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# Polyphenols and Neurodegenerative Diseases

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# Polyphenols and Neurodegenerative Diseases

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**Abstract**

With the expansion of the aged population, the prevalence of age-associated disorders like Alzheimer's and Parkinson's disease is growing, as well as the economic burden of its care and treatment. In this light, the preventive and therapeutic benefits of dietary polyphenols may directly improve human life and healthcare costs. Polyphenols display the capacity to protect neurons against oxidative stress, an ability to suppress neuroinflammation, and the potential to promote memory, learning and cognition. The anti-aging and neuroprotective aptitude of these dietary-derived phytochemicals counteract the environment in which neurodegenerative diseases arise. And while the mechanisms by which these effects occur are yet to be fully understood, it is evident that further investigation may yield a potential use for polyphenols as nutritional and pharmacological interventions against specific age-associated diseases. The focus of this review is aimed at presenting the classification, bioavailability and metabolism of polyphenols, as well as the mechanisms of action underlying their neuroprotective features.

**Keywords:** Alzheimer, diet, inflammation, Parkinson, polyphenols.

## Introduction

Ageing is a highly complex process marked by succeeding events that promote alterations in the normal functioning of an individual organism over time.[1] The overall decline in function of entire organs or systems with subsequent vulnerability to oxidative and inflammatory insults, is known to play a key role in both ageing and the complex etiology of certain age-associated diseases such as Alzheimer's and Parkinson's disease.

The aim of this article is to give an overview on the dynamic capacity of polyphenols to protect the central nervous system, by exerting antioxidant activities, suppressing neuroinflammation, and improving cognitive function.

## Polyphenols: classification, bioavailability and metabolism

Polyphenols (i.e. several hydroxyl groups on aromatic rings) are secondary metabolites of plants, that were initially identified as the plant's defensive response against stress from ultraviolet radiation, pathogens, and physical damage.[2] They also contribute to their pigmentation, and are responsible for the astringency and bitterness of plant derived food and beverage.[3]

About 10,000 phenolic compounds of plant origin have been characterized, ranging from simple molecules to highly polymerized compounds. They can be broadly divided

into two categories, flavonoids and non-flavonoid polyphenols, depending on the number of phenol rings and the chemical groups that bind these rings to one anothor (Table 1).[4]

Flavonoids comprise the largest and most important single group of polyphenols. They are found ubiquitously in plants and dietary sources include fruits, vegetables, cereals, tea, wine and fruit juices.[5] Flavonoids consist of two aromatic carbon rings, benzopyran (A and C rings) and benzene (B ring), and may be divided into six subgroups based on the degree of oxidation of the C-ring, the hydroxylation pattern of the ring structure and the substitution of the 3-position.[5] The main dietary groups of flavonoids are (1) flavonols (e.g. kaempferol, quercetin), which are found in onions, leeks, and broccoli; (2) flavones (e.g. apigenin, luteolin), which are found in parsley and celery; (3) isoflavones (e.g. daidzein, genistein), which are mainly found in soy and soy products; (4) flavonones (e.g. hesperetin, naringenin), which are mainly found in citrus fruit and tomatoes; (5) flavan-3-ols (e.g. catechin, epicatechin, epigallocatechin, epigallocatechin gallate), which are abundant in green tea, red wine, and chocolate; and (6) anthocyanidins (e.g. pelargonidin, cyanidin, malvidin), whose sources include red wine and berry fruits.[6]

Among the non-flavonoid polyphenols there are 4 distinct groups: (1) phenolic acids (e.g. caffeic acid, gallic acid); (2) lignans (e.g. secoisolariciresinol); (3) stilbenes (e.g. resveratrol); and (4) curcuminoids (e.g. curcumin).

Two classes of phenolic acids can be distinguished: derivatives of benzoic acid and derivatives of cinnamic acid. The benzoic acid content of edible plants is generally very low, with the exception of certain red fruits, black radish, onions and tea leaves (gallic acid). The cinnamic acids are more common and consist chiefly of p-coumaric, caffeic,

ferulic and sinapic acids . Blueberries, kiwis, plums, cherries and apples possess the highest content of cinnamic acids, being caffeic acid the most abundant phenolic acid.[5]

Lignans are formed of 2 phenylpropane units. The richest dietary source is linseed, which contains secoisolariciresinol and low quantities of matairesinol. Lentils, triticale, wheat, garlic, asparagus, carrots, pears and prunes are minor sources of lignans.[5]

Stilbenes are molecules of two phenolic rings connected by an ethene molecule. Resveratrol is the main stilbene and can be found in grapes, red wine, berries, pistachios and peanuts. There are two isomeric forms of resveratrol, *cis*-resveratrol and the most biologically active *trans*-resveratrol (*trans*-3,4,5-trihydroxystilbene).[7]

Curcuminoids are major chemical components of turmeric, a commonly used spice derived from the rhizome of the plant *Curcuma longa*, used to give specific flavor and yellow color to Indian curries and in food preservation. Curcumins in turmeric include curcumin I (77%), demethoxycurcumin (curcumin II, 17%), and bisdemethoxycurcumin (curcumin III, 3%).[8]

Bioavailability of polyphenols varies widely from one compound to another, so it is important to realize that the polyphenols that are most common in the human diet are not necessarily the most active within the body. Chemical structure, which determines their rate and extent of intestinal absorption is the main factor responsible for their biological activities. Other variables, such as intestinal absorption, excretion of glucuronides toward the intestinal lumen, metabolism by the microflora, intestinal and hepatic metabolism, plasma kinetics, the nature of circulating metabolites, binding to albumin, cellular uptake, intracellular metabolism, accumulation in tissues, and biliary and urinary excretion are also very important, and should be integrated when determining polyphenols bioavailability and be considered in bioactivity research.[5]

Natural polyphenols occur in conjugated form, with one or more sugars, generally bound to the hydroxyl group. Glycosylation influences their physical, chemical, or biological properties, and determines their absorption by the small intestine, which is also affected by their molecular size, degree of polymerization (tannin formation), binding to proteins, or dietary fibers, and solubility.[3] Polyphenols present as aglycones can be absorbed from the small intestine, however most of them are present in the form of esters, glycosides, or polymers and are not easily absorbed in their natural form.[9-11] It is generally accepted that the breakdown of these conjugates to aglycones by acid hydrolysis in the stomach and by the microflora in the gut is required to produce the bioactive compounds that are readily bioavailable to the body.[4] However, relatively little is known about the ability of these aglycone forms to reach the target cells or what the influence of further metabolism in the body has on their spectra of biological activities.[4]

The intestinal absorption of polyphenols can be high, however the plasma concentration of any individual molecule only ranges from 0 to 4 μmol/L after the consumption of 50 mg of aglycone equivalents.[10] Therefore, the maintenance of a high plasma concentration requires repeated ingestion over time. Measurement of the plasma antioxidant capacity suggests that more phenolic compounds are present, largely in the form of unknown metabolites, produced either in our tissues or by the colonic microflora.[9-11] The activities of microbial metabolites must be examined in further studies to determine active structures, available concentrations, and potential modulation of the capacity of the microflora to produce such metabolites.[5] Changes in the composition of the colonic microflora could explain the large interindividual variations in polyphenols bioavailability.[9-11]

The methods surveying the occurrence in food of the various types of polyphenols are not well-standardized, consequently only partial information is available on the quantities of polyphenols that are consumed daily throughout the world. Precise measurements have been done regarding flavonols, flavones, isoflavones, and phenolic acids. Consumption of flavonols has been estimated at ≈ 20 – 25 mg/d in the United States, Denmark, and Holland.[12-14] In Japan, an average dietary intake of 30 – 40 mg/d for isoflavones was determined.[15-16] The mean consumption of flavonones was 28,3 mg/d in Finland, in addition, anthocyanidin consumption was found to be 82 mg/d on average, reflecting the high consumption of berries that is customary in this country.[5] Consumption of soya in the Asian countries is ≈ 10 – 35 g/d, which is equivalent to a mean intake of 25 – 40 mg isoflavones/d.[15-17] In Spain the total consumption of catechins and proanthocyanidin dimers and trimers has been estimated at 18 – 31 mg/d, and the main sources are apples, pears, grapes, and red wine.[5] Consumption of hydroxycinnamic acids may vary highly according to coffee consumption. Some persons who drink several cups per day may ingest as much as 500 – 800 mg hydroxycinnamic acids/d, whereas subjects who do not drink coffee and also eat small quantities of fruit and vegetables do not ingest >25 mg/d.[5] A German study estimated daily consumption of hydroxycinnamic acids and hydroxybenzoic acids at 211 and 11 mg/d, respectively. Caffeic acid intake alone was 206 mg/d, and the principal sources were coffee (which provides 92% of caffeic acid) and fruit and fruit juices combined (source of 59% of *p*-coumaric acid).[18]

The addition of the mean values of flavonols, flavanones, flavan-3-ols, and isoflavones intakes gives a total daily consumption of 100 – 150 mg in Western populations, to which must be added the considerably variable intake of hydroxycinnamic acids, anthocyanidines, and proanthocyanidines.[5] Flavonoids account

for two thirds of total dietary phenols, and phenolic acids account for the remaining third.[9] Finally, the total polyphenol intake probably reaches 1 g/d in people who eat several servings of fruit and vegetables per day.[5] The polyphenols that are most well absorbed in humans are isoflavones and gallic acid, followed by catechins, flavanones, and quercetin glucosides. The least well absorbed polyphenols are the proanthocyanidines, the galloylated tea catechins, and the anthocyanidins.[10]

Paramount importance for the relevance of food polyphenols in the protection of the aging brain is the ability of these compounds to cross the blood-brain barrier (BBB), which controls the entry of xenobiotics into the brain and the maintenance of the brain's microenvironment.[19-21] The BBB is formed by the endothelium of brain microvessels, under the inductive influence of associated cells, especially astrocytes.[19-21] Polyphenols penetration through the BBB is dependent on the degree of lipophilicity of each compound,[22] with less polar polyphenols or metabolites (i.e., O-methylated derivatives) capable of greater brain uptake than the more polar polyphenols and/or metabolites (i.e., sulfated and glucuronidated derivatives), and their interactions with specific efflux transporters expressed in the BBB, such as the multidrug resistance-associated proteins (MRPs).[23]

Several studies have indicated that the flavonones hesperetin, naringenin and their relevant *in vivo* metabolites, as well as some dietary anthocyanidins, cyanidin-3-rutinoside and pelargonidin-3-glucoside, are able to traverse the BBB.[22-25] Green tea catechins are brain permeable,[26-27] and, after oral administration, could be found in the rat brain as glucuronide and 3'-O-methyl epicatechin glucuronide.[28] Anthocyanidines have also been detected in the brain after oral administration,[29-30] with several anthocyanidines being identified in regions of rat brain after the animal were fed with

blueberries.[31] Curcumin is highly lipophilic and crosses the BBB to reach the brain, but it's bioavailability is very low, since the drug is rapidly metabolized by conjugation.[32]

Although it is clear that polyphenols can reach the brain, the precise brain distribution of polyphenols after oral administration is less well studied. It has been reported that anthocyanidins were detected in the cerebellum, cortex, hippocampus, and striatum of blueberry-supplemented rats,[33] and several anthocyanidins have been identified in various regions of the rat[34] and pig[35-36] brain after berry supplementation. Such flavonoid localization has been correlated with increased cognitive performance, suggesting a central neuroprotective role for these compounds.[31]

**Oxidative stress, inflammation and neurodegenerative diseases**

There is a common character for age-related neurodegenerative diseases: all of them are connected with oxidative stress-induced neuronal apoptosis. Oxidative stress (OS) experienced during normal metabolism, and the accumulated damage to important cellular components and structures, is one of the primary contributors to the ageing process and senescence at the cellular level.[37]

Free radicals can be defined as molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals. These unpaired electrons give a considerable degree of reactivity to free radicals. Reactive oxygen species (ROS) (hydrogen peroxide - $H_2O_2$, or superoxide anion - $O_2^-$), as well as reactive nitrogen species, are products of normal cellular metabolism, mainly energy production processes like the electron transport chain in mitochondria, and play a dual role in both

deleterious and beneficial effects, especially in numerous signal transduction mechanisms. OS results from the shift toward ROS production in the equilibrium between ROS generation and the antioxidant defense system, which includes enzymes such has superoxide dismutase, catalase, glutathione peroxidase, as well as low molecular weight compounds, such as glutathione, generally found at levels sufficient enough to defend cells from oxidative insult.[38] The high metabolic rate, the low concentrations of glutathione and catalase, and the high proportion of polyunsaturated fatty acids, make brain tissue particularly susceptible to oxidative damage.[39]

Mounting evidence suggests that increased OS occurs in the aging brain, including reductions in redox active iron,[40-42] as well as increases in Bcl-2, membrane lipid peroxidation, and cellular hydrogen peroxide.[42] Additionally, there is significant lipofuscin accumulation,[38] along with alterations in membrane lipids.[43] The consequences of these increases in OS at several levels may result in disruption of calcium homeostasis, alterations in cellular signaling cascades, and changes in gene expression,[44-48] which combine to contribute to the increased vulnerability to OS seen in the ageing population,[49] and which is elevated in neurodegenerative diseases, such as Alzheimer's disease (AD)[50-51] and Parkinson's disease (PD).[52-54]

AD is the most common type of dementia in the elderly, with an incidence of about 2% in the industrialized countries, affecting 15 – 20 million people worldwide.[55] It is associated with progressive memory loss and cognitive impairment, due to neurodegeneration. Besides genetic factors, which comprise around 7% of familial AD patients, epigenetic and environmental factors are known to play an important role in the onset of sporadic AD.[55]

Common pathological hallmarks for AD are the accumulation of amyloid plaques and neurofibrillary tangles in the neocortex.[56] Amyloid beta (Aβ), a peptide of 39 – 43 amino acids, is the main constituent of amyloid plaques, and is the product of the aberrant fragmentation of a membrane protein, the Amyloid Precursor Protein (APP).[57-58] APP can be alternatively processed by cleavage by α-secretase (a harmless process whose physiological role has not been clarified yet), or by the sequential proteolysis carried out by β-secretase and γ-secretase, leading to the release of Aβ that can then be aggregated in the oligomeric form.[2,55] The Aβ peptide has been proven to generate free radicals through the production of hydrogen peroxide, through metal ion reduction (especially Zn, Cu and Fe), with concomitant release of thiobarbituric acid-reactive substances (TBARS), a process probably mediated by formation of hydroxyl radicals with concomitant stimulating of inflammatory cells.[59] Oligomeric Aβ can confer oxidative insult to neurons and glial cells and initiate changes in synaptic plasticity, events occurring long before their deposition to form amyloid plaques.[60] Furthermore, in the AD brain, tau-protein, a microtubule-associated protein becomes hyperphosphorylated and oxidized, forming intracellular proteinaceous deposits, the neurofibrillary tangles.[61]

Oligomeric Aβ is able to confer specific action on the N-methyl-D-aspartic acid (NMDA) receptors, which not only regulate synaptic plasticity, and memory function, but up on their activation are coupled with ROS production.[62-66] Thus , NADPH oxidase may be common in NMDA- and Aβ-induced ROS production, and activation of signaling pathways including protein kinase C (PKC) and mitogen-activated protein kinase (MAPK), which in turn, lead to the activation of cytosolic phospholipase A2 and release of arachidonic acid.[66] Arachidonic acid not only is a precursor for synthesis of prostaglandins, but is also known to serve as a retrograde transmitter in regulating

synaptic plasticity.[67] Intracellular Aβ may target cytoplasmic signaling pathways and impair mitochondrial function.[68] Aβ-mediated ROS production is also linked to increased inflammatory responses, including increased production of cytokines, nitric oxide, and eicosanoids.[69-71]

PD is a chronic progressive neurodegenerative movement disorder characterized by a profound and selective loss of dopaminergic neurons in the substancia nigra pars compacta, and it affects approximately 1% of the population over the age of 50.[54,72] Clinical manifestations of PD include motor impairment involving resting tremor, a slowing of physical movement (bradykinesia), postural instability, gait difficulty, and rigidity.

The most probable origin of the etiology of dopaminergic neuronal demise is a combination of genetic susceptibilities and environmental factors, including heavy metals and herbicides.[73-74] Oxidative stress has been widely believed to be an important pathogenetic mechanism of neuronal apoptosis in PD.[75] The majority of PD cases are sporadic (90 – 95%), while familial cases account for 5 – 10% of PD.[76]

One of the pathological hallmarks of PD is the presence of intracellular inclusions called Lewy bodies that consist of aggregates of the presynaptic soluble protein called α-synuclein.[77-78] The toxic effects of α-synuclein include impaired endoplasmic reticulum, Golgi fragmentation, sequestration of anti-apoptotic proteins into aggregates, and the formation of pores on cellular membranes.[79] The onset of PD is accompanied by the dramatic depletion of levels of glutathione in substancia nigra , resulting in a selective decrease in mitochondrial complex I activity (a major hallmark of PD) and a marked reduction in overall mitochondrial function.[80] The harm to mitochondrial

complex I causes α-synuclein aggregation, which contributes to the death of dopamine neurons, leading to a dopamine deficit in the striatum.

The features of enhanced oxidative stress linked with PD are supported by postmortem studies, and by studies demonstrating the capacity of oxidative stress to induce nigral cell degeneration.[81] In addition, other important factors, involving inflammation, toxic action of nitric oxide, defects in protein clearance, and mitochondrial dysfunction all contribute to the etiology of PD.[82]

Iron content alterations have been described in the brains of PD and AD patients, which may be caused to a large extent, by endogenous dysregulation of iron uptake, transport, distribution , and storage.[83-86] Iron is one of the most essential transition metals involved in the formation of ROS, owing to its interaction with hydrogen peroxide through Fenton chemistry and generation of the aggressively reactive hydroxyl radical. Accumulation of iron, specifically in the substancia nigra pars compacta, is one cardinal feature of PD, and is considered to be a major contributor to OS.[87] Analysis of AD brains indicates iron accumulation within specific brain regions, displaying selective vulnerability to neurodegeneration, such as the hippocampus and cerebral cortex.[88-89] Damage to brain cells in Parkinson's, Alzheimer's and other neurodegenerative diseases seems to result from the combination of a number of damaging factors including excessive inflammation and increased levels of iron, both of which lead to increased free radical production, exhaust the brain's supply of protective antioxidants and trigger the production of certain proteins, such as Aβ.

**Polyphenols display neuroprotective effects**

One of the most important aspects of current polyphenol research is the focus on the neuroprotective capacity that is a characteristic feature of this broad family of compounds. There is increased interest in uncovering efficient antioxidants to reduce the risk of AD, PD, and other neurodegenerative disorders, since current therapeutic approaches are merely symptomatic, without any disease-modifying activity. Because many diseases of ageing can be directly linked to repeated oxidative stress and chronic inflamation,[90] therapies that can diminish such effects have become an important tool in seeking more effective treatments for diseases such as Alzheimer's and Parkinson's.[53,91]

Continuing research highlights the dynamic capacity of polyphenols to protect against age-associated disorders through a variety of important mechanisms. The chemical antioxidant activity of polyphenols is correlated with the number of hydroxyl groups present on the aromatic A and B rings, and with the presence of a C2-C3 double bond, the most active ones containing between 3 and 6 hydroxyl groups.[52] The antioxidant mechanism is based on the donation of a hydrogen and the formation of a phenoxyl radical that undergoes stabilization either by release of a further hydrogen, or by reaction with another radical.[3] In general, polyphenols have the capacity to chelate metal ions and to quench free radical species.[53] The ability of flavones and flavan-3-ol polyphenols to chelate redox-active transition metal ions, such as iron or copper, depends on the presence of their carboxylic and hydroxylic groups and may contribute to their antioxidant activity, because it prevents metals from catalyzing free radical formation.[54]

Green tea is an extremely popular drink in eastern countries, and green tea polyphenols known as catechins, are natural plant flavonoids found in the tea leaves. The major tea catechins include, epicatechin (EC), epigallocatechin (EGC), EC gallate (ECG), and EGC gallate (EGCG).[92] Other compounds in green tea are the flavonols (quercetin, kaempferol, and rutin), caffeine, phenolic acids, and theanine.[93] Catechins are especially concentrated in green tea, which account for 30 – 40% of the dry weight of the leaves.[94-95] All four tea catechins have been demonstrated to be potent antioxidants, resulting from their direct oxygen and nitrogen species scavenging properties, induction of endogenous antioxidant enzymes, and the capacity to bind and chelate excess of divalent metals, such as iron and copper.[96-97] The rank order of antioxidant abilities of green tea components is EGCG>ECG>EGC>EC.[98] Catechins are well absorbed after oral administration, and are biotransformed in the liver to their conjugated metabolites, i.e., glucuronidated, methylated, sulfated derivatives.[1] By simply drinking green tea, polyphenols can cross the BBB and have neuroprotective effects.[99]

Nutritional studies demonstrated that a consumption of green tea could have a beneficial role in reducing the risk of PD.[100] The mechanisms underlying this beneficial role were the capacity of EGCG to act as an iron chelator,[101] and increase the activity of two major antioxidant enzymes, superoxide dismutase and catalase, further helping to decrease free radical damage.[102] EGCG has also been shown to competitively inhibit the uptake by the presynaptic or vesicular transporters of metabolites from the neurotoxin MPTP (*N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).[103] This competition could protect dopaminergic neurons against MPTP induced injury.[104]

In AD, EGCG has been reported to interfere with an early step in the amyloid formation cascade by binding directly to the natively unfolded α-synuclein and Aβ

pollypeptides, thus inhibiting their fibrilogenesis and redirecting them into an alternative "off pathway" before they become toxic.[105] EGCG has recently been found to convert large, mature α-synuclein and Aβ fibrils into smaller, amorphous non-toxic protein aggregates.[106] In addition, EGCG exerts neuroprotection by modulating intracellular signaling pathways such as MAPK,[107] PKC,[108-110] and PI-3K/Akt[111] which will be discussed later in this review, and inhibit the activation of nuclear factor kappaB[112] (NF-κB) and pro-apoptotic pathways.[113]

Several studies using dietary supplements with either spinach, strawberries, or blueberries extracts have been reported to reduce some neurological deficits in aged animals (Morris water maze performance).[114-118] In addition, blueberries supplementation was also effective in reversing cognitive declines in object recognition.[119] Catechin, epicatechin, and anthocyanidins are the main polyphenols present in blueberries, and there is a significant positive correlation between their serum content and postprandial antioxidant status.[120] Aged rats with blueberries supplemented diet had significantly lower levels of NF-κB than aged control diet rats,[119] revealing that the neuroprotection conceded might involve more than the blueberries extract antioxidant actions. Blueberries extract supplementation could also reduce the volume of infarction in the cerebral cortex, and increase the post-stroke locomotor activity induced by isquemia/reperfusion,[118] as well has protect against neuronal loss in the CA1 and CA2 regions of the hippocampus after cerebral isquemia.[121] Additionally, blueberries supplemented APP/PS1 mice exhibited greater levels of hippocampal extracellular signal regulated kinase (ERK), as well as striatal and hippocampal PKCα, when compared with transgenic mice maintained on a control diet.[122]

Resveratrol is the main non-flavonoid polyphenol found in grapes and red wine, and it has been reported to possess antioxidant, anti-inflammatory, antimutagenic, and

anticarcinogenic effects,[123-124] as well as a beneficial effect against AD pathology by promoting anti-amyloidogenic mechanisms.[100] Several epidemiological studies indicate that a moderate consumption of wine is associated with a lower incidence of AD.[125-127] Resveratrol not only possesses the capacity to directly scavenge free radical species, but also regulates the cytotoxic effects of Aβ oligomers and fibrils via phosphorylation of PKC, which activates the transmembrane protein α-secretase.[128-129] α-secretase catalyzes the formation of a soluble, non-amyloidogenic (non-plaque forming) protein from APP , and thus does not allow for the formation of neuritic plaques. Modulation of NF-κB activity, or NF-κB/SIRT1 pathway could also be implicated in the neuroprotective effect of resveratrol, since activation of SIRT1 by resveratrol inhibits NF-κB signaling by promoting deacetylation of lys310 of RelA/p65[130], thereby protecting cells against the Aβ peptide.[131-132]

Genistein, the most active component of soy isoflavone, is a phytoestrogen that is capable of crossing the BBB,[133] manifesting potent antioxidative properties,[134-135] and neuroprotective activity.[59] Genistein has been shown to protect neurons form Aβ-induced damages largely via a estrogen receptor mediated pathway, as well as by its antioxidative properties.[59]

Curcumin has been used for centuries in Asia as a food additive and a traditional herbal medicine, and it has been revealed that besides its potent antioxidative, and anti-inflammatory properties, it also exhibits anti-amyloidogenic effects.[136] Epidemiological studies have raised the possibility that the properties of this molecule are responsible for the significantly reduced (4.4 fold) prevalence of AD in India compared to the United States of America.[137] These observations could be explained by the ability of curcumin to reduce IL-1β,[138] a proinflammatory cytokine, inhibit β-secretase and Aβ aggregation,[7,139] and bind to the redox-active metals iron and copper.[140] The

neuroprotective effects of curcumin relevant to PD are likely to be associated with its antioxidant and anti-inflammatory properties.[141-142] Acute oral administration of curcumin results in poor bioavailability due to its rapid conversion to glucuronides, suggesting that very small doses of curcumin are necessary for its neuroprotective effect.[2] In addition, it is worth noting that excessive application of curcumin may produce pro-oxidative effects.[143]

The flavonoid-rich ginkgo biloba has been used for 5000 years in traditional Chinese medicine. EGb 761 is a standardized extract of ginkgo biloba, whose flavonoid content is composed of quercetin, kaempferol, and isorhamnetin. Several studies have highlighted the potential of EGb 761 and its constituents to prevent lipid oxidation,[144] and to act as antioxidants and free radical scavengenrs.[145-146] Ginkgo biloba also exerts a combination of anti-amyloidogenic, and anti-apoptotic effects particularly in connection with age related dementias and AD.[147-149] EGb 761 is able to inhibit Aβ fibrils formation due to its iron chelating properties,[147,150] and is able to rescue primary hippocampal neurons and PC12 cells against the toxicity of the Aβ peptide.[150-151]

**Polyphenols improve memory**

With ageing, neuronal populations and synaptic connections are lost over time, resulting in diminished efficiency in the processing and storage of sensory information, however, emerging evidence suggests that polyphenols are able to induce improvements in memory acquisition, consolidation, storage, and retrieval. There is strong evidence that flavonoid intake is associated with better cognitive evolution, i.e. the preservation of cognitive performance with ageing.[152] Furthermore, flavonoids found in fruits and

fruit juices (most notably flavan-3-ols, flavanones, and anthocyanins) have the capacity to improve memory.[30,153-155] A number of animal intervention studies, using diets containing between 1 and 2% (w/w) freeze-dried fruit/fruit juice, have indicated that grape, pomegranate, strawberry, and blueberry, as well as pure flavonoids (epicatechin and quercetin), are capable of affecting several aspects of memory and learning, notably rapid[156] and slow[157-160] memory acquisition, short-term working memory,[153,161-164] long-term reference memory ,[165] reversal learning,[156,161] and memory retention/retrieval.[166] For example, fruits such as strawberry, blueberry, and blackberry (all rich in anthocyanidins and flavan-3-ols) have been shown to be beneficial in retarding functional, age-related central nervous system and cognitive behavioral deficits.[157,167-168] There is also extensive evidence that blueberries are effective at reversing age-related deficits in spatial working memory.[153,163,165,168-173]

The ability of polyphenols to reverse age-related declines in memory, relies on their potential to interact with the cellular and molecular architecture of the brain responsible for memory. In general, the short-term storage of both implicit and explicit memory involves functional changes in the strength of pre-existing synaptic connections, whilst their long term storage requires the synthesis of new protein and the growth of new connections.[5] The capacity of polyphenols to interact with, and effectively modify the pathways within neurons and synapses leading to changes in the efficiency of *de novo* protein synthesis, will allow for the likelihood to affect the process of memory.[5]

Long-term potentiation (LTP) is widely considered to be one of the major mechanisms by which the brain learns and maintains memories.[174-175] It refers to a persistent increase in the chemical strength of a synapse, and is known to contribute to "synaptic plasticity" or the increased strength of the connection between two neurons, a process thought to underlie memory.[176-177] Various signaling pathways have been linked

with the control of *de novo* protein synthesis in the context of LTP, synaptic plasticity and memory: (1) cAMP-dependent protein kinase (protein kinase A);[178] (2) protein kinase B (PKBAkt);[179] (3) PKC;[180] (4) calcium-calmodulin kinase (CaMK);[181] and (5) ERK.[182-183] All five pathways converge to signal to the cAMP-response element-binding protein (CREB), a transcription factor which binds to the promoter regions of many genes associated with synapse re-modeling, synaptic plasticity and memory (Figure 1).[185-185] The importance of CREB activation in the induction of long-lasting changes in synaptic plasticity and memory is highlighted by studies which show that disruption of CREB activity specifically blocks the formation of long-term memory,[186] whereas agents that increase the amount or activity of CREB accelerate the process.[187] Furthermore, CREB is known to be a critical transcription factor linking the actions of neurotrophins, such as BDNF, to neuronal survival, differentiation, and synaptic function.[188-189] BDNF belongs to the neurotrophin family of growth factors and affects the survival and function of neurons in the central nervous system. It's secretion from neurons is under activity dependent control and is crucial for the formation of appropriate synaptic connections during development, and for learning and memory in adults.[190] Decreases in BDNF and pro-BDNF have been reported in AD,[191-192] and the importance of pro-BDNF has been emphasized by the finding that a polymorphism that replaces valine for methionine at position 66 of the pro-domain is associated with memory defects and abnormal hippocampal function in humans.[193] Ultimately, CREB activation and neurotrophyn synthesis are able to induce synaptic plasticity, and represents a vital stage in converting brief afferent signals into long lasting memory.[5] The increase in synaptic receptor, and neuronal spine density and morphology are hallmarks of synaptic plasticity ,[194-195] and constitute integral events in LTP.[5]

Flavonoids through the interactions within MAPK pathways, such as the ERK pathway are believed to influence memory,[196] since ERK is associated with pro-survival and pro-neurotrophin signaling through the activation of CREB.[197-199] Fisetin, a flavonoid found in strawberries, has been shown to improve LTP and to enhance object recognition in mice by a mechanism dependent on the activation of ERK and CREB.[200] Similarly, the flavan-3-ol (-)epicatechin induces both ERK ½ and CREB activation in cortical neurons and subsequently increases CREB regulated gene expression,[201] whilst nanomolar concentrations of quercetin are effective at enhancing CREB activation.[202] The citrus flavanone hesperetin is also capable of activating ERK ½ signaling in cortical neurons,[203] and EGCG is capable of restoring both PKC and ERK ½ activities in 6-hidroxydopamine treated and serum deprived neurons.[109,204] These effects on the ERK pathway are highly concentration-dependent, with high affinity receptor agonist-like actions at low concentrations, and direct enzyme inhibition at high concentrations.[205-206] In addition, the finding that anthocyanidins and flavan-3-ols appear in the hippocampus following blueberry supplementation may indicate that changes in memory are linked directly to flavonoids and their action on the ERK-CREB-BDNF pathway.[207]

Another mechanism that may exert beneficial effects on memory consists on the ability of flavonoids to activate the Akt/PKB pathway, which also has the potential to activate CREB. Hesperetin can activate the Akt/PKB pathway, as well as inhibit pro-apoptotic proteins such as ASK1, Bad, caspase-9, and caspase-3 in cortical neurons.[203]

Flavonoid-induced activation of CREB and enhancement of BDNF expression in neurons will ultimately lead to the activation of PI3 kinase/Akt signaling pathway *via* the binding of BDNF to pre- or post-synaptic TrkB receptors.[208] These events trigger the activation of the mTOR pathway and the increased translation of specific mRNA subpopulations,[209] including the activity-regulated cytoskeletal-associated protein

(Arc/Arg3.1). Arc/Arg3.1 expression, which is under regulatory control of both BDNF[210] and ERK signaling,[211] has been shown to facilitate changes in synaptic strength, and stimulate the growth of small dendritic spines into large mushroom-shaped spines through a mechanism dependent on actin polymerization.[212] In support of this, dietary supplementation with blueberries has been shown to increase hippocampal Arc/Arg3.1,[4] and specific flavan-3-ols have been shown capable of inducing neuronal dendrite outgrowth.[109] Furthermore, nobiletin, a poly-methoxylated flavone found in citrus peel, also induces neurite outgrowth[213] and synaptic transmission [214] *via* its ability to interact directly with MAPK and PKA signaling pathways.[215]

Flavonoid-rich foods may also influence memory by improving cerebral blood flow (CBF), which is decreased in patients with dementia[216-217] and is significantly lower in patients with AD .[218] Such vascular effects seem to be mediated by flavonoids potential to induce nitric oxide production in the endothelium, along with rapid vasodilatation leading to improved peripheral blood flow.[219-220] Increased cerebrovascular function is known to facilitate adult neurogenesis in the hippocampus,[221] with new hippocampal cells appearing clustered near blood vessels, which proliferate in response to vascular growth factors.[222] In support of this, flavonol-rich foods have been shown to cause significantly increased CBF in human subjects, one to two hours postintervention,[223-224] and an increase in CBF through the middle cerebral artery has been reported after the consumption of flavan-3-ol-rich cocoa using trans-cranial Doppler ultrasound.[224]

**Polyphenols inhibit neuroinflammation**

Sustained neuroinflammatory processes may contribute to the cascade of events culminating in the progressive neuronal damage observed in many neurodegenerative disorders , most notably AD and PD,[225-226] and also with neuronal injury associated with stroke.[227] As such, the use of non-steroidal anti-inflammatory drugs, like ibuprofen, has been proposed to delay or even prevent the onset of such neurodegenerative disorders,[228-229] and epidemiological studies have indicated that the risk for developing AD was reduced in regular users of anti-inflammatory drugs.[230] Glial cells mediate the endogenous immune system within the microenvironment of the CNS, and their activation which increases in the normal ageing brain, is the hallmark of inflammation in the brain.[231-232] Activated microglia produce proinflammatory molecules, such as cytokines (IL-1, IL-6, TNF-α), growth factors, and complement proteins, that in turn activate other cells to produce additional signaling molecules that further activate microglia in a positive feedback loop to perpetuate and amplify the inflammatory signaling cascade.[233-235]

There is a growing body of evidence to suggest that flavonoids and flavonoid-rich foods may be capable of counteracting such neuronal injury, thereby delaying the progression of these diseases.[22,223,236-237] To date, evidence relating to the inhibition of neuroinflammation by flavonoids indicate that they may act through, (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; and (4) a capacity to down-regulate

the activity of pro-inflammatory transcription factors such as NF-κB (Figure 2).[238] Furthermore, the potential to influence these events appear to be mediated by their influences on a number of glial and neuronal signaling pathways , such as the MAPK cascade.[238]

EGCG has been shown to attenuate neurodegeneration induced by the parkinsonian toxin 6-hidroxydopamine[239] and MPTP,[240] and hippocampal injury induced by transient global isquemia.[241] In addition, EGCG has been noted to interact with and modulate signaling pathways involved in neuroprotection, notably PKC and PI3-kinase.[242-245] *In vitro* studies have also indicated that flavonoids commonly found in oranges, berries, apples, and grapes, might act to prevent PD pathology because of their ability to prevent the formation of the endogenous neurotoxin 5-S-cysteinyldopamine.[246-249] It has been shown that aged male Fischer 344 rats fed a blueberries supplemented diet showed reductions of age-induced increases in NF-κB expression, compared to those of aged nonsupplemented controls in the frontal cortex, hippocampus, and the striatum.[119]

The citrus flavanone naringenin has been found to be highly effective at reducing lipopolisaccharide/interferon-γ-induced glial-cell activation and resulting neuronal injury, via inhibition of p38 and signal transducers and activators of transcription family-1, and a reduction in inducible nitric oxide synthase expression.[249] Other flavonoids have been shown to partially alleviate neuroinflammation through the inhibition of TNF-α production.[250] Flavonoids present in blueberries have also been shown to inhibit NO·, IL-1β, and TNF-α production in microglia cells,[251] while the flavonol quercetin[252] and the flavan-3-ols catechin and EGCG[253] have all been shown to attenuate microglia- and/or astrocyte-mediated neuroinflammation.

It should be mentioned that much of the existing *in vitro* data has utilized non-physiological concentrations of polyphenols, making it difficult to extrapolate these results to the *in vivo* scenario, however, *in vivo* evidence and select *in vitro* data have clearly indicated a potential for polyphenols to inhibit neuroinflammation and the neurodegeneration associated with it.[238]

## Conclusion

The substantial number of naturally occurring dietary polyphenols represent an emerging and promising tool in the prevention and treatment of neurodegenerative diseases such as AD and PD, as well as the deleterious effects of ageing. Polyphenols have often been generically referred to as "antioxidants" for their ability to react with and quench ROS produced during metabolic processes, however, the emerging view is that polyphenols can exert beneficial effects on cells not only through their antioxidant potential but also through an ability to suppress neuroinflammation, and the potential to promote memory, learning, and cognitive function.

The beneficial effects of polyphenols may prove to be a valuable asset in the quest to develop a new generation of drugs capable of counteracting neuroinflammation and associated neurodegenerative diseases, however, the research in this field is still incomplete. Many questions are still unanswered, especially regarding the transfer of the findings of the *in vitro* studies to the *in vivo* application, furthermore, to date there is not enough data to clearly associate flavonoid consumption with improvements in neurological health.[254] A first point of attention is that the bioavailability of the various food polyphenols is not yet completely known, and can be different for the same

molecule depending on its source and on food preparation, indeed, the quantity of polyphenols found in the plasma represents only a small percentage of the intake.[255] In addition, *in vitro* studies on the biological activity of polyphenols use the original molecule instead of the *in vivo* metabolites produced upon digestion, whose biological activities may differ from the parent compounds. Also, the side effects of polyphenols must be better understood since they display a biphasic behavior, acting as prooxidants at high concentrations, with inhibition of enzymes responsible for cell survival or activation of enzymes leading to cell death.[256]

For the obtention of a causal relationship between the consumption of polyphenols and their behavioral outcomes, future intervention studies will be required to utilize better-characterized intervention materials, more appropriate controls, and more rigorous clinical outcomes. For example, it would be highly advantageous to directly link behavioral responses to changes in hippocampal volume and density, changes in neural stem cell and progenitor cell populations, molecular changes related to synaptic plasticity, and alterations in CBF using MRI and fMRI techniques.[254] Functional MRI measures may be used to assess changes in blood flow that underlie improved cognitive functioning as a result of polyphenol supplementation.[254]

Despite the need for these additional studies, the ability of polyphenols to activate the CREB pathway in addition to their antioxidant and anti-inflammatory properties, establish them as potential precursor molecules in the quest to develop a new generation of drugs capable of counteracting and perhaps even reversing age-related losses in cognitive performance. Additionally, nutritional interventions may be designed to prevent or delay the age-related neurodegenerative diseases.

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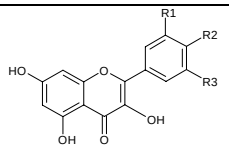
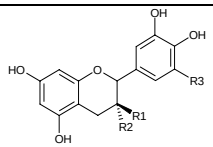
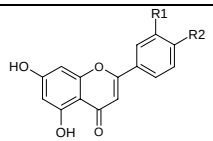
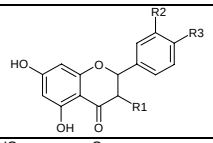
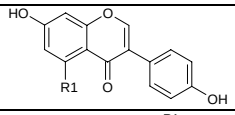
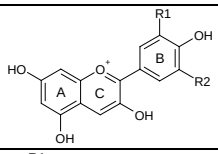
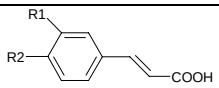
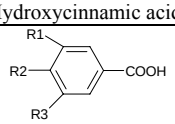
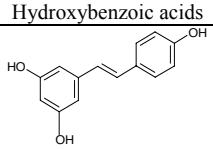
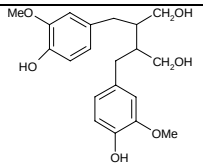
**Table 1** – Chemical structures of main groups of polyphenols.

| | | | | |
|---|---|---|---|---|
| Polyphenols | Flavonoid | Flavonols |  | R1=H; R2=OH; R3=H: kaempferol<br>R1=OH; R2=OH; R3=H:quercetin<br>R1=OH; R2=OH; R3=OH: myricetin |
| | | Flavan-3-ols |  <br>Monomeric | R1=H; R2=OH; R3=H: (+)-catechin<br>R1=OH; R2=H; R3=H: (-)-epicatechin<br>R1=OH; R2=OH; R3=OH: (+)-gallocatechin |
| | | Flavones |  | R1=H; R2=OH: apigenin<br>R1=OH; R2=OH:luteolin |
| | | Flavanones |  | R1=H; R2=H; R3=OH: naringenin<br>R1=OH; R2=OH; R3=OMe: hesperetin |
| | | Isoflavones |  | R1=H: daidzein<br>R2=OH: genistein |
| | | Anthocyanidins |  | R1=H; R2=H: pelargonidin<br>R1=OH; R2=H: cyanidin<br>R1=OH; R2=OH: delphinidin<br>R1=OMe; R2=OH: petunidin<br>R1=OMe; R2=OMe: malvidin |
| | Non-flavonoid | Phenolic acids |  <br>Hydroxycinnamic acids | R1=H; R2=OH: *p*-coumaric acid<br>R1=OH; R2=OH: caffeic acid<br>R1=OMe; R2=OH: ferulic acid |
| | | |  <br>Hydroxybenzoic acids | R1=OH; R2=OH; R3=H: protocatechuic acid<br>R1=OH; R2=OH; R3=OH: gallic acid |
| | | Stilbenes |  | resveratrol |
| | | Lignans |  | secoisolariciresinol |

**Effects of polyphenols on memory, learning and cognition.**

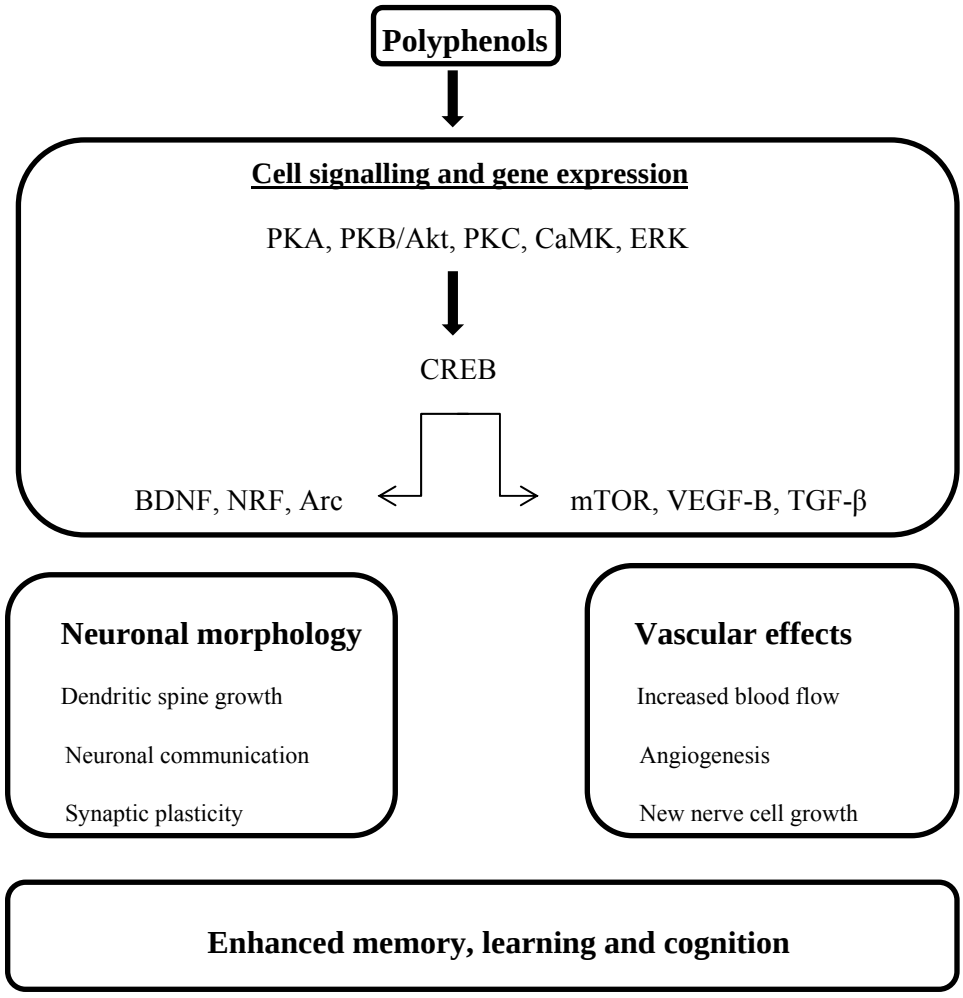



**Figure 1.** Polyphenol-induced activation of neuronal signalling and gene expression in the brain, may lead to changes in synaptic plasticity and neurogenesis in the brain which ultimately influence memory, learning and cognition. Adapted from Spencer JPE (Ref. 218).

**Effects of polyphenols on neurodegeneration and brain ageing.**

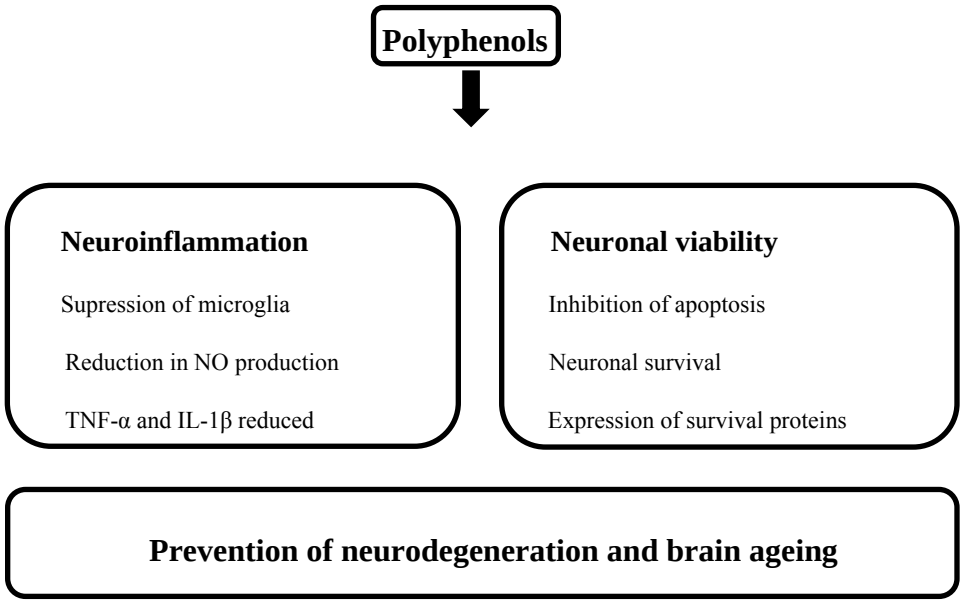



**Figure 2**. The polyphenol-induced inhibition of pro-apoptotic signalling in neurons, and reduction of neuroinflammatory reactions in microglia, may prevent neurodegeneration and brain ageing. Adapted from Spencer JPE. (Ref. 218).