REVIEW

The neuroprotective potential of flavonoids: a multiplicity of effects

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Abstract Flavonoids exert a multiplicity of neuroprotective actions within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning and cognitive function. These effects appear to be underpinned by two common processes. Firstly, they interact with critical protein and lipid kinase signalling cascades in the brain leading to an inhibition of apoptosis triggered by neurotoxic species and to a promotion of neuronal survival and synaptic plasticity. Secondly, they induce beneficial effects on the vascular system leading to changes in cerebrovascular blood flow capable of causing angiogenesis, neurogenesis and changes in neuronal morphology. Through these mechanisms, the consumption of flavonoid-rich foods throughout life holds the potential to limit neurodegeneration and to prevent or reverse age-dependent loses in cognitive performance. The intense interest in the development of drugs capable of enhancing brain function means that flavonoids may represent important precursor molecules in the quest to develop of a new generation of brain enhancing drugs.

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Introduction

Recently, there has been intense interest in the potential of flavonoids to modulate neuronal function and prevent against age-related neurodegeneration. The use of flavonoid-rich plant or food extracts in humans and animal dietary supplementation studies have shown improvements in cognition function possibly by protecting vulnerable neurons, enhancing existing neuronal function or by stimulating neuronal regeneration [134]. Their neuroprotective potential has been shown in both oxidative stress [41] and Aβ-induced neuronal death models [65]. Evidence also exists for the beneficial and neuromodulatory effects of flavonoid-rich ginkgo biloba extracts, particularly in connection with age-related dementias and Alzheimer's disease [7]. Furthermore, individual flavonoids such as the citrus flavanone tangeretin, has been observed to maintain nigro-striatal integrity and functionality following lesioning with 6-hydroxydopamine, suggesting that it may serve as a potential neuroprotective agent against the underlying pathology associated with Parkinson's disease [24]. In addition, flavonoids may also exert beneficial effects on memory and may prevent cognitive losses associated with ageing and even reverse certain age-related declines [45, 46]. This review will highlight the neuroprotective mechanisms of flavonoids and other polyphenols, in particular their ability interact with neuronal signalling pathways [91, 97] and their potential to inhibit neuro-inflammatory processes in the brain [17, 48].

Flavonoid: sources and structure

Flavonoids are major constituents of fruit, vegetables and beverages, such as wine, tea, cocoa and fruit juices. Most commonly, flavonoids share a common structure consisting of two aromatic rings (A and B), which are bound together by three carbon atoms, forming an oxygenated heterocycle (ring C) (Fig. 1). Based on variations in the saturation of the basic flavan ring system, their alkylation and/or glycosylation and the hydroxylation pattern of the molecules, flavonoids may be divided into seven subclasses: flavonols, flavones, flavanones, flavanonols, flavanols, anthocyanidins, and isoflavones (reviewed by Manach et al. [67]).

The flavanols, sometimes referred to as flavan-3-ols, are found predominantly in green and black teas, red wine and chocolate. Variations in their structures lie in the hydroxylation pattern of the B ring and the presence of gallic acid in position 3. The lack of a double bond at the 2–3 position and the presence of a 3-hydroxyl group on the C-ring create two centres of asymmetry. Typical dietary flavanols include catechin, epicatechin, epigallocatechin (EGC) and epigallocatechin gallate (EGCG) (Fig. 1). Flavanols exist also as oligomers or polymers, referred to as condensed tannins or proanthocyanidins, which are found in high concentration in cocoa, tea, red wine and fruits such as apples, grapes and strawberries. These differ in nature based on their constitutive units (e.g. catechins and epicatechin), their sequence and the position of interflavanic linkages. The sources of anthocyanins such as pelargonidin, cyanidin and malvidin include red wine and berry fruits such as blueberries, blackberries cherries and strawberries. These compounds exist as glycosides in plants, are water-soluble and appear red or blue according to pH. Individual anthocyanins arise from the variation in number and arrangement of the hydroxyl and methoxy groups around the three rings (Fig. 1). Flavones such as apigenin, luteolin are found in parsley, chives, artichoke and celery. Hydroxylation on position 3 of the flavone structure gives rise to the 3-hydroxyflavones also known as the flavonols (e.g. kaempferol, quercetin), which are found in onions, leeks, broccoli (Fig. 1). The diversity of these compounds stems from the varying positions of phenolic –OH groups around the three rings. Dietary flavanones include naringenin, hesperetin and taxifolin and are found predominantly in citrus fruit and tomatoes. Hydroxylation of flavanones in position 3 of C-ring gives rise to the flavanonols (Fig. 1). Finally, isoflavones such as daidzein and genistein are a subclass of the flavonoid family found in soy and soy products. They have a large structural variability and more than 600 isoflavones have been identified to date and are classified according to oxidation level of the central pyran ring (Fig. 1).

Absorption, metabolism and distribution of flavonoids

Although flavonoids have been identified as powerful antioxidants in vitro [84–86], their ability to act as antioxidants in vivo is limited by the extensive biotransformation and conjugation which occurs during their absorption from the gastrointestinal (GI) tract, in the liver and finally in cells (reviewed in [103, 107]). In the small intestine and liver, dietary flavonoids (and other polyphenols) are substrates for phase I (hydrolysing and oxidizing) and phase II (conjugating and detoxifying), meaning that they are de-glucosylated and metabolised into glucuronides, sulphates and O-methylated derivatives [99, 103, 104]. Further metabolism occurs in the colon, where the enzymes of the gut microflora induce the breakdown of flavonoids to simple phenolics acids that may then undergo absorption and further metabolized in the liver [88]. Furthermore, flavonoids may undergo at least three types of intracellular metabolism: (1) Oxidative metabolism, (2) P450-related metabolism and (3) Conjugation with thiols, particularly GSH [100]. Circulating metabolites of flavonoids, such as glucuronides, sulphates and conjugated O-methylated forms, or intracellular metabolites like flavonoid-GSH adducts, have significantly reduced antioxidant potential relative to the forms found in plants [102]. Indeed, studies have indicated that although such conjugates and metabolites may participate antioxidant reactions and may scavenge reactive oxygen and nitrogen species in the circulation, their effectiveness to do so is reduced compared to their parent aglycones [22, 70, 94, 117, 132].

In order for flavonoids to access the brain, they must first cross the blood brain barrier (BBB), which controls entry of xenobiotics into the brain [2]. Flavanones such as hesperetin, naringenin and their in vivo metabolites, along with some dietary anthocyanins, cyanidin-3-rutinoside and pelargonidin-3-glucoside, have been shown to traverse the BBB in relevant in vitro and in situ models [135]. Their degree of BBB penetration is dependent on compound lipophilicity [133], meaning that less polar O-methylated metabolites may be capable to greater brain uptake than the more polar flavonoid glucuronides. However, evidence exists to suggest that certain drug glucuronides may cross the BBB [1] and exert pharmacological effects [52, 112], suggesting that there may be a specific uptake mechanism for glucuronides in vivo. Their brain entry may also depend on their interactions with specific efflux transporters expressed in the BBB, such as P-glycoprotein [63] which appears to be responsible for the differences between naringenin and quercetin flux into the brain in situ [135]. In animals, flavanones have been found to enter the brain following their intravenous administration [79], whilst epigallocatechin gallate [115], epicatechin [3] and anthocyanins [26, 116] are found in the brain after their oral
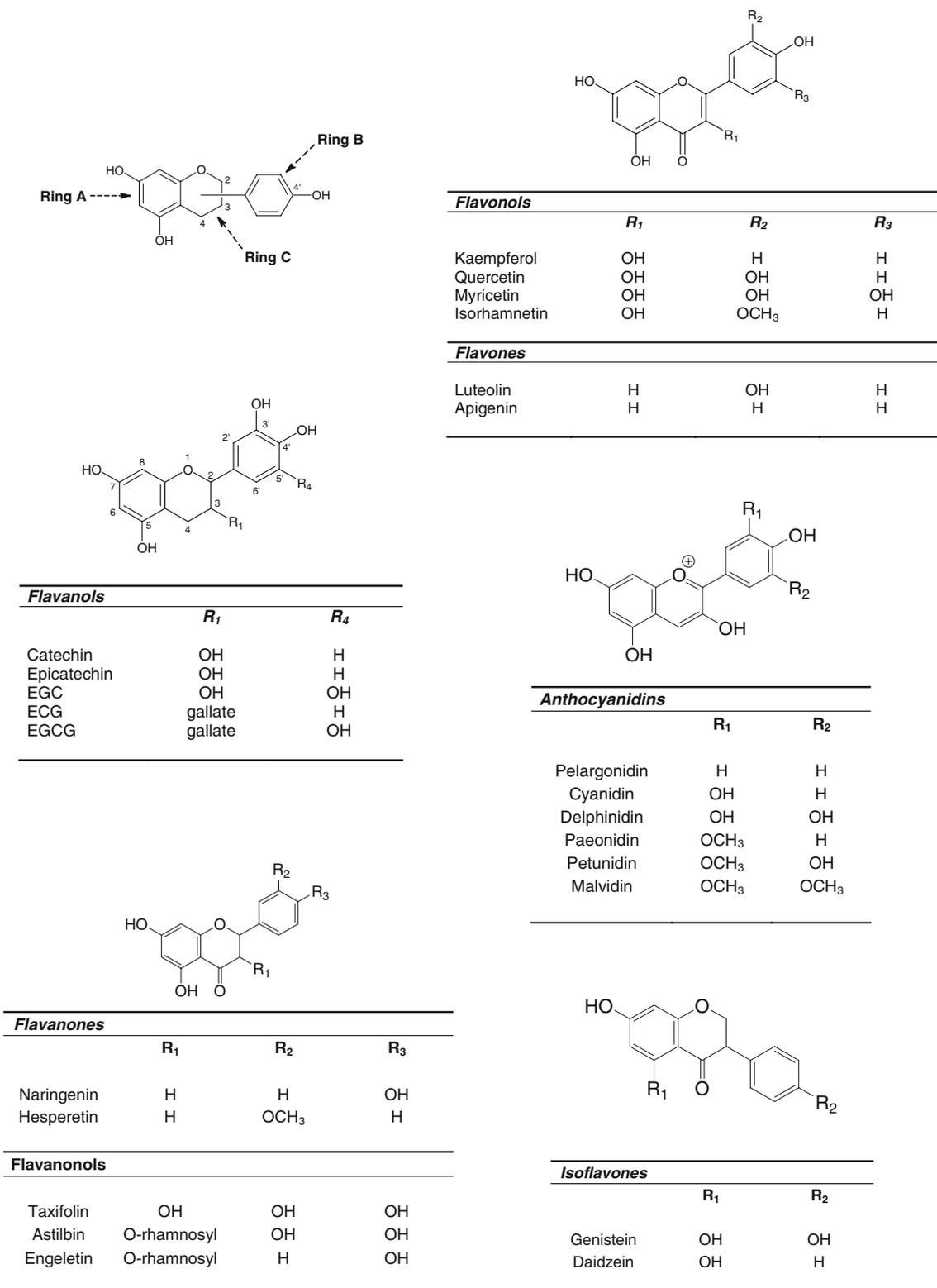
Flavonols

	R_1	R_2	R_3
Kaempferol	OH	H	H
Quercetin	OH	OH	H
Myricetin	OH	OH	OH
Isorhamnetin	OH	OCH$_3$	H

Flavones

Luteolin	H	OH	H
Apigenin	H	H	H

Flavanols

	R_1	R_4
Catechin	OH	H
Epicatechin	OH	H
EGC	OH	OH
ECG	gallate	H
EGCG	gallate	OH

Anthocyanidins

	R_1	R_2
Pelargonidin	H	H
Cyanidin	OH	H
Delphinidin	OH	OH
Paeonidin	OCH$_3$	H
Petunidin	OCH$_3$	OH
Malvidin	OCH$_3$	OCH$_3$

Flavanones

	R_1	R_2	R_3
Naringenin	H	H	OH
Hesperetin	H	OCH$_3$	H

Flavanonols

Taxifolin	OH	OH	OH
Astilbin	O-rhamnosyl	OH	OH
Engeletin	O-rhamnosyl	H	OH

Isoflavones

	R_1	R_2
Genistein	OH	OH
Daidzein	OH	H

Fig. 1 The structures of the main classes of flavonoids. The major differences between the individual groups reside in the hydroxylation pattern of the ring-structure, the degree of saturation of the C-ring and the substitution of in the 3-position: **a** general structure of flavonoids, **b** structure of flavonols and flavones, **c** structure of flavanols, also referred as flavan-3-ols, **d** structure of anthocyanidins, **e** structure of flavanones and flavanonols and **f** structure of isoflavones

administration. Furthermore, several anthocyanins have been identified in different regions of the rat [78] and pig brains [47] of blueberry fed animals, with 11 intact anthocyanins found in the cortex and cerebellum. Studies have indicated that the accumulation of flavonoids in the brain is not dependent on the brain region, with levels of anthocyanins reaching 0.45 ± 0.12 nmol/g in the hippocampus and 0.46 ± 0.11 nmol/g in the cortex following intervention with a 2% w/w blueberry diet for 12 weeks [129]. Flavanols have been shown to accumulate at significantly higher levels (Hippocampus: 2.65 ± 0.17 nmol/ g tissue; cortex levels were 2.54 ± 0.18), following the same dietary intervention. These results indicate that flavonoids traverse the BBB and are able to localize in the brain, suggesting that they are candidates for direct neuroprotective and neuromodulatory actions.

Protection against neuronal injury induced by neurotoxins

Neurodegeneration in Parkinson's, Alzheimer's, and other neurodegenerative diseases appears to be triggered by multi-factorial events including neuroinflammation, glutamatergic excitotoxicity, increases in iron and/or depletion of endogenous antioxidants [6, 44, 113]. There is a growing body of evidence to suggest that flavonoids may be able to counteract the neuronal injury underlying these disorders [68, 98, 105]. For example, a Ginkgo biloba extract has been shown to protect hippocampal neurons from nitric oxide- and beta-amyloid-induced neurotoxicity [65] and studies have demonstrated that the consumption of green tea may have beneficial effect in reducing the risk of Parkinson's disease [16]. In agreement with the latter study, tea extracts and (−)-epigallocatechin-3-gallate (EGCG) have also been shown to attenuate 6-hydroxydopamine-induced toxicity [61], to protect against hippocampal injury during transient global ischemia [56] and to prevent nigral damage induced by MPTP [60].

The death of nigral neurons in Parkinson's disease is thought to involve the formation of the endogenous neurotoxin, 5-S-cysteinyl-dopamine [108, 109]. Recent investigations have shown that 5-S-cysteinyl-catecholamine conjugates possess strong neurotoxicity and initiate a sustained increase in intracellular reactive oxygen species (ROS) in neurons leading to DNA oxidation, caspase-3

Fig. 2 Involvement of neuroinflammation, endogenous neurotoxins and oxidative stress in dopaminergic neurodegeneration. Structures of the 5-S-cysteinyl-dopamine (5-S-Cys-DA) and the dihydrobenzothiazine-1 (DHBT-1) are shown
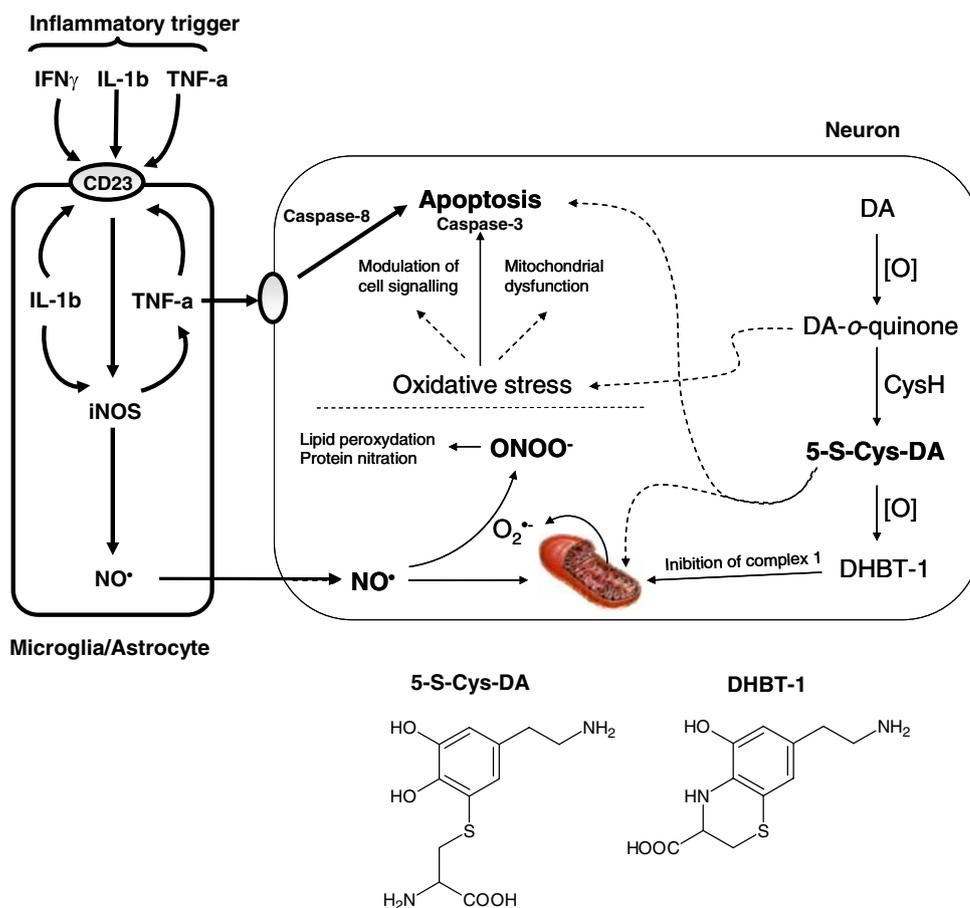
activation and delayed neuronal death [37, 111] (Fig. 2). Such adducts may be generated by reactive species [121] and have been observed to be been elevated in the human substantia nigra of patients who died of Parkinson's disease [108], suggesting that such species may be potential endogenous nigral toxins. However, 5-S-cysteinyldopamine-induced neuronal injury is counteracted by nanomolar concentrations of various flavonoids including pelargonidin, quercetin, hesperetin, caffeic acid, the 4′-O-Me derivatives of catechin and epicatechin [121]. Furthermore, in presence of the flavanol, (+)-catechin, tyrosinase-induced formation of 5-S-cysteinyl-dopamine was inhibited by a mechanism linked to the capacity of catechin to undergo tyrosinase-induced oxidation to yield cysteinyl-catechin adducts [123]. In contrast, the inhibition afforded by flavanones, such as hesperetin, was not accompanied with the formation of cysteinyl-hesperetin adducts, indicating that it may inhibit via direct interaction with tyrosinase [123].

Reactive oxygen and nitrogen species have also been proposed to play a role in the pathology of many neurodegenerative diseases [44] (Fig. 2). There is abundant evidence that flavonoids are effective in blocking this oxidant-induced neuronal injury, although their potential to do so is thought not to rely on direct radical or oxidant scavenging [98, 102, 110]. Instead, they are believed to act by modulating a number of protein kinase and lipid kinase signalling cascades, such as the PI3 kinase (PI3 K)/Akt, tyrosine kinase, protein kinase C (PKC) and mitogen-activated protein kinase (MAP kinase) signalling pathways [98, 130]. Inhibitory or stimulatory actions of these pathways are likely to profoundly affect neuronal function by altering the phosphorylation state of target molecules, leading to changes in caspase activity and/or by gene expression [130]. For example, flavonoids have been observed to block oxidative-induced neuronal damage by preventing the activation of caspase-3, providing evidence in support of their potent anti-apoptotic action [91, 92, 102]. The flavanols epicatechin and 3′-O-methyl-epicatechin also protect neurons against oxidative damage via a mechanism involving the suppression of JNK, and downstream partners, c-jun and pro-caspase-3 [91]. Flavanones, such as hesperetin and its metabolite, 5-nitro-hesperetin, have been observed to inhibit oxidant-induced neuronal apoptosis via a mechanism involving the activation/phosphorylation of signalling proteins important in the pro-survival pathways [122]. Similarly, the flavone, baicalein, has been shown to significantly inhibit 6-hydroxydopamine-induced JNK activation and neuronal cell death and quercetin may suppress JNK activity and apoptosis induced by hydrogen peroxide [42, 124], 4-hydroxy-2-nonenal [119] and tumour necrosis factor-alpha (TNF-alpha) [49].

Inhibition of neuroinflammation

Neuroinflammatory processes in the CNS are believed to play a crucial role in the development of neurodegenerative diseases such as Alzheimer's and Parkinson's disease [39] as well as with neuronal injury associated with stroke [137]. Glial cells (microglia and astrocytes) activation leads to the production of cytokines and other inflammatory mediators which may contribute to the apoptotic cell death of neurons observed in many neurodegenerative diseases. In particular, increases in cytokine production (interleukin-1β, IL-1β; tumor necrosis factor-alpha, TNF-α) [50], inducible nitric oxide synthase (iNOS) and nitric oxide (NO), and increased NADPH oxidase activation [4] all contribute to glial-induced neuronal death (Fig. 2). These events are controlled by MAPK signalling which mediate both the transcriptional and post-transcriptional regulation of iNOS and cytokines in activated microglia and astrocytes [9, 69]. Whilst ibuprofen, a non-steroidal anti-inflammatory drug, has been shown to delay the onset of neurodegenerative disorders, such as Parkinson disease [14], the majority of existing drug therapies for neurodegenerative disorders has failed to prevent the underlying degeneration of neurons. Consequently, there is a desire to develop alternative strategies capable of preventing the progressive neuronal loss resulting from neuroinflammation.

Flavonoid-rich blueberry extracts have been observed to inhibit NO, IL-1β and TNF-α production in activated microglia cells [53, 54], whilst the flavonol quercetin [17], the flavones wogonin and bacalein [55], the flavanols catechin and epigallocatechin gallate (EGCG) [62], and the isoflavone genistein [125] have all been shown to attenuate microglia and/or astrocyte mediated neuroinflammation via mechanisms that include inhibition of: (1) iNOS and cyclo-oxygenase (COX-2) expression, (2) NO production, (3) cytokine release, and (4) NADPH oxidase activation and subsequent reactive oxygen species generation, in astrocytes and microglia. Flavonoids may exert these effects via direct modulation of protein and lipid kinase signalling pathways [98, 105, 130], for example via the inhibition of MAPK signalling cascades, such as p38 or ERK1/2 which regulate both iNOS and TNF-α expression in activated glial cells [9]. In this respect, fisetin inhibits p38 MAP kinase phosphorylation in LPS-stimulated BV-2 microglial cells [136] and the flavone luteolin inhibits IL-6 production in activated microglia via inhibition of the JNK signalling pathway. The effects of flavonoids on these kinases may influence downstream pro-inflammatory transcription factors important in iNOS transcription. One of these, nuclear factor-Kappa B (NF-κB), responds to p38 signalling and is involved in iNOS induction [8], suggesting that there is interplay between signalling pathways, transcription factors and cytokine

production in determining the neuroinflammatory response in the CNS. However, flavonoids have also been shown to prevent transcription factor activation, with the flavonol quercetin able to suppress NF-κB, signal transducer and activator of transcription-1 (STAT-1) and activating protein-1 (AP-1) activation in LPS- and IFN-γ-activated microglial cells [17].

Flavonoid-induced improvements in memory, learning and cognitive performance

There is a growing interest in the potential of phytochemicals to improve memory, learning and general cognitive ability [105, 106]. A recent prospective study aimed at examining flavonoid intake in relation to cognitive function and decline, has provided strong evidence that dietary flavonoid intake is associated with better cognitive evolution, i.e. the preservation of cognitive performance with ageing [59]. In this PAQUID study (Personnes Agées QUID), a total of 1,640 subjects (aged 65 years or older) free from dementia at baseline and with reliable dietary assessment data were examined for their cognitive performance (Mini-Mental State Examination, Benton's Visual Retention Test, "Isaacs" Set Test) four times over a 10-year-period. After adjustment for age, sex, and educational level, flavonoid intake was found to be associated with significantly better cognitive performance at baseline and with a significantly better evolution of the performance over time. In particular, subjects included in the two highest quartiles of flavonoid intake had better cognitive evolution than subjects in the lowest quartile and after 10 years follow-up, subjects with the lowest flavonoid intake had lost on average 2.1 points on the Mini-Mental State Examination, whereas subjects with the highest quartile had lost 1.2 points. Such data provides a strong indication that regular flavonoid consumption may have a positive effect on neuro-cognitive performance as we age.

There has been much interest in the neuro-cognitive effects of soy isoflavones (Fig. 1), primarily in post-menopausal women [10, 28, 57, 128]. Isoflavone supplementation has been observed to have a favourable effect on cognitive function [13], particularly verbal memory, in postmenopausal women [51] and a 6 and 12-week supplementation was observed to have a positive effect of frontal lobe function [27]. Furthermore, animal studies have also indicated that isoflavones are capable of improving cognitive function [58, 64, 77]. However, there is still uncertainty regarding their effects as some large intervention trials have reported that isoflavone supplementation does not lead to cognitive improvements [30]. The rationale behind the potential of isoflavones to exert positive effects on cognitive function is believed to lie primarily in their potential to mimic the

actions and functions of oestrogens in the brain [10]. For example, postmenopausal women who undertake oestrogen-replacement therapy have a significantly lower risk for the onset of Alzheimer's disease than women who do not [38]. They may also be effective by affecting the synthesis of acetylcholine and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in hippocampus and frontal cortex [75, 76].

There is also extensive evidence that berries, in particular blueberries, are effective at reversing age-related deficits in motor function and spatial working memory [5, 12, 45, 46, 129]. In addition to spatial memory, blueberry supplementation has been shown to improve 'object recognition memory' [34] and 'inhibitory fear conditioning learning' [5]. Blueberry appears to have a pronounced effect on short-term memory [82] and has also been shown to improve long-term reference memory following 8 weeks of supplementation. [12]. Tests using a radial arm maze have supported these findings and have provided further evidence for the efficacy of blueberries [129]. Indeed, these have shown that improvements in spatial memory may emerge within 3 weeks, the equivalent of about 3 years in humans. The beneficial effects of flavonoid-rich foods and beverages on psychomotor activity in older animals have also been reported [95, 96]. In addition to those with berries, animal studies with tea [15] and pomegranate juice [36], or pure flavonols such as quercetin, rutin [80] or fisetin [66] have provided further evidence that dietary flavonoids are beneficial in reversing the course of neuronal and behavioural aging.

The flavonoid-rich plant extract, *Ginkgo Biloba* has also been shown to induce positive effects on memory, learning and concentration [19, 20, 25]. *Ginkgo Biloba* has a prominent effect on brain activity and short-term memory in animals and humans suffering from cognitive impairment [43, 93, 131] and promotes spatial learning in aged rodents [40, 114, 126, 131]. Furthermore, *Ginkgo Biloba* promotes inhibitory avoidance conditioning in rats with high-dose intake leading to short-term, but not long-term, passive avoidance learning in senescent mice [114, 118]. However, the pharmacological mechanisms by which *Ginkgo Biloba* promotes cognitive effects are unclear, with its ability to elicit a reduction in levels of ROS [72, 73], to increase cerebral blood flow [33], to modulate brain fluidity [114], to interact with the muscarinic cholinergic system [18] and to protect the striatal dopaminergic system [81] all being suggested as possible mechanisms of brain action.

The effects of flavonoid-rich foods on neuro-cognitive function have been linked to the ability of flavonoids to interact with the cellular and molecular architecture responsible for memory and learning [105, 106], including those involved in long-term potentiation and synaptic plasticity [98] (Fig. 3). These effects are likely to lead to the

Fig. 3 Signalling pathways underlying neuronal survival and cognitive performance. Flavonoids activate ERK-CREB pathway and the PI3 kinase-mTOR cascade leading to changes in synaptic plasticity. They are also capable of influencing neurogenesis through the activation of PI3 kinase-Akt-eNOS
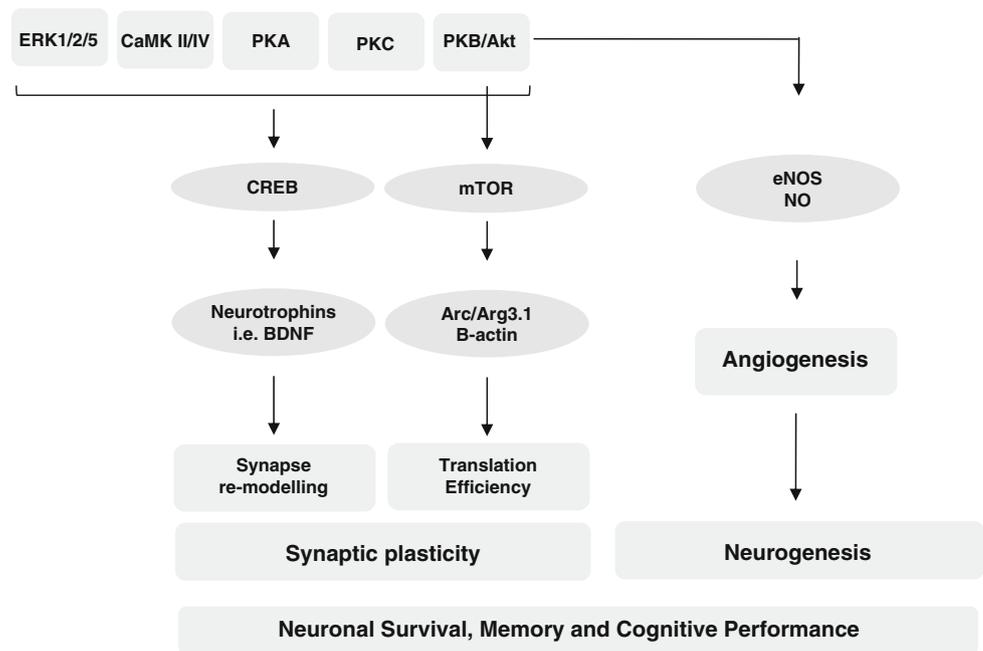
enhanced neuronal connection and communication and thus a greater capacity for memory acquisition, storage and retrieval [106]. For example, the flavanol (-)-epicatechin, especially in combination with exercise, has been observed to enhance the retention of rat spatial memory by a mechanism involving increased angiogenesis and neuronal spine density in the dentate gyrus of the hippocampus, and an up-regulation of genes associated with learning in the hippocampus [120]. Fisetin, a flavonoid found in strawberries, has been shown to improve long-term potentiation and to enhance object recognition in mice by a mechanism dependent on the activation of ERK and CREB [66]. Similarly, the flavanol (-)-epicatechin induces both ERK1/2 and CREB activation in cortical neurons and subsequently increases CREB regulated gene expression [89], whilst nanomolar concentrations of quercetin are effective at enhancing CREB activation [101]. Blueberry-induced improvements in memory have been shown to be mediated by increases in the phosphorylation state of ERK1/2, rather than that of calcium calmodulin kinase (CaMKII and CaMKIV) or protein kinase A [129]. Other flavonoids have also been found to influence the ERK pathway, with the citrus flavanone hesperetin capable to activating ERK1/2 signalling in cortical neurons [122] and flavanols such as EGCG restoring both protein kinase C and ERK1/2 activities in 6-hydroxy dopamine toxicity and serum deprived neurons [61, 83].

Cerebrovascular effects of flavonoids

Dementia is a serious degenerative disease effecting predominantly elderly people with the two most common forms of this illness being Alzheimer's and vascular dementia. The factors affecting dementia are age, hypertension, arteriosclerosis, diabetes mellitus, smoking, atrial fibrillation and those with the ApoE4 genotype [11]. There is evidence to suggest that flavonoids may be capable of preventing many forms of cerebrovascular disease, including those associated with stroke and dementia [21, 23]. There is powerful evidence for the beneficial effects of flavonoids on endothelial function and peripheral blood flow [90] and these vascular effects are potentially significant as increased cerebrovascular function is known to facilitate adult neurogenesis in the hippocampus [32] (Fig. 3). Indeed, new hippocampal cells are clustered near blood vessels, proliferate in response to vascular growth factors and may influence memory [74]. As well as new neuronal growth, increases in neuronal spine density and morphology are considered vital for learning and memory [35]. Changes in spine density, morphology and motility have been shown to occur with paradigms that induce synaptic, as well as altered sensory experience, and lead to alterations in synaptic connectivity and strength between neuronal partners, affecting the efficacy of synaptic communication. These events are mediated at the cellular and molecular level and are strongly correlated with memory and learning.

Efficient cerebral blood flow is also vital for optimal brain function, with several studies indicating that there is a decrease in cerebral blood flow (CBF) in patients with dementia [71, 87]. Brain imaging techniques, such as 'functional magnetic resonance imaging' (fMRI) and 'trans-cranial Doppler ultrasound' (TCD) has shown that there is a correlation between CBF and cognitive function

in humans [87]. For example, cerebral blood flow velocity is significantly lower in patients with Alzheimer disease and low CBF is also associated with incipient markers of dementia. In contrast, non demented subjects with higher CBF were less likely to develop dementia. Flavonoids have been shown to exert a positive effect on cerebral blood flow (CBF) in humans [29, 31]. After consumption of a flavanol-rich cocoa drink, the 'flow oxygenation level dependent' (BOLD)-fMRI showed an increase in blood flow in certain regions of the brain, along with a modification of the BOLD response to task switching. Furthermore, 'arterial spin-labelling sequence magnetic resonance imaging' (ASL-MRI) [127] also indicated that cocoa flavanols increase CBF up to a maximum of two hours after ingestion of the flavanol-rich drink. In support of these findings, an increase in cerebral blood flow through the middle cerebral artery has been reported after the consumption of flavanol-rich cocoa using TCD [29].

Conclusion

The neuroprotective actions of dietary flavonoids involve a number of effects within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning and cognitive function. This multiplicity of effects appears to be underpinned by two common processes. Firstly, they interact with important neuronal signalling cascades in the brain leading to an inhibition of apoptosis triggered by neurotoxic species and to a promotion of neuronal survival and differentiation. These include selective actions on a number of protein kinase and lipid kinase signalling cascades, most notably the PI3 K/Akt and MAP kinase pathways which regulate pro-survival transcription factors and gene expression (Fig. 3). It appears that the concentrations of flavonoids encountered in the brain may be sufficiently high to exert such pharmacological activity on receptors, kinases and transcription factors. Secondly, they are known to induce beneficial effects on the peripheral and cerebral vascular system, which lead to changes in cerebrovascular blood flow. Such changes are likely to induce angiogenesis, new nerve cell growth in the hippocampus and changes in neuronal morphology, all processes known to important in maintaining optimal neuronal function and neuro-cognitive performance (Fig. 3).

The consumption of flavonoid-rich foods, such as berries and cocoa, throughout life holds a potential to limit neurodegeneration and prevent or reverse age-dependent deteriorations cognitive performance. However, at present the precise temporal nature of the effects of flavonoids on these events is unclear. For example, it is presently unclear

as to when one needs to begin consuming flavonoids in order to obtain maximum benefits. It is also unclear which flavonoids are most effective in inducing these changes. However, due to the intense interest in the development of drugs capable of enhancing brain function, flavonoids may represent important precursor molecules in the quest to develop of a new generation of brain enhancing drugs.

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