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Neuroprotective effects of anthocyanins on learning and cognitive abilities

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Abstract

Anthocyanins represent a remarkable class of compounds belonging to the group of polyphenols. Anthocyanins are glucosides of the anthocyanidins, flavonoid derivatives produced by the phenylpropanoid pathway. These compounds are natural water-soluble vacuolar pigments in different fruits, flowers, and vegetative organs. A lot of *in vitro*, animal, and human studies have evaluated the biological and pharmacological potential of anthocyanins. Their results have demonstrated that these compounds may counteract oxidative stress via free-radical scavenging capacity and activating antioxidant enzymes. They can act as antimicrobial substances, modulate inflammatory cytokines signalling and regulate different pathways to prevent or reduce the progression of numerous diseases such as cardiovascular, metabolic, and neurodegenerative diseases. Several studies have indicated that anthocyanins and anthocyanin-enriched extracts can improve learning and memory, but also relieve the motor and cognitive deficits associated with neurodegenerative diseases.

Introduction

Anthocyanins are red, blue, or purple pigments found in plants, especially flowers, fruits, and tubers. In plants they occur in the form of glycosides, and their aglycone part is referred to as anthocyanidin. The red pigment of anthocyanins manifests itself in acidic environments, while the blue pigment exists in alkaline conditions. Anthocyanins belong to the flavonoids even if they have a positive charge on the oxygen atom of the C-ring of the flavonoid structure. In addition to anthocyanins, the group of flavonoids also includes flavonols, flavan-3-ols, flavones, and flavonones. The stability of anthocyanin depends on pH, light, temperature, and its structure (Yoshida *et al.* 2009, Khoo *et al.* 2017). They are among the most consumed flavonoids in the normal diet. Since they can also be easily and safely incorporated into the diet, anthocyanins may be promising agents for the prevention and supported treatment of various diseases, including neurodegenerative diseases. It has been shown that they are rapidly taken up into vascular endothelial cells in a bilitranslocase-dependent manner (Ziberna *et al.* 2012). Furthermore, anthocyanins may interact with P-glycoprotein transporters, and gain entrance into the brain in this manner (Youdim *et al.* 2003). Upon

transport into the central nervous system, anthocyanins have been shown to accumulate in brain parenchymal tissue, striatum, hippocampus, cerebellum, and cortex (Andres-Lacueva *et al.* 2005, El Mohsen *et al.* 2006).

Anthocyanins have been shown to affect brain function in several ways. A number of pathways are thought to work together to prevent brain degeneration, as well as improve cognition. Anthocyanins are primarily effective antioxidants, and the high content of antioxidants in plants and fruits can scavenge free radicals. In addition, anthocyanins increase the activity of antioxidant enzymes. In fact, these effects contribute to reducing inflammation in the brain. Anthocyanins in plants and fruits also have the potential to inhibit cell death of neurons and improve neuron connections, particularly in areas of the hippocampus associated with learning and memory (Rendeiro *et al.* 2013, 2014). Anthocyanins can also disrupt the aggregation of amyloid beta (Aβ) in the brain, thereby preventing the formation of amyloid plaques and preventing Alzheimer's disease (Winter & Bickford 2019).

Structure and function

Anthocyanins are formed by a flavylium cation backbone hydroxylated in different positions which gives rise to different anthocyanidins. The general molecular structure of anthocyanin is shown in Figure 1. Even if these molecules contain an oxonium group in their structure, the flavonoid skeleton maintains its ring nomenclature with the charged oxygen atom on the C ring (Mattioli *et al.* 2020). Among most frequently naturally occurring anthocyanins are the glycosides of cyanidin, delphinidin, pelargonidin, and malvidin (Figure 1).

Anthocyanins and anthocyanidins, similarly as other polyphenols and flavonoids, may act as free radical scavengers against harmful oxidants such as reactive oxygen and nitrogen species (Nimse & Pal 2015). A central role of the antioxidant activity is the oxidation of anthocyanin phenolic hydroxyl groups. In particular, para- and ortho- phenolic groups are important for the formation of semiquinones and for the stabilization of one-electron oxidation products (Ali *et al.* 2016, Mattioli *et al.* 2020). However, the 1,4 and the 1,2 conjugations are not the only electronic systems able to offer stabilizing condition for radicals on flavonoids. Substituents 3,5,7 and 3´and 4´ on rings C, A and B are essential for the formation of different electronic delocalized and oxidized structures (Duchowicz *et al.* 2019, Ali *et al.* 2016, Mattioli *et al.* 2020).

After consumption of anthocyanin, absorption occurs along the gastrointestinal tract, the distal lower bowel being the place where most of the absorption and metabolism occurs. In the intestine, anthocyanins undergo extensive microbial catabolism followed by absorption, metabolism, and production of different molecular intermediates that may possess specific properties and biological activities. (Mattioli *et al.* 2020, Tian *et al.* 2019). Anthocyanins, however, have low bioavailability, and short systemic circulation which is restrained its clinical application (Gonçalves *et al.* 2022). To overcome these limitations and enhance the bioavailability, nanoparticle-based delivery systems have been developed and intensively studied (Gonçalves *et al.* 2022, Dayar and Pechanova 2021, Pechanova *et al.* 2020, Kim *et al.* 2017).

Health benefits of anthocyanins have been widely described, especially in the prevention of diseases associated with oxidative stress, such as cardiovascular (Pechanova *et al.* 2004, Cebova *et al.* 2017, Cebova & Pechanova 2020, Galleano *et al.* 2010, 2013, Lietava *et al.* 2019), metabolic (Dayar *et al.* 2020, 2021), and neurodegenerative diseases (Jagla & Pechanova, 2015, 2020, Kovaczova *et al.* 2010). Recent evidence suggests that health-promoting effects attributed to anthocyanins may also be related to anticancer activity (Kopustinskiene *et al.* 2020) and modulation of gut microbiota (Tian *et al.* 2019). Most of the studies reported the neuroprotective effects are however dedicated to cyanidin and its glycosides. Limited studies have been done to determine the neuroprotective benefits of other anthocyanidins and anthocyanins like delphinidin, pelargonidin, and malvidin (Roghani *et al.* 2010, Kim *et al.* 2019, Xiao *et al.* 2022, Khoo *et al.* 2017). Kim *et al.* (2012) showed the neuroprotective effect of a mixture of three major anthocyanins such as cyanidin-3-glucoside, delphinidin-3-glucoside, and petunidin-3-glucoside against cell death.

Learning and memory

Several preclinical studies have demonstrated that anthocyanins improve learning and memory in different mammalian species (Afzal *et al.* 2019, Vauzour *et al.* 2021). Andres-Lacueva *et al.* (2005) demonstrated that anthocyanins are able to cross the blood brain barrier and localize in various brain regions important for learning and memory. Correlational analyses revealed a relationship between Morris water maze performance in blueberry supplementation rats and the total number of anthocyanin compounds found in the brain cortex (Andres-Lacueva *et al.* 2005). These findings indicate that anthocyanidins may deliver their antioxidant and signaling modifying capabilities centrally.

Anthocyanin-rich blueberry intake shown to induce spatial memory improvement in young rats (Rendeiro *et al.* 2014, 2012) and ameliorate age-related cognitive decline in aged rats (Rendeiro *et al.* 2013, Williams *et al.* 2008). The behavioural improvements in young rats were linked to increased levels in the polysialylated form of the neural adhesion molecule (PSA-NCAM) in the dentate gyrus of the hippocampus, which is known to be required for the establishment of durable memories. The authors observed parallel increases in hippocampal N-methyl-D-aspartate (NMDA) recep-

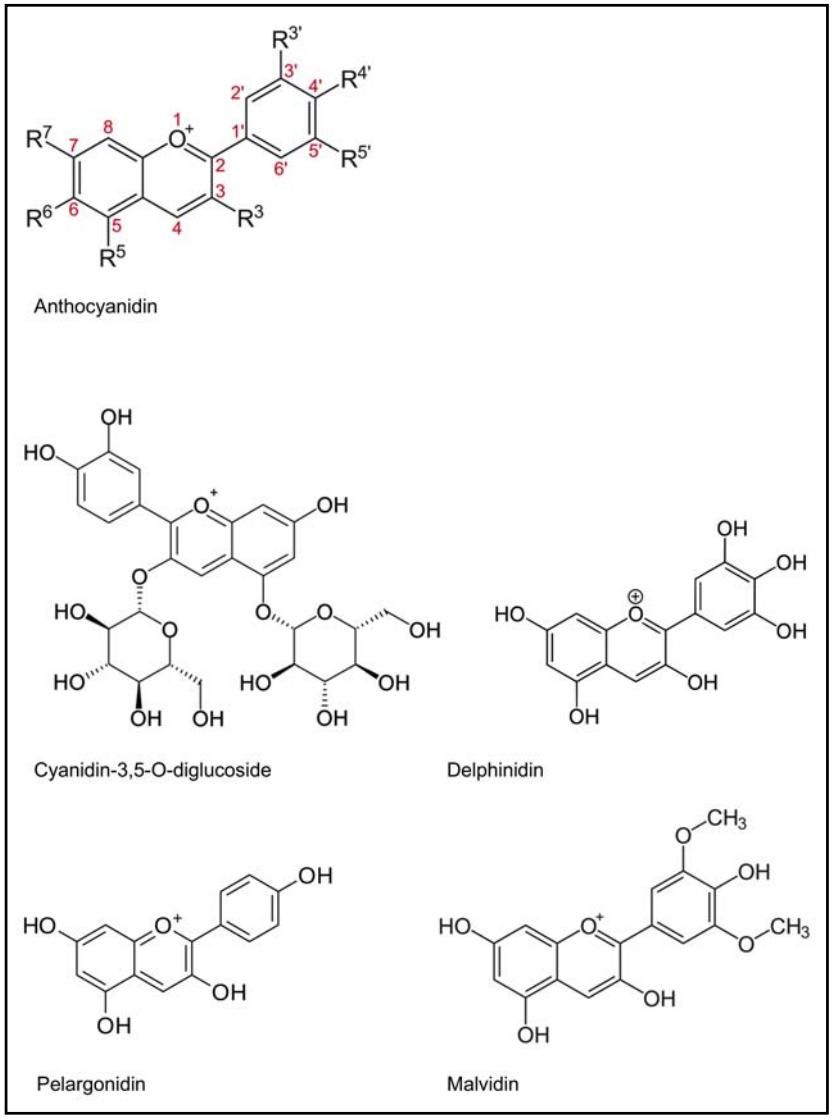

Fig. 1. The basic chemical structure of anthocyanidin and cyanidin-3,5-O-diglucoside, delphinidin, pelargonidin, and malvidin.

tors containing the NR2B subunit, suggesting an enhancement of glutamate signaling following anthocyanin intervention (Rendeiro *et al.* 2014). In aged rats the changes in spatial working memory were linked predominantly to the effects of anthocyanins on the extracellular signal-related kinase - cAMP-response element-binding protein - brain-derived neurotrophic factor (ERK-CREB-BDNF) pathway (Rendeiro *et al.* 2013, Williams *et al.* 2008). Vauzour *et al.* (2021) demonstrated that over the course of the 6-week shaping phase, aged rats receiving the anthocyanin extract performed better in the cross-maze apparatus, indicating an enhancement of learning capabilities. In addition, performance in the cross-maze apparatus was independent of the improvement of motor skills, indicating a clear cognitive impact of the anthocyanin treatment.

In lipopolysaccharide (LPS)-treated mice anthocyanins reversed the activation of c-Jun N-terminal kinase (JNK), prevented neuroinflammation by lowering the levels of inflammatory markers like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), tumor necrosis factor α (TNF-α), and interleukin IL-1β. Furthermore, they reduced neuronal apoptosis by decreasing the expression of Bax, cytochrome c, cleaved caspase-3, and cleaved poly [ADP-ribose] polymerase 1 (PARP-1), while increasing the level of survival proteins p-Akt, p-serine/threonine protein kinase (p-GSK3β), and anti-apoptotic Bcl-2 protein. By this way anthocyanin treatment increased the levels of memory-related pre- and post-synaptic proteins and improved the hippocampus-dependent memory (Khan *et al.* 2009). In the shuttle-box test, ovariectomized rats showed increased latency time and total errors and decreased number of avoidances in the learning sessions. But the group of ovariectomized rats treated with anthocyanins had significantly increased number of avoidances and decreased latency time and total errors during the learning sessions. These results suggest that anthocyanins improve learning and memory of rats with estrogen deficit caused by ovariectomy (Varadinova *et al.* 2009).

Current human studies are in agreement with preclinical research findings (Devore *et al.* 2012, Letenneur *et al.* 2007). Indeed, a cognitive improvement after the intake of anthocyanins have been demonstrated in the short-term memory, long-term memory, learning, lexical-semantic memory, and working memory systems of postpartum women (Miranda *et al.* 2021). Increased berry anthocyanin consumption was also associated with improved cognitive functions amongst young healthy adults (Whyte *et al.* 2019). Kent *et al.* (2022) in the Rey Auditory Verbal Learning Test (RAVLT) showed that the group of participants with the highest anthocyanins intake (median, 35.5; IQR, 71.5 mg/d) recalled a greater number of words after a short delay and forgot less words after a long delay of 20 minutes.

Neurocognitive benefit of anthocyanins was also confirmed by functional magnetic resonance imaging in a study where blueberry diet supplementation enhanced neural responses during working memory challenges in older adults with cognitive decline (Boespflug *et al.* 2018). Improvement in working memory performances was also observed in individuals undergoing mild cognitive decline by consuming grapes twice a day (Lee *et al.* 2017). Anthocyanins also improve brain perfusion and activation in brain areas associated with cognitive function in healthy older adults supplemented with blueberries (Bowtell *et al.* 2017) and with *Vitis vinifera* fruit extract (Calapai *et al.* 2017).

The neuroprotective effects of anthocyanins also led to memory improvement. This enhancement was confirmed by Western blot analysis of the memory-associated presynaptic and postsynaptic protein markers and by behavioural tests. Anthocyanins improved memory-related pre- and postsynaptic protein markers and memory functions in the Alzheimer's disease (AD) mice model (Ali *et al.* 2018). The authors also showed that anthocyanin-loaded polyethylene glycol-gold nanoparticles inhibited apoptosis and neurodegeneration in the $A\beta_{1-42}$-injected mice (Ali *et al.* 2017). Improvement of learning and memory by anthocyanin treatment has been confirmed by the Morris water maze (Ali *et al.* 2017, Tan *et al.* 2014), Y-maze (Rehman *et al.* 2017), novel object recognition (Carvalho *et al.* 2017, Bensalem *et al.* 2018) and passive avoidance (Tan *et al.* 2014) tests as well.

Neuroprotection and cognition

Neurodegenerative diseases, like Alzheimer's disease, Huntington's disease, Parkinson's disease, prion disease, and amyotrophic lateral sclerosis, are a group of disorders that share the abnormal accumulation of intraneuronal or extraneuronal misfolded/unfolded proteins (Taalab *et al.* 2018). Although pathophysiological pathways including oxidative stress, apoptosis, autophagy, mitochondrial dysfunction, have been identified in different neurodegenerative diseases, there are different functional mechanisms in each disease which represent the focus of research interest. Anthocyanins have the ability to protect neurons against oxidative stress, suppress neuroinflammation and modulate cell signalling pathways, thus have the potential to prevent/improve neurodegenerative conditions. Several studies have indicated that anthocyanins and anthocyanin-enriched extracts can relieve the cognitive deficits associated with Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.

Studies using 6-hydroxydopamine model of Parkinson's disease (6-OHDA) have demonstrated that this compound causes significant oxidative damage and neuronal death in neuronal populations associated with Parkinson's disease (Simola *et al.* 2007). Rats treated with 6-OHDA showed decreased numbers of dopaminergic neurons within the lesioned *substantia nigra* and increased lipid peroxidation (Rogha *et al.* 2010). These effects were essentially eliminated by administration of the anthocyanin derivative, pelargonidin and also corresponded with motor function improvement. A diet rich in blueberries in the similar rat model led to a transient increase in reactive microglia that had resolved one month post-lesion, which correlated with recovery of dopaminergic neurons as indicated by tyrosine hydroxylase immunoreactivity in striatal tissue (Stromberg *et al.* 2005). Concerning human studies, findings of Gao *et al.* (2012) suggest that intake of flavonoids rich in anthocyanins may reduce Parkinson's disease risk, particularly in men, but a protective effect of other constituents of plant foods cannot be excluded.

Anthocyanin-rich extracts have also been shown for the treatment of Alzheimer's disease and age-related cognitive impairment (Williams & Spencer 2011). Several studies pointed to the fact that anthocyanins and anthocyanin extracts attenuate many of the aspects associated with amyloid beta toxicity, like decreases in cellular viability, increased oxidative stress, elevated intracellular calcium, beta-secretase expression, down-regulation of pro-survival proteins, and elevation of pro-apoptotic signalling proteins (Belkacemi & Ramassamy 2015, Badshah *et al.* 2015, Ali *et al.* 2018, Amin *et al.* 2017). Anthocyanin treatment also significantly reduces markers of inflammation such as NF-κB, inducible nitric oxide synthase, cyclooxygenase-2 (COX-2) and TNF-α expression, and JNK activation in the BV-2 microglial cell line (Kim *et al.* 2017).

In the mouse model of AD, anthocyanins regulated the phosphorylated-phosphatidylinositol 3-kinase-Akt-glycogen synthase kinase 3 beta (p-PI3K/Akt/GSK3β) pathways and consequently attenuate amyloid beta oligomer (AβO)-induced elevations in oxidative stress via stimulating the endogenous antioxidant system of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (Nrf2/HO-1) pathways. They also prevent apoptosis and neurodegeneration

by suppressing the apoptotic and neurodegenerative markers such as caspase-3 and PARP-1 expression (Ali *et al.* 2018). AD might be also reversed by adenine nucleotide translocators through the mitochondrial apoptotic pathway, by regulating Bax, Cyto-C, caspases-9 3, tau-proteins, and BACE-1 (Wu *et al.* 2019, Badshah *et al.* 2015).

In participants developed Alzheimer's dementia, higher strawberry intake was associated with reduced risk of Alzheimer's dementia. In separate adjusted models, higher intake of pelargonidin and total anthocyanidins were each associated with lower Alzheimer's dementia risk (Agarwal *et al.* 2019). A 12-week randomized clinical trial conducted in older adults with mild to moderate AD, found consumption of 200 ml/day of cherry juice resulted in improvements in verbal fluency, short term memory, and long-term memory compared to the control group, which consumed a juice with negligible anthocyanin content (Kent *et al.* 2017).

Older adults with mild memory decline who consumed grape juice rich in anthocyanins showed reduced semantic interference on memory tasks. Relatively greater activation in anterior and posterior regions of the right hemisphere was also observed with functional magnetic resonance imaging in the grape juice treated subjects. These findings provide further evidence that anthocyanins may improve neurocognitive function also in adults with mild memory decline (Krikorian *et al.* 2012).

Conclusion

Anthocyanins belong to flavonoid widespread in nature that display a wide array of beneficial effects on human health. Several signalling pathways affected by anthocyanin specific interactions have been shown to increase the expression of neuroprotective proteins and increase the number or strength of connections between neurons. Decrease of oxidative stress and PI3-kinase/Akt signalling pathways belong among them. Through increased brain blood flow and an ability to initiate neurogenesis in the hippocampus they may also lead to enhancements in cognitive performance. Furthermore, in neurodegenerative disorders and AD-like pathology anthocyanins may have potential to inhibit neuronal apoptosis and neuroinflammation or disrupt amyloid β aggregation and affect amyloid precursor protein processing through the inhibition of β-secretase and activation of α-secretase and thus to prevent the progression of neurodegenerative pathologies and to promote cognitive performance. Anthocyanins in food may also interact with other polyphenols, and nutrients and combinations of foods may lead to synergistic effects. As shown in the literature and also in this review, an adequate daily intake of these substances may provide protection from numerous diseases including neurodegenerative diseases.

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Conflict of interest

The author declare that there is no conflict of interest.

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