Chapter 7
Polyphenols as an Effective Therapeutic Intervention Against Cognitive Decline During Normal and Pathological Brain Aging

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1 Introduction

Globally, an alarming increase in the elderly population has had profound implications, not only on the individuals' health but also for society and the economy. A prediction based on statistics by the World Health Organisation has indicated an enormous increase of the global population over 60 years of age to 22% by 2050 [1]. However, as attempts to improve the longevity of the population are increasing, the burden of the increasing incidences of age-related neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, is on the rise. Alongside this rise are the crucial and fundamental questions that need to be resolved, i.e. at what age do these brain diseases occur and what are the age-related factors that predispose patients to neurodegenerative diseases?

In this review, we focus specifically on middle-age as an important risk factor for cognitive decline in normal aging subjects and how this decline is further impacted by neurons in specific regions of the brain leading to neurodegenerative diseases in subjects over 80 years of age. However, vigorous efforts towards any preventive measure against the onset of various brain disorders should also consider prioritising mechanisms related to normal aging such as inflammatory processes and impaired redox balance as essential tissue factors responsible for initiating the loss of neurons in sub-fields of the brain that are specific for cognitive functions. The literature on intervention studies has described in mechanistic terms polyphenols' effects through interactions with cellular signal transduction pathways. In addition, polyphenol-rich foods, such as fruit and vegetables, have been shown to either protect or slow down the progression of cerebrovascular diseases, such as strokes, and

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many neurological disorders, including dementia [2–5] and cognitive impairment in elderly populations. Polyphenol consumption in middle-age is also related to better cognitive function much later in life [6].

2 Polyphenols

Polyphenols are secondary metabolites in plants. The main components of polyphenols are phenolic acids, anthocyanins, flavonoids and simple and complex flavonoids as well. Flavonoids are the largest group of polyphenols that can be further classified into four main classes: flavonoids, phenolic acids, stilbenes, and lignans. A detailed classification of polyphenols has been reviewed by Archivo and his coscientists [7]. Of particular interest are the flavonoid anthocyanins, which impart red and blue colours to berries, grapes, and red wine. The beneficial effects of grape seeds on human health lie in the fact that they have highest concentrations of antioxidant activities in comparison with many other polyphenolic extracts from plants [8] and this is largely related to its flavan-3-ols and condensed tannins [9]. The flavonoids include gallic acid, the monomeric flavan-3-ols catechin, epicatechin, gallocatechin, epigallocatechin, and epicatechin 3-O-gallate. In addition, they contain procyanidin dimers, trimers, and more highly polymerised procyanidins. Of these, the simplest are dimeric proanthocyanidins, possessing ten to eight linked monomers [10–12]. Using liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique, we have shown the bioavailability of tannins, (+)-catechin, and (−)-epicatechin in the hippocampus [13] and prefrontal cortex [14] of grape seed proanthocyanidin extract (GSPE)-supplemented young and middle-aged male Wistar rats.

Polyphenols supplied by the diet as functional foods are providing several benefits, especially for the elderly populations across the globe. In fact, some studies have demonstrated an interest of the consumers in such foods enriched with antioxidants, and these are now referred to as ‘nutraceuticals’ [15–17]. There is active intestinal absorption of the polyphenols following ingestion of polyphenol-rich foods [18, 19]. Polyphenols possess distinctive physiologically-supportive properties that are described as anti-diabetic, anti-inflammatory, anti-thrombotic, anti-hypertensive, and more importantly, anti-oxidant [20, 21]. In fact, experimental evidence has described polyphenols as micronutrients with anti-aging properties. Polyphenols are often perceived as pleiotropic, exerting their antioxidant and anti-inflammatory potential against several disease-relevant biological pathways [16]. Studies have shown that polyphenols and their metabolites in mammals can pass across the blood brain barrier (BBB) into the brain and bolster neurological functions [22–26]. Furthermore, the bioavailable concentrations of certain polyphenols such as anthocyanins have been identified in the hippocampus and cortex of rats supplemented with blueberry for 8 weeks [27] and 4 weeks in pigs [28]. In addition, the study also showed that the extent of deposition of anthocyanin in the brain is not in proportion to that of the plasma levels when measured immediately after consumption of the berry, thus concluding that uptake of polyphenols in the brain can also happen by

mechanisms other than passive diffusion. However, it is uncertain whether polyphenols and its metabolites primarily enter via simple or facilitated diffusion [29, 30]. Interestingly, uptake of the monomer constituents of GSPE, (+)-catechin and (−)-epicatechin, is through an isomer-selective transport in endothelial cells of the BBB [31]. In addition, Liang and co-workers [32] have demonstrated the accumulation of a product of catechin metabolism, 3-*O*-Me-catechin-5-*O*-glucuronide, in the rat brain. However, the limited bioavailability of polyphenols in the brain has been related to the selective permeability of the BBB, weak absorption, and rapid elimination from circulation [25].

3 Polyphenols and the Normal Aging Brain

Brain aging is associated with loss in volume and dendritic atrophy in the hippocampus (HC) and medial prefrontal cortex (mPFC) in rats [33] and humans [34–36]. Middle-aged rats experience reductions in neuronal number, volume, and density in the anterior cingulate cortex (ACC) and prelimbic cortex (Prl) of the dorsomedial prefrontal cortex (dmPFC) [14]. Studies have shown that young rats of 4–6 months of age have longer dendritic trees, elevated levels of synaptic markers, and better cognition compared to older rats 22–24 months-old, which have shorter dendrites and lower levels of synaptic markers [37, 38]. These age-related morphological changes represent an imbalance between generation and degeneration of dendrites in the old and their role in pathological neurodegeneration [39].

The brain is characterised by high levels of polyunsaturated fatty acids and oxidative stress (OS) is highly prevalent in normal aging. Some areas related to cognition, such as the PFC and HC, become dysfunctional as a result of increased oxidative injury by macromolecules that are essential for neuronal functions. As a result, several cytotoxic free radicals (FRs) contribute to the formation of lipid peroxides within the neurons [40]. Thus, neurons of aging brains suffer from a loss of intracellular concentrations of micronutrients and ions which leads to weak synaptic plasticity. Oxidative stress is highly related to cognitive impairments in aging humans and is largely a result of an imbalance between reactive oxygen and nitrogen species (RONS) and the antioxidant defence system. The heightened OS occurring in the aging brain is concomitantly accompanied by reductions in redox-active iron [41] with significant lipofuscin accumulation [14, 42].

Among the flavonoid polyphenols, proanthocyanidins are excellent scavengers of superoxide radicals and hydroxyl radicals [43]. Inhibition of oxidative DNA damage in the neural tissue has been reported in rats that were supplemented with GSE (100 mg/kg b.wt.) for 30 days [44] along with a decreased incidence of FR-induced lipid peroxidation (LPO) in the central nervous system of aged rats [45]. Better cognitive performance with reduced acetylcholine esterase (AChE) activity has been reported for adult mice following intra-peritoneal (i.p.) supplementation for 7 days with the polyphenol-rich blueberry extract [46] and in adult and middle-aged rats orally supplemented for 8 weeks with proanthocyanidin-rich GSE at 400 mg/kg body weight [47].

Normal aging of the brain is largely confined to the frontal and temporal lobes compared to the parietal and occipital lobes [48] with a progressive decline in cognition due to disturbances in the hippocampal circuit, including the dentate gyrus (DG) and the PFC [49]. It is known that the functional changes in the pre-existing synaptic connections and the synthesis of new proteins and more importantly, their capacity for establishing new connections, are critical for short-term and long term memory storage. It is made possible due to their potential to interact with the molecular components in the brain sites for memory. Alterations in cognition with age are manifested by a significant decline in spatial and working memory as evidenced by a delayed retrieval of a learned task. Polyphenols, when supplemented daily, can reverse age-related declines in memory because of their potential to interact with the molecules in cognitive sites and modify the pathways within neurons and synapses, as well as facilitate *de novo* protein synthesis, and in turn, are effective in improving the process of memory [50].

Animal studies on cocoa and tea flavanol supplementation have also demonstrated that dietary polyphenols are beneficial in reversing the course of neuronal and behavioural aging [51]. For instance, human studies have shown that cocoa flavanol consumption improved working memory and attention [52].

The anti-aging effects of GSE are attributable to the polyphenolics in reversing the neurobehavioral aging. Animal studies have shown that polyphenol extracts and individual polyphenols can benefit older and impaired rats that suffer cognitive deficits as a result of age, brain insults, or induced pathologies [53, 54]. The possible mechanisms that can be attributed to polyphenolic protection involve neurogenesis in the DG [55–57].

Polyphenolic activity in scavenging FRs can protect the brain tissue from oxidative injury. The evidence for this comes from behavioural studies in 19–21 month-old rats that consumed 10% grape juice wherein improvements were detected in the release of dopamine from striatal slices and improved cognitive performance in the Morris water maze [58], and from studies where 12 month-old rats were on a daily oral dose of GSPE at 75 mg/kg body weight for 30 days and had better cognition and memory as seen in a T-maze test [42]. Grape seed proanthocyanidin extract can neutralise FRs [59], protect against oxidative damage [60], and reduce the occurrence of diseases. Ample evidence through human and experimental studies on polyphenols and their beneficial effects for improving cognitive ability, more so, in normal aging and those with neurodegenerative disorders [47, 61–65] has led to the new term, neuro-nutraceutical.

4 Polyphenols and Neurodegenerative Diseases

As scientists are trying to achieve longevity in the lifespan, the incidence of several disorders, including neurodegenerative diseases, especially in ages above 70 years, is on the rise. Therefore, attempts in increasing the retention of cognitive functions have also been equally important. It is relevant to emphasise the significance of

sirtuin 1 (SIRT1) which is notably expressed in brain neurons with a role not only in neuronal plasticity but in protection against neuronal disorders [66, 67]. Numerous studies have proven a role of SIRTs in DNA repair, antioxidant defence, and anti-inflammatory mechanisms. Resveratrol has neuroprotective action through alleviating oxidative stress and inflammation, by enhancing vascular function and activating longevity genes and SIRTs [63].

Alzheimer's disease has been seen often, the incidence being about 15–20% in the world population [68]. Among Alzheimer's disease patients, 7% are of familial genetic patterns while environment and epigenetics have a role in the sporadic onset of the disease. Oxidative stress initiates the accumulation of amyloid plaques, a product of the membrane amyloid precursor protein (APP) being fragmented into β-amyloid (Aβ), with 39–43 amino acids being the pathological hallmark in the neocortex of AD patients [69]. As the disease advances, tau-laden tangles, referred to as neurofibrillary tangles (NFT), enlarge with a loss of neurons and synapses in the cerebral cortex and subcortical regions [70–72] followed by cognitive decline and memory loss [73]. The situation is further aggravated through the activation of microglia and astrocytes [74, 75]. The AChE inhibitory activities of grape skin anthocyanin (GSA) extract and the oligomerisation of Aβ by GSPE may be important considerations for designing therapeutic drugs against Alzheimer's disease [76], thus preventing the onset and progression of cognitive deterioration in Alzheimer's disease.

Parkinson's disease is now recognised as the second most prevalent neurodegenerative disease in elderly subjects with a similar economic and social impact as that of Alzheimer's disease. Individuals over the age of 85 years have at least a 5% risk of developing Parkinson's disease [77–79]. The symptoms of Parkinson's disease appear as a result of cell loss in the substantia nigra (SN) that is necessary for motor function, the dopaminergic neurons of the pars compacta are lost. It is also notable hat normal aging is accompanied by pathological changes in other regions of the brain which is exacerbated further in Parkinson's disease [80, 81]. Advanced age promotes a loss of neurons and a loss key mitochondrial proteins and mitochondrial potential, and fragmentation of mitochondrial network. All of these effects lead to loss of neurons with aging. Importantly, in these neurons is a summation effect of reactive oxygen species (ROS) within the mitochondria and OS due to the metabolism of dopamine within them [82]. Reeve and his co-scientists [83] have reviewed extensively on dopaminergic neurons of the pars compacta and advanced age as an important risk factor for the aetiology and pathophysiology of Parkinson's disease in humans.

Despite the fact that Alzheimer's and Parkinson's disease have different clinical symptoms, they have similar pathological mechanisms. In Alzheimer's disease, protein aggregation and accumulation of plaques of Aβ peptide and intracellular NFT of tau protein occurs and Parkinson's disease is marked by appearance of Lewy bodies and Lewy neuritis of intracellular α-synuclein (αS) inclusions. In contrast to these diseases that have minor genetic factors but larger environmental stressors during one's lifetime, amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) are neurodegenerative disorders which have stronger genetic predispositions [84].

Table 7.1 lists a few representative studies on flavonoid and non-flavonoid polyphenols as enhancers of cognitive ability in animal and human studies.

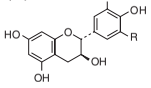
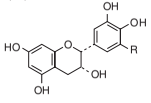
5 Polyphenols and Exercise for Aging Brain

Pure (−)-epicatechin (500 μg/g of food) has been observed to enhance the retention of spatial memory, especially when combined with exercise, in 8–10-week old C57BL/6 mice due to angiogenesis and increased spine density in the DG of the HC [85]. Further, our studies on male Wistar rats have demonstrated that GSPE intervention singly at a dose of 400 mg/kg body weight/day over a period of 16 weeks, in combination with swimming training, was beneficial in protecting the dmPFC [14] and HC [13] by alleviating mitochondrial FRs, and lipid and protein oxidations, as well as ameliorating the cytosolic antioxidant defences. The combined interventions imply a possible synergism between the two especially in middle-aged rats that are vulnerable to OS-induced mitochondrial functions (Fig. 7.1).

6 Conclusions

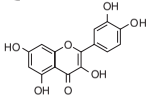
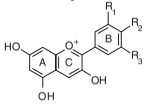
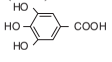
The normal age-related decline in the cognitive abilities in terms of learning and memory is largely traceable to a sizeable number of changes in the biochemical and molecular pathways at specific sites in the brain (HC, PFC, and amygdala). Such modifications are confirmed by several animal and human studies, wherein rigorous approaches have been attempted to delay the further progression towards pathological aging. Some are through dietary interventions related to natural products. Among these, the polyphenolic compounds have been found to have positive effects on brain health and cognitive function. Studies from our laboratory have revealed improved acquisition and retrieval of a learned task with aging by alterations at the biochemical, molecular, and anatomical levels through flavonoid-containing grape seed extract. The emerging evidence is that polyphenols have potential as a natural therapeutic product for treating neurodegenerative diseases. A flavonoid such as GSPE could be an appropriate ingredient for the manufacture of functional and neuro-nutraceutical food products for the elderly. However, these findings underline the physiological complexity that must be examined in designing therapeutic interventions to evoke similar responses in clinical situations.

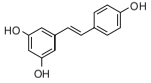
Table 7.1 Representative studies on dietary polyphenols with possible therapeutic use in age-related neurodegenerative diseases

Polyphenols Flavanoids Major constituents	Dietary sources	Effects	Study model	Type of study	References
(+)-Catechin 	Green tea Red wine	Prevent the formation of the endogenous neurotoxin 5-S-cysteinyldopamine in PD similar to in vivo conditions	Cysteinyl-dopamine adducts were formed by reaction of dopamine (100 lM) and L-cysteine (400 lM) in the presence of mushroom tyrosinase (250 U/ml) and catechin	*In vitro*	[86]
	Blue berry (BB)	Better performance in Morris water-maze. 14-unit T-maze. Kainic acid-treated rats impaired learning reduces with BB diet	Young male Fischer-344 rats	*In vivo*	[87]
(−)-Epicatechin (+)-Catechin  (−)-Epicatechin	Grape seed (GSE)	Prevents Aβ deposition in AD	Mice	*In vivo*	[88, 89]
		A noncovalent interaction of polyphenols with proline residues in the proline-rich domain of tau, with Pin1 sites at P213 and P232 Disintegration of PHF	Human brain	Frontal lobe temporal lobe, and parietal lobe of AD patients	[90]
		Improves climbing in *Drosophila*	Drosophila PD model	*In vivo*	[91]
	Grape seed and skin extract (GSSE)	GSSE acts at multiple levels to protect dopamine neurons from degeneration in a 6-OHDA-induced model of PD.	Mice	In vivo and in vitro Mesencephalic primary cell culture	[92]

(continued)

Table 7.1 (continued)

Polyphenols Flavanoids Major constituents	Dietary sources	Effects	Study model	Type of study	References
Quercetin 	Onion Buckwheat Tea Red wine	Brain-targeted polyphenol metabolites, quercetin-3-*O*-glucuronide,reduced the generation of Aβ peptides	Mice	Primary neuron cultures generated from the Tg2576 AD mouse model *In vitro*	[93]
		Reduces Aβ accumulation and protect against neurotoxicity and OS	Rat	Hippocampal neurons	[94]
Anthocyanidins  Anthocyanin	Red wine Berry fruits Cherry juice	Aged rats had lower levels of NF-κB than control animals	Aged Fischer-344 rats	*In vivo* Brain regions	[95]
		Improved short-and long-term memory	Humans	Randomized	[96]
Non-Flavanoids					
Gallicacid (GA) 	Red fruits Black radish Onions Tea leaves	Reduces HC neural damage Reduces FRs Inhibits oligomerization of Aβ	Adult *Wistar* rats	*In vivo* 1 μg/μL $A\beta_{1-42}$-induced AD	[97]
		Reduced ChEs and BACE-1 activity, ROS and MDA levels	Transgenic *D. melanogaster* expressing human amyloid precursor protein and β-secretase (BACE 1) genes as AD flies.	In vivo	[98]

Resveratrol 	Grapes Red wine Berries Pistachios peanuts	RESV and pharmacological activation of AMPK have therapeutic potential against Alzheimer disease.	Non-neuronal and neuronal cells, mouse primary neurons	*In vitro*	[99, 100]
		Anti-amyloidogenic activity of RESV	HEK293 cells stably transfected with human APP695	*In vitro*	[101]
		RESV diminished plaque formation	RESV fed for 45 days to transgenic	*In vitro*	[102]
		RESV negatively controls microglial inflammation triggered by Aβ	Mice	*In vitro* and *In vivo*	[103]
		RESV reduces amyloid protein enhances proteolytic cleavage due to its allosteric activity on the sirtuins	Murine microglial cell line BV-2	*In vitro*	[104]
		RES lowers motor and cognitive deficits	A53T α-synuclein mouse model of PD	*In vitro*	[105]
		Carbidopa / levodopa with + trans RESV improved cognition and movement	75 year old female with PD	*In vitro*	[106]
		RESV with an adjunct (dasatinib) against mitochondrial dysfunction and CDK5 dysregulation in neurodegeneration	Rotenone induced SH-SY5Y cell line models of Parkinson's disease.	*In vitro*	[107]
		RESV to rotenone exposed cells lowered cellular ROS, apoptosis, and increased survival rates	SH-SY5Y cell line models of PD	*In vitro*	[108]

Aβ amyloid beta, *AD* Alzheimer's disease, *AMPK* AMP-activated protein kinase, *APP* amyloid precursor protein, *BACE-1* β-secretase, *ChEs* Choline esterases, *LTP* long-term potentiation, *MDA* malondialdehyde, *NF-κB* (nuclear factor kappa-light-chain-enhancer of activated B cells, *OS* oxidative stress, *6-OHDA* 6-hydroxydopamine, *PD* Parkinsons' disease, *PHF* paired helical filaments, *RESV* resveratrol, *ROS* reactive oxygen species

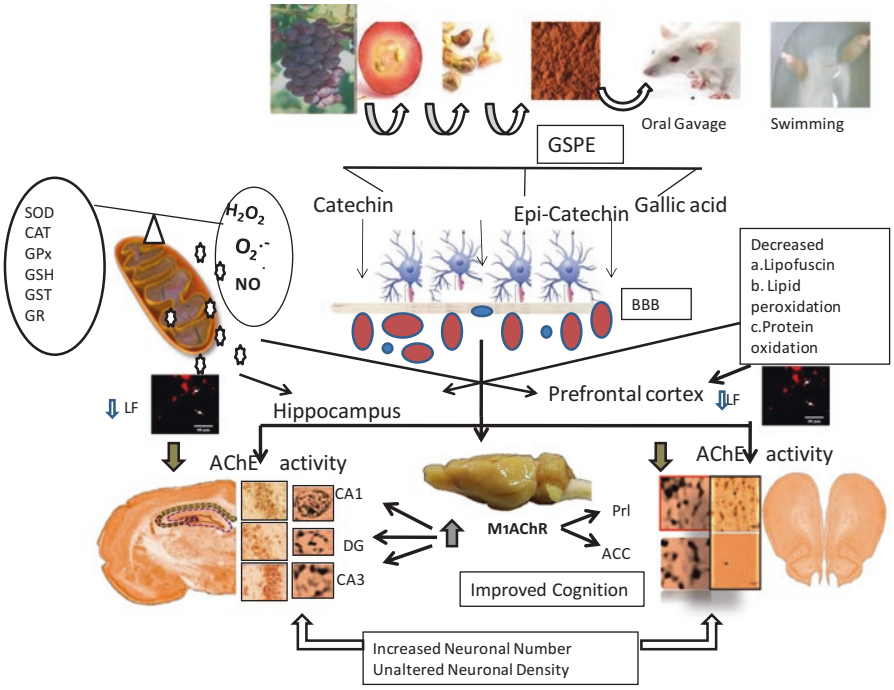


Fig. 7.1 Neuroprotection from grape seed proanthocyanidin extract and swimming training in middle-aged male Wistar rat. AChE, acetylcholine esterase; ACC, anterior cingulated cortex; BBB, blood brain barrier; CAT, catalase; CA1, cornus ammonis 1; CA3, cornus ammonis 3; DG, dentate gyrus; GSH, glutathione; GPx, glutathione peroxidase; GR, glutathione reductase; GSPE, grape seed proanthocyanidin extract; GST, glutathione-S-transferase; H2O2, hydrogen peroxide; LF, lipofuscin; M1AChR, muscarinic acetylcholine receptor NO•, nitric oxide;; O2•-, superoxide; Prl, prelimbic cortex; SOD, superoxide dismutase

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