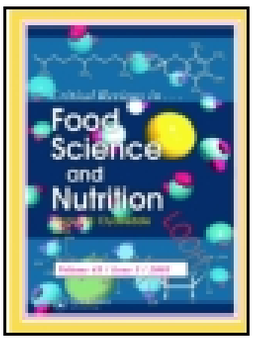

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REVIEW

Anthocyanins: From plant pigments to health benefits at mitochondrial level

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ABSTRACT

Anthocyanins are water-soluble pigments providing certain color for various plant parts, especially in edible berries. Earlier these compounds were only known as natural food colorants, the stability of which depended on pH, light, storage temperature and chemical structure. However, due to the increase of the in vitro, in vivo experimental data, as well as of the epidemiological studies, today anthocyanins and their metabolites are also regarded as potential pharmaceutical compounds providing various beneficial health effects on either human or animal cardiovascular system, brain, liver, pancreas and kidney. Many of these effects are shown to be related to the free-radical scavenging and antioxidant properties of anthocyanins, or to their ability to modulate the intracellular antioxidant systems. However, it is generally overlooked that instead of acting exclusively as antioxidants certain anthocyanins affect the activity of mitochondria that are the main source of energy in cells. Therefore, the aim of the present review is to summarize the major knowledge about the chemistry and regulation of biosynthesis of anthocyanins in plants, to overview the facts on bioavailability, and to discuss the most recent experimental findings related to the beneficial health effects emphasizing mitochondria.

KEYWORDS

Biosynthesis; bioavailability and metabolism; neuro- and cardioprotection; hepatoprotection; kidney and pancreas; oxidative phosphorylation

Introduction

Anthocyanins are water-soluble pigments that provide blue, purple and red color for various parts of plants, especially in fruits and blooms, and are also involved in plant adaptability to environmental factors. They belong to a large subgroup of polyphenols, known as flavonoids. Chemically, anthocyanins are glycosides whose aglycones are polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium salts (Figure 1). Over the last few years these natural compounds have attracted increasing attention due to their potential health benefits. It has been proposed that the consumption of dietary plants and fruits or products rich in anthocyanins can provide potent protective effects on either human or animal brain, liver and kidney, and, moreover, can be of value for the prevention of cardiovascular diseases, obesity control or cancer therapy (Kelly et al. 2017; de Pascual-Teresa 2014; Li et al. 2016; Cassidy 2018; Raj et al. 2017; Smeriglio et al. 2016; Dias et al. 2017; McNamara et al. 2018; Pounis et al. 2018; Giampieri et al. 2018; Blando et al. 2018). Many of these therapeutic effects have been attributed to the radical scavenging and antioxidant activities of anthocyanins. However, recent evidence has suggested that these compounds can also exert an intracellular antioxidant action through the modulation of cellular antioxidant defense systems (Sandoval-Acuña, Ferreira, and Speisky 2014). In addition to the mentioned antioxidant mechanisms of action, there is an increasing interest in the potential of certain anthocyanins and their metabolites to sustain the structural integrity and functional activity of mitochondria that are the main source of energy in cells (Sandoval-Acuña, Ferreira, and Speisky 2014; Teixeira et al. 2018a; Liobikas et al. 2016). Moreover, mitochondria are also regarded as the convergence center of multiple extra- and intracellular signaling pathways leading to cell death or survival. Thus, the development of mitochondria-targeted polyphenolic-based compounds intended to prevent mitochondrial damage and sustain their functions could be regarded as a promising pharmacological strategy. Therefore, the present review will summarize the principal knowledge about the chemistry, biosynthesis and bioavailability of anthocyanins, and discuss the most recent experimental findings related to the health benefits emphasizing mitochondria.

Natural sources of anthocyanins

Anthocyanins occur in all plant tissues, however, an extensive amount of anthocyanins is produced in fruits and vegetables. Typical consumption of anthocyanins is 9 mg/day on average in the United States, and the main sources of anthocyanins include berries (39%), wine (18%), banana (12%),

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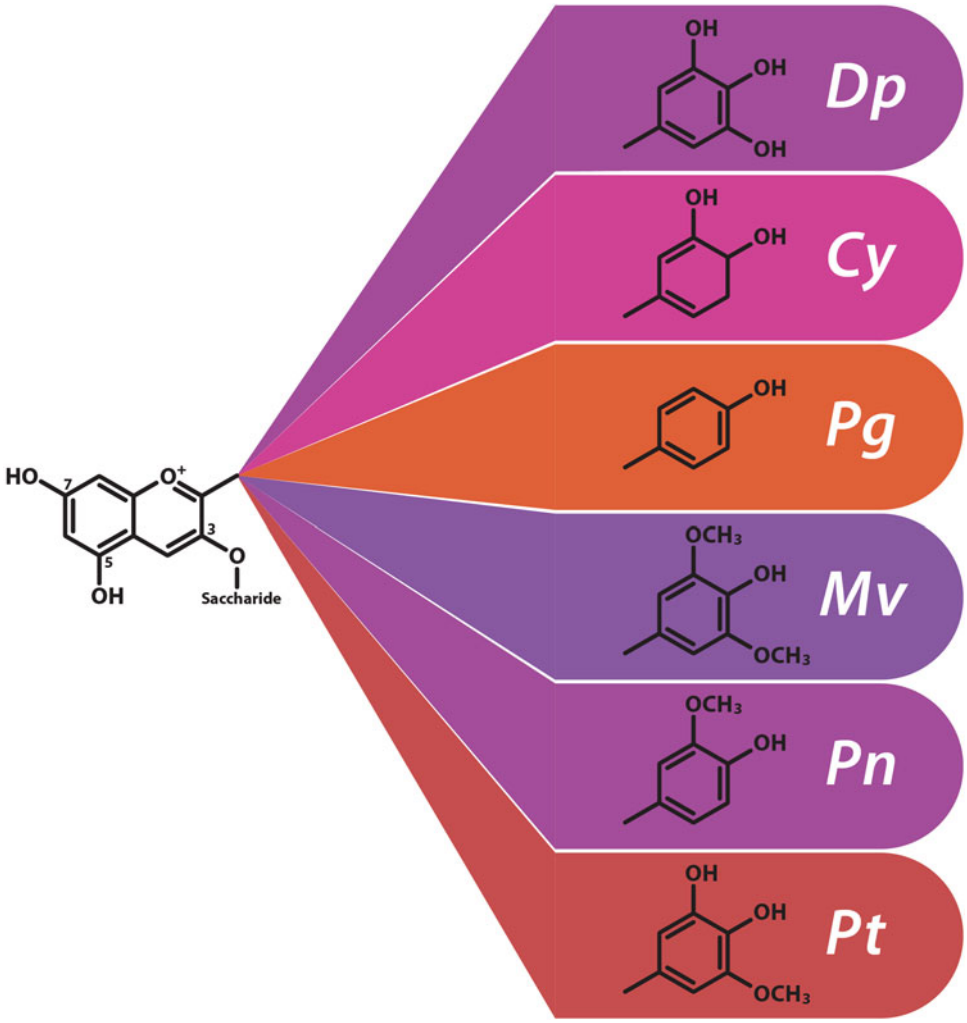

Figure 1. Chemical structure of anthocyanidin 3-*O*-glycosides. Dp, delphinidin; Cy, cyanidin; Pg, pelargonidin; Mv, malvidin; Pn, peonidin; Pt, petunidin; Saccharide, glucose, rutinose (rhamnosyl glucose), arabinose, galactose, sambubiose (xylosyl glucose) or xylose.

vegetables (9%), fruits (9%) and other food sources (Kim, Vance, and Chun 2016). In Europe the usual consumption of anthocyanins is higher corresponding to 19 mg/day, and even constituting 28 mg/day in some countries (Vogiatzoglou et al. 2015), whereas the main sources of anthocyanins are similar: berries (43%), wine (22%), pome fruits (19%) and other food sources. The largest proportion of anthocyanins in human diet comes from berries of *Vaccinium*, *Ribes*, *Prunus*, *Sambucus*, which contain a particularly high amount of anthocyanins (Table 1).

However, the amount of anthocyanins in berries varies from 10 mg/100 g fresh weight (FW) in wild strawberry to 772.4 mg/100 g FW in bilberry (Table 1). Thus, the amount and composition of anthocyanins may vary depending on the cultivar or the ripening stage, and the synthesis in berries may be affected by temperature, UV-B or light wavelength (Wang et al. 2016; Mattila et al. 2016; Bendokas et al. 2017; Jaakola et al. 2017; Pervaiz et al. 2017; Silva et al. 2017; Stanys et al. 2019).

Modulation of anthocyanin synthesis in plants

Anthocyanins are produced in a specific branch of the flavonoid pathway, and their synthesis, which is regulated at different levels, starts from phenylalanine conversion to cinnamic acid (Figure 2) which through a series of reactions catalyzed by cinnamate 4-hydroxylase (C4H) and 4-coumaroyl CoA ligase (4CL) is transformed into the main anthocyanin precursor 4-coumaroyl CoA. Then, a molecule of 4-coumaroyl CoA and three molecules of malonyl CoA are condensed into chalcones by chalcone synthase (CHS). Subsequently, a cascade of enzymatic reactions results in the production of principal anthocyanins (Rahim, Busatto, and Trainotti 2014; Rahim et al. 2018; Zhang et al. 2014).

The expression of anthocyanin-specific genes is regulated by the conserved MYB-bHLH-WD40 (MBW) complex of transcription factors, the regulatory proteins that modulate the expression of specific groups of genes. MBW complex is composed of the transcription factors characterized by the R2R3-type MYB domain (MYB), basic helix-loop-helix (bHLH), and WD40-Repeat protein (WD40) subunits. However, in different plant species the composition of this complex varies. Various MBW complexes differentially regulating the synthesis of anthocyanins in different plant tissues are assembled when cytosolic, constant member of the complex WD40 protein associates with different members of MYB and bHLH families. MYB is the main family of the transcription factors that are implicated in inhibition or

Table 1. Individual amount of anthocyanins (mg 100 g^{-1} of fresh weight [FW]) in berries.

Source	Maximum anthocyanin amount mg/100 g FW	Dominant anthocyanins	Reference
Bilberry	772.4	Dp3gal, Dp3glc, Dp3ara, Mv3glc, Cy3gal, Cy3glc, Cy3ara	(Veberic et al. 2015)
Blackberry	130.2	Cy3glc, Cy3rut, Cy3xyl	(Ivanovic et al. 2014)
Blackcurrant	478.6	Dp3rut, Cy3rut, Dp3glc, Cy3glc	(Šikšnianas et al. 2013)
Chokeberry	401.5	Cy3gal, Cy3glc, Cy3ara, Cy3xyl	(Veberic et al. 2015)
Elderberry	580.0	Cy3sam, Cy3glc	(Mikulic-Petkovsek et al. 2014)
Golden currant	615.5	Cy3rut, Cy3glc, Pn3rut	(Šikšnianas et al. 2013)
Gooseberry	379.2	Cy3rut, Cy3glc, Dp3glc, Dp3rut	(Šikšnianas et al. 2013)
Redcurrant	66.7	Cy3glc, Cy3rut, Cy3sam	(Šikšnianas et al. 2013)
Sour cherry	147.0	Cy3rut	(Bendokas et al. 2017)
Sweet cherry	244.0	Cy3rut, Pn3rut	(Blackhall et al. 2018)
Wild strawberry	10.0	Pg3glc, Cy3glc	(Rugienius et al. 2016)

Cy, cyanidin; Dp, delphinidin; Mv, malvidin; Pg, pelargonidin; Pn, peonidin; ara, arabinoside; gal, galactoside; glc, glucoside; rut, rutinoside; sam, sambubioside; xyl, xyloside.

activation of gene transcription in plant kingdom (He et al. 2018; Henry-Kirk et al. 2018; James et al. 2017; Liu et al. 2017; Sun et al. 2018). It is worth mentioning that proteins of MYB family are the most plentiful and the most variable members of the MBW complex participating in the regulation of secondary metabolism, signal transduction, development, and other pathways (Starkevič et al. 2015). Regulation of anthocyanin biosynthesis genes is different in monocotyledonous and dicotyledonous plants. Thus, MBW complex regulates anthocyanin biosynthesis genes as one unit in monocotyledons. In dicotyledons, for example *A. thaliana*, early biosynthesis genes can be activated only by MYB transcription factors, and late biosynthesis genes are activated by MBW complex (Rahim et al. 2018) (see Figure 2).

Anthocyanin synthesis and accumulation are also controlled by epigenetic changes in plants, by regulation of gene expression, and by post-translational modifications of proteins modulating the transcription factor activity (Maier et al. 2013; Guerra et al. 2015; Wang et al. 2015; Zhang et al. 2016; Zhou et al. 2017; Gao et al. 2018; Nabavi et al. 2018).

Bioavailability for human health

The unique pharmacokinetics of anthocyanins

Upon ingestion of anthocyanin-rich food or pure molecules, a few minutes later anthocyanins appear in plasma in tiny amounts (<100–200 nM) (Pojer et al. 2013; Celli, Ghanem, and Brooks 2017). This absorption pattern distinguishes anthocyanins from other flavonoids, which later appear in plasma as glucuronides or sulfate esters. Indeed, anthocyanins are not substrates of either cytosolic β-glycosidase (Berrin et al. 2002) or membrane-bound lactase-phlorizin hydrolase (Németh et al. 2003), the essential enzymatic step prior to second-phase metabolism.

Anthocyanins are structurally complex hydrophilic molecules (see Figure 1). Hence, they cannot passively diffuse across biological membranes at a rate observed in vivo (Kell 2015). Rather, one or more membrane transporters expressed on the digestive epithelium must be in place to control their net flux across the digestive epithelium towards the blood, as to be discussed later on. In addition, a quick appearance of anthocyanins in blood may result from their gastric absorption (Passamonti 2019).

The "fitness" of anthocyanins for the stomach is manifested at all levels of the stomach. In the acidic gastric juice, they occur as flavylium cations, i.e., the most stable species. The negatively charged mucus layer favors charge interactions with flavylium cations and their electrostatic guidance towards the epithelial surface (Passamonti 2019). The latter is made by a single layer of cells resting on a highly vascularized submucosa. Some cell types (i.e., surface mucous cells and acid-secreting parietal cells) express bilitranslocase, the anthocyanin-specific membrane transporter (Zuperl et al. 2011), and a limited number of other membrane transporters. The process of absorption continues in the intestine (Williamson, Kay, and Crozier 2018).

The time of maximal plasma concentrations has been calculated in the range of 0.5–2 hours (T_{max}) by applying a physiologically-based, multi-compartmental pharmacokinetic (PBMK) model to data from manifold experiments (Celli, Ghanem, and Brooks 2017). The same pattern was again observed with pure Cy3glc administered orally to human volunteers and followed by its ^{13}C labeling (de Ferrars et al. 2014). After T_{max}, anthocyanins disappear from plasma as fast as they appear. Noteworthy, catabolites of parent anthocyanins such as protocatechuic acid and vanillic acid were detected as early as the parent compounds (Mueller et al. 2017; de Ferrars et al. 2014), which suggests that peak plasma concentrations (C_{max}) might be underestimated as a consequence of delayed timing of blood sampling. Indeed, when pure Cy3glc was intravenously administered in the rat (Fornasaro et al. 2016), so to bypass the gastro-intestinal absorption step, it disappeared very rapidly: in 15 s after the injection its plasma concentration was only 52% of the injected dose, and a number of methylated metabolites were co-detected, indicating a rapid distribution into other organs and simultaneous efflux as second-phase metabolites. The pharmacokinetic parameters enabled to estimate that 0.2% of Cy3glc was present in plasma, while 99.8% was distributed beyond plasma. Thus, under these conditions it is probably impossible to accurately estimate the bioavailability in vivo, because the parent compound and/or its catabolites may be sequestered in tissues (Fang 2014; Lila et al. 2016). A recent human study showed that retention of anthocyanins prior to a "wash-out" period influenced both their

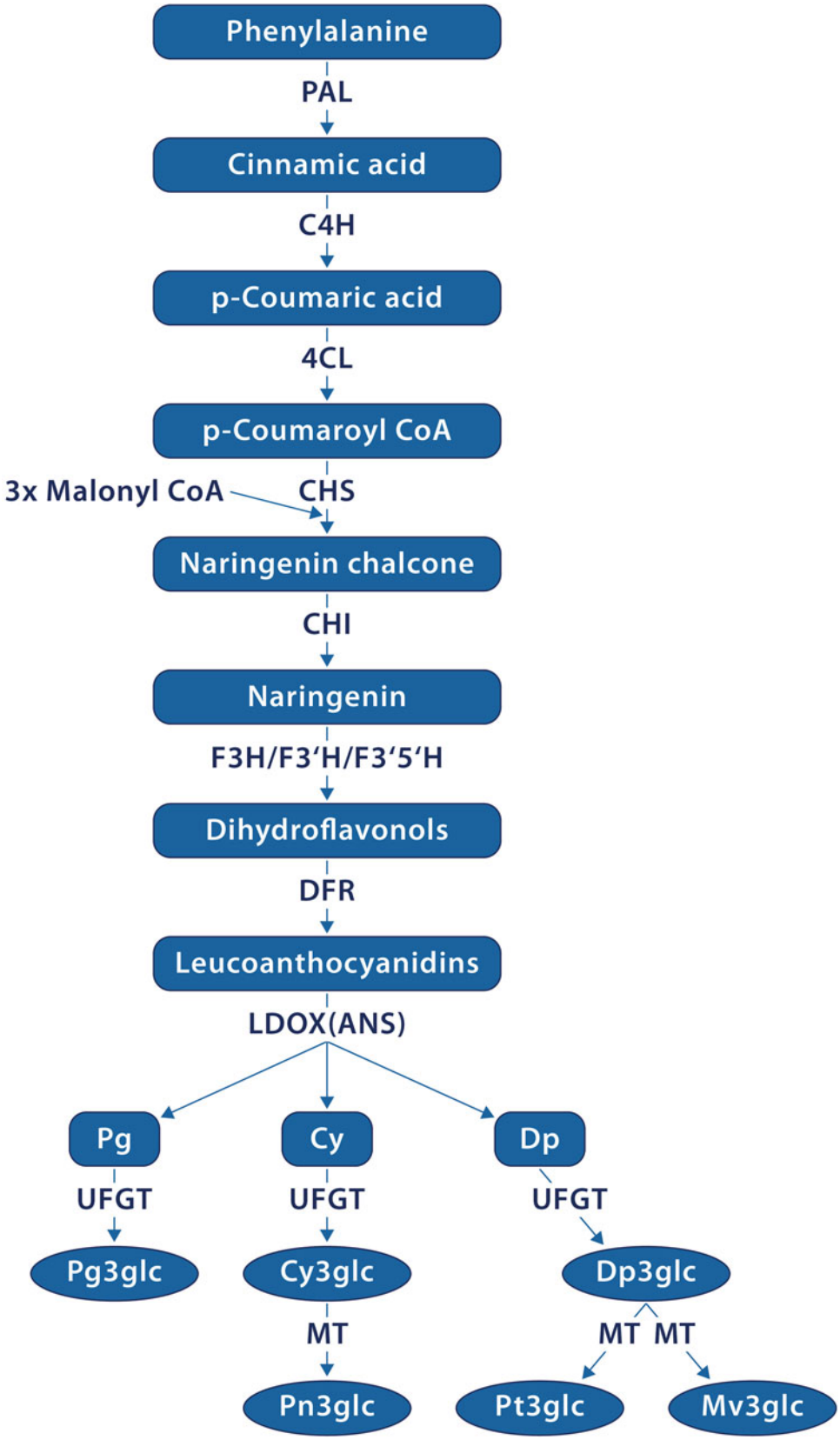

Figure 2. Scheme of anthocyanin biosynthesis via phenylpropanoid pathway. Amino acid phenylalanine is converted into the main anthocyanin precursor 4-coumaroyl CoA by phenylalanine ammonia lyase (PAL), cinnamate 4-hydroxylase (C4H) and 4-coumaroyl CoA ligase (4CL) catalyzed reactions. Then three molecules of malonyl CoA and a molecule of 4-coumaroyl CoA are condensed into naringenin chalcone by chalcone synthase (CHS). Subsequently, the series of reactions resulting in certain anthocyanidins are catalyzed by chalcone isomerase (CHI), flavanone 3-hydroxylase (F3H), flavonoid 3-hydroxylase (F3′H), flavonoid 3′5′-hydroxylase (F3′5′H), dihydroflavonol 4-reductase (DFR), and leucoanthocyanidin dioxygenase (LDOX) also known as anthocyanidin synthase (ANS). Finally, pelargonidin (Pe3glc), cyanidin (Cy3glc) and delphinidin 3-*O*-glucosides (Dp3glc) are produced by UDP-flavonoid glucosyl transferase (UFGT), whereas peonidin (Pn3glc), petunidin (Pt3glc) and malvidin 3-*O*-glucosides (Mv3glc) are produced by methyltransferase (MT) from their appropriate precursors. The regulation of anthocyanin biosynthesis is performed by a so called MBW complex, a complex of transcription factors: MYB (R2R3-MYB), bHLH (basic helix-loop-helix) and WD40 repeats. All those genes itemized above are regulated by the whole MBW complex in monocotyledons. However, in dicotyledons, the early biosynthesis genes like *CHS, CHI and F3H* are regulated solely by MYB, whereas the late genes (*F3′H*, *DFR*, *LDOX* (*ANS*) and *UFGT*) are regulated by MBW complex (detailed in Rahim et al. 2018).

absorption and elimination, thus contributing to individual variability of bioavailability parameters (Kalt et al. 2017).

An extensive target tissue of anthocyanins is the vascular endothelium, where they are transported by bilitranslocase (Maestro et al. 2010; Ziberna et al. 2012, 2013a, 2013b), and can activate endothelial nitric oxide synthase signaling as well as reduce oxidative stress (Cutler, Petersen, and Anandh Babu 2017). As a result, anthocyanins act as vasodilating agents (Fairlie-Jones et al. 2017). However, they can also be transported into cardiomyocytes and protect them against oxidative stress (Liobikas et al. 2016; Petroni et al. 2017).

Perhaps the most striking demonstration of the capacity of anthocyanins to distribute in tissues and organs is their detection in the brain of living animals that received anthocyanins via diverse routes of administration (Passamonti et al. 2005; Chen et al. 2015; Kalt et al. 2008; Janle et al. 2010; Fornasaro et al. 2016). Both the blood–brain barrier and neurons are selectively permeable to these molecules which attenuate oxidative stress, modulate cell signaling and ultimately counter neurodegeneration (Pacheco et al. 2018; Ali et al. 2018; Khan et al. 2019).

The urinary elimination of anthocyanins is also extremely rapid. In humans, orally administered Cy3glc appeared in the urine, together with a number of metabolites and catabolites, as early as in blood, i.e., 30 min after ingestion (de Ferrars et al. 2014). In rats, Cy3glc and other methylated metabolites were co-detected already 15–20 s after an intravenous injection (Vanzo et al. 2011; Fornasaro et al. 2016). Indeed, very quickly Cy3glc was already found in the kidney with different degrees of conversion to Pn3glc and other methylated species (Vanzo et al. 2011; Fornasaro et al. 2016). Anthocyanins are also excreted in the bile (Talavera et al. 2003; Vanzo et al. 2011), and may establish enterohepatic circulation (Hashimoto, Han, and Fukushima 2017). Both in the urine and in the bile the concentration of Cy3glc and Pn3glc are 30–90 times higher than in the renal and hepatic parenchyma which shows that anthocyanins are transported against their concentration gradient by the primary active transporters (Vanzo et al. 2011).

Membrane transporters as molecular factors of anthocyanin bioavailability

The activity of specific membrane transporters is a requirement for the diffusion of anthocyanins across biological membranes and cellular barriers. Indeed, these molecules are stereo-chemically complex, with an absolutely hydrophilic moiety, i.e., the glycosyl adduct. Even for lipophilic or amphipathic molecules biological membranes constitute more a trap than a pathway towards new compartments (Kell 2015). So far, research on anthocyanin-specific transporters has been very limited. Bilitranslocase was the first described anthocyanin-specific transport mechanism. Drug screening enabled to build up a QSAR model that was based on the property of the transporter to establish a network of hydrogen bonds with transport substrates in the planar configuration afforded by the quinoidal tautomer (Zuperl et al. 2011). The role of the bilitranslocase-mediated membrane transport of anthocyanins has been demonstrated in vascular endothelial cells (Maestro et al. 2010), in isolated porcine coronary artery rings (Ziberna et al. 2013b), and in isolated rat hearts (Ziberna et al. 2013a). As mentioned above, bilitranslocase is expressed in stomach epithelium, and on the brush border of small intestine as well (Passamonti et al. 2009).

Other studies tested the effect of anthocyanins on glucose uptake in Caco-2 cells, and outlined the inhibition under different conditions that allowed to speculate that GLUT2 may be involved in the intestinal absorption of anthocyanins (Faria et al. 2009). It has been shown that Cy3glc was taken up by both sodium-dependent (SGLT1) and sodium-independent (GLUT2) glucose transporters in Caco-2 cells (Zou et al. 2014), however, the results were in disagreement with the previous ones obtained with jejunum patches mounted on Ussing chamber (Walton et al. 2006). Hence, a different uptake system in the intestine was claimed (Walton et al. 2006). Nevertheless, in both models (Caco-2 cells and jejunum patches) uptake rates were slow and did not match the observed in vivo pharmacokinetic features (de Ferrars et al. 2014), which revealed a super-fast absorption of Cy3glc. The role of glucose transporters was put in doubt by the demonstration that anthocyanins acted as noncompetitive glucose uptake inhibitors (Manzano and Williamson 2010; Kottra and Daniel 2007), which means they were not engaged in the active site of glucose transporters. Altogether, anthocyanins rather seem to act as both inhibitors and regulators of intestinal glucose absorption (Alzaid et al. 2013) and post-prandial glycemia (Dreiseitel et al. 2009).

Regarding primary active transporters expressed on the luminal side of the intestinal cells, a study demonstrated that several anthocyanins and anthocyanidins interacted with Breast Cancer Resistance Protein ABCG2, which suggests that they may be transported from the cells back to the lumen, and thus their bioavailability is limited (Dreiseitel et al. 2009).

Metabolites and catabolites of anthocyanins

Anthocyanins are rapidly metabolized by methylation of the B ring, arguably in all tissues where they can be transported and where the enzyme catechol *O*-methyltransferase (COMT) is expressed; the methyl group donor S-adenosyl methionine must also be available. Methylation of Cy3glc to Pn3glc (and other congeners) was detected in excretory organs, liver and kidney only after 15 s following an intravenous injection (Fornasaro et al. 2016). These methylation products were simultaneously found in blood, which suggests that they were transported from tissues back to the circulation by a high-performing membrane transporter (presumably bilitranslocase (Vanzo et al. 2008)). It is noteworthy that within 1 min the cellular uptake of Cy3glc, methylation to Pn3glc and efflux back to the medium was displayed in vascular endothelial cells, too (Ziberna et al. 2012). Glucurono- and sulfo-conjugates of Cy3glc were also

found in blood some time later after the administration (Williamson, Kay, and Crozier 2018).

When pure Cy3glc was administered to humans (de Ferrars et al. 2014), glucuronides (and no sulfates) of Cy and methyl-Cy were detected only in urine. In serum, next to the parent compound, two catabolites ("degradants") were identified, i.e., protocatechuic acid and pholoroglucinaldehyde. The first gave rise to 13 derivatives, with vanillic acid and hippuric acid being the main ones. Pholoroglucinaldehyde produced a single catabolite, i.e., ferulic acid. Other nine catabolites were detected in the urine and feces, but not in the serum. The fact that Cy3glc constituted only 2% of the sum of its catabolites detected in the serum embodies the most significant outcome of this study, i.e., anthocyanin concentration values in serum and urine provide an incomplete picture of anthocyanin oral bioavailability (Kay et al. 2017). Even more, vanillic acid and hippuric acid were identified in the serum at their maximal concentration after 30 min following the ingestion of the parent compound, when the latter was not yet or no longer detectable (de Ferrars et al. 2014). Indeed, it is speculated that anthocyanins undergo ring fission and conversion to phenolic fragments in the small intestine, either in its lumen or epithelium (Kay et al. 2017). Moreover, Cy3glc reappears in the circulation only when the metabolizing capacity of the target tissues is saturated or exhausted (de Ferrars et al. 2014). Noteworthy, an estimation of anthocyanin bioavailability and distribution within various organs can be derived only from studies on experimental animals. A recent systematic review (Sandoval-Ramirez et al. 2018) has noted the kidneys, liver and lungs as the organs with the highest capacity to accumulate these pigments (up to 0.1 µmol/g of tissue), whereas the heart and the brain can retain some nmol/g of tissue. However, the experimental data suggest (as it is presented below) that the level of anthocyanins together with their metabolites reached at various subcellular compartments, e.g., in the vicinity of or even within mitochondria, might be sufficient to modulate the activity of intracellular targets.

Targeting mitochondria

Neuroprotective activity at mitochondrial level

Epidemiological evidence suggests that diets containing fruits rich in anthocyanins and proanthocyanidins may reduce the risk of neurodegenerative diseases and cognitive decline (Gao et al. 2012; Krikorian et al. 2010). As mentioned above, anthocyanins have been detected in the brain tissue, which indicate that they are able to cross the blood-brain barrier (Fornasaro et al. 2016). Scientific literature highlights various mechanisms by which anthocyanins may exert neuroprotective effects, including pro-survival signaling pathway activation, suppression of microglial activation and neuroinflammatory processes (Zhang et al. 2019). The focus of this sub-chapter is on the less investigated field, i.e., the interactions of anthocyanins with mitochondria, and how such effects may be beneficial for neuronal survival in various pathological states.

In general, the effects of anthocyanins on mitochondria can be ascribed to their antioxidant properties, and this is often considered to be the main biological effect of these compounds. Oxidative and nitrosative stress, particularly when it is long-lasting, has been implicated in the pathogenesis of various neurodegenerative diseases. An excessive generation of reactive oxygen (ROS) or nitrogen species (RNS) that is not counteracted by cellular antioxidant defense system creates oxidative or nitrosative stress. Brain tissue is especially sensitive to ROS and RNS due to its high oxygen demand and relatively low antioxidant defense capacity, which becomes even more depleted with aging (Ataie, Ataie, and Shadifar 2016; Kelly, Vyas, and Weber 2017). It is worth to note that aging is considered one of the main risk factors for most of the neurodegenerative diseases. Chemical structure of anthocyanins (aromatic rings with one or several hydroxyl groups) allows them to accept unpaired electrons from ROS or RNS. Thus, anthocyanins are considered to be involved in the detoxification of ROS/RNS that come from mitochondria as one of the important sources of ROS generation (Brown and Borutaite 2012). Moreover, polyphenols with the structure similar to anthocyanins were evidenced to accumulate in mitochondria (Fiorani et al. 2010; Schroeder et al. 2009) suggesting that anthocyanins might also be suitable for the removal of toxic mitochondrial ROS/RNS. Several studies have reported that anthocyanins or anthocyanin-rich extracts may prevent neuronal death by scavenging mitochondrial ROS. At the cellular level, Cy3glc was shown to be able to prevent glutamate-induced neuronal death by inhibiting glutamate-induced Ca^{2+} overload, ROS generation and mitochondrial depolarization (Yang et al. 2015). Similar prevention of mitochondrial depolarization in primary cortical neurons exposed to oxygen and glucose deprivation was reported for mulberry Cy3glc (Bhuiyan et al. 2011) and black soybean Cy3glc (Bhuiyan et al. 2012). Another study on excitotoxic neuronal death induced by kainic acid (a non-degradable analog of glutamate and an agonist of AMPA/kainate receptors) demonstrated that anthocyanins extracted from black soybeans prevented Ca^{2+} overload, mitochondrial depolarization and ROS generation as well as neuronal death (Ullah, Park, and Kim 2014). At the animal level, orally consumed Cy3glc, that was isolated and purified from cherries, revealed a neuroprotective effect in the cerebral artery occlusion model of ischemia in mice, as it reduced brain superoxide levels, infarct size, and improved neurological functions (Min et al. 2011). In addition, Cy3glc was found to be almost equally protective when applied before or after ischemic insult. These findings suggest the potential anthocyanin use in clinical therapeutic stroke interventions.

Besides the direct scavenging of ROS, anthocyanins have been shown to act as mild uncouplers of the oxidative phosphorylation system (Skemiene et al. 2013) causing a mild mitochondrial depolarization which may prevent ROS generation by mitochondria, as ROS production depends on the mitochondrial membrane potential. In this respect, Dp3glc was found to be the most effective uncoupler in the micromolar range of concentrations, although other compounds

like Cy and Cy3rut (but not Cy3glc or Pg3glc) at concentrations higher than 50 μM also increased the non-phosphorylating (Leak) respiration which is an indicator of uncoupling (Skemiene et al. 2013; Liobikas et al. 2016). Whether such mechanism of anthocyanin action is valid in neuronal cells promoting their survival has not yet been experimentally confirmed.

It is worth to note that anthocyanins and other flavonoids in the in vitro studies exert protective effects in the range of relatively low (1–20 μM) concentrations, which do not correlate with their free radical scavenging capacities (Skemiene et al. 2013; Nichols et al. 2015; Lagoa, Samhan-Arias, and Gutierrez-Merino 2017). This observation indicates that these compounds may have a more specific mechanism than mere general antioxidant actions in cells. There is also a possibility that the modulation of certain signaling pathways of cell death and pro-survival regulation that may involve mitochondria. In isolated cortical neurons from adult mouse brain Cy3glc has been shown to protect mitochondria specifically against apoptosis inducing factor (AIF) release but not against cytochrome c release (Min et al. 2011). Anthocyanins and anthocyanin-rich fruit extracts have been shown to exert neuroprotective effects in Parkinson's disease (Strathearn et al. 2014) and beta amyloid-induced toxicity in Alzheimer's disease models (Brewer et al. 2010; Fuentealba et al. 2011) at least partially by mechanisms involving interactions with mitochondria. A study by Strathearn et al. (2014) used rotenone-treated midbrain cell cultures as a model of Parkinson's disease. Rotenone suppressed the activity of complex I of the mitochondrial oxidative phosphorylation system, the dysfunction of which is thought to be involved in Parkinson's disease pathogenesis. It was indicated that certain anthocyanins (Mv, Cy and Dp glycosides) and anthocyanin-rich fruit extracts were more effective in preventing rotenone-induced neuronal death than extracts enriched with other polyphenolic compounds (Strathearn et al. 2014). The protective effect of anthocyanins was found to be related to the amelioration of rotenone-induced mitochondrial dysfunction, which might be due to the displacement of rotenone from its binding site on mitochondrial complex I and the prevention of ROS production (Strathearn et al. 2014; Lagoa et al. 2011). However, there may be other explanations for the protective effect of anthocyanins. For example, Cy3glc and Dp3glc have been shown to serve as electron acceptors from complex I stimulating NADH oxidation by NADH dehydrogenase (Skemiene, Liobikas, and Borutaite 2015). With regard to this mechanism of action anthocyanins may overcome the rotenone-induced inhibition of complex I and support oxidative phosphorylation in mitochondria. Therefore, anthocyanins acting as substrates for complex I and transferring electrons to cytochrome c in the mitochondrial electron transfer system may provide neuroprotective effects not only in Parkinson's disease, but also in the brain affected by ischemic stroke where the inhibition of mitochondrial complex I is one of the earliest pathological events (Borutaite, Toleikis, and Brown 2013).

Cardioprotective effects

A number of prospective cohort studies have shown the association between habitual anthocyanin intakes and cardiovascular disease (CD). Coronary heart disease and myocardial infarction were examined in five studies, the four of which revealed that increased habitual intakes of anthocyanins were significantly related to the reduction of CD by 12–32% (Cassidy et al. 2013; McCullough et al. 2012; Mink et al. 2007). There is also evidence suggesting that daily fruit intake decreases systolic blood pressure, blood glucose levels, and decreases incident major coronary events by 34%, while cardiovascular mortality is respectively decreased by 40% (Du et al. 2016). In addition, human feeding studies have shown beneficial effects of anthocyanin-rich foods on blood flow and flow-mediated vasodilation (Hooper et al. 2008). However, there are no data available about the distribution of anthocyanins in human organs.

Thus, anthocyanins were reported to maintain cardioprotective effects, and one of the main mechanisms is to scavenge ROS, although the exact protective mechanism of anthocyanins against oxidative stress remains elusive (Ziberna et al. 2012). Some evidence has been presented that ROS production is associated with the impairment of mitochondrial respiratory chain and inhibition of electron transport through complexes I and II. Fang and colleagues have indicated that Cy3glc restored the activity of mitochondrial complex I and II and significantly attenuated ROS production induced by endotoxin LPS in mice (Li et al. 2018). This observation was further supported by experiments on primary cardiomyocytes when Cy reduced the LPS-induced mitochondrial ROS production (Li et al. 2018). Similar effects of anthocyanins on mitochondrial complex activities were revealed in our previous studies (Skemiene, Liobikas, and Borutaite 2015). On the other hand, important protective effects of certain anthocyanins have been observed in heart ischemia-induced mitochondria-mediated cell death pathway, where the release of cytochrome c (an important element of the electron transport chain) into cytosol is considered to be the central pathological event (Skemiene et al. 2013; Skemiene, Liobikas, and Borutaite 2015). In cytosol cytochrome c can trigger the activation of caspases in apoptosome (Acehan et al. 2002). However, the redox state of cytochrome c is an important factor in the regulation of caspase activation in apoptosome, as it was determined that a reduced form is much less potent than the oxidized form of cytochrome c (Brown and Borutaite 2008). Anthocyanins, as redox-active compounds, are able to reduce cytochrome c, though they differ in their reducing capacity: the highest cytochrome c reducing activity was observed with Dp3glc, Cy3glc and Cy, whereas Mv3glc, Pn3glc and Pg3glc were found to be weak reductants (Skemiene et al. 2013; Lagoa, Samhan-Arias, and Gutierrez-Merino 2017). Cy was found to be a more potent reductant of cytochrome c than ascorbate at the same concentration (Lagoa, Samhan-Arias, and Gutierrez-Merino 2017). Interestingly, anthocyanins with the highest cytochrome c-reducing capacity were revealed to be the best protectors against ischemia-induced apoptosis and necrosis in a perfused heart, though none of the investigated

anthocyanins was able to inhibit the loss of cytochrome c from mitochondria (Skemiene et al. 2013; Skemiene, Liobikas, and Borutaite 2015) suggesting that the reduction of cytosolic cytochrome c by Cy and Dp glucosides might prevent caspase activation and ischemia-induced cell death in the myocardium.

Recent study by Lagoa et al. (2017) has proposed another mechanism of protection against mitochondria-mediated cell death by flavonoids, including anthocyanins. Researchers found that Cy and certain flavonols with high cytochrome c reducing capacity at low micromolar concentrations were able to inhibit the pro-apoptotic cardiolipin-induced peroxidase activity of cytochrome c. Cy was indicated to be the most potent inhibitor of cytochrome c peroxidase activity. As reported by the researchers, pharmacological regulation of cardiolipin-induced peroxidase activity of cytochrome c might become an attractive mechanism for the new mitochondria-targeted anti-apoptotic drugs useful in cardiac pathologies (Lagoa, Samhan-Arias, and Gutierrez-Merino 2017). And anthocyanins are among them.

Health benefits at mitochondrial level in liver, kidney and pancreas

Besides the neuro- and cardioprotective activities anthocyanins have been shown to be beneficial on liver, kidney and pancreas as well (Dias et al. 2017; Mafra et al. 2018). However, scientific studies on the effects of anthocyanins at the level of mitochondria are rather fragmented and scarce. Nevertheless, it could already be proposed that anthocyanins protect mitochondria against oxidative stress acting as ROS scavengers, and, consequently, preserving mitochondrial functions and protecting cells from apoptosis. For instance, it was demonstrated that blueberry anthocyanin-rich extract (with Cy3glc as the main component) protected mice liver mitochondria against acrylamide-induced mitochondrial oxidative stress in vivo by inhibiting the formation of ROS (Zhao et al. 2015). Moreover, the administration of extract resulted in a reduced mitochondrial membrane lipid peroxidation, protected against mitochondrial swelling and diminished the release of cytochrome *c*, recovered the activities of mitochondrial electron transport chain, and thus sustained mitochondrial membrane potential. At the cellular level the hepatoprotective effects of Cy3glc on primary mouse hepatocytes against high glucose-induced apoptosis were associated with the preservation of mitochondrial membrane potential, reduced generation of ROS, inactivation of caspase-3 and -9, and down-regulation of the pro-apoptotic Bax protein (Jiang et al. 2014). In addition, another study on the effects of dietary anthocyanins from strawberries against doxorubicin-induced toxicity in rats (Diamanti et al. 2014) outlined both a significant improvement in liver antioxidant enzyme activities and mitochondrial capacity, and a significant reduction of mitochondrial ROS level. It is worth mentioning that beneficial effects of anthocyanins on mitochondrial functions have been recently identified in human hepatocyte HuH7 and HepG2 cell lines as well (Mogalli et al. 2018; de Sales et al. 2018).

It was also demonstrated that anthocyanins and anthocyanidins may positively affect mitochondrial functions in kidney. Bankoglu et al. (2018) revealed that a 3-deoxyanthocyanin tricetinidin and Dp restored the depolarization of the mitochondrial membrane and stimulated the expression of the antioxidant enzyme heme oxygenase-1, and the increase of the intracellular glutathione level in NRK epithelial rat kidney cells affected by antimycin A and insulin. Anthocyanidin Dp was also found to suppress the high glucose-induced mitochondrial superoxide generation in mouse mesangial CRL-1927 cell culture (Song et al. 2016). Furthermore, it has been recently reported that Cy3glc sustained the mitochondrial membrane potential, decreased the intracellular level of ROS and, consequently, protected human HK-2 cells from high glucose induced apoptosis (Wei et al. 2018).

Besides, Cy3glc has reduced the H_2O_2-induced cell death in mouse MIN6N pancreatic β-cells (Lee et al. 2015). This anthocyanin affected the level of intrinsic apoptotic pathway-associated proteins: it decreased the level of activated caspase 3, sustained Bcl-2 family proteins at the control level, and induced a dose-dependent inhibition of the release of cytochrome c from pancreatic mitochondria. Noteworthy, the authors of the present review would like to highlight that to the best of their knowledge the study performed by colleagues (Cesna et al. 2015) was the first to reveal that treatment with Cy3glc decreased the proliferation rate of ethanol-activated human pancreatic stellate cells, decreased cell oxygen consumption rate and reduced ATP synthesis to the control levels. Thus, the results provided new insights for the usage of Cy3glc in the prevention of pancreatic fibrosis. However, further studies are needed to clarify the anthocyanin action mechanism.

Mitochondria-targeted anthocyanin-based molecules as potential therapeutics

Mitochondria play the key role in the regulation of cellular bioenergetics and metabolic homeostasis, therefore mitochondrial dysfunction contributes to the rise or development of a range of pathologies and diseases (Pagano et al. 2014; Srivastava 2017). Consequently, there is a considerable interest in targeting small molecules to mitochondria in order to ameliorate the mitochondrial dysfunction. Mitochondria are known to be the source of ROS, as well, they are susceptible to oxidative damage. Therefore, the biggest attention has been focused on the development of mitochondria-targeted antioxidants (Finichiu et al. 2015; Pezzini, Mattoli, and Ciofani 2017; Feniouk and Skulachev 2017). In addition, some of the mitochondria-targeted compounds are either phytochemicals as plastoquinone conjugates (SkQs) (Zakharova et al. 2017), or are based on natural (poly)phenols, like MitoApocynin, caffeic acid, curcumin and quercetin (Apostolova and Victor 2015; Teixeira et al. 2017; Teixeira et al. 2018a). Since anthocyanins together with other polyphenols also constitute important dietary components with a potential beneficial effect on mitochondrial functions, the development of mitochondria-targeted

anthocyanin-based antioxidants might be considered as a further challenging task. It has been well documented that the antioxidant activity and chemical stability of anthocyanins are related to the number and position of hydroxyl and methoxyl groups in the flavylium B ring, and to the extent of modifications of a sugar moiety (Zhao et al. 2014; Ereminas et al. 2017; Blando et al. 2018). Hence, the most redox active Dp3glc and Dp3rut were found to be the least chemically stable among the tested anthocyanins (Ereminas et al. 2017). Therefore, the increase in stability and preservation of antioxidant activity of certain anthocyanins might be achieved through the formation of complexes between anthocyanins and selected biodegradable nanocarriers (Klimaviciute et al. 2015; Navikaite et al. 2016). The use of methylated anthocyanins or their metabolites, e.g., Mv3glc and syringic acid that bear sufficient hydrophobicity to cross the cell membrane and reach mitochondria would constitute another option (Skates et al. 2018). Moreover, the synthesis of several mitochondrially targeted derivatives of protocatechuic and gallic acids, which are the major metabolites of Cy and Dp anthocyanins, respectively, has recently been reported (Parihar et al. 2014; Teixeira et al. 2017). These new molecules were found to present a higher lipophilicity than the parent compounds, and similar antioxidant properties. Interestingly, AntiOxBEN$_3$, another mitochondria-targeted derivative of gallic acid besides its prominent antioxidant activity, inhibited the opening of calcium ion-dependent mitochondrial permeability transition pore (mPTP) (Teixeira et al. 2018b). Thus, more mitochondria-targeted polyphenol- or anthocyanin-based multifunctional molecules are likely to be designed and tested in the nearest future.

Concluding remarks and future perspectives

Within the last several years anthocyanins, the water-soluble pigments produced in a specific branch of the flavonoid pathway in plants, have become an object of increasing attention due to their potential health benefits. Many of these effects on brain, heart, liver, kidney or pancreas are attributed to the free-radical scavenging and antioxidant properties of anthocyanins. However, constantly growing experimental data indicate that anthocyanins may have more specific mechanisms than just general antioxidant actions in cells. Thus, they can act as uncouplers of the oxidative phosphorylation system causing a mild mitochondrial depolarization which may prevent ROS generation by mitochondria. Moreover, certain anthocyanins can maintain the activity of electron transport chain, and, consequently, sustain the mitochondrial membrane potential and support ATP production. Anthocyanins, as redox-active molecules, can also be regarded as anti-apoptotic agents preventing mitochondrial apoptotic pathway via their effects on cytochrome c. In addition, the low concentrations of anthocyanins and their metabolites found in serum and tissues appear to be sufficient for these compounds to affect intracellular targets. Thus, all this information aims at encouraging more detailed studies on the application of various anthocyanins and their metabolites to the clinical intervention or prevention of pathological conditions or diseases related to mitochondrial dysfunctions (e.g., ischemic insult, myocardium infarction, neurodegenerative diseases) or to the bypass surgery to prevent ischemia/reperfusion-induced cell death and to support mitochondrial functions. Search for new delivery platforms like encapsulation and complex formation between anthocyanins and nanocarriers in order to increase the stability and bioavailability of anthocyanins in humans are to be stimulated as well (Tan et al. 2018; Mueller et al. 2018; Navikaite et al. 2016; Celli and Brooks 2019). Introduction of chemical modifications to anthocyanins that can facilitate their way to the final intracellular targets might also contribute to the desirable health-promoting effects (Teixeira et al. 2018a). The production of food rich in anthocyanins plays a central role in this strategy, since the enhanced food is the source of anthocyanin-rich extracts for pharmaceutical use or food fortification. To conclude, ample directions and opportunities exist for future research.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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