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;
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 (Commenge 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 Aβ1–42 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 appraise 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 are 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 (Impney 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 (Bourchuladze et al., 1994; Impney 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/Ang3.1) (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 neuroinflammatory 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 huAPPsw/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**

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


