces the elimination of Aβ peptides, regulates the microglial responses to Aβ, and attenuates neuroinflammation related to Aβ levels (Boccardi *et al.* 2019). Neuroinflammation has a direct contribution to the progression of AD, and at this point the PCB could neutralize the disease by effectively modulating the expression of genes mainly related to the immune response. Moreover, the expression of TGF-β1, a trophic factor involved in synaptic plasticity and neuronal development (Estrada *et al.* 2018), was also positively modulated by the PCB (Marín-Prida *et al.* 2013). Transgenic overexpression of TGF-β1 decreased the Aβ load in an AD mouse model by promoting microglial clearance of Aβ (Heppner *et al.* 2015). Another gene evaluated was C/EBPβ, which regulates delta-secretase transcription, an enzyme that cleaves both APP and Tau involved in amyloid plaque formation and neurofibrillary tangle in AD (Zhang *et al.* 2014, 2015b). Overexpression of C/EBPβ in young 3xTg mice increases delta-secretase expression and accelerates the pathological features, while C/EBPβ depletion in aged 3xTg or 5XFAD mice diminishes delta-secretase and reduces AD pathologies (Wang *et al.* 2018). Moreover, by using a high-throughput screening, Zhang *et al.* (2017) were able to identify a non-toxic and selective delta-secretase inhibitor, termed compound 11, that reduces tau and APP cleavage, ameliorates synapse loss and augments long-term potentiation in 5XFAD mice. These pieces of evidence support the view that the restriction of delta-secretase activity mediated either by decreasing C/EBPβ levels or by specific chemical inhibition of this enzyme, may provide effective memory enhancement and cerebral tissue health in AD. In this sense, the PCB treatment significantly reduced the cerebral C/EBPβ mRNA levels in hypoperfused rat brains, accompanied by the reduction of cerebral oxidative stress (Marín-Prida *et al.* 2013). Interestingly, compound 11 suppressed delta-secretase activity in cultured neurons under oxygen-glucose deprivation and promoted neuronal survival (Zhang *et al.* 2017). Thus, these results suggest that PCB may induce neuroprotection in AD by curtailing the activity of delta-secretase secondary to the diminished expression of brain C/EBPβ.

Several studies have indicated that biomarkers of endothelial dysfunction, such as ICAM-1, are elevated in AD, and that endothelial cells, astrocytes and microglia express increased levels of ICAM-1 in pathological conditions, playing a role in neuritic plaques in the process of neurite growth and neurodegeneration (Walker *et al.* 2017; Drake *et al.* 2018; Frohman *et al.* 1991). As well as chemokines such as CXCL2 act through the chemokine receptor (CXCR2) in neurons where they play a pathophysiological role in AD (De Paola *et al.* 2007). The mRNA expression levels of both markers were significantly decreased after PCB treatment in ischemic rats (Marín-Prida *et al.* 2013), and therefore, this suggest that a similar counteracting effect on AD may ameliorate ICAM-1 and CXCL2-mediated injury in this pathology.

We have also reported the decrease in the inflammatory component after C-PC treatment in MS models. In an EAE model, mice treated with C-PC showed a significant decrease in the number of inflammatory foci present in the spinal cord (Pentón-Rol *et al.* 2016). This result is of interest in this pathology since it has been described that inflammatory processes are closely related to axonal degeneration in the brain and spinal cord in AD disease (Wirths *et al.* 2010). Th17 cells and their signature cytokine IL-17 are implicated in the pathogenesis behind various inflammatory diseases, such as MS, rheumatoid arthritis and psoriasis, but their possible contribution to brain diseases has recently been exposed associated with cognitive decline (Cipollini *et al.* 2019). Novel scientific evidence

suggests that cognitive impairment and neuroinflammation induced by Aβ could be improved by administering anti-IL-17 antibodies and neutralizing the IL-17 cytokine (Cristiano *et al.* 2019). In this sense, our group reported that the treatment of animals with C-PC significantly decreased the expression of IL-17 mRNA in the brain in the EAE model (Pentón-Rol *et al.* 2016). C-PC is a selective inhibitor of the enzyme cyclooxygenase-2 (COX-2) (Reddy *et al.* 2000). COX-2 is an enzyme responsible for the formation of prostaglandins located in the hippocampus, which in pathological conditions is activated by astrocytes and microglia causing chronic inflammation of neurons. Its high expression in the brains of AD patients is related to neuronal plaques and neurofibrillary tangles, including the worsening of dementia and the progression of AD to clinical stages (Joob and Wiwanitkit 2019; Ho *et al.* 2001).

In animal models of AD, regulatory T cells (Treg) have been shown to play an important role (Gan-Or *et al.* 2015), but their precise contribution is complex and remains unclear. Also, previous studies have reported that Treg cells are a neuroprotective and immunomodulatory intervention in AD (Yang *et al.* 2013). Transient depletion of Treg cells accelerates the onset of cognitive deficits and is associated with modulation of the microglial response to Aβ peptide deposits (Dansokho *et al.* 2016). In another study using anti-CD25 for a period of 4 months in 3xTg-AD mice there was a depletion of the Treg cells that resulted in an increase in the deposition of Aβ on the extracellular plaques, an increase in the number of microglia/macrophages in the CA1 and CA3 regions of the hippocampus and a significant worsening in spatial learning deficits (Baek *et al.* 2016). Furthermore, it was showed that peripheral therapy with IL-2, which stimulates Treg cell proliferation, improves synaptic plasticity, reduces spine density and restores cognitive function in animal models of AD disease (Alves *et al.* 2017). Our group studied the expression of Treg cell markers (CD25, Foxp3, TGF-β and IL-10) in PBMC with MS and healthy controls treated *in vitro* with C-PC by qRT-PCR (Pentón-Rol *et al.* 2011b). The results showed that, 4 hours after the administration of C-PC, and up-regulation of all the Treg cell markers was present. The effect on the induction of a subset of Treg cells was evaluated by flow cytometry, revealing that 72 hours after stimulating PBMC from MS patients, C-PC promoted a positive regulation of the $CD4^{+}CD25^{high}$ subset in comparison to PBMC from healthy humans control (Pentón-Rol *et al.* 2011b). Based on this immunomodulatory potential of C-PC/PCB, we can propose it as a possible candidate for therapy against AD disease targeting the neuroinflammatory stage.

4.6 *C-Phycocyanin and Phycocyanobilin in remyelination*

Due to the important role of myelin in the CNS, where by wrapping axonal segments it promotes acceleration in the propagation of nerve impulses and provides trophic and mechanical support to fragile neuronal processes (Raasakka *et al.* 2019); it transports the necessary trophic support to neuronal axons and reduces the energy consumed by neuronal axons (Lee *et al.* 2012; Nave 2010). Degeneration of myelin also contributes to the cognitive deterioration characteristic of AD, due to its crucial role in the speed and integrity of axonal transmission (Lorenzini *et al.* 2020). Several studies corroborate that demyelination reinforces the accumulation of Aβ, hyperphosphorylated Tau, synaptic dysfunction and neuronal loss in AD (Sun *et al.* 2017). Chu *et al.* (2017) described the effect on the destruction and loss of myelin in AD, and other authors have also reported evidence supporting the close association between the loss of myelin and the cognitive impairment observed in patients with this disease (Bouhrara *et al.* 2018; Dong *et al.* 2018). Such evidence gives a view that by promoting remyelination in patients with AD, it may accelerate the recovery of the structure and functioning of neuronal axons and the improvement of cognition.

In this line of thinking, our group has studied C-PC and PCB as remyelinating molecules in both prophylactic and therapeutic schemes, in models of different diseases. In rats with EAE, C-PC given by intraperitoneal route, not only significantly decreased the maximal clinical score but also protected the myelin sheaths of the brain by promoting its more compact structure, a solid myelin without signs of axonal decomposition (Pentón-Rol *et al.* 2011b). More recently, we reported a similar protective action of oral C-PC on the structural integrity of cerebral myelin, an effect that was concomitant with its anti-lipid peroxidation activity (Cervantes-Llanos et al. 2018). As C-PC is a specific inhibitor of COX-2, an enzyme involved in the oxidative injury to oligodendrocytes precursor cells in different toxic environments (Shiow *et al.* 2017), it is reasonable to point out that this property could also mediates its myelin protective action. We determined the *g* ratio (ratio of the diameter of the axon to the diameter of the myelinated axon), as a quantitative parameter for remyelination induced by C-PC. The

EAE vehicle-treated rats showed a significantly higher *g* ratio compared to healthy control group (mean ± S.E.M.: 0.88 ± 0.004 and 0.66 ± 0.017, respectively), while in EAE animals treated with C-PC, the level of the ratio g (0.67 ± 0.007) was similar to the control level (Pentón-Rol *et al.* 2018). Normal myelinated axons has a typical *g* ratio ranging from 0.6 to 0.8, while a demyelinated axon has a *g* ratio between 0.8 and 1.0 value, the latter indicating a complete loss of myelin (Olsen and Akirav 2015). Thus, our results confirm that the treatment with C-PC promotes the remyelination in the brain of EAE rats.

On another hands, the qRT-PCR assessment of genes expression modulated by the treatment of PCB in rats with acute hypoperfusion, revealed evidence regarding the effects of this molecule on myelin. PCB up-regulated the expression of *Mal* gene in brain areas (Marín-Prida *et al.* 2013), which encodes for a protein found in the compact myelin and has been implicated in the biogenesis and proper myelin functioning (Bijlard *et al.* 2016). Additionally, we have showed that oral PCB treatment in animals with EAE negatively regulates the expression of demyelination-related genes (LINGO1, Notch-1) and up regulates genes involved in remyelination (MAL, CXCL12) (Pentón-Rol and Cervantes-Llanos 2018). The LINGO-1 antibody has been reported to promote CNS remyelination and recovery of spatial learning and memory in mice with EAE, indicating that lowering the amounts of LINGO-1 could also probably improve cognition in patients with AD (Sun *et al.* 2017). By studying a Tg rodent models of AD, researchers showed that chronic Notch-1 activation can accelerate Aβ accumulation and lead to spatial memory deficits (Cuello *et al.* 2019). In this sense, Cho *et al.* (2019) demonstrated that the plasma levels of Notch-1 correlate with cognitive deterioration in patients with dementia and that there is accumulation of Notch-1 and co-localization with Aβ plaques in the brain of the patient with AD. Conversely, an increase in protein MAL and CXCL12 levels is a promising sign of remyelination. MAL is a proteolipid located in the compact myelin of cells of the nervous system and has been implicated in the biogenesis and/or function of myelin and CXCL12 improves the proliferation of oligodendrocyte precursor cells and increases myelin expression during remyelination (Patel *et al.* 2012; Pal *et al.* 2012). Remyelination provided by the PCB can promote the recovery of cognition and movement, increasing locomotor activity and maintaining energy homeostasis in AD brains (Sun *et al.* 2017). Myelin largely reduces the energy consumption of axons during action potentials and provides them with the necessary vitality (Sun *et al.* 2017).

5. Conclusion

Due to the continuous increase of aged population worldwide and the high incidence of AD, it is essential to find effective disease-modifying treatments as well as preventive strategies that can also be cost affordable for all people affected by this devastating condition. PCB is a natural compound with many advantages since it modulates several processes involved in the pathogenic cascade of AD, that can be administered safely by oral or parenteral routes and therefore could be commercially offered as a nutraceutical supplement or as a pharmaceutical drug. Our results in various neurodegenerative disease models indicate that PCB treatment can have a relevant clinical impact in AD. PCB mitigates neuronal cell damage by blocking various targets in the disease's mechanisms of action. PCB is able to prevent the oxidative damage, modulate neuroinflammation, protect brain mitochondria, maintain energy homeostasis, prevent axonal loss, inhibit apoptosis-inducing mediators, reduce microglial and astrocytes activation and promote remyelination. In conclusion, PCB attenuates the neurodegenerative processes typical of neurological conditions such as AD, which increases its value for drug development.

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