Chapter

Anthocyanins: Dietary Sources, Bioavailability, Human Metabolic Pathways, and Potential Anti-Neuroinflammatory Activity

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Abstract

The objectives of this chapter are to summarize and discuss (i) the anthocyanins structure and content in foodstuffs and their dietary intake (ii) the anthocyanins bioavailability and human metabolic pathways and (iii) the *in vitro* and *in vivo* potent anti-neuroinflammatory effects of anthocyanins and their metabolites. Indeed, anthocyanins are polyphenolic compounds belonging to the group of flavonoids, and are one of the most commonly consumed polyphenols in a normal diet. They are responsible of red, blue and purple color of several fruits and vegetables and their intake has been related with several human health benefits. The anthocyanins structures diversities as well as their content in various fruits, vegetables and cereals is addressed. Moreover, despite the growing evidence for the protective effects of anthocyanins, it is important to highlight that the *in vivo* bioavailability of these compounds is relatively low in comparison to their more stable metabolites. Indeed, after consumption, these bioactives are subjected to substantial transformations in human body. Phase I and II metabolites generated by intestinal and hepatic enzymatic reactions, and phenolic acids produced by gut microbiota and their metabolized forms, are the most important metabolic anthocyanins forms. For this reason, the study of the biological properties of these circulating metabolites represents a more *in vivo* realistic situation. Although the anthocyanin bioavailability researches in humans are limited, they will be discussed together with a global metabolic pathway for the main anthocyanins. Moreover, several works have demonstrated that anthocyanins can cross the blood brain barrier, and accumulate in brain endothelial cells, brain parenchymal tissue, striatum, hippocampus, cerebellum and cortex. Consequently, the study of anthocyanins as potent therapeutic agents in neurodegenerative diseases has gained relevance and the principal and the most recent studies are also discussed in the book chapter.

Keywords: anthocyanin, metabolites, neuroinflammation, phenolic acids, bioactives

1. Introduction

Anthocyanins (deriving from the Greek *anthos* means flower, and *kyanos* means blue) are one of the most important pigments in the plant kingdom

after chlorophyll. Anthocyanins belong to the widespread family of flavonoid polyphenolic compounds and are responsible of red, purple and blue colors of a great numbers of vegetables and fruits [1]. Although several hundred of natural anthocyanins has been identified (more than 600), they all derived from 31 naturally known anthocyanidins (anthocyanins aglycone) [2, 3]. When looking at the human diet (fruits, vegetables and cereals), the number of anthocyanidins can be reduce to only six different anthocyanidins which are: pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin. Among these, cyanidin represents the most widespread anthocyanidin in plants (50%). Cyanidin, delphinidin and pelargonidin are the non-methylated anthocyanidins whereas peonidin, malvidin and peonidin possess *O*-methylation. However, as free aglycones are considerable unstable, anthocyanins (the glycosylated forms) are more usually present in natural sources [1, 4].

Apart of being responsible for the color of many foods and beverages, anthocyanins also have numerous health benefits resulting of their antioxidant and anti-inflammatory activities, among others. Although the dietary intake of anthocyanins depends on the nutritional habits [5], they have received less attention than other flavonoids compounds. This may be due to the fact that anthocyanins are poorly absorbed, highly metabolized, and rapidly excreted in the urine [6]. In addition, their bioavailability and the metabolites formed by intestinal, hepatic enzymatic reactions, and gut microbiota depend on the chemical structure of anthocyanin.

This book chapter will summarize and discuss (i) the anthocyanins structure and content found in fruits, vegetables and cereals as well as the global dietary intake (ii) the anthocyanin bioavailability and human metabolic pathways and (iii) the *in vitro* and *in vivo* anti-neuroinflammatory effects of anthocyanins and their metabolites.

2. Anthocyanins: chemistry, intake and dietary sources

From a structural point of view, anthocyanins are glycosylated, polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium (or flavylium cation) containing two benzoyl rings (A and B) separated by a heterocyclic (C). The number of hydroxyl groups and their degree of methylation, the nature and number of the sugar and the position of the attachment, as well as the nature and number of aliphatic or aromatic acids attached to the sugars, determine their different structural variations [3, 7].

Regarding sugars, they can be attached at different positions: 3-monoglycosides, 3-diglycosides, or 3-triglycosides, 3,5-diglycosides and to a lesser extent 3,7-diglycosides. Glucose is the most common sugar moiety but other monosaccharides as rutinoside, rhamnose, galactose, arabinose, xylose are found. Furthermore, the disaccharides as sambubioside or sophoroside and as well as trisaccharides like as xylosilrutinoside or glucosylrutinoside can also be present [8, 9]. The linking of acyl substituents to sugars make possible a further degree of complexity of anthocyanins. Among them, aliphatic (acetic, malonic, succinic, malic) and cinnamic acids (*p*-coumaric, ferulic, sinapic) are the most predominant [10]. Both glycosylation and acylation affects the chemical and physical properties of anthocyanins. Thus, glycosylation improves water solubility whereas acylation have the contrary effect [11].

Anthocyanins are sensible to different factors such as temperature, light, oxygen or enzymes but pH represent one of the most important factors affecting them. Four different equilibrium species can co-exist, the flavylium cation (red; pH 1),

the quinonoidal base (bleu, pH 4), the carbinol pseudobase (colorless or pale yellow, pH 5) and the chalcone (–*cis* and -*trans*) (colorless; pH 6). At pH values higher than 7, anthocyanis are degraded. Generally, anthocyanins are more stable and more soluble at low pH [12]. Among anthocyanidins, pelargonidin is the most stable compounds because of its B ring substituents and the presence of hydroxyl or methoxyl groups decrease the stability. However, the glycosylation confers to the molecules a higher stability at neutral pH, since the presence of sugar avoid the degradation into phenolic acid and aldehyde compounds [13].

The determination of the dietary intake of flavonoids, and among them, the mean consumption of anthocyanins has been the subject of several studies over the last two decades. In United States the daily consumption of these compounds in adults has been estimated in 12.5 mg/day, representing cyanidin anthocyanins the 44.7% of the total intake followed by delphinidin, malvidin, petunidin, peonidin and pelargonidin anthocyanidins [14]. Another study in adults (17900 individuals) showed a lower anthocyanidin intake, 9.20 ± 0.79 mg/day. In addition, they stated differences among anthocyanin consumption according to gender (women's consume higher anthocyanins than men's) and sociodemographic and lifestyle factors such as education, alcohol consumption and activity levels [15]. Concerning European data, the European Prospective Investigation into Cancer and Nutrition (EPIC) study estimated a mean of anthocyanin intake of 31 mg/day. At the same time, they also observed that these values vary according to the country, age, sex, body mass index (BMI), level of education, smoking status and physical activity level [5]. Between European countries, significant differences were reported. Indeed, Italy, France and Germany displays the greater mean values, from 35.1 to 42.3 mg/day, whereas Netherlands and Sweeden are the countries with a lower anthocyanin consumption (22.6 and 20.9 mg/day, respectively). More recently, after the study of the dietary habits of 30000 subjects in 14 European countries the mean intake of anthocyanins was estimated to be 19 mg/day [16]. In other continents and countries such as Australia (12153 subjects) or China (1393 subjects) the estimated anthocyanin mean intake was calculated at 24.2 mg/day and 27.6 mg/day, respectively, which are very closed values to European levels [17, 18].

Apart of being present in many colored fruits and vegetables they appeared also in beverages as red wine or juices and in processed foods as jams. Both, the type and the concentrations of anthocyanins are influenced by genetics (cultivar, species), cultivation, climate, soil, and processing [19]. However, one of the best sources of anthocyanins are berries. Among them, bilberries, blueberries and blackcurrants can be reach values greater than 1000 mg/100 g of fresh weight (FW) (**Table 1**). Among vegetables and cereals, red cabbage, cauliflower and colored corn and rice represent good sources of anthocyanins. The most common anthocyanins are cyanidin glucosides, but some fruits contain other predominant anthocyanin (**Table 1**). For example, pelargonidin-3-*O*-glucoside is the principal anthocyanin of strawberries, whereas malvidin-3-*O*-glucoside predominates in grapes and cyanidin-3,5-diglucoside is the major one in pomegranates [29–31]. Generally, the main anthocyanins in vegetables and cereals are chemically more complex in comparison with fruits. In fact, acylated and diglucosylated anthocyanins such as cyanidin-3-(*p*-coumaroyl)-diglucoside-5-glucoside can be found [33]. In addition, others less conventional sugars like sophoroside (cauliflower and radish) or laminiaribioside (red onions) can be present [35, 36, 39]. Interestingly, the most common anthocyanin type in sorghum, are the 3-deoxyanthocyanidins luteolinidin and apigeninidin (characterized by the lack of hydroxyl group at C3 position) and their derivatives, which are not commonly found in higher plants [44].

Fruit	**Content**	**Main anthocyanin**	**Ref**
Apples (Red)	0.1–315 mg/Kg peel	Cy-3-gal	[20]
Apricot	1.9–230.4 mg/100 g FW	Cy-3-rut	[21]
Bilberry	933–1017 mg/100 g FW	Delp-3-gluc/ Delp-3-ara/ Delp-3-gal	[22, 23]
Blackberry	84–201 mg/100 g FW	Cy-3-gluc/ Cy-3-rut	[24]
Blueberry	232–438 mg/100 g FW	Mv-3-gluc/ Mv-3-gal/ Delp-3-gal/ Delp-3-ara	[22]
Cherry	6.3–60 mg/100 g FW	Cy-3-gluc/ Cy-3-rut	[25, 26]
Cranberry	12.4–207.3 mg/100 g FW	Cy-3-gal / Cy-3-ara/ Peo-3-gal / Peo-3-ara	[27]
Blackcurrant	146.15–403.66 mg/100 g FW	Cy-3-rut/Cy-3-gluc/Delp-3-rut/ Delp-3-gluc	[28]
Red grapes	11.5–29.8 g/Kg DM	Mv-3-gluc/ Mv-3-acetylgluc (*V. vinifera*)	[29]
		Mv-3,5-digluc (other than *V. vinifera*)	
Pomegranate juice	8.9–346.6 mg/L	Cy-3,5-digluc/ Cy-3-gluc/ Delp-3,5-digluc/ Delp-3-gluc/ Pel-3-gluc	[30]
Strawberry	8.5–66 mg/100 g FW	Pel-3-gluc/ Cy-3-gluc/ Pel-3-rut	[31]
Vegetables	**Content**	**Main anthocyanin**	**Ref**
Black beans	32 mg/g DW	Delp-3-gluc/ Pet-3-gluc/ Mv-3-gluc	[32]
Red cabbage	2.32 mg/g DW	Cy-3-digluc-5-gluc/ Cy-3-coumaroyldigluc-5-gluc/ Cy-3-sinapoyldigluc-5-gluc	[33]
Purple carrot	168.7 mg/100 g FW	Cy-3-xylosyl-coumaroylglucosyl-gal/ Cy-3-xylosyl-feruloylglucosyl-gal/ Cy-3-xylosyl-gal	[34]
Purple cauliflower	7.18–201 mg/100 g FW	Cy-3-coumarylsoph-5-gluc/ Cy-3-coumarylsoph-5-sinapylgluc	[35, 36]
Eggplant (skin)	12.1 mg/ 100 g DW	Delp-3-rut	[37]
		Delp-3-coumaroylrut-5-gluc	
Colored potatoes	14.42–25.79 mg/g DW	Pel-3-coumaroylrut-5-gluc/ Pel-3-feruloylrut-5-gluc (red)	[38]
		Pet-Pe and Mv-3-coumaroylrut-5-gluc (blue–purple)	
Red onions	48.5 mg/ 100 g FW	Cy-3-gluc/ Cy-3-laminaribioside/ Cy-3-malonylgluc/ Cy-3-malonyllaminaribioside	[14]
Radish	32 mg/100 g FW	Pel-3-coumaroylsoph-5-gluc/ Pel-3-feruloylsoph-5-gluc/Pel-3-feruloylsoph-5-malonylgluc/ Pel-3-coumaroylsoph-5-malonylgluc	[39]
Cereals	**Content**	**Main anthocyanin**	**Ref**
Colored Barley	8–679 mg/Kg DW	Cy-3-gluc/ Peo-3-gluc (purple and blue)	[40, 41]
		Dep-3-gluc/Peo-3-gluc/ Mv-3-gluc (purple)	
Purple, blue, Red, black corn	27–1439 mg/Kg DW	Cy-3-gluc/Cy-3-malonylgluc/ Cy-3-dimalonylgluc	[41, 42]

Fruit	Content	Main anthocyanin	Ref
Purple, red, black rice	68–5101 mg/Kg	Cy-3-gluc/Peo-3-gluc (black)/Mv (red)	[43]
		Cy-3-gluc/Peo-3-gluc/Cy-3-gal/Cy-3-rut (purple)	
Black and red sorghum	32–680 μg/g DW	3-deoxyanthocyanins (Luteolinidin and apigeninidin)	[44]
Purple, blue, black wheat	10–212 mg/Kg DW	Cy-3-gluc/Peo-3-gluc/ Cy-malonylgluc/ Cy-succinylgluc	[45]

Cy: cyanidin; Delp: delphinidin; Mv: malvidin; Peo: peonidin; Pel: pelargonidin; Pet: petunidin; gluc: glucoside; digluc: diglucoside; sam: sambubioside; gal: galactoside; ara: arabinoside; rut: rutinoside; soph: sophoroside; DW: dry weight; FW: fresh weight.

Table 1.
Content and main anthocyanins in foodstuffs.

3. Anthocyanins bioavailability and human metabolic pathways

To validate the prominent health-promoting effects revealed in many *in vitro* and *in vivo* models, it is necessary to consider the anthocyanin bioavailability. Anthocyanin bioavailability has been reported to be very low, with recoveries of less than 1% of the ingested anthocyanin dose. However, higher values have been reported reaching recoveries values of 12.4% [46, 47]. As will be described later, anthocyanin can be absorbed from the stomach and small intestine, but a non-negligible part of them can reach the large intestine where they undergo also an extensive catabolism resulting in several metabolites (phenolic acids, propionic acids). For this reason, anthocyanin bioavailability is estimated much greater taking into account not only the phase I and phase II metabolites but also the microbiota catabolites [6]. Although the currently anthocyanin bioavailability researches in humans are limited, they will be discussed below.

3.1 Anthocyanins absorption

Despite having different molecular sizes and types of sugars or acetylated groups attached, anthocyanins can be absorbed intact [48, 49]. Moreover, anthocyanins were found in the blood stream within minutes of consumption in humans [6] suggesting that they can be quickly absorbed from the stomach. This fact is supported by the fact that anthocyanin urine concentrations were fivefold higher when introduced through nasal tubes into the stomach as opposed to the jejunum in patients with colorectal liver metastases after administration of a bilberry extract [50].
In fact, thanks to the low stomach pH (1.5–4) the anthocyanin stability increase permitting their absorption under their glycoside forms. Because anthocyanins are hydrophilic molecules, an organic anion membrane carrier named bilitranslocase, which is expressed in the gastric mucosa has been proposed to mediate anthocyanin transport [51]. Another hypothesis is the involvement of glucose transporter 1 in the transport of anthocyanin glucosides [52]. However, the main site of anthocyanin absorption is the small intestine. They undergo deglycosylation mediated by β-glucosidase in the intestinal lumen and lactasephloridzin hydrolase in the brush border of the intestinal epithelial cells. Alternatively, anthocyanins can enter the enterocyte without deglycosylation via the sodium-coupled glucose transporter after which deglycosylation can occur by cytosol β-glucosidase [51]. These proposed mechanisms are based, in contrast, on *in vitro* studies. Thus, more studies are required in order to gain insight in human anthocyanin absorption.

3.2 Anthocyanins metabolism

Anthocyanin aglycones that enter the intestinal epithelial are metabolized before reaching portal circulation. This metabolism includes oxidation, reduction, and hydrolysis reactions (phase I metabolism) and conjugation reactions (phase II metabolism). In the intestine, anthocyanins can undergo methylation, sulfation, and glucuronidation by catechol-*O*-methyltransferase, sulfotransferase, and uridine-5′-diphospho-glucuronosyltransferase enzymes [53]. These reactions can also take place in the liver and the kidneys.

Anthocyanin aglycones can alternatively undergo degradation rendering different phenolic compounds within the intestinal lumen or epithelial cells. Anthocyanin fragmentation can also be a result of the colonic microbiota activity. The microbiota gut can release many deglycosylation enzymes giving rise to aglycones that further undergo ring-opening to produce different benzoic acids or aldehydes such as gallic, vanillic, protocatechuic and syringic acids or aldehydes [46, 54]. Consequently, the phenolics acids portion increases whereas ingested anthocyanin forms portion decreases along the gastrointestinal tract. These products of anthocyanin degradation may be absorbed from the intestine and be transported and further metabolized in the liver and kidneys [55]. The specific anthocyanins metabolism will be described below.

3.3 Anthocyanin's distribution

The protective effects of flavonoids have been associated with diseases occurring in various tissues, but such claims are mainly based on *in vitro* evidence using different types of cell lines.

Anthocyanin distribution in tissues has been evaluated in rodents and pig models but never in humans [56–59]. In a study in which Wistar rats were fed during 15 days with blackberry extract (370 nmol anthocyanin/day), total averaged anthocyanins concentrations were found in jejunum (605 nmol/g), in stomach (68.6 nmol/g), in kidney (3.27 nmol/L), in liver (0.38 nmol/g) and in brain (0.25 nmol/g) [60]. In pigs, anthocyanins were identified in the liver (1.30 pmol/g), in eyes (1.58 pmol/g), in cortex (0.878 pmol/g) and in cerebellum (0.664 pmol/g) after being supplemented with 0, 1, 2, or 4% w/w blueberries for 4 weeks [61]. In anesthetized rats received cyanidin-3-*O*-glucoside by intravenous injection, this compound has been detected within 15 seconds in the brain tissue and a concentration comparable to that in serum [62]. The results suggested that anthocyanins may provide protection for brain and eye tissues after crossing the blood–brain and blood-retinal barriers.

3.4 Anthocyanin excretion

Anthocyanins can be excreted in urine, bile and even though in air. Around 5% of ^{13}C-label was recovered from urine after the [^{13}C]-cyanidin-3-*O*-glucoside administration in humans [46]. The urinary excretion of pelargonodin-3-*O*-glucoside seems to be higher than that of cyanidin-3-*O*-glucoside [63, 64]. This may be related to the stability of pelargonidin-3-*O*-glucoside than its real higher absorption. Furthermore, anthocyanins can undergo extensive bile secretion in their original forms or as their phase II metabolites. In human studies enterohepatic recycling of a several xenobiotic could be revealed by a second peak on the plasma concentration *versus* time curve; This phenomenon can be observed in the literature for several anthocyanins (cyanidin-3-*O*-glucoside, peonidin-3-*O*-glucoside, delphinidin-3-*O*-glucoside) [49, 65].

Finally, volatile metabolites produced from [^{13}C]-cyanidin-3-*O*-glucoside have also been found in large quantities in breath (6.9% of the administrated dose) following oral administration of [^{13}C]-cyanidin-3-*O*-glucoside [46].

3.5 Anthocyanin's behavior *in vivo*

Researching the xenobiotic methylation and hydroxylation of anthocyanins is challenging based on MS/MS because anthocyanidins are themselves differentiated by hydroxyl and methyl groups on the B-ring. For example, 3'-*O*-methylation can convert cyanidin to peonidin, and delphinidin to petunidin and 5'-*O*-methylation converts petunidin to malvidin [66]. Moreover, the removal of functional groups will interconvert anthocyanidins. For example, if cyanidin loses the hydroxyl group in position 2″ from the B-ring, it gives rise to pelargonidin (**Figure 1**) [67]. As methylation and glucuronidation occurs on hydroxyl groups, abundant in anthocyanins, positional isomers of anthocyanin and anthocyanidin conjugates can be predicted and are indeed detected [64–68]. As a consequence, data on anthocyanins bioavailabitily in humans after ingestion is potentially more straight forward to interpret.

3.5.1 Cyanidin metabolism

Cyanidin is the best-studied anthocynidin as it is the most widely distributed. Isotopically-labeled cyanidin-3-*O*-glucoside (C3g) was used to examine the absorption and metabolism of ^{13}C cyanidin-3-*O*-glucoside in humans [46]. In this study, 44% of the ^{13}C label has been excreted in urine (5.4%), breath (6.9%) and feces (32.1%) at 48 hours after intake. That implies also that more than 50% of the ^{13}C label was still inside the body at that moment. The absorption, digestion, metabolism and excretion of cyanidin-3-*O*-glucoside concur that methylation and glucuronidation are major routes of cyanidin-3-*O*-glucoside conjugation *in vivo* [46, 67]. The metabolites detected in these studies included methyl and glucuronide conjugates of cyanidin-3-*O*-glucoside, methyl cyanidin-3-*O*-glucoside (peonidin-3-*O*-glucoside), and their aglycones cyanidin and peonidin.

Recently, a human study has been carried on to investigate the metabolic pathways and human bioavailability of anthocyanins of red-fleshed apple in which 22% of phenolic compounds are anthocyanins and the main is cyanidin-3-*O*-galactoside. As a result, cyanidin glycosides (galactoside and arabinose) have been detected in plasma and urine samples. Moreover, peonidin-3-*O*-galactoside as phase II metabolite of cyanidin-3-*O*-galactoside methylation by the action of catechol-*O*-methyltransferase enzyme has been also detected [69]. Methylation, as one of the first

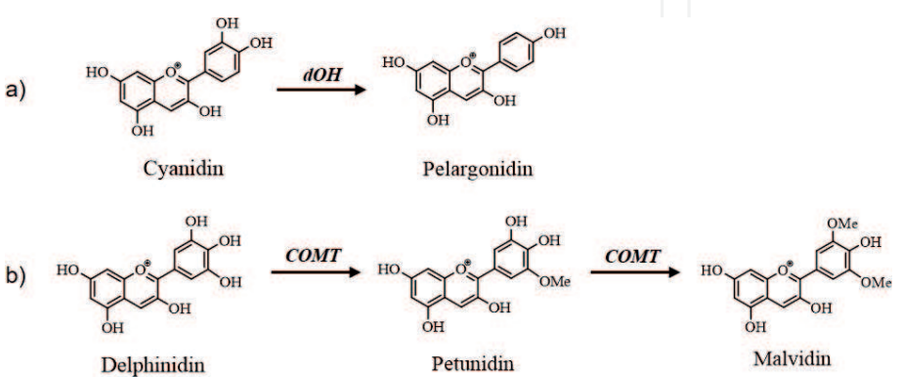

Figure 1.
*Interconversion reactions between anthocyanins: (a) dehydroxylation reaction to arise pelargonidin from cyanidin; (b) methylation pathway that could be carried on by the action of catechol-*O*-methyltransferase enzyme. Reactions:* dOH*, dihydroxylation;* COMT*, catechol-*O*-methyltransferase.*

metabolic reaction of cyanidin glycosides was also reported after the oral ingestion of 500 mg of ^{13}C-labeled cyanidin-3-*O*-glucoside [55].

Protocatechuic acid (PCA) and dihydroxyphenylpropionic acid (dihydrocaffeic acid) were respectively detected in these studies [55, 69]. PCA has been observed at maximum concentrations of 147 nM, thus suggesting that it is not a major metabolite of anthocyanins. The A-ring-derived degradation product, phloroglucinolaldehyde, was present at concentrations greater than either cyanidin-3-*O*-glucoside or PCA in the serum [55].

Hippuric acid has been identified as the major metabolite of anthocyanins, reaching a maximum concentration of 1962 nM in serum [55]. The detection of ^{13}C2-labeled hippuric acid in this study indicates that PCA and its conjugates are likely further metabolized to form benzoic acid, which is conjugated with glycine to form hippuric acid, or alternatively, formed from the α-oxidation and dihydroxylation of hydroxyphenylacetic acids [64]. PCA might have been formed by β-oxidation of dihydroxyphenylpropionic acid. Then, this phenolic acid could either be further degraded by the action of the gut microbiota to catechol metabolites (α-oxidation), pyrogallol metabolites (hydroxylation) and hydroxybenzoic acid (dehydroxylation), or methylated to vanillic acid [55, 69].

Colonic metabolism has long been speculated to be a major contributor to the overall metabolism of anthocyanins [70]. It has been proposed that phenylpropenoic acids arise from cyanidin-3-*O*-glucoside as a result of bacterial cleavage of the C-ring in the colon [71], which is supported by the detection of caffeic acid and its methyl metabolite, ferulic acid [55].

On the basis of the findings of these studies, the metabolic pathway of cyanidin-3-*O*-glucoside and peonidin-3-*O*-glucoside can be summarized as undergoing multiple biotransformation (**Figure 2**).

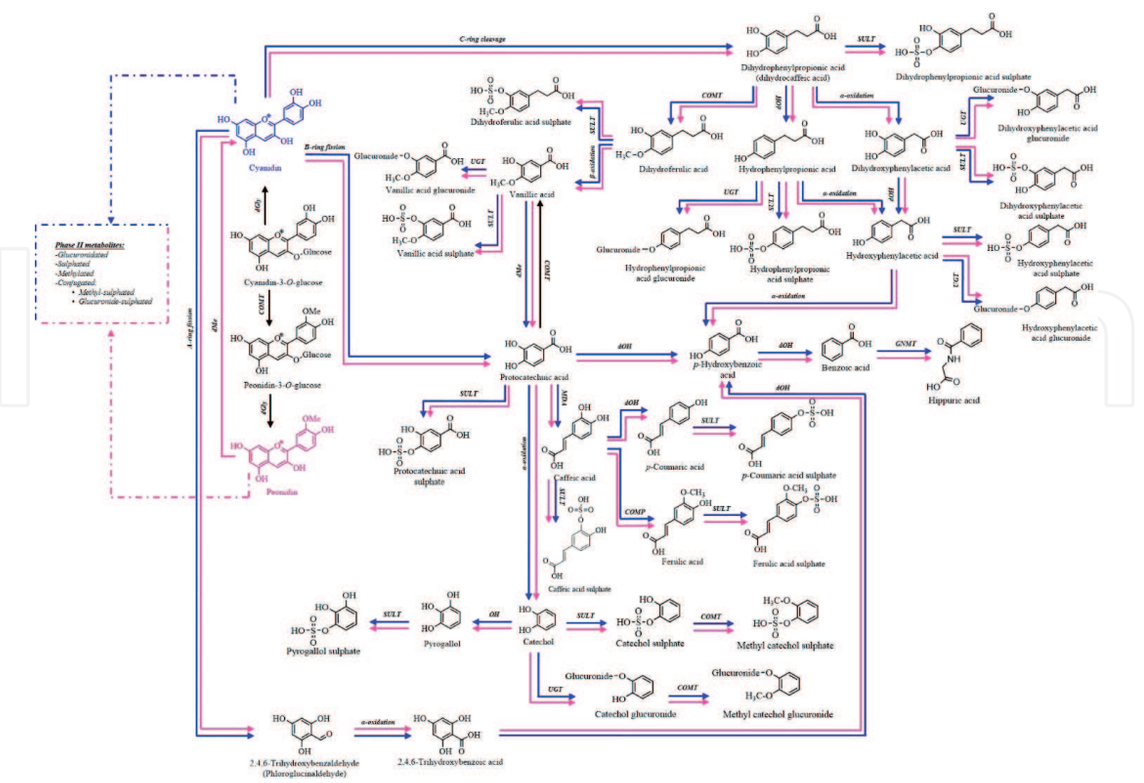

Figure 2.
Proposed metabolic pathway for cyanidin and peonidin glucosides. Reactions: dH, *dehydrogenation;* SULT, *sulphotransferase;* UGT, *glucuronosyl-transferase;* COMT, *catechol-O-methyltransferase;* dOH, *dehydroxylation;* dMe, *demethylation;* α-oxidation, *one decarboxylation;* β-oxidation, *two decarboxylation.*

3.5.2 Pelargonidin metabolism

As it was shown before, demethylation and dihydroxylation of highly substituted anthocyanins gives rise to pelargonidin, that helps to explain the high apparent recovery of pelargonidin-based metabolites [63]. Indeed, pelargonidin glucuronide has been detected in urine after the ingestion of boysenberry (rich in four cyanidin glycosides and without pelargonidin) in humans [67]. Furthermore, strawberry pelargonidin was found to be metabolized to 4-hydroxybenzoic acid in humans when 13 healthy volunteers consumed 300 g of fresh or stored strawberries [72]. In which 4-hydroxybenzoic acid plasma recovery was 23 and 17 mmol, corresponding to the percentages of 54 and 56% of pelargonidin-3-*O*-glucoside.

3.5.3 Delphinidin, petunidin and malvidin metabolism

After administration of Concord grape juice in humans, delphinidin-3-*O*-glucoside, petunidin-3-*O*-glucoside and malvidin-3-*O*-glucoside were found in blood or urine. Glucuronidated metabolites of aglycones have been identified as their major metabolites in urine [49]. In the urine of volunteers administered bilberry-lingonberry puree, a small amount of syringic acid, a potential metabolite of malvidin glycosides, was detected [73]. Recently, in a long-term study with humans consuming blueberry juice, 55 anthocyanin metabolites have identified. Among them, malvidin-3-*O*-glucoside, malvidin-3-*O*-galactoside and malvidin-3-*O*-arabinoside have been described representing around 5% of the total excretion [68]. *In vitro* experiments state that gallic acid is the major degradation product of delphinidin-3-*O*-glucoside. Moreover, syringic acid was described as the mean metabolite for malvidin-3-*O*-glucoside [13].

4. Anti-neuroinflammatory effects on anthocyanins and their metabolites

As it was discussed above, several works have demonstrated that anthocyanins can cross the blood brain barrier, and accumulate in brain endothelial cells, brain parenchymal tissue, striatum, hippocampus, cerebellum and cortex [74–76]. Consequently, the study of anthocyanins as therapeutic agents in neurodegenerative diseases has gained relevance.

Neuroinflammation is a common physiopathological hallmark in neurodegenerative diseases as Alzheimer, Parkinson or amyotrophic lateral sclerosis, among others. This process is mediated by microglial cells, the immune cells of central nervous system. Their functions are related with the host defense by destroying pathogens, promoting tissue repair and facilitating tissue homoeostasis [77]. Nowadays it is well establish that these cells can adopt different phenotypes depending on the brain environment to shift into pro-inflammatory/neurotoxic or anti-inflammatory/neuroprotective phenotypes. The stimulation agent will be the responsible of trigger one or another phenotype. Thus, when microglial cells are stimulated with lipopolysaccharide (LPS) and interferon gamma (IFN-γ), microglia develop a classically phenotype or M1, while when it is activated with IL-4 microglia show an alternative activated phenotype or M2 [78]. On the one hand, M1 microglia type is characterized by the production of nitric oxide (NO) by the inducible nitric oxide synthase (iNOS) [79, 80] and by the expression of inflammatory chemokines and cytokines, such as interleukin (IL)-6, IL-12, IL-1β, IL-23, and tumor necrosis factor (TNF)-α. All this culminates in the influx of new immune system cells to combat the infection. When neuroinflammation becomes chronic,

it can ultimately lead to neuronal cell death. On the other hand, M2 microglia is characterized by a suppression of IL-12 secretion and an induction of the release of IL-10, transforming growth factor beta (TGB-β), IL-1R [81]. Furthermore, the expression of arginase-1 instead of iNOS, switching arginine metabolism from production of NO to ornithine, and also the increase of polyamines production for extracellular matrix and collagen synthesis, promotes the neuroregeneration and tissue repair [82].

Several *in vitro* and *in vivo* studies have shown that anthocyanins, overall rich anthocyanins extracts, are able to be neuroprotective and counteract neuroinflammation [83, 84]. Regarding *in vitro* studies, a blueberry extract (25–50 μg/mL) have demonstrated to be able to diminish the release of NO, TNF-α, iNOS and cyclooxygenase-2 (COX-2) protein expression in LPS-stimulated BV2 cells [85, 86] and in LPS or IFNγ-stimulated N9 cells [87]. In addition, they proved that this effect is mediated by NF-κB signaling pathway, via the inhibition of Nuclear Factor Kappa B (NF-κB) nuclear translocation [88]. NF-κB is a key inflammation regulator located in the cell cytoplasm and their nuclear translocation trigger the expression of inflammation-related genes. Likewise, the anti-inflammatory effect of blueberry extract has been related with the activation of janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling (pathway activated after IFN-γ stimulation) [87]. Other study that evaluated the potential anti-neuroinflammatory effect of a large variety berries extracts (blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry), showed that the cranberry extract (20 μg/mL) was the most active diminishing the NO production and inhibiting the fibrillation of amyloid-β peptide (peptide responsible of the formation of senile plaques in brain Alzheimer's patients) [89]. Moreover, elderberry extracts (400 μg/mL, ethanol or ethyl acetate extracts) has also been proposed as a potent suppressor of NO release [90]. Mitogen-activated protein kinases (MAPKs) are a family of serine/threonine protein kinases that mediate fundamental cellular responses to external stress signals. In particular, p38 MAPK, is involve in the regulation of the synthesis of inflammation mediators being for that a potential target for anti-inflammatory therapeutics. In this context, an anthocyanin-enriched extract of acai berry and a mixture of anthocyanins isolated from black soybean seed coats (cyanidin-3-*O*-glucoside (72%), delphinidin-3-*O*-glucoside (20%) and petunidin-3-*O*-glucoside (6%)) have demonstrated that MAPK pathways can be also implicated in the decrease in inflammatory mediators and cytokines [91, 92]. Finally, this year, an article have been published showing that a black raspberry extract reduced the production of IL-18, IL-1β and reactive oxygen species (ROS) in LPS-induced BV2 microglia by down-regulating the level of NADPH oxidase 2 (NOX2) and its downstream factors, including thioredoxin-interacting protein (TXNIP) and NOD-like receptor protein 3 (NLRP3) inflammasome [93]. The complexity of these extracts containing several structurally diverse anthocyanins makes difficult the interpretation of results. For this, some papers have been published concerning the evaluation of the activity of pure anthocyanins. This type of studies provide insight into the plausible mechanism of single compounds facilitating the understanding. Some (although very few) studies, have been performed with pure anthocyanins. An interesting work published by Miraeles and collaborators demonstrated that cyanidin-3-*O*-glucoside, (1 μM) and also cyanidin-3-*O*-glucoside and a mixture of 3′-methyl-cyanidin-3-*O*-glucoside and 4′-methyl-cyanidin-3-*O*-glucoside, were able to decrease a great number of pro-inflammatory mediators. Indeed, TNF-α and IL-6 mRNA expression was decrease by and methyl-cyanidin-3-*O*-glucoside. Moreover, cyanidin reverted the IL-1β expression. This paper also shows that even though cyanidin and theirs different chemical forms, are not able to shift microglia to an M2, they can interact with microglia biology

increasing CX3C Motif Chemokine Ligand 1 (CX3CL1) expression [94]. Neurons can express this chemokine, which mediates microglial activation via interacting with its sole receptor CX3CR1 in microglia (axis CX3CL1/CX3CR1). Comparable results have been recently published, showing that the underlying responsible anti-neuroinflammatory mechanism of cynidin-3-*O*-glucoside is related with suppression of NF-κB and p38 MAPK signaling pathways [95]. Other pure anthocyanins as delphinidin-3-*O*-glucoside, malvidin-3-*O*-glucoside (20 μM) [86] and pelargonidin-3-*O*-glucoside (100 μM) [96] are also shown to be able to suppress the LPS/IFN-γ -induced phosphorylation of p38, p42/44 and MAPKs in BV2 cells and mouse C8-4B microglial cells.

Concerning *in vivo* studies, only around ten papers have been published about the effect of anthocyanins extracts/pure compounds in microglia-related diseases. The first paper published in 2015, evaluate the effect of a blackberry extract consumption at a dose of 25 mg/Kg in an standard or in a high fat diet, during 17 weeks in Wistar rats. The results showed that the intake of this fruit, in both dietary conditions, modulates CX3CL1 expression and the thymus chemokine TCK-1. In addition, they also found that blueberry can ameliorate synapse connectivity by regulating platelet-derived growth factor (PDGF)-AA, activin, vascular endothelial growth factor (VEGF) and agrin [97]. Another three works proved that the consumption of anthocyanins extracted of Korean black soybean (24–100 mg/Kg) inhibited the activation of astrocytes and neuroinflammation via suppression NF-κB, iNOS and TNF-α in the hippocampus and cortex regions of D-galactose and LPS treated rats brain [98–100].

Not only the reduction of IL-1β and TNF-α but also the reduction of IL-10 induced by LPS was observed after the treatment with 100 mg/Kg of anthocyanin obtained from *V. vinifera* grapes in mice [101]. Moreover, the addition of an enriched anthocyanin extract from purple corn in water (mean of 53 mg/Kg body weight) has proved to be able to reduce microglia size and Iba1 staining (marker of microglia activation) and IL-6, TNF-α, IL-1β, MCP-1 and iNOS. Interestingly, this papers showed that purple corn anthocyanins not only inhibit microglia activation but also promote their shift towards the production of anti-inflammatory mediators, such as arginase-1, IL-10, Fizz1, IL-13 and YM-1 (a marker of M2 microglia phenotype) [102]. In agreement, a diet based on anthocyanin-rich wheat during 6 months on Alzheimer and Parkinson disease mouse models, reduced the α-synuclein accumulation (protein responsible of the formation of Lewy bodies in Parkinson patients) [103].

Other rich anthocyanins fruits as bilberry has exhibited promising results. In fact, the administration in food or in water of an bilberry extract (20 mg/Kg day) on APP/PSEN1 mice and their littermates downregulates the expression of several inflammatory factors (TNF-α, NF-κβ, IL-1β, IL-6, COX-2, iNOS and cluster of differentiation 33 (CD33), the chemokine receptor CX3CR1, but also and for the first time, the microglia homeostatic factors (TREM2 and TYROBP) and the Toll-like receptors (TLR2 and TLR4) [104].

As was explained above, circulating concentrations of phenolic acid metabolites derived from anthocyanin degradation such as protocatechuic, gallic, syringic and ferulic acids have been observed at up to eight times to that of the parent anthocyanins [72]. Two papers have been very recently published showing that a mixture of anthocyanin metabolites can have anti-neuroainflammatory activities. Indeed, an *in vitro* digested blueberry and raspberry extracts (1.25–10 μg/mL) proved be able to reduce some key inflammatory markers (TNF-α and NO) and ROS in N9 cell line exposure to LPS and IFN-γ. This bioactivity has been related with the NF-κB and STAT1 molecular pathways [87, 105]. By using pure compounds, ferulic, caffeic and protocatechuic acids have been the most studied metabolites on

neurodegenerative diseases with an inflammatory component. The pre-treatment of BV2 microglial cells (1 and 4 hours) with PCA (2.5–10 μM) attenuated microglial activation by suppressing TLR4-mediated NF-κB and MAPKs (JNK, p38, ERK) activation and SIRT1 pathway [106, 107]. Other interesting paper displayed that PCA (3,4-dihydroxybenzoic acid), ant not 4-hydroxybenzoic acid can reduced NO production of BV2 cells, however, in this case, PCA concentrations are ten times higher (100 μM) [108]. Furthermore, Koga and their co-workers demonstrated that caffeic acid-treated mice exhibited significantly lower levels of 4-hydroxynonenal (oxidative stress marker) and fewer activated microglia [109]. A long-term treatment (4-weeks) with ferulic acid (in drinking water (0.006%)) for male mice prevented the $A\beta_{1-42}$-induced activation of microglia [110]. Ferulic acid has also demonstrated interfered with TLR4 interaction sites in mouse hippocampus and in BV2 cells by down streaming iNOS, COX-2, TNF-α, and IL-1β via JNK and NF-κB phosphorylation [111]. Furthermore, the intra-peritoneal injection of 30 mg/Kg of vanillic acid reversed LPS-induced glial cells activation, neuroinflammation (TNF-α, IL1-β, and COX-2) and amyloidogenic markers (β-site amyloid precursor protein (APP)–cleaving enzyme 1 (BACE1) and amyloid-β [112]. Finally, concerning gallic acid, two articles can be highlighted. This compound (at 5–50 μM concentration) in a co-culture system consisted on BV2 and Neuro-2A cells and in primary microglia resulted on the diminution of cytokine production induced by the Aβ peptide [113]. After the orally administration of gallic acid (100 mg/Kg) 1 hour prior to the LPS infusion and daily afterwards for 7 days, an attenuation of LPS-induced elevation in heme oxygenase-1 level and α-synuclein aggregation was observed. Moreover, this same work revealed that gallic acid diminished the iNOS gene expression and the NO production *in vitro* [114].

However, any anti-neuroinflammatory activity has been reported for glucuronidated, sulfated and *O*-methylated anthocyanins and their corresponding metabolites. This lack of studies can be explained due to the lack of commercial compounds which makes the chemical synthesis or hemy-synthesis as the only alternative available. Even if it is a challenge to obtain glucuronidated, sulfated and *O*-methylated anthocyanins some methodologies can be used and are reported in the literature. For example methylation of cyandin-3-*O*-glucoside can be carried out by the reaction with dimethylcarbonate [115]. Regarding the hemisynthesis of sulfated derivatives several approaches are possible by bringing the anthocyanins into contact with chlorosulfonic acid [116] or even with sulfur trioxide-N-triethylamine [117]. Finally, glucuronidated anthocyanin can be obtain by acidic aldo-condensation between trihydroybenzalhaldehyde and acetophenone which have been previously functionalized with the expected OH and OMe group as well as the glucuronic acid at the proper position [118].

5. Conclusion

Anthocyanins represents one the most consumed polyphenols in human diet. However, their type, complexity and quantities depends on the foodstuff. For example, anthocyanins in vegetables and cereals are chemically more complex in comparison with fruits, but berries are the major source of these compounds. Anthocyanin bioavailability has been reported to be very low, with recovery of less than 1% of the ingested anthocyanin dose. However, nowadays much greater bioavailability values have reported taking into account not only the phase I and phase II metabolites but also the microbiota catabolites. One of the peculiarities of anthocyanin metabolism is their capacity of interconversion between them. For example, dehydroxylation reaction can arise pelargonidin from cyanidin and methylation

reactions can convert delphinidin into petunidin and malvidin. For this reason, metabolism data after anthocyanin ingestion is more straight forward to interpret. Regarding metabolism, cyanidin is the most studied anthocyanin due to ubiquitous character in the nature. However, more studies are necessary to better understand the similarities and differences with the other less studied anthocyanins. Even though several papers have reported the potential anti-neuroinflammatory effect of rich anthocyanin extracts, anthocyanins or their metabolites, the number of papers are very scarce. The most important limitation to study the activity of anthocyanin metabolites is the lack of commercial phase II and microbiota catabolites compounds. Thus, the chemical synthesis is the most employed technique to obtain standards although more developments are requires in order to obtain greater quantities. Moreover, little is known about the molecular mechanisms implicated in the observed effects. Furthermore, the majority of works are based on the study of the microglia M1 phenotype, so more studies are necessary to know if anthocyanins and their metabolites are able to induce an anti-inflammatory phenotype. To sum up, more research is necessary to stablish if anthocyanins and their metabolites are efficacious in slowing the progression of brain aging or of neurodegenerative diseases with an inflammatory component.

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