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Review Article

Dietary Polyphenols as Modulators of Brain Functions: Biological Actions and Molecular Mechanisms Underpinning Their Beneficial Effects

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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. In particular, polyphenols have been reported to exert their neuroprotective actions through the potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning, and cognitive function. Despite significant advances in our understanding of the biology of polyphenols, they are still mistakenly regarded as simply acting as antioxidants. However, recent evidence suggests that their beneficial effects involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling and neurohormetic effects leading to the expression of genes that encode antioxidant enzymes, phase-2 enzymes, neurotrophic factors, and cytoprotective proteins. Specific examples of such pathways include the sirtuin-FoxO pathway, the NF-κB pathway, and the Nrf-2/ARE pathway. Together, these processes act to maintain brain homeostasis and play important roles in neuronal stress adaptation and thus polyphenols have the potential to prevent the progression of neurodegenerative pathologies.

1. Introduction

A gradual increase in human life span, with people over the age of 60, is expected to double between 2000 and 2050 [1]. As the elderly population expands, the prevalence of both Alzheimer's disease (AD) and Parkinson's disease (PD) is likely to augment, therefore having profound economical and social implications. Although the exact cause is not yet finally known, it has been postulated that the behavioural and neuronal declines associated with these age-related neurodegenerative disorders are triggered by multifactorial events including neuroinflammation, glutamatergic excitotoxicity, increases in iron, and/or depletion of endogenous antioxidants [2–4]. Therefore, it becomes imperative to develop drugs that possibly exert neuroprotective actions in order to prevent or even reverse age-related health disorders. One such possibility is the use of nutritional substances such as polyphenols [5, 6]. For example, a large number of dietary interventions using polyphenol rich foods or beverages, in particular those using tea [7–9], Gingko Biloba [10, 11], cocoa [12, 13] and blueberry [14–16], have demonstrated beneficial effects on memory and learning in both animals and humans. Furthermore, individual flavonoids such as the citrus flavanone tangeretin, have been observed to maintain nigrostriatal integrity and functionality following lesioning with 6-hydroxydopamine, suggesting that it may serve as a potential neuroprotective agent against the underlying pathology associated with PD [17]. While historically research focused on their antioxidant properties [18], recent data support the view that polyphenols, and their *in vivo* metabolites, do not act as conventional hydrogen-donating antioxidants but may exert modulatory actions in cells through actions at protein kinase and lipid kinase signalling pathways [19] and may even involve hormetic effects to protect neurons against the oxidative and inflammatory stressors [20]. This paper will describe the potential of polyphenols to modulate neuroinflammation, to counteract neurotoxins induced neurodegenerative disorders, and to enhance memory, learning, and cognitive performances. Neuroprotective mechanisms through the ability of polyphenols to interact

with neuronal signaling pathways and to mediate endogenous cellular defense systems including sirtuin, NF-κB, Nrfs, and related pathways will be also presented.

2. Sources and Structures of Polyphenols

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

2.1. Flavonoids. Flavonoids are polyphenolic compounds comprising 15 carbons, with two aromatic rings connected by a three-carbon bridge (C_6–C_3–C_6). Hydroxylation in position 3 of C-ring allows the differentiation of flavanonols from flavanones since they share a similar structure based on the 2,3-dihydro-2-phenylchromen-4-one skeleton. From these central intermediates, the pathway diverges into several side branches, each resulting in a different class of flavonoids. Flavonoids share a common feature which consists 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. Hydroxylation on position 3 of the flavone structure gives rise to the 3-hydroxyflavones also known as the (2) flavonols (e.g., kaempferol, quercetin), which are found in onions, leeks, and broccoli; (3) isoflavones (e.g., daidzein, genistein), which are mainly found in soy and soy products. These compounds 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; (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, and epigallocatechin gallate (EGCG), which are abundant in green tea, red wine, and chocolate. Flavanols are found both as monomers and oligomers referred to as condensed tannins or proanthocyanidins. 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; (6) anthocyanidins (e.g., pelargonidin, cyanidin, and malvidin), whose sources include red wine and berry fruits. 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 3 rings (Figure 1).

2.2. Nonflavonoids. The nonflavonoid group may be separated into two different classes: (1) the phenolic acids, including the hydroxybenzoic acids (HBAs; C_1–C_3 skeleton) and hydroxycinnamic acids (HCAs; C_3–C_6 skeleton) and (2) the stilbenes (C_6–C_2–C_6 skeleton).

The most common phenolic acids are not present in plants in a free state but occur as simple esters of glucose, tartaric acid, and quinic acid [21], and variations in the structure mainly lie in the hydroxylation and methoxylation pattern of the aromatic cycle [22]. HBAs are derivatives of the hydroxybenzoic acids such as *p*-hydroxybenzoic, protocatechuic, and gallic acids and are mostly present in the form of glucosides and some esters with glucose. However, gallic acid is mainly esterified to quinic acid or catechins and usually present in polymeric forms as soluble tannins [21]. HCAs are found in a variety of foods, the most common being caffeic and ferulic acids and their derivatives. They are mostly present in ester forms bound to quinic, shikimic, or tartaric acids. Caffeic acid is generally the most abundant phenolic acid and is mainly found as the quinic ester, chlorogenic acid, in blueberries, kiwis, plums, and apples [23]. However, very high intake of chlorogenic acid is common among coffee drinkers because of very high concentrations (50–150 mg of chlorogenic acids in one cup (200 mL) of instant coffee [24] (Figure 1).

Stilbenes possess a 1,2-diarylethenes structure based on the C_6–C_2–C_6 backbone and are usually synthesized in plants in response to infection or injury [25]. Resveratrol, the main stilbene, can be found in the *cis* or *trans* configurations, either glucosylated (piceid) or in lower concentrations as the parent molecule of a family of polymers such as viniferins, pallidol, or ampelopsin A [26]. Major dietary sources of resveratrol include grapes, wine, and peanuts. Resveratrol is found in low concentrations (0.3–7 mg aglycones/L and 15 mg glycosides/L) in red wine, and thus it seems unlikely to produce protective effects at normal nutritional intakes (Figure 1).

3. Brain Localisation of Polyphenols

Despite the increasing amount of evidence for the bioavailability of polyphenols in the systemic circulation [22, 27–29] only little information is available regarding their ability to reach the central nervous system (CNS). In order for polyphenols to access the brain, they must first cross a tightly regulated, selectively permeable endothelial cell layer which isolates the CNS tissue from the vasculature, the blood-brain barrier (BBB). The BBB is permeable to nutrients and actively excludes many substances from the central nervous system [30]. Using *in vitro* models, initial studies have demonstrated that polyphenols permeation through the BBB is dependent on the degree of lipophilicity of each compound with less polar polyphenols or metabolites (i.e., *O*-methylated derivatives) capable of greater brain uptake than the more polar ones (i.e., sulfated and glucuronidated derivatives) [31]. Their brain entry will also depend on their interactions with efflux transporters, such as P-glycoprotein (Pgp) [32] and their stereochemistry. For example, both catechin and epicatechin could cross a cellular model of BBB in a time-dependent and stereoselectivity manner with epicatechin $\gg$ catechin [33]. The amount of nutrient or drug that

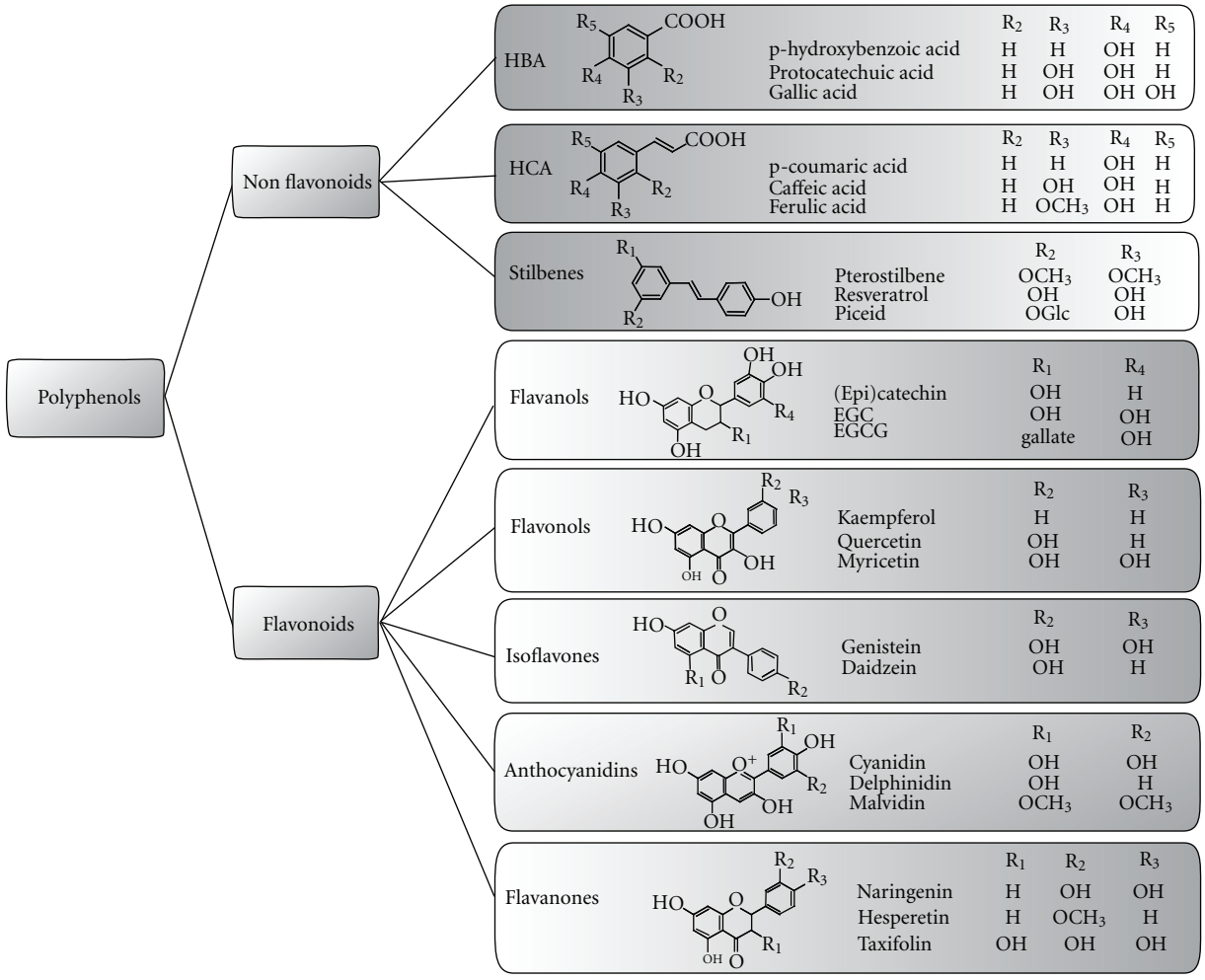

Figure 1: Structures of polyphenols. Polyphenols are a group of naturally occurring phytochemicals which are present in high amounts in fruits, vegetables, and natural products and are characterised by the presence of multiple hydroxyl groups on aromatic rings. These compounds are divided into two main categories, the flavonoids and non flavonoids, based on the number of phenol rings and the way in which these rings interact. For the flavonoid group, the major differences between the individual groups arise from the hydroxylation pattern of the ring-structure, the degree of saturation of the C-ring, and the substitution of the 3-position. HBAs, hydroxybennzoic acids; HCAs, hydroxycinammic acids.

penetrate into the brain was also investigated *in vivo*, with animal studies indicating that polyphenols are able to cross the BBB and to colocalise within the brain tissues independently of their route of administration. For example, naringenin was found in the brain following its intravenous administration [34], whilst epigallocatechin gallate [35], epicatechin [36], and anthocyanins [37, 38] were observed after oral administration. Although the uptake and distribution of dietary polyphenols within the brain are well documented, the question of the dose reaching the target tissues remains uncertain. Discrepancies in the findings mainly stem in the fact that studies reporting polyphenol brain uptake and concentrations often disregard residual blood as a potential confounder. Studies using exsanguinated, perfused animals or applying the recently published mathematical correction model [39] may therefore be more suitable for assessing polyphenol uptake and metabolism in the brain. Data deriving from such studies suggest that polyphenols usually localise in the brain at levels below 1 nmol/g tissue (see review by Schaffer and Halliwell [40]). Furthermore, several polyphenols have been identified in different regions of the rat [38, 41] and pig brains [42, 43] and usually accumulates in a nonregion-specificic manner [16, 44]. For example, recently, Janle et al. demonstrated that ^{14}C-labelled grape polyphenols did not show any regional differences in ^{14}C accumulation from anterior to posterior slices of the brain [44]. Collectively, these results indicate that polyphenols transverse the BBB and localise within the brain tissue, suggesting that they are candidates for direct neuroprotective and neuromodulatory actions. Nonetheless, our knowledge regarding polyphenol absorption, metabolism, tissue distribution, and intracellular accumulation and excretion remains insufficient, and future work is needed to better understand their biological effects.

4. Effect of Polyphenols on Memory, Learning, and Neurocognitive Performance

Accumulating evidence suggests that diet and lifestyle can play an important role in delaying the onset or halting the progression of neurodegenerative diseases and improving cognitive function [45–48]. With regards to diet, polyphenols have been associated with a reduced risk of developing dementia [45, 49], an improved cognitive performance in normal ageing [48] and an improved cognitive evolution [5]. More recently, high total polyphenol intake was also associated with better language and verbal memory but not with executive functioning. In particular, intake of catechins, theaflavins, flavonols, and hydroxybenzoic acids was positively associated with language and verbal memory, especially with episodic memory as assessed by the RI-48 test [50]. Although a positive correlation between dietary polyphenol consumption and cognitive decline has been mostly reported, a limited body of evidence is, however, suggestive that carrier of the *APOε4* genotype may influence the beneficial effect of polyphenols in relation to dementia and AD. For example, the frequent consumption of fruits and vegetables was associated with a decreased risk of all cause dementia (hazard ratio [HR] 0.72, 95% CI 0.53 to 0.97) especially amongst the *APOε4* noncarriers [51]. The relationship between polyphenols intake and *APOε* genotype is intriguing, and further work is required to gain a better understanding of the physiological and molecular mechanisms underlying such disparity.

Over the last years, there has been much interest in the neurocognitive effects of berries, in reversing age-related deficits in motor function and spatial working memory [14, 16, 52]. While the consumption of cranberry juice over a 6 weeks period in older adults has failed to report any cognitive benefits [53], consumption of both grape or blueberry juices in older adults with or without mild cognitive impairment (MCI) reported significant improvement in memory function after 12 weeks intervention [54, 55]. In addition to spatial memory, blueberry supplementation in aged animals has also been shown to improve "object recognition memory" [56] and "inhibitory fear conditioning learning" [57, 58]. Blueberry appears to have a pronounced effect on short-term memory [58] and has also been shown to improve long-term reference memory following 8 weeks of supplementation. [14]. Tests using a radial arm maze have supported these findings and have provided further evidence for the efficacy of blueberries [16]. Indeed, these have shown that improvements in spatial memory may emerge within 3 weeks, the equivalent of about 3 years in humans. Although not fully understood, evidence suggest that blueberry-derived polyphenols may enhance the efficiency of spatial memory by indirectly acting on the dentate gyrus (DG), an hippocampal subregion particularly sensitive to the effects of aging [59]. In particular, blueberry supplementation has been shown to significantly increase the precursor cells in the DG of aged rats [14]. Such link between hippocampal neurogenesis, cognitive performance, and aging may represent a potential mechanism by which polyphenol-derived foods may improve memory [60].

In addition to those with berries, human and animal studies with cocoa and tea flavanols have also provided further evidence that dietary polyphenols are beneficial in reversing the course of neuronal and behavioural aging [7, 61]. For example, two recent acute human studies have shown that cocoa flavanol consumption was able to improve working memory and attention [12, 13]. In addition, pure (−)-epicatechin (500 μg/g) was also observed to enhance the retention of mice spatial memory, especially when combined with exercise [62], suggesting that polyphenols may be causal agents in inducing the behavioural effects. Although the exact mechanisms underlying such behavioural changes remain to be elucidated, evidence suggests that flavanol-rich foods improve peripheral blood flow and surrogate markers of cardiovascular function [63–65]. In addition, CNS imaging studies in humans have demonstrated that the consumption of flavanol-rich cocoa may improve cerebral blood flow (CBF) in healthy older adults [66] and in young adults in response to a cognitive task [67]. These effects are particularly significant, as increased cerebrovascular function is known to facilitate adult neurogenesis [68] and to enhance vascularisation [69, 70], two events important in the maintenance of cognitive performances.

The flavonoid-rich plant extract, *Ginkgo biloba,* has also been shown to induce positive effects on memory, learning, and concentration [71, 72]. *Ginkgo biloba* has a prominent effect on brain activity and short-term memory in animals and humans suffering from cognitive impairment [11, 73] and promotes spatial learning in aged rodents [74, 75]. However, the pharmacological mechanisms by which *Ginkgo biloba* promotes cognitive effects remain unclear, although its ability to elicit a reduction in levels of reactive oxygen species (ROS) [76], to increase cerebral blood flow [77], to modulate membrane fluidity [78], to interact with muscarinic cholinergic receptors [79], to protect the striatal dopaminergic system [80], and to upregulate AMPA, calcium and chloride channels, and growth hormones [81] have been suggested as possible mechanisms underlying its actions in the CNS. Together, these data provide a strong indication that regular polyphenol consumption may have a positive effect on neurocognitive performance as we age (Figure 2).

5. Polyphenol Protection against Neuronal Injury Induced by Neurotoxins

There are a number of epidemiological studies which suggest that plant-derived polyphenol-rich foods or supplements might delay the initiation and progression of AD, PD, and related neurodegenerative disorders [5, 82]. With regard to AD, most of the preclinical studies of the effects of polyphenols have focused on models where there is increased production of beta-amyloid (Aβ), a small protein produced by the enzymatic cleavage of amyloid precursor protein (APP) [83]. For example, the chronic consumption of ferulic acid with the drinking water protected mice from the deleterious effects of an intracerebral injection of β-amyloid peptide [84]. More recently, using transgenic mouse models, studies have started to address the potential effect of polyphenol-rich diets on AD. Oral administration of

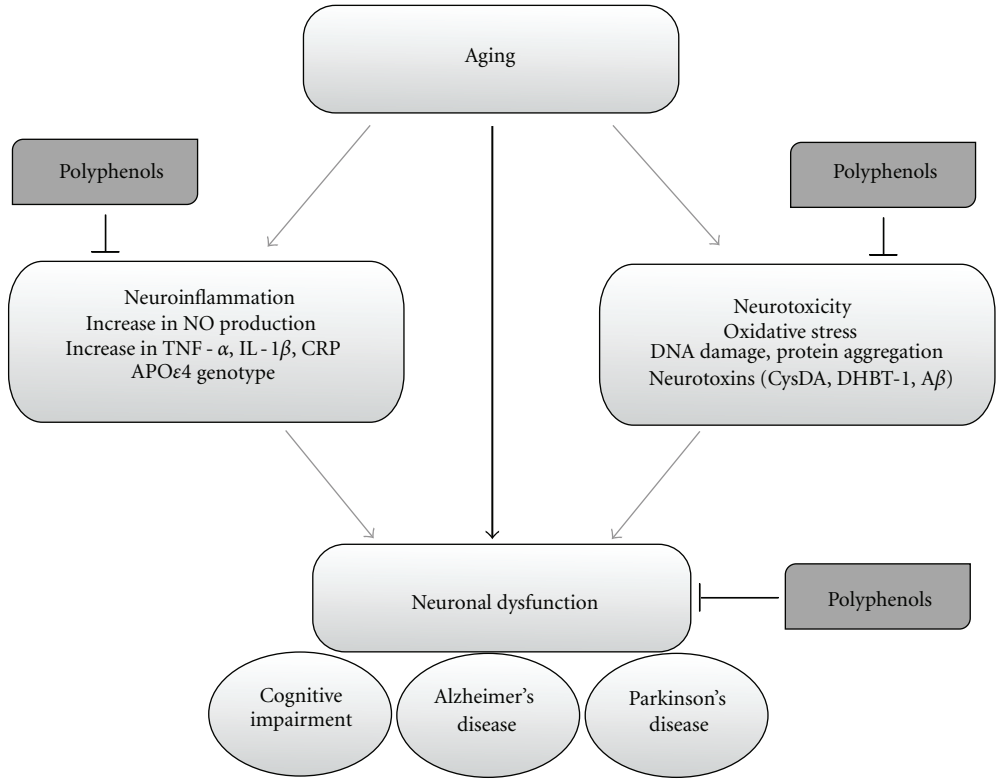

Figure 2: Modulation of neuronal dysfunction by dietary polyphenols. In ageing and neurodegenerative diseases, neuronal death can be triggered by specific genetic mutations, neurotoxins, and/or neuroinflammation. Initiating factors promote cellular alterations, including increases in oxidative stress, protein aggregation, DNA damage, and activation of apoptotic cascades. Dietary polyphenols have been observed to protect the brain against such cellular alteration through the modulation of neuronal function against endogenous neurotoxins and inhibition of glial-induced neuroinflammation. Aβ, amyloid beta; CysDA, 5-S-cysteinyldopamine; DHBT1, dihydrobenzothiazine 1; TNF-α, tumor necrosis factor alpha; IL-1β, interleukine-1 beta; CRP, C reactive protein; NO, nitric oxide.

epigallocatechin-3-gallate (EGCG) for 6 months in mice which overexpress the Swedish mutation of APP (APPsw), reduced Aβ pathology and improved cognition [85]. Similarly long-term green tea catechin administration 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 [86]. The antiamyloidogenic activity is not unique to EGCG and a number of other polyphenols bind to Aβ fibrils and prevent further fibrillization [87–89]. For example, gallic acid and catechin-rich grape seed polyphenolic extract (GSPE) inhibited cognitive deterioration coincident with reduced levels of soluble high molecular weight oligomers of Aβ [88]. Repeated intraperitoneal injection of nobiletin has similar effects [90]. The mechanisms underlying these changes are not clear but might be linked to increased nonamyloidogenic processing of APP, through stimulating the activity of α-secretase, which cleaves APP at a site which prevents the formation Aβ species [91, 92]. Alternatively, it is conceivable that polyphenols reduce Aβ plaque pathology by inhibiting amyloid aggregation and fibrillization either as a result of metal chelation activity [93–95] or by favouring the formation of nontoxic oligomers [96]. Additional mechanisms have been also suggested for the ability of polyphenols to delay the initiation of and/or slow the progression of AD-like pathology, including a potential to inhibit neuronal apoptosis triggered by neurotoxic species (e.g., oxidative stress and neuroinflammation) or disrupt amyloid β aggregation and effects on amyloid precursor protein processing through the inhibition of β-secretase (BACE-1) [97] and/or activation of α-secretase (ADAM10) (See review by Williams and Spencer [98]).

The potential utility of polyphenols in neurodegeneration extends beyond AD, and there is also considerable interest in their therapeutic potential in PD [47, 99]. There is good evidence to suggest that the consumption of green tea may have a beneficial effect in reducing the risk of PD [82], as has been extensively reviewed elsewhere [100, 101]. The efficacy of green tea is likely to be mediated by the effects of EGCG, which has been shown to attenuate the selective degeneration of dopamine neurons in animal models of PD induced by toxins including 6-hydroxydopamine [102] and MPTP [103]. In addition, the citrus flavonoid tangeretin has also been observed to be neuroprotective against 6-hydroxydopamine lesioning in a rat model of PD [17]. *In vitro* studies have also indicated that polyphenols might act to prevent PD pathology via their ability to prevent the formation of the endogenous neurotoxin, 5-*S*-cysteinyl-dopamine

(CysDA) [104, 105]. Such adducts may be generated by reactive species [105] and have been observed to be elevated in the human substantia nigra of patients who died of PD [104], suggesting that such species may be potential endogenous nigral toxins. However, CysDA-induced neuronal injury is counteracted by nanomolar concentrations of various polyphenols including pelargonidin, quercetin, hesperetin, caffeic acid, tyrosol, *p*-coumaric acid, and the 4′-*O*-Me derivatives of catechin and epicatechin [105, 106]. Furthermore, in presence of the flavanol, (+)-catechin, tyrosinase-induced formation of CysDA was inhibited by a mechanism linked to the capacity of catechin to undergo tyrosinase-induced oxidation to yield cysteinyl-catechin adducts [107]. In contrast, the inhibition afforded by flavanones, such as hesperetin, was not accompanied with the formation of cysteinyl-hesperetin adducts, indicating that it may be inhibited via direct interaction with tyrosinase [107]. Furthermore, the stilbene resveratrol also had a small inhibitory effect; however, its reaction with tyrosinase in the presence of L-cysteine led to the formation of dihydrobenzothiazine (DHBT-1) [107], a strong neurotoxin known to selectively inhibit the respiratory chain complex I, the alpha-ketoglutarate dehydrogenase (alpha-KGDH), and the pyruvate dehydrogenase complexes (PDHC) [108] (Figure 2). Collectively, these studies suggest that polyphenols have the potential to confer benefit in diverse neurodegenerative disorders. Some of the major neuroprotective mechanisms are discussed in more detail below.

6. Role of Polyphenols in Preventing Neuroinflammation

Although neuroinflammation plays a critical role in brain host defence, it also contributes to the underlying neuronal loss in neurodegenerative disorders, such as PD, AD [109–111] and to damages associated with cerebral ischemia [112]. Neuroinflammation is "driven" by activated resident glial cells (astrocytes and microglia) which result in invasion of circulating immune cells and the production of proinflammatory cytokines (TNF-α, IL-1β, and IL-6), nitric oxide ($NO^{\bullet}$), prostaglandin E2, chemokines, and reactive oxygen species (ROS). Amongst the numerous factors released by activated glial cells, excessive $NO^{\bullet}$ production has been reported to induce neuronal cell death by damaging the mitochondrial electron transport chain function in neurons [113] therefore resulting in neuronal ATP synthesis disruption and in increased generation of ROS [114]. Furthermore, NADPH oxidase activation, an important event in activated microglia-induced neurotoxicity, has also been suggested to mediate both superoxide ($O_2^{\bullet -}$) production and to release proinflammatory molecules such as TNF-α [115]. $NO^{\bullet}$ produced in microglia or astrocytes may react with $O_2^{\bullet -}$, produced by NADPH oxidase [116, 117], to generate the neurotoxic peroxynitrite radical ($ONOO^-$) [116]. $ONOO^-$ has been observed to inhibit mitochondrial respiration, induce caspase-dependent neuronal apoptosis, and to induce glutamate release resulting in excitotoxicity and neuronal death [116, 118]. Additionally, glial cytokine production may also play a deleterious role in neurodegenerative diseases by binding to specific cell surface receptors expressed in neurons and activating apoptotic pathways. For example, TNF-α binds to the tumour necrosis factor receptor-1 (TNFR1) which may lead to neuronal apoptosis [119, 120].

Since long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to lower the risk of AD in later life [121], there has been much interest in the development of new drugs capable of preventing neuroinflammatory-mediated brain injury. Emerging evidence suggests that dietary polyphenols may exert neuroprotective effects by suppressing the activation of microglia, which mediates inflammatory processes in the CNS. Although rather complex, the main anti-inflammatory properties of polyphenols include: (1) an inhibitory role on the release of cytokines, such as IL-1β and TNF-α, from activated glia; (2) an inhibitory action against iNOS induction and subsequent nitric oxide production in response to glial activation; (3) an ability to inhibit the activation of NADPH oxidase and subsequent ROS generation in activated glia; (4) a capacity to downregulate the activity of proinflammatory transcription factors such as NF-κB through their influences of a number of glial and neuronal signaling pathways, such as MAPK cascade (discussed in details below) [122, 123].

For example, the commonly consumed flavonol quercetin has been reported to inhibit neuroinflammation by attenuating nitric oxide production and iNOS gene expression in microglia [117, 124] and by preventing inflammatory cytokine production, thus preventing neuronal injury [125, 126]. However, one of the major physiological metabolites of quercetin, quercetin-3′-sulfate, failed to demonstrate any anti-inflammatory action [117]. Nevertheless, these studies have employed quercetin concentrations (10–50 μM) much higher than of those found in plasma after ingestion [28]. In contrast to this, epicatechin and catechin (10–300 nM) were observed to inhibit TNF-α release but not iNOS expression or nitric oxide production in primary glial cells [127] suggesting that flavanols at physiologically relevant concentrations may hold the potential to exert anti-inflammatory effects in the central nervous system. Polyphenols present in blueberry have also been reported to inhibit $NO^{\bullet}$, IL-1β and TNF-α production in activated microglia cells [128], and the flavanone naringenin was observed to be highly effective in reducing LPS/IFN-γ-induced glial cell activation [127]. Dietary polyphenols are also potent inhibitors of NADPH oxidase activity *in vitro*. A study comparing 45 polyphenolic compounds indicated that whilst both the flavanols (+)-catechin and (−)-epicatechin failed to inhibit NADPH oxidase, their relevant methylated metabolites exhibited strong NADPH oxidase inhibition through an apocynin-like mechanism [129]. Interestingly, other apocynin-like phenolic compounds, such as, ferulic acid, homovanillin alcohol, caffeic acid, tyrosol, and vanillic acid were also observed to inhibit NADPH oxidase activity, therefore indicating that smaller polyphenols, more structurally related to some colonic metabolites, may also serve as novel therapeutic agents in neuroinflammation (Figure 2).

There is also data which shows encouraging positive effects of polyphenols in animal and *in vitro* models relevant to multiple sclerosis (MS), a chronic debilitating disease which is characterised by demyelination, progressive

irreversible axonal damage and inflammation [130]. For example, EGCG delivered orally reduces symptom severity in the autoimmune encephalomyelitis model of relapsing-remitting MS by reducing inflammation and increasing neuroprotection [131]. Quercetin has also been reported to be effective in the Experimental Autoimmune Encephalomyelitis (EAE) mouse model, and reduces T-cell proliferation *in vitro* at concentrations exceeding 10 μM [132]. Micromolar concentrations of luteolin, apigenin, fisetin, and quercetin (but not morin or hesperetin) were reported to suppress the production of the cytokine interferon-gamma (IFNγ) from lymph-node-derived T cells but, paradoxically, worsen clinical severity in the EAE model. More recently, resveratrol protection against EAE was associated with rises in IL-17/IL-10 and with repressed macrophage IL-6 and IL-12/23 p40 expression [133]. Thus, the studies to date show promising proof of concept of beneficial effects of polyphenols in suppressing immune and inflammatory responses in models of MS.

7. Mechanisms Underpinning the Beneficial 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* [134–137]. 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 therefore reducing their antioxidant potential [19]. During the last years, a new realisation of how nutritional antioxidants may function has been envisaged, and recent findings have suggested that in lower amounts, typical of those attained in the diet, polyphenols may activate one or more adaptive cellular stress responses pathways [93, 138–140]. Activation of such hormetic pathways in neurons results in the production of several types of cytoprotective proteins including neurotrophic factors, protein chaperones, antioxidant and phase II enzymes, and antiapoptotic proteins [141, 142]. One particular protective pathway which is receiving considerable attention in regard to hormesis in the nervous system involves the transcription factor NF-E2-related factor-2 (Nrf2). Nrf2 binds to the antioxidant-responsive element (ARE) with high affinity and plays a central role in the upregulation of genes implicated in the regulation of the cellular redox status and the protection of the cell from oxidative insult [143, 144]. Under basal conditions, Nrf2 interacts with a cytosolic repressor protein Keap1 (Kelch ECH associating protein) limiting Nrf2-mediated gene expression [145]. In cells exposed to oxidative stress, Nrf2 is released from Keap1 and translocates to the nucleus, where it activates ARE-dependent transcription of phase II and antioxidant defence enzymes, such as glutathione-S-transferase (GST), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1) [146].

Most polyphenols have been reported to respond in a bell-shaped dose-response manner, presenting cellular toxicity at high concentrations while inducing light chemical stress at lower doses with activation of physiological hormesis in cells [142], resulting in overexpression of defensive genes such as those activated by Nrf2. For example, resveratrol was observed to protect PC12 cells against H_2O_2-mediated oxidative stress [147] and to attenuate cerebral ischemic injury in rat [148] via the activation of Nfr2 and the upregulation of HO-1. The caffeic acid phenethyl ester (CAPE), the active component of propolis, protected nigral dopaminergic neurons in an experimental mouse model of dopaminergic neurodegeneration through the modulation of heme oxygenase-1 and brain-derived neurotrophic factor (BDNF) [149]. The ethyl ferulate (EFE), a lipophilic polyphenol also found in propolis, was observed to protect rat neurons against oxidative stress via the induction of Nrf2/HO-1 [150]. The flavanol (−)-epicatechin prevented stroke damage through the Nrf2/HO1 pathway [151], and increased glutathione levels in primary astrocytes through an upregulation of ARE-mediated gene expression [152]. Although a positive correlation between dietary polyphenol consumption and brain function has been mostly reported, evidence is also suggestive that *APOε4* carriers may not benefit from the frequent consumption of fruits and vegetables rich in such phytochemicals. Indeed, previous findings suggest that *APOε4* carriers are less responsive towards the anti-inflammatory, paraoxanase-1 inducing, and blood pressure lowering activity of quercetin [153–155]. Such diminished responsiveness of the *APOε4* versus *APOε3* genotype (approximately 55–60% of the Caucasians population are homozygotes for the *ε3* allele) may be attributed to an impaired Nrf2 signalling and to a lower activity of Nrf2 target genes including glutathione-S-transferase, heme oxygenase-1, and NAD(P)H dehydrogenase, quinone 1 [156].

Several upstream signaling cascades may either individually, or in a combined manner, activate Nrf2. These include selective actions on a number of protein kinase and lipid kinase signalling cascades, most notably the PI3K/Akt and MAP kinase pathways which regulate prosurvival transcription factors and gene expression [19]. In general, *in vitro* studies have reported that polyphenols, at submicromolar concentrations, activate ERK, as determined by measuring increased phosphorylation of this enzyme. For example, both the flavanol (−)-epicatechin (0.1 and 0.3 μM) [139] and the citrus flavanone hesperetin at nanomolar concentrations [140] were observed to activate ERK1/in cortical neurons. Furthermore, EGCC was reported to restore ERK1/2 activities in 6-hydroxydopamine-treated or serum-deprived neurons [102]. ERK activation often leads to the activation of CREB, a transcription factor considered to be critical in the induction of long-lasting changes in synaptic plasticity and memory [157, 158]. CREB activation regulates the expression of a number of important genes, including BDNF, thus playing a pivotal role in controlling neuronal survival and synaptic function in the adult central nervous system [159, 160]. Regulation of BDNF is of particular interest as it is linked with the control of synaptic plasticity and long-term memory [161], and 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 [58]. Fisetin,

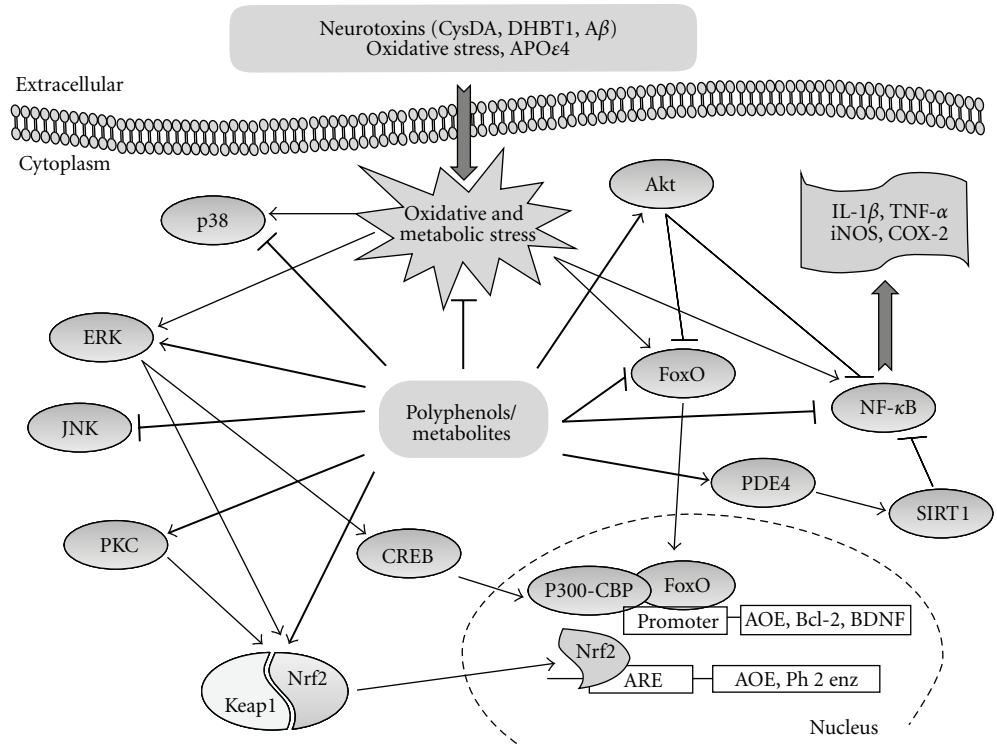

Figure 3: Mechanisms underlying the biological effects of polyphenols. Polyphenols and their *in vivo* metabolites activate cellular stress-response pathways resulting in the upregulation of neuroprotective genes. For example, both PKC and ERK can activate the nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 then translocates to the nucleus and binds to the antioxidant response element (ARE) in genes that encode cytoprotective proteins such as antioxidant enzymes (AOE) and phase 2 (Ph2) enzymes. The transcription factor cAMP-response-element-binding protein (CREB) is also activated by ERK, which induces the expression of brain-derived neurotrophic factor (BDNF), a mediator of neurohormesis. In addition, polyphenols can also regulate the transcription factor NF-κB, which can mediate adaptive cellular stress responses by reducing the expression of inflammatory cytokines. Activated SIRT1 may also inhibit NF-κB and so can reduce the cellular stress response. Another important pathway activated by metabolic and oxidative stress involves transcription factors of the forkhead (FoxO) family, which modulate genes that encode antioxidant enzymes and other stress-response proteins.

a polyphenol found in strawberries, has also 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 [162].

As well as effects on the ERK/CREB/BDNF axis, polyphenols are also known to modulate the activity of an enzyme system associated with neuroprotection, Akt (also known as PKB). One of the major enzymes which controls Akt/PKB activity is the lipid kinase, PI3K. In cortical neurons, polyphenols such as the citrus flavanone hesperetin (0.1 and 0.3 μM) cause the activation of Akt/PKB and the consequent inhibition of proteins associated with cell death such as apoptosis signal-regulating kinase 1 (ASK1), Bad, caspase-9 and caspase-3 [140]. The activation of Akt by flavonoids in hippocampal neurons has been shown to trigger the increased translation of specific mRNA subpopulations [163], including the activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) [58]. Arc is also under the regulatory of control of both BDNF [164] and ERK signalling [165]. Increased Arc expression may facilitate changes in synaptic strength, and the induction of morphological changes in dendritic spines [166]. In support of this, studies have indicated that changes in neuronal morphology occur in response to flavonoid supplementation [8], and that certain polyphenols can influence neuronal dendrite outgrowth *in vitro* [167–169].

In addition to the previously described signalling systems, two additional pathways that are known to play important roles in neuronal stress adaptation are those involving the transcription factor NF-κB and the protein sirtuin-1 (SIRT1) [170]. In neurons activation of NF-κB can prevent cell death induced by a range of insults including exposure to excitotoxins and oxidative stress [171]. Numerous polyphenols have been shown ascribe to inhibit NF-κB in different cell types. For example, quercetin (50 μM) suppresses NF-κB in a microglial cell line [117]. Apigenin (5–15 μM) blocks LPS stimulation of the NF-κB pathway in RAW 246.7 macrophages and reduces κB-transcriptional activity [172]. Catechin (0.13–2 mM) has been reported to increase mouse microglial cell survival following exposure to the oxidative agent tert-butylhydroperoxide (tBHP) by suppressing NF-κB activation [173]. The flavone wogonin (50 μM) was shown to reduce NF-κB activation in C6 glioma cells and prevent microglial activation [174], and baicalein is reported to inhibit NO. Production in and NF-κB activity in microglia [175, 176]. Although these data give proof of principle that NF-κB is a potential target of polyphenols, the concentrations

required for positive effects of those particular compounds *in vitro* are supraphysiological and difficult to be achieved through the diet. While it is likely that the antioxidant effects of the polyphenols used in those studies account for the positive effects on suppressing NF-κB activation, at dietary relevant concentrations (0.1–1 μM), different classes of polyphenol were unable to suppress NF-κB-signaling pathways in primary astrocytes [177]. Despite the fact that polyphenols may be effective compounds at suppressing neuroinflammation *in vitro*, the NF-κB signalling system is unlikely to be regarded as the primary signalling system responsible for their effects *in vivo*.

The protein SIRT1 can also be activated by polyphenols resulting in cell proliferation and cell survival. Cellular substrates of SIRT1 include the tumor suppressor p53, the transcription factor NF-κB, the forkhead box class O (FoxO) family of transcription factors, the peroxisome proliferator-activated receptor (PPAR)-γ, the PPAR-γ coactivator 1α (PGC-1α), and endothelial nitric oxide synthase (eNOS) [178]. In the realm of polyphenols, resveratrol has been the most extensively studied for its ability to modulate SIRT1 both *in vivo* and *in vitro* [179, 180]. However, the observed activation of SIRT1 by resveratrol *in vitro* now appears to be an artefact of the assay used, therefore raising doubt on the direct resveratrol-SIRT1 connection [181]. Recently, further insight into the mechanisms by which resveratrol interact with sirtuins has been proposed. Using a model of aged-related metabolic phenotype, Park et al. identified phosphodiesterase (PDE) enzymes as direct targets and proposed that resveratrol indirectly activates SIRT1 through a signaling cascade involving cAMP, Epac1, and AMPK [182]. Although these results provide important new mechanisms by which resveratrol interacts with sirtuins, the supraphysiological dose used in these experiments must be taken with caution when translating these results to *in vivo* dietary intervention. SIRT1 also plays an important role in the regulation of neurodegenerative disorders [183], and several findings have now converged on the notion that activation of sirtuins by polyphenols could be extended to degenerating neurons. For example, resveratrol, was observed to protect both *C. elegans* and mouse neurons against the cytotoxicity of the mutant polyglutamine protein huntingtin through a mechanism involving Sir-2.1 and SIRT1 activation, respectively [184]. Furthermore, resveratrol decreased cell death associated with neurons cultured from a mutant huntingtin (109Q) knock-in mice, in a manner that is reversible by two SIRT1 inhibitors, sirtinol and nicotinamide [183]. Finally, overexpression of SIRT1 and resveratrol treatment markedly reduced NF-κB signaling stimulated by Aβ and had strong neuroprotective effects, therefore linking SIRT1-NF-κB activity to AD [185] (Figure 3).

8. Conclusion

The neuroprotective actions of dietary polyphenols 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. While many of the mechanisms underpinning their beneficial effects remain to be elucidated, it has become clear that they in part involve decreases in oxidative/inflammatory stress signaling increases in protective signaling, and may also involve hormetic effects to protect neurons against oxidative and inflammatory stressors. Most of the dietary polyphenols that have been shown to be protective against age-related disease are all chemically reactive and nearly all are electrophilic. Such chemical features renders these molecules capable of influencing the redox potential of their target cells and to modulate series of transcriptions factors that result in the activation of phase I and phase II metabolism genes. Nonetheless, much of the data obtained on their bioactivity derived from short-term basis *in vitro* or *in vivo* studies where the dose used was not of nutritional relevance. Although at the moment, the balance of evidence that does suggest that polyphenol effects contribute to the benefits of a high intake of fruits and vegetables, the extent of their contribution *in vivo*, and at physiological relevant concentrations remains uncertain. More work needs to be done to prove whether this class of compounds is most likely to result in health benefits and to determine their beneficial effects in slowly developing neurodegenerative disorders. In view of their multiple biological activities, the consumption of polyphenol-rich foods throughout life holds a potential to limit neurodegeneration and to prevent or reverse age-dependent deteriorations in cognitive performance. However, the therapeutic and pharmacological potential of these natural compounds still remains to be translated in humans in clinical conditions. Moreover, efficacy in RCT is also needed to support the relatively consistent epidemiological and mechanistic evidence. Despite this lack of efficacy data and the uncertainty of their effects *in vivo*, investigations into the absorption and metabolism of various polyphenols in humans indicate that there are common pathways for the metabolism of the majority of polyphenols, notably via their bacterial metabolism in the large intestine [186, 187]. Consequently, research on developing dietary polyphenols for applications in neurodegenerative disorders should prioritise investigations of smaller polar polyphenols for brain bioavailability and bioactivity. 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 metabolites have efficacy in individuals affected by dementia and other neurodegenerative conditions.

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