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REVIEW OPEN ACCESS

Polyphenols and brain health

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Abstract – Accumulating evidence suggests that diet and lifestyle can play an important role in delaying the onset or halting the progression of age-related health disorders and to improve cognitive function. A growing number of dietary intervention studies in humans and animals and in particular those using polyphenol-rich diets have been proposed to 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 a potential to promote memory, learning, and cognitive functions. These effects appear to be underpinned by two common processes. First, they are capable of interactions 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. Second, they induce beneficial effects on the vascular system, leading to changes in cerebrovascular blood flow capable of causing enhance vascularisation and neurogenesis, two events important in the maintenance of cognitive performances. Together, these processes act to maintain brain homeostasis and play important roles in neuronal stress adaptation and thus polyphenols might have the potential to prevent the progression of neurodegenerative pathologies.

Keywords: flavonoids / ageing / neuroinflammation / cognition / signalling pathways

1 Introduction

Over the last decade, a vast and growing research literature has been focusing on the potential of dietary polyphenols for aiding preservation of cognitive function during ageing while reducing risk for neurodegenerative disorders (Letenneur *et al.*, 2007; Nurk *et al.*, 2009; Gu *et al.*, 2010; Nooyens *et al.*, 2011; Solfrizzi *et al.*, 2011; Loef and Walach, 2012; Vauzour, 2012). For example, the regular dietary intake of polyphenol-rich foods and/or beverages has been associated with 50% reduction in the risk of dementia (Commenges *et al.*, 2000), a preservation of cognitive performance with ageing (Morris *et al.*, 2006; Letenneur *et al.*, 2007), a delay in the onset of Alzheimer's disease (Dai *et al.*, 2006; Pasinetti *et al.*, 2015) and a reduction in the risk of developing Parkinson's disease (Checkoway *et al.*, 2002; Chen *et al.*, 2015). It is now widely accepted that the biological actions of polyphenols within the nervous system are not solely due to their classical hydrogen donating antioxidant activity (Williams *et al.*, 2004). Rather, it has become evident that polyphenols are more likely to exert beneficial effects in the brain (at low and physiological concentrations) by preventing neurodegeneration, inhibiting neuroinflammation and reducing age-related cognitive decline (Vauzour *et al.*, 2008; Vauzour, 2012). In particular, these interactions include an ability to activate signalling pathways, critical in controlling synaptic plasticity and a potential to induce vascular effects capable of causing new nerve cell growth in the hippocampus (Spencer *et al.*, 2009; Vauzour, 2012). This review will describe the potential of polyphenols to modulate brain functions and will summarise the possible mechanisms implicated in such beneficial effects.

2 Polyphenols structure and occurrence

Polyphenols are a group of naturally occurring phytochemicals which are present in high amounts in fruits and vegetables. These compounds are characterised by the presence of multiple hydroxyl groups on aromatic rings and are divided into two main categories, the flavonoids and non-flavonoids, based on the number of phenol rings and the way in which these rings interact.

Flavonoids have a C6–C3–C6 structure and share a common feature which consist of two aromatic carbon rings, benzopyran (A and C rings) and benzene (B ring), and may be divided in various subgroups based on the degree of the oxidation of the C-ring, the hydroxylation pattern of the ring structure and the substitution of the 3-position. The main dietary groups of flavonoids are: (1) flavones (*e.g.* apigenin, luteolin), which are found in parsley and celery; (2) flavonols (*e.g.* kaempferol, quercetin), which are found in onions, leeks, broccoli;

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(3) isoflavones (*e.g.* daidzein, genistein), which are mainly found in soy and soy products; (4) flavanones/flavanonols (*e.g.* hesperetin, naringenin/astilbin, engeletin), which are mainly found in citrus fruit, herbs (oregano) and wine; (5) flavanols (*e.g.* (+)-catechin, (−)-epicatechin, epigallocatechin, epigallocatechin gallate (EGCG)), which are abundant in green tea, red wine, chocolate; and (6) anthocyanidins (*e.g.* pelargonidin, cyanidin, malvidin), whose sources include red wine and berry fruits.

The non-flavonoid group may be separated into two different classes: (1) the phenolic acids, including the hydroxybenzoic acids (C1–C3 skeleton; *i.e.* protocatechuic and gallic acids) and hydroxycinnamic acids (C3–C6 skeleton; *i.e.* caffeic and chlorogenic acids) together found in many fruits and vegetables; (2) the stilbenes (C6–C2–C6 structure; *i.e.* resveratrol) found in grapes, wine, peanuts. For further details of the structures and occurrence of these compounds readers should consult Rodriguez-Mateos (Rodriguez-Mateos *et al.*, 2014), along with the ever expanding Phenol-Explorer database which includes comprehensive information of the polyphenol content of foods (Neveu *et al.*, 2010).

3 Effects of polyphenols on age-related cognitive decline and neurodegenerative disorders

Ageing is a normal and inevitable process in life. It progresses more or less rapidly depending on our lifestyle habits (sedentary, western-type diet, alcohol, and smoking). The normal brain ageing affects the frontal and temporal lobes more than the parietal and occipital lobes (Bentourkia *et al.*, 2000) and is characterised by a progressive decline in cognitive abilities mainly in hippocampal circuit, including the dentate gyrus, and the prefrontal cortex (for long-term memory) (Morrison and Baxter, 2012). In addition, past and recent research shows that the ageing process causes declines in both motor and cognitive functions even in absence of neurodegenerative disease, in both animals (Ingram *et al.*, 1994; Shukitt-Hale *et al.*, 1998) and humans (West, 1996; Muir, 1997). Alterations in cognition appear to occur primarily in secondary memory systems, such as memory performance (*e.g.* delayed recall of a story presented once) (Dixon *et al.*, 2004), processing, working memory (Corona *et al.*, 2013), and executive function (Siedlecki *et al.*, 2005). Increased fruits and vegetables intake has been associated with improved cognitive function (Sofi *et al.*, 2010; Tangney *et al.*, 2011; Lamport *et al.*, 2016), and may be in large part attributable to intake of polyphenols (Barberger-Gateau *et al.*, 2007). In particular, increased consumption of polyphenols was positively associated with better language and episodic memory in middle-aged healthy adults (45–60 years old) (Kesse-Guyot *et al.*, 2012) and with a greater cognitive performance at baseline and less decline across the follow-up assessments in non-demented adults aged 70 and over (Letenneur *et al.*, 2007). Similarly, greater intakes of blueberries and strawberries anthocyanins were associated with slower rates of cognitive decline in non-demented adults aged 70 and over (Devore *et al.*, 2012). Blueberry appears to have a pronounced effect on short-term (Ramirez *et al.*, 2005) and long-term memory (Casadesus *et al.*, 2004), and animal studies have provided further evidence for the efficacy of blueberries (Williams *et al.*, 2008; Rendeiro *et al.*, 2012), indicating that improvements in spatial memory may emerge within 3 weeks, the equivalent of about 3 years in humans. In addition, pure (−)-epicatechin (500 μg/g) was observed to enhance the retention of spatial memory in C57BL/6 mice (8–10 week old), especially when combined with exercise (van Praag *et al.*, 2007), similarly to green tea catechins (0.025–0.1% w/v) (Li *et al.*, 2009a). The mechanisms seem to involve an indirect action on the dentate gyrus (DG) (Casadesus *et al.*, 2004; Burke and Barnes, 2006; Rendeiro *et al.*, 2012; Rendeiro *et al.*, 2013). Such link between hippocampal neurogenesis, cognitive performance and ageing may represent a potential mechanism by which polyphenol-derived foods may improve memory (Stangl and Thuret, 2009). However, although epidemiological and pre-clinical studies have lent some support to the neurocognitive potential of polyphenols, human intervention results are less clear (Scholey *et al.*, 2010; Field *et al.*, 2011) and further work is still necessary to confirm these preliminary observations (Vauzour *et al.*, 2016).

In addition to age-related cognitive decline, epidemiological, preclinical and clinical studies have also explored the neuroprotective effect of natural compounds in clinical conditions (Commenges *et al.*, 2000; Letenneur *et al.*, 2007; Pasinetti, 2015; Pasinetti *et al.*, 2015). Verbal learning was improved in older adults with mild cognitive impairment (MCI) after consumption of Concord grape juice (Krikorian *et al.*, 2010a), blueberry juice (Krikorian *et al.*, 2010b) and flavanols (Desideri *et al.*, 2012). Although the exact mechanisms underlying these improvements are not clear, it has been suggested that polyphenols may delay the initiation of and/or slow the progression of Alzheimer's Disease (AD)-like pathology, including a potential to inhibit neuronal apoptosis triggered by neurotoxic species (*e.g.* oxidative stress and neuroinflammation) (Vauzour *et al.*, 2007a; Mori *et al.*, 2012; Cox *et al.*, 2015). Polyphenols can reduce amyloid-beta (Aβ) plaque pathology (Hirohata *et al.*, 2007; Amit *et al.*, 2008; Ehrnhoefer *et al.*, 2008; Ono *et al.*, 2008; Wang *et al.*, 2014), and therefore they could have utility in AD beyond anti-Aβ processing (Wang *et al.*, 2015). For example, oral administration of epigallocatechin-3-gallate (EGCG, 50 mg/kg) for 6 months in mice which over-express the Swedish mutation of APP (APPsw; 8 months old), reduced Aβ pathology and improved cognition (Rezai-Zadeh *et al.*, 2008). Long term green tea catechin administration (0.05–0.1% w/v) also improved spatial learning and memory in senescence prone mice, by decreasing $A\beta_{1-42}$ oligomers and upregulating synaptic plasticity-related proteins in the hippocampus (Li *et al.*, 2009b). However, a recent investigation reported a cognitive-enhancing effect of a polyphenol-rich without changes in either Aβ or Tau pathologies, therefore suggesting that polyphenols-rich extracts may prevent memory impairment associated with age-related diseases, without significant effects on classical AD neuropathology (Dal-Pan *et al.*, 2017). Further work is therefore required to fully apraise whether polyphenols have efficacy in individuals affected by dementia.

4 Cellular and molecular interactions underlying the cognitive effects of polyphenols

It has generally been assumed that the health benefits of polyphenols were linked to their capacity to directly scavenge

free radicals and other nitrogen species *in vitro* (Pannala *et al.*, 1997; Visioli *et al.*, 1998; Russo *et al.*, 2000; Halliwell, 2006). However, the concentrations at which they exert such antioxidant activity is unlikely to be easily achieved *in vivo* as many polyphenols have very limited bioavailability and are extensively metabolised in the gut and the liver (Rodriguez-Mateos *et al.*, 2014). Instead, recent findings have suggested that in lower amounts, typical of those attained in the diet, polyphenols may exert pharmacological activity within the cells with mechanisms that go beyond the classic antioxidant scavenging mechanisms (Williams *et al.*, 2004; Vauzour *et al.*, 2010). In particular, polyphenols are capable of modulating intracellular signalling cascades (Spencer *et al.*, 2009; Vauzour *et al.*, 2010; Kuo *et al.*, 2015), gene expression and interactions with mitochondria (Schroeter *et al.*, 2001; Schroeter *et al.*, 2007; Vauzour *et al.*, 2007b; Mandel *et al.*, 2008). By affecting such pathways, they have the potential to induce new protein synthesis in neurons and thus an ability to induce morphological changes, which have a direct influence on memory acquisition, consolidation and storage. Alternatively, their well established effects on the vascular system may also induce increases in cerebral blood flow capable of impacting on acute cognitive performance, or may lead to an increase hippocampal vascularisation capable of inducing new neuronal growth.

4.1 Polyphenols affect signalling cascades involved in synaptic plasticity maintenance

The activation of various signalling pathways have been linked with the control of synaptic plasticity and memory (Spencer *et al.*, 2009) which all converge to the cAMP-response element-binding protein (CREB), a transcription factor which binds to the promoter regions of many genes associated with synapse re-modelling, increases in neuronal spine density and synaptic plasticity (Impey *et al.*, 2004; Barco *et al.*, 2006). Such interactions may lead to improvements in memory through induction of synapse growth and connectivity, increases in dendritic spine density and the functional integration of old and new neurons. As such, nutrients which interact with these pathways may also be capable of reducing the neurodegenerative injury associated with major brain diseases.

There is much evidence to support the actions of polyphenols on the ERK pathway (Schroeter *et al.*, 2007; Vauzour *et al.*, 2007b), which often leads to the activation of CREB (Corona *et al.*, 2013), a transcription factor considered to be critical in the induction of long-lasting changes in synaptic plasticity and memory (Bourtchuladze *et al.*, 1994; Impey *et al.*, 1998). Indeed, CREB activation regulates the expression of a number of important genes, including the brain derived neurotrophic factor (BDNF), thus playing a pivotal role in controlling neuronal survival, and synaptic function in the adult central nervous system (Finkbeiner, 2000; Tully *et al.*, 2003). Regulation of BDNF is of particular interest as it is linked with the control of synaptic plasticity and long-term memory (Finkbeiner *et al.*, 1997; Carito *et al.*, 2014). Additionally, interactions are suggested to exist between BDNF, age-related cognitive decline and other cognitive-behavioural disorders. For example, age-related hippocampal atrophy is associated with memory-impairment, and therefore it is hypothesised that lower BDNF levels partly mediate this physiological change (Erickson *et al.*, 2012). Recent studies have shown that spatial memory performance in rats supplemented with blueberry, correlates well with the activation of CREB and with increases of BDNF in the hippocampus (Ramirez *et al.*, 2005; Wang *et al.*, 2011). In agreement with these observation, two recently conducted clinical trials reported concurrent changes in serum BDNF levels and global cognition scores following high polyphenol consumption, therefore suggesting a role for BDNF in polyphenol-induced cognitive improvements (Neshatdoust *et al.*, 2016). As well as effects on the ERK/CREB/BDNF axis, polyphenols are also known to modulate the activity of Akt (also known as PKB), triggering the increased translation of specific mRNA subpopulations (Vlahos *et al.*, 1994), including the activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) (Ramirez *et al.*, 2005), facilitating changes in synaptic strength, and the induction of morphological changes in dendritic spine density and outgrowth (Waltereit *et al.*, 2001).

4.2 Polyphenols mitigate neuroinflammation

Growing evidence is also suggestive that cognitive decline is in part mediated by an increase in neuroinflammatory stimuli linked to over-production of microglia-derived pro-inflammatory cytokines and reactive oxygen species. For example, increased neuroinflammation and oxidative stress can perturb the proper function of brain neurons, they can impede the efficiency of long term potentiation required for new memory formation, they can amplify the production and potentiate the effects of the Aβ protein. Since evidence emerged that non-steroidal anti-inflammatory drugs may be effective in delaying the onset of neurodegenerative disorders (Moore and O'Banion, 2002), there has been much interest in the development of new drugs capable of preventing neuro-inflammatory mediated brain injury. Over the last years, efforts have been made at investigating the effect polyphenols on neuroinflammation. Although not exhaustive, the main anti-inflammatory properties of polyphenols may be summarised by (1) a capacity to downregulate the activity of pro-inflammatory transcription factors such as NF-κB, Nrf2 or STAT through their influences on a number of glial and neuronal signalling pathways, (2) an inhibitory role on the release of cytokines, such as interleukin IL-1β and TNF-α, from primed microglia, (3) an inhibitory action against the production of NO and PGE2 in response to microglia activation, (4) an ability to inhibit the activation of NADPH oxidase and subsequent ROS generation in activated glia, and (5) an inhibitory action against microglia priming through toll-like receptors (TLR) activation (Gonzalez-Gallego *et al.*, 2010; Vauzour, 2014). For example, fisetin (0.05%, 6 months) reduced the protein expression of inflammatory markers in huAPPswe/PS1ΔE9 transgenic mice in an ERK-p25-mediated pathway without affecting the mRNA expression of NF-κB1 (Currais *et al.*, 2014). Similarly, kaempferol-3-O-rutinoside (10 mg/kg) and kaempferol-3-O-glucoside (7.5 mg/kg) reduced the neuroinflammatory response by inhibiting signal transducer and activator of transcription 3 (STAT3) and NF-κB following an ischemic brain injury in rats (Yu *et al.*, 2013). In addition, intervention trial with an anthocyanin

extract from blueberries (300 mg/d for 3 weeks) significantly reduced the plasma concentration of NF-kB-related pro-inflammatory cytokines and chemokines (IL-4, IL-13, IL-8 and IFN-α) in a group of 120 men and women aged 40–74 years (Karlsen *et al.*, 2007). However, no significant effect has been observed in plasma levels of CRP or ICAM-1 among healthy volunteers consuming diets rich or poor in berries and apple for 6 weeks (Freese *et al.*, 2004). Equally, a 4-week administration of quercetin significantly increased plasma levels of quercetin, but did not alter *ex vivo* LPS-induced TNF-α levels (Boots *et al.*, 2008). Although work carried out in cells or animal models have lent some support to the anti-inflammatory effect of polyphenols, the inconsistent outcome of various clinical trials on the preventive anti-inflammatory effect of polyphenols reinforces the necessity for more prospective randomised trials with larger sample sizes, longer follow-up in both healthy volunteers and in clinical conditions.

4.3 Polyphenols-induced change in (cerebro)vascular functions

Compelling evidence derived from human clinical studies is suggesting that polyphenols can positively affect peripheral (Hooper *et al.*, 2008; Kay *et al.*, 2012) and cerebrovascular blood flow (Schroeter *et al.*, 2006; Heiss *et al.*, 2007; Sorond *et al.*, 2008; Jagla and Pechanova, 2015), which may be an indirect effective mechanism by these molecules could impact on brain health and cognition. For example, a high-flavanone citrus juice (70.5 mg/500 ml) was associated with significantly increased regional perfusion in the inferior and middle right frontal gyrus at 2 h relative to baseline and the control drink in young healthy volunteers (Lamport *et al.*, 2016). Similarly, significant increases in regional perfusion across the brain were observed following consumption of a high flavanol drink relative to the low flavanol drink, particularly in the anterior cingulate cortex and the central opercular cortex of the parietal lobe (Lamport *et al.*, 2015). Longer-term interventions (3 months) also with cocoa flavanols in aged subjects revealed increases in cerebral blood volume (fMRI) in the DG of the hippocampus, which was highly correlated with improvements in performance in the DG-dependent Modified Benton task (Brickman *et al.*, 2014). Furthermore, ageing is known to impair vascularisation, endothelial function and decreases endothelial progenitor cell recruitment, which could adversely affect neurogenesis. Therefore, the influence of dietary agents on angiogenesis (van Praag *et al.*, 2007) and the production of vascular derived factors are also likely to influence neurogenesis (Casadesus *et al.*, 2004). Ultimately, the effects of polyphenols on the hippocampus are likely to be very dependent on local concentration and, at present, it remains unclear whether polyphenols induce global changes in hippocampal (and other brain region) morphology/function, or are capable of inducing changes within specific hippocampal sub-regions. However, if such effects prove possible, then diet would have the potential to not only slow the progression of neurodegeneration and cognitive decline, but also to potentially reverse disease and cognitive impairment *via* the re-population of neurons in the hippocampus. In summary, despite clear evidence regarding the acute vascular effects of flavonoids shown in humans (Macready *et al.*, 2010) and medium-term changes in synaptic plasticity markers demonstrated in animal studies (Spencer, 2009), the basic mechanisms of action of polyphenols in humans remains unclear, due to a lack of precise causative/mechanistic data. Future work should strive to determine the mechanistic basis of polyphenol-induced improvements in cognitive function by investigating the degree to which peripheral- and cerebral blood flow induced by polyphenol metabolites plays in determining improvements in human cognitive performance, in particular attention and episodic memory.

5 Conclusion

Decline on cognitive abilities with age occurs in healthy individuals and spreads through adult lifespan. The mechanisms contributing to normal aging, including oxidative stress, neuroinflammation and vascular dysfunction are the same than those contributing to the development of neurological diseases. However, in pathological conditions these mechanisms are exacerbated and are triggered by different factors which might be genetic or environmental. The consumption of polyphenol-rich foods throughout life holds a potential to limit neurodegeneration and prevent or reverse age-dependent deteriorations in cognitive performance. However, the therapeutic and pharmacological potential of these natural compounds still remains to be fully translated in humans and in clinical conditions. The challenge ahead therefore, is to proceed cautiously until rigorous randomized controlled clinical trials have been undertaken to determine empirically whether polyphenols and/or their *in vivo* metabolites have efficacy in individuals affected by dementia and other neurodegenerative conditions.

Abbreviations

AD	Alzheimer's disease
APP	amyloid precursor protein
Arc/Arg3.1	activity-regulated cytoskeleton-associated protein (also known as Arg3.1)
Aβ	amyloid beta
BDNF	brain derived neurotrophic factor
CREB	c-AMP-response element binding protein
CRP	C reactive protein
DG	dentate gyrus
EGCG	epigallocatechin-3-gallate
ERK	extracellular signal-regulated kinases
fMRI	functional magnetic resonance imaging
ICAM-1	Intercellular Adhesion Molecule 1
IL-1b	interleukin 1 beta
LPS	lipopolysaccharide
NF-Kb	nuclear factor-κB
NO	nitric oxide
Nox	NADPH oxidase
Nrf2	nuclear factor erythroid-related factor 2
PGE2	prostaglandin E2
ROS	reactive oxygen species
STAT3	signal transducer and activator of transcription 3
TLR	toll-like receptor
TNFa	tumour necrosis factor alpha

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