Food & Function

ROYAL SOCIETY OF CHEMISTRY

REVIEW

Cite this: *Food Funct.*, 2021, **12**, 10356

Phenolic compounds that cross the blood–brain barrier exert positive health effects as central nervous system antioxidants

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Received 25th June 2021,
Accepted 10th September 2021

DOI: 10.1039/d1fo02017j

rsc.li/food-function

The blood–brain barrier (BBB) is a physical structure whose main function is to strictly regulate access to circulating compounds into the central nervous system (CNS). Vegetable-derived phenolic compounds have been widely studied, with numerous epidemiologic and interventional studies confirming their health-related bioactivities across multiple cells, organs and models. Phenolics are non-essential xenobiotics, and should theoretically be unable to cross the BBB. The present work summarizes current experimental evidence that reveals that not only are phenolic compounds able to cross the BBB and bioaccumulate in the brain, but there is some stereoselectivity, which suggests the presence of specific transporters that allow them to reach the brain. Some molecules cross the BBB intact, while others do so only after being biotransformed or metabolized elsewhere. Once inside the CNS, they prevent or counter oxidative stress, which maintains the molecular, cellular, structural and functional integrity of the brain, and subsequently, overall human health.

Introduction

In 1885, Paul Ehrlich identified what he later named the blood–brain barrier (BBB) after injecting water-soluble dyes into the blood of animals and finding that all organs were dyed, except for the brain and spinal cord. It is now known that the BBB is a complex structure that protects the brain from foreign substances,[1,2] regulating which molecules can reach the central nervous system (CNS) and which cannot. Therefore, the role of this barrier is to maintain the brain's homeostasis by permitting access only to essential molecules, such as nutrients, while impeding it to potentially toxic substances or xenobiotics that may be transported in the bloodstream.[3–5]

The BBB carries out its functions due to its complex structure, which results in a strong physical barrier. A neurovascular unit (NVU) consists of a monolayer of brain endothelial cells (BECs) that coat brain capillaries, pericytes, astrocytes, neurons and muscle cells. BECs make up a continuous membrane, while all components of the NVU are linked, providing a more effective system that regulates blood flow.[5] The specificity of BECs arises because they have a different behavior, as compared to most other cells, which is due to tight (TJs) and adherens junctions (AJs). TJs in the space of BECs are produced by transmembrane proteins, which interact and seal the paracellular pathway, resulting in the impermeability of the BBB. AJs are responsible for the structural support of the endothelia among other functions. Both AJs and TJs contribute to produce tightness in the BBB and to maintain its stringent selective permeability.[6]

The main site for molecular transport is through BECs, cells that are meticulously specialized in the BBB. These are permeable to oxygen, CO_2, inert gases and inhalable anesthetics, but are impermeable to most polar molecules by passive diffusion.[7,8] This makes it necessary for BECs to express various transporters that allow access to essential polar molecules, such as glucose, amino acids and hormones.[9–11]

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Such stringent control exerted by the BBB limits the access of xenobiotic molecules to the brain, such as phenolic compounds, to prevent potential toxicity or organ damage.

Entry of compounds into the brain occurs by four mechanisms: passive transfer, solute carrier proteins, efflux transporters, and transport systems for macromolecules. (1) Passive transfer: lipophilic and small molecules can cross the BBB by a passive transfer mechanism,[12] for example, molecules of 300–600 Da, but they must have a low hydrogen bonding potential to allow penetration.[13,14] When the molecule is positively charged, it interacts with the glycocalyx and phospholipids, thereby enabling an easier entry.[14,15] (2) Solute carrier proteins: these are specialized proteins that grant access to essential molecules; there are five different transport systems for metabolic fuels, amino acids, neuro/glio-transmitters, organic anions and nucleic acids.[16] (3) Efflux transporters: these are part of the ABC transporter family, of which P-glycoproteins are among the most important; they are abundant in the luminal membrane of brain endothelia. These transporters prevent the accumulation of lipophilic compounds and most xenobiotics.[12,16] (4) Systems for macromolecule transport: BECs transport large molecules, like albumin, through pinocytosis. Negative charges in BECs interact with positively charged molecules and cause adsorptive endocytosis.[17] When the molecule is too large, it must be transported by receptor-mediated endocytosis, of which several spread throughout the BBB.[18–20] In contrast, molecules that do enter into the CNS tend to share some general attributes, such as a low molecular weight, a low hydrogen bonding potential or performing an essential function within it.[21] Nevertheless, some studies have demonstrated that other non-essential molecules can reach the brain and exert beneficial health effects to this organ, such as preventing oxidative stress, as will be discussed in the following sections.

Phenolic compounds that can cross the BBB and reach the brain

It has been estimated that less than 2% of low molecular weight organic molecules can cross the BBB,[22] but, regardless of this low value, the presence of phenolic compounds in the brain has been confirmed by several authors. Due to the ease with which reactive oxygen species (ROS) exert damage to the CNS, the presence of phenolic compounds herein appears to be of great importance to maintain redox homeostasis. This section summarizes current studies that have demonstrated which phenolic compounds can cross the BBB and gain access to the brain. It will also propose potential molecular features that a phenolic compound should have or should lack in order to cross the BBB. Phenolic compounds and most other orally consumed molecules are subjected to first pass metabolism, mainly in the small intestine and liver, where they are likely to be significantly transformed into other molecular species, in addition to metabolism by gut microbiota. These are all components of the gut–liver–brain axis, and have a significant impact on which precise metabolites reach the BBB, in addition to exerting health effects along the way, in fact, a phenolic may not strictly require access to the brain, since it can induce indirect health effects on this organ by acting on peripheral tissues.[23] The role of this axis and the reactions that take place therein are beyond the scope of the present work, although we have discussed it in detail elsewhere.[24,25]

Grape seed phenolics

Ferruzzi *et al.* (2009)[26] analyzed the bioavailability of phenolic compounds from a grape seed polyphenol extract (GSPE) in male Sprague Dawley rats. Rats were administered (intragastric gavage) 50, 100 or 150 mg of GSPE per kg body weight for a ten-day period, values equivalent to 483, 967 and 1451 mg, respectively, for a 60 kg human. The authors found twelve major compounds in GSPE (gallic acid, catechin, epicatechin, and their derivatives), while also determining the kinetics of their bioavailability in plasma and in the brain. Only free monomers were detected in plasma, and only methylated derivatives were found in the brain when the dose was increased. Quantifiable levels of free catechin and epicatechin were found in the brain (290.7 and 576.7 pg g^{-1} of tissue, respectively), while only traces of free gallic acid and methylated forms of catechins were detected. According to these results, the authors confirm that low molecular weight compounds found in GSPE, like catechin monomers, are bioaccumulated in the brain.

Distribution of GSPE flavonoids in rat tissues was evaluated by Margalef *et al.* (2015)[27] Wistar rats were administered varying doses of GSPE (0–1000 mg per kg body weight) *via* oral gavage, with results showing that flavonoids and their metabolites were present at different concentrations in each tissue. Only glucuronide, methylglucuronide, and some methylated forms accumulated at a dose-dependent rate, while the concentration of epicatechin metabolites was higher than their catechin analogs. The authors concluded that methyl-sulfated metabolites can cross the BBB and have better access to the brain. A similar pattern of better access of epicatechin over catechin demonstrated in the previous study has also been reported by Faria *et al.* (2011)[28] who showed the stereoselective entry of flavonoids. These reports suggest that metabolites of GSPE flavonoids can reach the brain in a dose-dependent manner; moreover, stereoselectivity suggests that they cross the BBB with the aid of an unspecified transporter, and not through passive diffusion. Transporter-mediated stereopreference has been documented for other compounds, for example, (+)-pioglitazone preferentially accumulates over (−)-pioglitazone in mice brain, due to the effect of P-glycoprotein expressed on the BBB.[29] In contrast, a monocarboxylate transporter (MCT) is responsible for regulating phenytoin transport across the BBB, with no involvement of P-glycoprotein.[30] This suggests that both uptake and excretion of phenolics (as well as other compounds) may be due to the concerted effect of these and other transporters, whose stereopreference for phenolics will dictate their net accumulation in the brain.

Resveratrol

The bioactivities of some phenolic compounds in the CNS have been studied, for example, resveratrol has shown significant neuroprotective effects related to its ability to cross the BBB and alter the redox environment, prevent cognitive decline and other effects. However, even with the amount of data gathered about its bioactivities, the presence of specific transporters that allow it to cross the BBB (in addition to passive diffusion) remains to be conclusively demonstrated.[31] This suggests that additional investigations are required to determine which transporters mediate phenolic transport, with a particular need to determine the stereopreference documented for some of them. Some studies have been performed, although most are focused primarily on pharmaceutical compounds, but not on dietary phenolics.[32] The ample structural variability of phenolics supports the notion that multiple transporters may be involved, thus, elucidating these transporters and their selectivity towards the different types will provide valuable information in this research area.

Danshesu and curcumin

Danshen is a dry root and rhizome of *Salvia miltiorrhiza*. Zhang *et al.* (2011)[33] administered danshen extract by an intragastric gavage to male Sprague Dawley rats, taking blood samples every 15 min for 4 h after ingestion, and dissected the brain after the experimental period. The phenolic compounds danshesu, protocatechuic acid and protocatechuic aldehyde were detected in the blood and brain with a similar concentration, even when the dosage was increased. Pharmacokinetics of danshesu and protocatechuic acid showed a brain/blood distribution ratio of 25 and 9%, respectively, suggesting that these molecules can cross the BBB, while, conversely, protocatechuic aldehyde cannot, because it is quickly oxidized to protocatechuic acid. The fact that danshesu has a better ability to cross the BBB, as compared to protocatechuic acid, could be due to its structure, since danshensu has two more carbon atoms than protocatechuic acid, making it more hydrophobic, suggesting increased access to hydrophobic molecules.

Curcumin access across the BBB was analyzed by Garcia-Alloza *et al.* (2007)[34] using *in vivo* multiphoton microscopy (MPM) in adult male and female mice (APPswe/PSIdE9). The methodology consisted on an *in vivo* and *ex vivo* staining; for the *ex vivo* assay, brain sections were dehydrated and treated with different concentrations of curcumin for 20 min; for the *in vivo* assay, mice were treated for seven days with 7.5 mg kg^{-1} day^{-1} of curcumin *via* the tail vein. The *ex vivo* study demonstrated the presence of curcumin in the brain, while the *in vivo* study confirmed the ability of curcumin to cross the BBB. After a single dose, there were undetectable levels of curcumin in the brain, but its concentration was significantly higher after the seventh day of treatment, leading to the conclusion that curcumin is able to cross the BBB and, apparently, is bioaccumulated in the brain, exerting health benefits therein.

According to the experiments of Garcia-Alloza *et al.* (2007)[34] and Zhang *et al.* (2011),[33] non-flavonoids danshensu and curcumin can cross the BBB and bioaccumulate in the brain. Although their molecular structure is similar, curcumin has a higher molecular weight and less hydrogen bonding potential, making it more hydrophobic. Log *P* of curcumin is higher than that of danshensu, at 2.30 and −0.25, respectively, further supporting the notion that hydrophobicity is a key factor that influences a phenolic compound's ability to cross the BBB. This is expected since the brain is rich in fatty acids, thus, the lipophilic structure of curcumin should allow it to be deposited and stored therein.

Anthocyanins

Kirakosyan *et al.* (2015)[35] evaluated the presence of tart cherry anthocyanins in the cerebral cortex of Wistar rats that were fed diets supplemented with 1 or 10% tart cherry powder. Tart cherry powder contained cyanidin, peonidin and pelargonidin derivatives, as identified by UPLC. Cyanidin, cyanidin-3-rutinoside-5-β-D-glucoside and peonidin-3-rutinoside accumulated in the brain in a dose-dependent manner. There was also evidence that cyanidin-3-rutinoside-5-β-D-glucoside, which is a more polar form of cyanidin-3-rutinoside, was found in the brain, which can be a result of the endogenous anthocyanin metabolism. Also, peonidin-3-rutinoside can enter the brain, but cyanidin-3-rutinoside cannot; their structure differs by a methoxyl group in the B-ring, indicating that even a minor structural modification can significantly affect a compound's ability to reach the brain. This may suggest the presence of specific transporters on the BBB that are yet to be identified. This study confirms the ability of anthocyanins to cross the BBB, and the influence of polarity and molecular structure as determining factors that regulate the entry of anthocyanins and other phenolics into the brain. Other studies have shown that chokeberry anthocyanins (cyanidin-3-galactoside, -glucoside, -arabinoside and -xyloside) reach the cerebrospinal fluid (CSF) of adult Polish Lowland sheep (5% powdered chokeberry, 10 mg cyanidin kg^{-1}, intraruminal route), with metabolites (methylated, glucuronidated and sulfated derivatives) predominating over native molecules.[36]

The distribution pattern of cyanidin-3-glucoside (C3G) was evaluated by Fornasaro *et al.* (2016)[37] who administered the compound to Wistar rats *via* penile vein injection. Rats were euthanized after 0.25, 5, 10, 15, and 20 min of injection; UPLC was then used to analyze its concentration in plasma and brain. Plasma concentration decreased with time, with the highest values of C3G and other anthocyanins (glucosides of delphinidin, peonidin, petunidin, malvidin, and pelargonidin) found at 0.25 min. The mean half-life of anthocyanins varied by compound, with that of C3G being <7 min. The brain concentration of C3G was dose-dependent and decreased with time, from 40.46 to 2.21 pmol g^{-1} tissue. A similar pattern was found for petunidin-3-*O*-glucoside and peonidin-3-*O*-glucoside, whose concentration was detectable after 2 min and decreased with time. A time-dependent decrease of brain anthocyanins suggests that these compounds cannot accumulate due to their hydrophilic nature. The presence of C3G in the brain correlated with the plasma concentration, suggesting that it could be an indicator of C3G in this organ. In contrast, there was no

correlation between other anthocyanins' access to the brain and the structure of their metabolites, suggesting a possible BBB selectivity for C3G.

Flavonoids

Yang *et al.* (2014)[39] evaluated the active transport of flavonoids across the BBB. The authors evaluated puerarin, rutin, hesperidin, quercetin, genistein, kaempferol, apigenin and isoliquiritigenin using rat BBB and Caco-2 cell line models. Cells were incubated with flavonoid solutions, and their transport was expressed as the apparent permeability coefficient (P_{app}, $\times 10^{-6}$ cm s^{-1}). In the BBB cell model, permeation was in the order quercetin > rutin > hesperidin > kaempferol > puercetin > apigenin > isoliquiritigenin > genistein, with P_{app} in the range 13.44–2.20. The order was similar in Caco-2 cells, except for rutin which had the lowest permeability, and in general, transport rates correlated with increased concentration. The authors concluded that the flavonoids studied permeate the cell layer through a passive diffusion mechanism, and they also suggest that glycation and the presence of hydroxyl groups reduce their permeability, arguing in favor of increased permeability for hydrophobic compounds. Furthermore, they stated that *o*-hydroxybenzene moieties increase permeability, as compared to *m*-hydroxybenzene. Preference for one isomer instead of another affirms, once again, shows the presence of specific transporters on the BBB.

Flavan-3-ols

Faria *et al.* (2011)[28] evaluated the transmembrane transport of catechin and epicatechin across the BBB, using an immortalized cell line of rat capillary cerebral endothelial cells (RBE-4) and hCMEC/D3. The results showed that transport was stereoselective, favoring epicatechin over catechin. Furthermore, endothelial cells were able to metabolize flavan-3-ols; this was confirmed because plasma levels of catechin and epicatechin were lower when compared to other reports, but those of methylated, sulfated and glucuronidated forms were high. The authors concluded that flavan-3-ols cross the BBB through a stereoselective transport mechanism. It is apparent that the same rules that regulate the entry of flavonoids to the brain also affect the permeability of anthocyanins across the BBB, which is more permeable to conjugated forms and lipophilic compounds. In addition, methylation of flavonoids and anthocyanins results in increased permeability. Both types of compounds have a time- and dose-dependent response when crossing the BBB, where longer exposure times increases their brain concentration. These results indicate that it is easier for hydrophobic molecules to cross the BBB, while increased hydrophobicity also promotes accumulation. Furthermore, preference for methylated metabolites suggests the presence of specific transporters found on the BBB.

Figueira *et al.* (2017)[40] analyzed the bioaccessibility of phenolic compounds across the BBB using immortalized human brain microvascular endothelial cells (HBMEC). The results confirmed, for the first time, the presence of ABC-type efflux transporters in HBMEC, that may contribute to the transport of phenolic compounds across the BBB. Also, they appear to be regulated by metabolites of phenolic compounds, suggesting that one compound may alter the bioavailability of another.[41] Structural modifications of the tested phenolics by HBMEC, showed that the less modifications on the compound, the greater its absorption. This process begins when the compound is ingested and continues in the liver through phase I and II enzymes, which alter their molecular structure and subsequent BBB-crossing potential.[40] The authors also report that modifications exerted by the HBMEC may facilitate their elimination from the brain or delivery to other neuronal cells.

Anthocyanins, flavan-3-ols and flavonols

The transport of anthocyanins, flavan-3-ols, and flavonols in a BBB model was evaluated by Faria *et al.* (2014)[38] in the immortalized human cerebral microvessel endothelial cell line (hCMEC/D3 cells). For anthocyanins, the authors used three compounds with different polarities: delphinidin-3-*O*-glucoside, cyanidin-3-*O*-glucoside and malvidin-3-*O*-glucoside; all three were able to cross the BBB model, but with different efficiencies. As with other compounds discussed, access of anthocyanins depended on their hydrophobicity, with efficiency decreasing in parallel with hydrophilicity. The authors also evaluated the methylated forms of anthocyanins, showing that these can more efficiently cross the BBB. In contrast, quercetin and quercetin-3-*O*-glucuronyl transport was evaluated, showing that both compounds are absorbed in a time-dependent manner, but absorption of the metabolite is more efficient, as compared to the parent compound. To probe the efficiency of flavan-3-ols, the authors evaluated epicatechin and its metabolites, showing that metabolized forms can cross the BBB in a more efficient way than epicatechin itself. The authors suggest that quercetin transport probably involves a phosphorylation/dephosphorylation mechanism.

The interaction and permeability of various molecules (hesperetin, naringenin, hesperetin glucuronide, naringenin glucuronide, cyanidin-3-rutinoside, pelargonidin-3-glucoside, epicatechin, methylated epicatechin and epicatechin glucuronide) were evaluated in *in vitro* models (b.END5 mouse brain and RBE4 rat n cells) by Youdim *et al.* (2003).[42] Cells were incubated with compounds of interest for up to 18 h, confirming the entry of flavonoids and their metabolites into BECs. Hesperetin, naringenin and their metabolized forms, as well as evaluated anthocyanins, permeated across the BBB, with hesperetin and naringenin showing the highest values. Data also suggested that compounds may accumulate in brain cells. The authors analyzed permeability as a function of their Log *P*, with naringenin and hesperetin (the ones with the highest permeability) showing the highest values (2.61 and 2.44, respectively), followed by their glucuronidated metabolites and anthocyanins. The authors concluded that certain types of flavonoids and their *in vivo* metabolites can cross the BBB, while in the case of aglycones, this was attributed to their lipophilicity.

Human data

There is evidence of some phenolic compounds or their metabolites crossing the BBB, due to them being detected in

the CSF. For example, Grabska-Kobylecka *et al.* (2020)[43] analyzed the CSF of 28 patients (18 females, 10 males, age 46 ± 16) who had undergone a diagnostic lumbar puncture and peripheral blood sampling (both under fasting conditions). Samples were subjected to a solid-phase extraction and subsequent HPLC analysis (electrochemical and UV-Vis detectors), which revealed the presence of various phenolic compounds. Homovanillic acid, caffeic acid, 3-hydroxyphenyl acetic acid, dihydrocaffeic acid, vanillic acid, hippuric acid and 3,4 dihydrobenzoic acid were detected in the plasma of at least one patient; however, only homovanillic acid, caffeic acid and 3-hydroxyphenyl acetic acid were also detected in CSF. The authors note that homovanillic acid and 3-hydroxyphenyl acetic acid may be derived from non-dietary sources, for example, homovanillic acid is derived from endogenous catecholamine (dopamine, epinephrine and norepinephrine) metabolism. Catecholamine metabolism also produces other phenolic acids in the brain and elsewhere, such as vanillylmandelic acid, 3,4-dihydroxymandelic acid and 3,4-dihydroxyphenylacetic acid, and are therefore expected in normal brain tissue and CSF.[44] As for 3-hydroxyphenyl acetic acid, although it is a metabolite of various phenolic compounds produced by intestinal bacteria,[45] endogenous tyrosine and tyramine metabolism is also known to produce it, thus, it cannot be confirmed as being a food-derived phenolic compound.[46] On the other hand, caffeic acid is not produced endogenously, and was therefore confirmed to be a phenolic compound of exogenous origin that is able to cross the BBB and be detectable after an overnight fast. Its plasma (0.03 ± 0.01 μmol L^{-1}) and CSF (0.02 ± 0.01 μmol L^{-1}) concentrations were similar, but the values showed no significant correlation, which the authors cautiously interpreted as evidence against passive or facilitated transport across the BBB.

In contrast to this data, Zini *et al.* (2006)[47] were unable to detect flavan-3-ols or their metabolites after an acute ingestion of green tea (250 mL, consumed 1 h before blood collection and lumbar puncture) in human subjects (3 male, 3 female, 41 years old, range 34–61 years), according to HPLC-DAD-MS^2 data. Because the presence of various circulating compounds and their metabolites was confirmed, the authors propose that detecting them in blood is not enough to assume that they are also in the brain. However, they also acknowledge the limitations of their study, such as a small sample size, single dose and single sample, but comment about the intolerable invasiveness of another protocol.

Others have also analyzed the composition of human blood and CSF, where phenolic compounds were shown to be a major molecular class of metabolites quantified in both fluids.[48] Interestingly, the authors highlight the observed tendency of finding a higher phenolic concentration in CSF than in blood, although their exogenous origin was not conclusively established. This is congruent with the observations made by Grabska-Kobylecka *et al.* (2020)[43] and Zini *et al.* (2006),[47] regarding the discrepancies between these two fluids, and why detecting a compound in circulation is not enough evidence to assume that it will reach the brain.

Phenolic concentration data obtained from human brain and CSF is scarce, which can be attributed to the highly invasive nature of sampling the CNS. Because of this, most evidence to date comes from *in vitro* or *in vivo* models, where the viability of obtaining brain and CSF samples is higher. The need for human data is still significant, since no other tool can fully replicate the knowledge gained from it.

Possible transport mechanisms

The actual mechanism by which phenolic compounds cross the BBB is not fully defined. The potential ability to cross the BBB of phenolic sulfates was evaluated by Figueira *et al.* (2017),[40] demonstrating that these metabolites can be transported across the BBB. They propose a different transport mechanism for each tested metabolite, which can be related to the rank of modifications in its structure. For example, the permeability of gallic acid and catechol derivatives is enhanced by methylation and sulfation; however, pyrogallol derivatives show a different behavior. The authors utilized QikProp analysis, which predicts which molecules can cross the BBB, demonstrating that all methylated and sulfated forms of gallic acid, catechol and pyrogallol can cross passively, but also suggesting the presence of some form of active transport. The results of the *in silico* analysis suggested that entry of phenolics cannot be explained by passive transport only, possibly requiring active transport as well. Similarly, Faria *et al.* (2011)[28] evaluated the mechanism of molecules' access to the brain, reporting that it can be by passive diffusion and through a specific transporter, similar to previously mentioned studies. However, the elucidation of the possible active transport mechanisms requires additional investigations of molecules of interest, such as those of the phenolic family and their metabolites.

Lipinski's rule of five partially predicts which molecules can cross the BBB, proposing that those without a specific transporter with more than 5 hydrogen bond donors, 10 hydrogen bond acceptors, molecular weight >500 Da and Log *P* > 4.15 are poorly absorbed. These rules can be applied to phenolic compounds previously discussed according to the properties listed in Table 1, and whose chemical structures are shown in Fig. 1.

It is apparent that most compounds listed in Table 1 have a molecular weight <500 Da, this can explain why simple phenolic compounds have the ability to cross the BBB. For example, rutin and hesperidin have the highest molecular weight and the lowest permeability, as reported by Yang *et al.* (2014).[39] The Log *P* values suggest that all compounds listed are able to cross the BBB. Some molecules, particularly those of higher molecular weight, tend to have more hydrogen bond donors, which would theoretically make it less likely that they can cross the BBB. The ability of a compound to form hydrogen bonds restricts it from passively diffusing across a hydrophobic barrier (such as the BBB), thus, the requirement for a specific transporter increases. This is better illustrated for metabolites with a polar moiety attached, such as sulfated or glucuronidated ones, since these modifications are made with

Table 1 Lipinski's rule of five values for selected phenolic compounds

Number	Compound	MW	Log *P*	H-Bond donors	H-Bond acceptors
1	Danshensu	198.17	−0.25	4	5
2	Genistein	270.24	2.27	3	5
3	Pelargonidin	271.25	−0.26	4	5
4	Naringenin	272.26	2.12	3	5
5	Kaempferol	286.23	2.17	4	6
6	Catechin	290.27	1.37	5	6
7	Peonidin	301.27	−0.44	4	6
8	Quercetin	302.24	1.68	5	7
9	Malvidin	331.30	−0.42	4	7
10	Curcumin	368.38	2.30	2	6
11	Cyanidin-3-glucoside	484.83	−2.79	8	11
12	Cyanidin-3-rutinoside	595.53	−3.49	10	15
13	Rutin	610.52	−1.06	10	16
14	Hesperidin	610.56	−0.55	8	15

MW: molecular weight; H-bond: hydrogen bond. Numbering is based according to increasing molecular weight. Their chemical structures are shown in Fig. 1.

the purpose of increasing the hydrogen bond-forming potential of the molecule. This decreases the likelihood of a potentially toxic compound crossing a biological barrier, by allowing it to remain in circulation and promoting its excretion.[49] In contrast, methylation increases the lipophilicity of a compound by decreasing its hydrogen bond-forming potential, thereby promoting its ability to cross the BBB and accumulate in the CNS.[38]

For compounds that do not fulfill Lipinski's rules regarding their hydrogen bond-forming potential, the presence of specific transporters is possible. For example, curcumin has six hydrogen bond acceptors, and is able to accumulate in the brain,[34] probably due to transporters or other factors that promote its uptake and accumulation, although increasing its delivery into the CNS remains a challenge.[50] The number of hydrogen bond acceptors are within the theoretical range to be absorbed for most compounds considered, except for rutin, hesperidin, C3G and cyanidin-3-rutinoside. The fact that rutin and hesperidin have many hydrogen bond acceptors may be related to their the poor absorption to the brain, nevertheless, C3G is able to enter, even though it only fulfills three of five criteria. Therefore, it should be stated that Lipinski's rules are not absolute, but there are additional factors that precisely modulate a compound's potential to cross the BBB, which is likely to differ according to its structure and bioactivities.

As discussed in this section, many phenolic compounds are able to cross the BBB, even though some of them do not fulfil all the required characteristics established by Lipinski's rule of five. This fact, along with experimental evidence of stereoselectivity, suggests the presence of specific receptors, as proposed by several authors. However, the nature of these receptors must be elucidated with additional experimentation, as well as the main structural characteristics that influence their interactions with them. It should be stated that when a compound is administered intravenously or intraperitoneally, as reported in various documents discussed in the present work, its circulating concentration will likely be significantly higher, as compared to when consuming it orally. This will drive the diffusion of the said compound across the BBB down a concentration gradient, a phenomenon that is likely to vary from the oral intake route. Thus, conclusions drawn from these types of studies should take this into account.

Metabolic transformations suffered by these compounds (in the periphery or in the brain itself) may drastically alter their bioactivity, by making a metabolite significantly more or less accessible and/or bioactive than the parent compound. For example, Carregosa *et al.* (2020)[51] discuss some effects exerted by various known phenolic metabolites, such as benzene diols and triols, benzoic acids, cinnamic acids, phenylacetic acids and phenylpropionic acids, showing that they are capable of exerting neuroprotective effects *in vitro*. They also cite the case of certain compounds (such as caffeic acid phenethyl ester, CAPE) with significant bioactivities but poor bioavailability, and thus propose that analyzing the effects of some specific metabolites under physiological conditions is a more appropriate approach. Carecho *et al.* (2021)[52] comment on the presence of phase I and II enzymes inside the brain, suggesting that certain phenolics or their metabolites may suffer additional transformations therein, further altering their potential bioactivities. These observations highlight the need to consider the role of metabolites when analyzing a compound's distribution or bioactivity, since they may be responsible for most effects, particularly for larger phenolics that are unlikely be transported intact.

The mere absorption of phenolic compounds into the brain would not be noteworthy if they did not exert a significant effect once there, thus, the following discussion focuses on oxidative stress in the brain and the antioxidant effect of phenolic compounds on this organ.

Oxidative stress in the brain

An aerobic energy-yielding metabolism generates ROS as byproducts, whose deleterious effects on the cell must be prevented and/or countered by antioxidants. The term oxidative stress refers to a state where the balance of ROS/antioxidants is disrupted by an increase of ROS, a decrease of antioxidants or both. Under these conditions, excess ROS oxidize the cell's lipids, enzymes/proteins, nucleic acids and most other molecules, which causes cell damage through lipid peroxidation, protein misfolding/aggregation or genetic mutations.[53,54]

The brain satisfies its energy demands through a high aerobic metabolism, consuming approximately 20% of the organism's oxygen.[55] Due to its high metabolic requirements, a deficient antioxidant defense system and particular characteristics of neurons, the brain is extremely vulnerable to oxidative stress, as compared to most other organs. The brain is rich in several different polyunsaturated fatty acids, which are easily oxidized by ROS and free radicals, a process that can lead to damage, disruption and breakdown of the BBB. At the

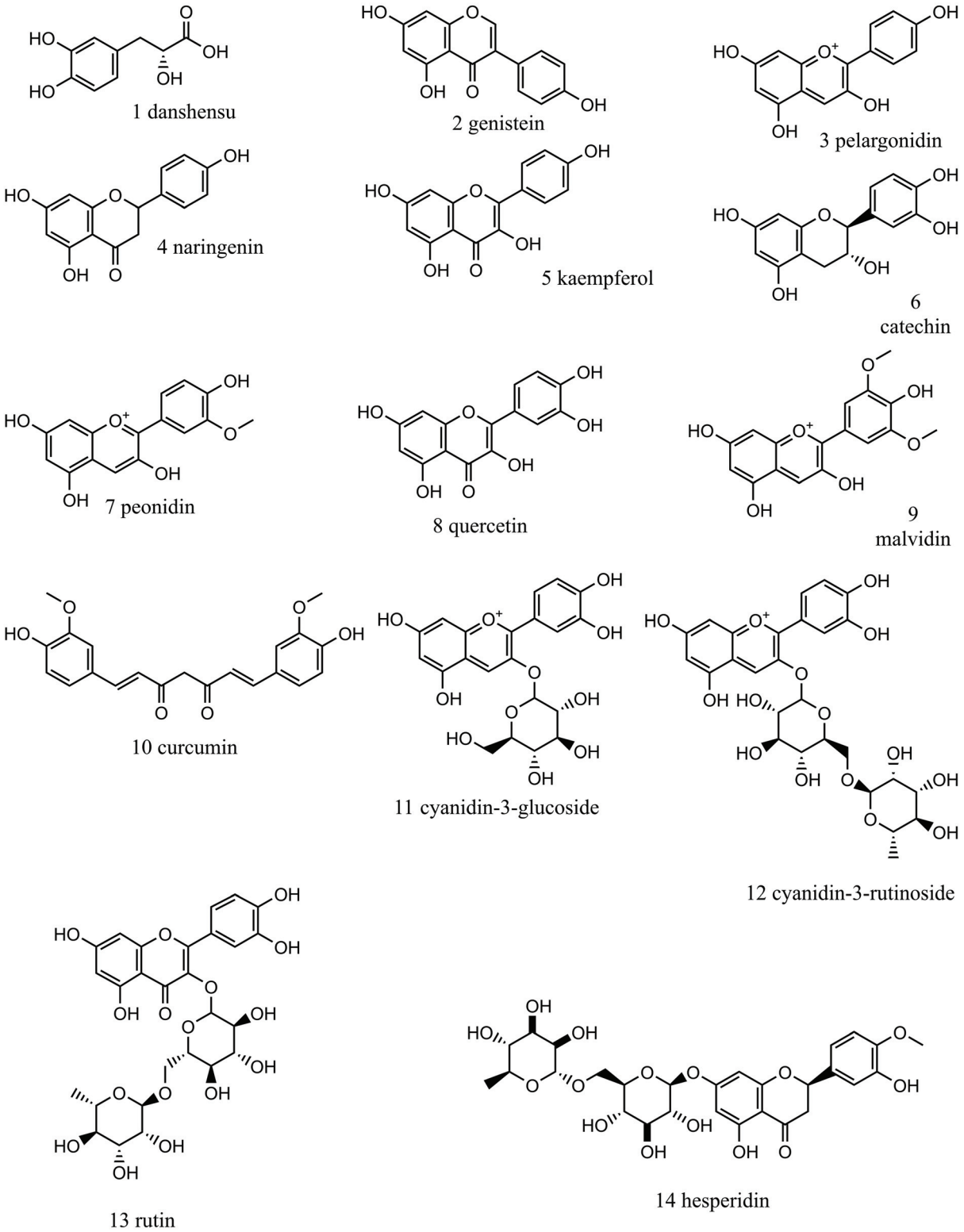

Fig. 1 Chemical structures of selected phenolic compounds that are able to cross the BBB. Numbering is the same as in Table 1, and is based on increasing molecular weight.

same time, matrix metalloproteases (MMPs) that can catabolize the BBB's basal lamina can be activated by ROS, hence, the generation of ROS can further promote BBB breakdown. When the lamina breaks down, TJs and AJs are down-regulated causing ischemia, a pathology that affects the intra and extracellular concentration of Ca^{2+}, which can subsequently

increase the BBB's permeability by creating changes in transport pathways and TJ modifications.[56–60] Damage to the BBB and a high ROS generation in the brain are conditions that have been implicated in the development of many pathologies, such as cancer and neurodegenerative diseases like Alzheimer's, Parkinson's and others.[61,62] Some phenolic compounds like curcumin and quercetin form a quinone, which depletes endogenous antioxidants like glutathione. The cellular response is then to ramp up glutathione production, thereby making them indirect antioxidants according to their ability to induce an adaptive response to oxidative stress.[63,64]

Maintaining redox homeostasis is essential for life and overall health.[65] Because ROS are naturally generated by various metabolic processes, their oxidative damage is kept under strict control by the antioxidant defense system, while failure to control it has been linked to different pathologies.[66] This is based on the precise regulation of endogenous antioxidants or on increasing the concentration of those of exogenous origin, mainly through diet;[67] the former strategy is under the cell's control, but the latter is under the individual's conscious control through dietary choices. Li *et al.* (2013)[61] and other authors have suggested that using exogenous antioxidants as neuroprotective and preventive adjuvants could be a promising strategy that has to be profoundly studied; however, it appears that this neuroprotective effect is not as beneficial when the damage or disease is already advanced. We previously observed that the most efficient neuroprotective effects of antioxidants are preventive rather than therapeutic.[68,69]

Effects of phenolic compounds on oxidative stress biomarkers in the brain

The effects of phenolic compounds have been less studied in the brain, as compared to other organs, even while it is highly vulnerable to oxidative stress. As previously stated, only some phenolic compounds or their metabolites are able to reach the brain because of the BBB; this has led to an interest in defining precisely which ones do and promoting their use to exert a beneficial impact on brain and overall health. Therefore, the importance of studying the beneficial effects of phenolic compounds and/or diets rich in them on oxidative stress biomarkers in the brain is highlighted. The present section focuses on the protective effect of phenolic compounds regarding antioxidant-related actions, since this is perhaps the most characteristic bioactivity for which they are known, but it should also be noted that they are also capable of exerting numerous other health-related effects that are independent of their antioxidant potential.[70,71] For example, they can increase insulin sensitivity,[72] they can modulate the composition of the intestinal microbiota[73] and regulate peripheral lipid metabolism,[74] among other effects, all of which can be exerted independently of any antioxidant actions. Moreover, these effects can be neuroprotective in and of themselves, meaning that a phenolic compound can have a significant impact on the brain without actually crossing the BBB.

The effect of curcumin on injury-induced oxidative stress in the brain has been analyzed in different models, reporting an overall improvement of these biomarkers. For example, Siddique *et al.* (2014)[75] analyzed the brains of transgenic flies expressing human α-synuclein, a protein related to the development of Parkinson's disease, that generates oxidative stress. After 25 days of treatment with three different doses of curcumin, the authors observed a dose-dependent reduction of lipid peroxidation, as compared to the control. This finding could be attributed to a remodeling effect exerted by certain flavonoids that convert α-synuclein fibrils into smaller aggregates, thus preventing the generation of ROS, in addition to curcumin's direct antioxidant effects. Furthermore, while evaluating its effect on rats with oxidative stress alterations induced by different pathological conditions, the authors found that high doses or curcumin significantly decreased malondialdehyde (MDA) concentration, while also increasing glutathione (GSH) and decreasing antioxidant enzyme degradation and oxidative index, as compared to the control. Based on these findings, it was proposed that curcumin can ameliorate oxidative stress in the brain by maintaining antioxidant homeostasis. The antioxidant effects of curcumin (50 and 100 mg kg^{-1}) in this organ have been shown to protect against acrylamide-induced neurotoxicity *in vivo* (Sprague Dawley rats, 40 mg aceylamide per kg), according to decreased oxidative and inflammatory markers [TNF-α, IL-1β and MDA] and increased components of the antioxidant system [glutathione, superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities].[76] The effectiveness of curcumin on brain health has been such that synthetic derivatives are currently being tested as potential treatments for Parkinson's disease, with a mechanism of action related to modulating the endogenous antioxidant system.[77] These findings could be used to complement conventional treatments for Parkinson's, Alzheimer's and other neurodegenerative diseases where oxidative damage is relevant.

Zhang *et al.* (2017)[78] induced aneurysmal subarachnoid hemorrhage on Sprague-Dawley rats, a pathology characterized by a loss of BBB stability and structure. After administering free and nanoencapsulated curcumin, the authors observed a protective effect on the BBB structure by preserving TJs, as well as decreased concentrations of ROS, MDA and 8-oxo-2′-deoxyguanosine (8-OHDG). In addition, curcumin normalized SOD and GPx activity, as well as reversed catalase (CAT) inhibition. These results showed that curcumin mitigated pathologically derived oxidative stress in the brain, by improving its overall antioxidant status.

Yonguc *et al.* (2015)[79] administered grape seed extract (GSE) to streptozotocin-induced diabetic rats, on hippocampal oxidative stress. After a six-week treatment, the authors determined that brain antioxidant status had improved, while also showing anti-apoptotic effects in the hippocampus. Moreover, Bedhiafi *et al.* (2018)[80] evaluated the effects of grape seed extract on rats fed high fat diets, which increased oxidative stress and lipid peroxidation. The addition of high doses (4000 mg kg^{-1}) of GSE reversed and ameliorated diet-induced oxidative stress and lipid peroxidation, as well as improved

antioxidant enzyme activity. These results suggest that phenolic compounds present in grape seed cross the BBB, as previously discussed, and are able to exert health effects therein.

Devi *et al.* (2011)[81] evaluated the effects of GSE on age-related oxidative stress, in an *in vivo* rat model. The authors showed that a brief treatment with high doses (12 weeks, 75 mg kg^{-1}) significantly improved brain's antioxidant status by reducing H_2O_2 (−46%) and MDA (−41.5%) concentrations, while also increasing CAT activity (38%). These results were more pronounced in middle-aged, rather than in older animals, suggesting that the preventive effects of GSE consumption are more effective, as compared to consuming it once deterioration has already occurred. Other authors administered GSE to rats with lithium-induced oxidative stress. After a one-month treatment, protein carbonylation, MDA and oxidized glutathione significantly decreased, while SOD and CAT activities increased.[82] According to their findings, the authors argue that GSE can be effective against oxidative stress, which can prevent the development of oxidative stress-related CNS diseases. The potential of GSPE to prevent and/or treat ischemia-reperfusion injuries (such as those that occur during a stroke) has been studied, showing significant positive results according to decreased cell death, anti-inflammatory and antioxidant effects.[83] This suggests that their accumulation in the brain and antioxidant-related actions can lead to significant neuroprotection, thereby preventing oxidative damage, such as that found on Parkinson's and Alzheimer's disease, among others.

Danshen is widely used in traditional South Asian medicine to treat cardiovascular and cerebrovascular diseases, with various validated effects on the cardiovascular system. Although danshensu, one of its main phenolic compounds, is able to effectively cross the BBB (as previously discussed), there are few studies evaluating its effects on the brain. Jing *et al.* (2016)[84] performed *in vivo* (C57BL mice) and cell line (human neuroblastoma SH-SY5Y cells) experiments to determine the effect of this compound on oxidative stress biomarkers. The results showed that 6-hydroxydopamine (6-OHDA) induced oxidative stress by promoting ROS synthesis, which danshensu was able to prevent, in addition to increasing glutathione and inhibiting Nrf2 transcriptional activity and neuronal death. The neuroprotective actions of danshen phenolics have been studied *in vivo*, showing significant protection against ROS in *C. elegans* and against aggregation of amyloid-beta in a *Drosophila melanogaster* model of Alzheimer's disease.[85,86]

The effect of naringenin, the main flavonoid of several citrus fruits, has been evaluated on the brain to determine its effects on oxidative stress. Wang *et al.* (2017)[87] evaluated the neuroprotective effect of this flavonoid at three different concentrations (20, 40 and 80 μM) on cultured neurons from neonatal Sprague-Dawley rats exposed to oxygen deprivation. The authors found a significant reduction of ROS and MDA levels, while SOD1 and glutathione increased in the highest-dosage group. The same effects were also observed in a different study using male Swiss mice with social defeat-induced oxidative

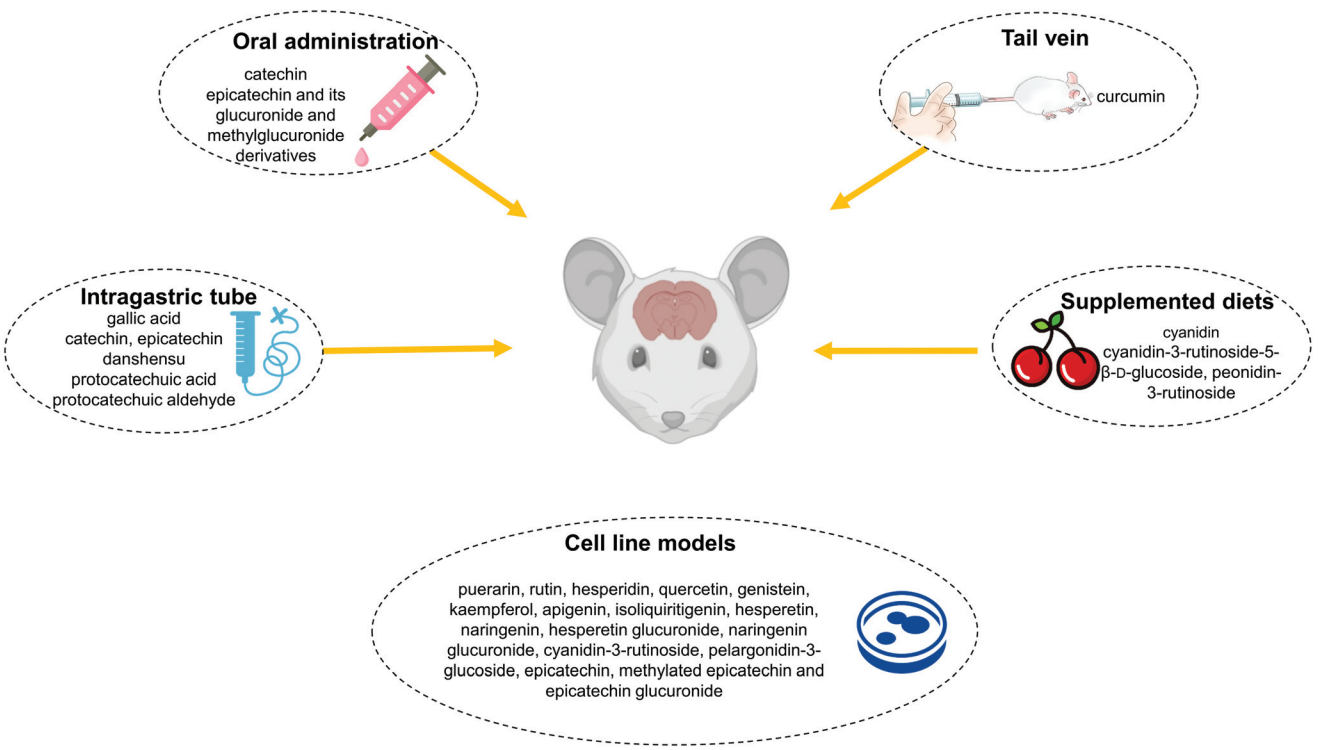

Fig. 2 Overview of phenolic compounds discussed in the main text that cross the BBB and exert antioxidant bioactivities in the brain. Most experimental evidence was obtained from murine models.

stress, where an increased CAT activity was found in the medium and high dosage groups.[88] In addition, a significant decrease in MDA was found when naringenin was evaluated in an Alzheimer's disease murine model that was pretreated with an intraperitoneal injection of this flavonoid.[89]

Adedara *et al.* (2016)[90] analyzed the neuroprotective effects of quercetin against manganese-induced damage. Wistar rats were treated with manganese (15 mg per kg BW) or manganese and quercetin (10 and 20 mg per kg BW). The authors report decreased SOD and CAT activity and increased H_2O_2 and lipid peroxidation in the manganese group, which quercetin was able to normalize to values similar to those of the healthy control. In addition to this study, Kanimozhi *et al.* (2017)[91] evaluated the effect of quercetin against hyperammonemic stress by administering ammonium chloride (100 mg per kg BW) or ammonium chloride and quercetin (100 and 50 mg per kg BW) to Wistar rats for a 56-day period. The results showed that hyperammonemia increased lipid peroxidation and hydroperoxides, effects that were significantly countered by quercetin. Antioxidant enzyme activity was also normalized by the quercetin treatment. According to their results, the authors concluded that quercetin exerts an antioxidant effect in the brain of hyperammonemic rats. These results suggest that quercetin is able to cross the BBB in order to exert an antioxidant effect against manganese-induced and ammonia-induced oxidative damage.

A brief graphical representation of molecules that cross the BBB to exert antioxidant bioactivities in the brain is presented in Fig. 2. It is of great interest to study and elucidate the possible mode of action and mechanisms involved in the preventive effects of hydrophylic and hydrophobic molecules present in various foods. The study of transport kinetics of molecules through the BBB is of relevance, as well as the possible molecular interactions with other compounds that can reduce or increase their passive or active crossing.

Conclusion

Entry of phenolic compounds through the BBB into the CNS is highly relevant, since they can exert significant neuroprotection if regularly consumed. Experimental evidence suggests that low molecular weight, hydrophobicity and low hydrogen-binding potential are physicochemical properties that allow them to across the BBB. Furthermore, methylation, sulfation and glucuronidation of phenolic compounds also facilitate access to some species, as compared to the parent compound, in addition to altering their bioactivities. Some studies show stereospecific preference for some molecules, which suggests that there are specific transporters that enable them to cross the BBB; however, these have been poorly studied. Once inside the CNS, they exert bioactivities like mitigating and treating oxidative stress, which is key in preserving the integrity and health of the brain, due to its high susceptibility to oxidation. Because of the major role of metabolized phenolic compounds in the brain and overall health, further studies regarding their mechanism of entry into the CNS through the BBB and bioactivities therein are warranted. Although it should be noted that phenolic compounds may still exert an effect on the CNS, even if they are unable to cross the BBB. Conclusive evidence for the presence of active transporters is particularly required, since the information currently available does not definitively prove or disprove it.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This work was supported by Instituto de Bebidas de la Industria Mexicana de Coca-Cola through project "Inducción de saciedad y modulación de la digestión intestinal de lípidos ejercidos por los compuestos fenólicos de aguacate Hass" (Premio Nacional en Ciencia y Tecnología de Alimentos 2019) and by Centro de Investigación en Alimentación y Desarrollo (CIAD) A. C.

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