

Protective effects of berry polyphenols against age-related cognitive impairment

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Abstract. A growing body of evidence suggests that dietary interventions may delay or halt the progression of age-related health disorders and cognitive decline. Among the components of the human diet, polyphenols from berries are essential micronutrients that have been particularly studied for improving cognitive functions. In the present review, we highlight the health impact of major polyphenolic classes found in berries: flavanols, anthocyanins and stilbenes, focusing on resveratrol. The reports of beneficial effects of berry consumption on age-related cognitive decline and associated neurobiological processes in animals and human are underscored. We then discuss the potential benefit of each category of polyphenols on memory impairment and in neurodegenerative diseases. Berry polyphenols improve several types of memory and have a global effect on brain plasticity, partly through their antioxidant activity and/or their effect on neuronal signal transduction and neuroinflammation. Interestingly, accumulated bioavailability data suggest that most polyphenols, or at least key metabolites, can access the brain in sufficient concentrations. Collectively, the data accumulated so far suggest that dietary polyphenols can modulate brain health and function, and strengthen the importance of fruit consumption for a healthy brain aging and the prevention of age-related diseases. However, further preclinical work is needed to determine the most neuroactive nutraceutical formulations, whether through the diet or supplement, to subsequently design and perform informative clinical trials.

Keywords: Polyphenols, flavonoids, flavanols, anthocyanins, resveratrol, berries, memory, plasticity, aging, neurodegenerative disease

1. Introduction

Old age is well known to be associated with cognitive impairment and neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's

disease (PD) [1]. As the elderly population increases, so will the prevalence of these age-related disorders [2–4]. In order to improve the quality of life of the elderly and to alleviate the social and economic burdens caused by dependence, it is important to develop strategies to reverse, or at least minimize, age-related cognitive decline and delay the onset of neurodegenerative diseases. To this end, nutrition-based preventive strategies are currently being attempted to avoid or delay the evolution towards dementia and thus maintain a stable cognitive state and

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satisfactory wellness in elderly subjects. In recent years, we have observed an intensification of research dedicated to understanding the relationship between nutrition and “healthy aging”. Among foods that are potentially capable of protecting against age-related degenerative diseases, fruits and vegetables rich in polyphenols have been put forward as possible tools to delay age-related physiological and functional deficits [1, 5, 6].

Polyphenols, particularly flavonoids, have been shown to ameliorate learning and memory processes and are today extensively studied for their potential to prevent age-related cognitive decline in both animals [7–11] and humans [12–17]. Although the mechanisms of action of flavonoids remain unclear, there is evidence that they modulate cellular and molecular processes involved in learning and memory [18]. Among the different polyphenols found in berries, those which have been particularly studied for their effect on brain function are flavonoids—particularly flavanols and anthocyanins— and among the stilbene family, resveratrol. Other stilbenes are present in berries, but few or no data is available concerning their neuroactivity. Indeed, resveratrol is considered among the most potent biologically active nutrient. Initially studied for its presence in red wine and its link with the “French paradox” [19], resveratrol has been shown to partially mimic caloric restriction, to extend the lifespan and to improve cognitive function and delay age-related cognitive impairment [20–25]. Together, these data suggest that high polyphenol consumption could help prevent age-related cognitive decline.

2. Polyphenol classification, chemical structure and food content

Polyphenols are phytochemicals now considered essential micronutrients. Polyphenols can be divided into four main classes based on their structure (Fig. 1): flavonoids, phenolic acids, stilbenes and lignans [26]. Flavonoids possess a common structure consisting of two aromatic rings bound by three carbon atoms to form an oxygenated heterocycle ($C_6-C_3-C_6$). Based on the hydroxylation pattern of the oxygenated heterocycle and the arrangement of the hydroxyl groups, flavonoids can be divided into four subgroups: 1) flavanols, found in onions, broccoli and chocolate, 2) chalcones, 3) flavones, present in apples, and 4) anthocyanins, found in blueberries, strawberries, red wine and common beans [27, 28]. Flavones can be

further divided into four subclasses: i) flavanones, present in citrus fruits and oregano, ii) flavanols, which are abundant in green tea, red wine and chocolate, iii) flavones, found in parsley, celery and olives, and iv) isoflavones, which are mainly found in soy [27, 28]. Flavanols may be polymerized to generate flavanoids, also known as tannins or proanthocyanidins (PAs). Phenolic acids can be further classified into derivatives of benzoic acid ($C_6-C_{1,2}$), found in blackberries, red wine or black tea and massively in nuts such as chestnut, and derivatives of cinnamic acid (C_6-C_3), found in red wine, plums and olives [27, 28]. Stilbenes, found in lingonberries and cranberries [27, 28], are in turn composed of two aromatic rings bound by a methylene bridge and can be found in *cis* and *trans* forms, which have different chemical and biological properties. Interconversions between *trans* and *cis* forms are observed with heat or UV radiation. Resveratrol can also occur in dimer or trimer forms as viniferins, found in red wine. Polyphenols also include lignans, which are precursors of parietal plant polymers that constitute factors of defense against pathogens and are characterized by a 1,4-diarylbutane structure. They are found in olive oil and sesame seeds and oil [27, 28].

As mentioned above, in this review we will focus on polyphenols from berries for their interest in the prevention of age-related cognitive decline and also of the most prevalent age-related neurodegenerative diseases. Specifically, we will review and synthesize current knowledge regarding flavanols such as catechins and epicatechins and their oligomers, the PAs, which are found in grapes, as well as anthocyanins, mainly studied in relation to blueberries. Finally, we will focus on a particular stilbene, resveratrol, known to be present in grapes and at the center of considerable interest in the scientific community in recent years.

3. Cognitive impairment

3.1. Aging brain

Cognitive aging is characterized by an age-related decrease in elementary and advanced mental abilities such as concentration, working and long-term memory, reasoning, judgment, problem solving and speed of information processing [29]. This affects different abilities in individuals and can lead to decreased self-esteem and quality of life and take a “natural” or pathological form. Age-related cognitive decline is

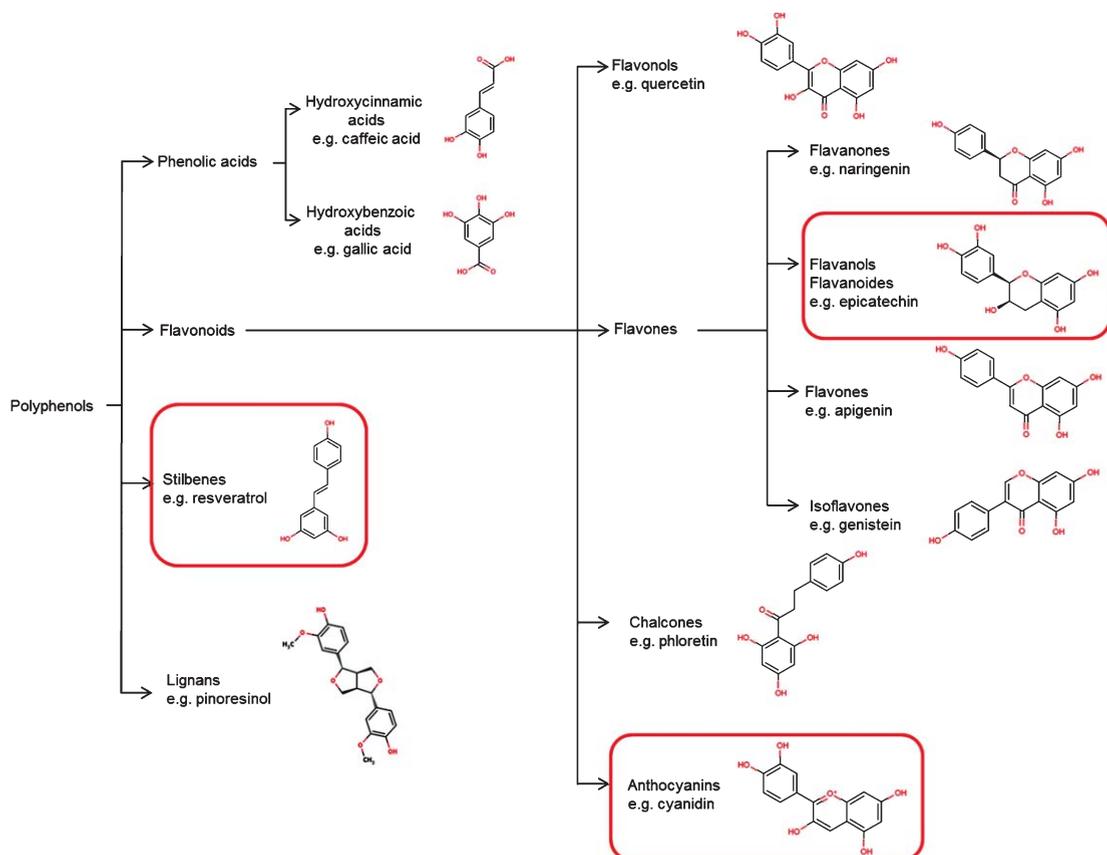


Fig. 1. Classification and chemical structure of the main classes of polyphenols (modified from Spencer et al., 2008 [209]).

the term used to describe the non-pathological form of memory deterioration, and identifies the decline in cognitive function consequent to the aging process that is within normal limits, given a person's age. It is a complex process, with the first signs emerging in humans in midlife (between 35 and 65 years), even without specific neurodegenerative lesions. Some pathological forms of aging may occur in addition to this "normal" cognitive decline. Among them, AD, the most common cause of dementia, affecting more than 24 million individuals worldwide [30], is irreversible in our present state of knowledge, as the only available treatments are purely symptomatic [31].

The aged brain exhibits numerous structural and functional alterations, which could underlie the decline of cognitive and motor abilities. Furthermore, cerebral lesions characteristic of AD (amyloid plaques and neurofibrillary tangles) are frequently observed during "normal" brain aging, in individuals with no cognitive symptoms [32, 33]. It is widely admitted that dementia is an unavoidable process beyond a certain stage of aging, and that a con-

tinuum exists between "normal" cognitive decline during aging and dementia [34], which could thus be considered an "exaggeration" or "acceleration" of aging. Thus, pathological cognitive aging appears to overlap with non-specific processes related to the "normal" aging of the brain, which also lead to cognitive impairment, and the relationship between the two is still unclear. Even the relevance of differentiating between the two processes with respect to the expression of cognitive symptoms is controversial. It has been shown that multiple brain lesions that are found in dementia also appear with normal aging; although their density and distribution are usually lower in healthy subjects [35]. Before the development of irreversible dementia, progressive cognitive decline is noticeable by the occurrence of minor cognitive problems that affect 15 to 20% of the population aged 65 years or more, but which represent an unstable state [36]. The natural evolution of this mild cognitive impairment could still be influenced by the implementation of secondary preventive measures.

In this context, modifying environmental factors such as food and nutrition offers great opportunities for primary preventive strategy during the asymptomatic phase. Hence, any nutritional strategy defined should aim to prevent or delay the evolution toward dementia, in order to promote the maintenance of a satisfactory cognitive state and to avoid the dependence of elderly citizens in our modern society.

3.2. Neurodegenerative diseases

3.2.1. Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in the world, exerting an escalating socioeconomic burden on modern society [37, 38]. Most often, AD is diagnosed in people over 65 years of age [39], who develop a progressive pattern of cognitive and functional impairments [40, 41] that gradually increase as the disease advances. Memory impairment, in particular the loss of the ability to form and retain new episodic memories, is a hallmark of early AD and may help in differentiating AD from common age-related cognitive decline. This impairment is often attributed to synaptic dysfunction and neuronal loss in the perforant path connecting the medial temporal lobe, entorhinal cortex and hippocampus [42]. Accordingly, cognitive changes in AD start with specific difficulties in the encoding and storage of new information, also indicative of a deficiency in semantic memory [43–45] and executive function impairment [46]. The etiology of AD is not well understood, except in 1 to 5% of cases in which genetic differences can be identified [47]. It is increasingly recognized that AD is a proteinopathy characterized by specific neuropathological markers: amyloid deposits, tau-laden tangles and the loss of neurons and synapses in the cerebral cortex and subcortical regions, associated with gross atrophy of the affected regions [48–55]. The accumulation of amyloid beta (A β) fragments is thought to be due to the uncontrolled cleavage and defective clearance of amyloid precursor protein [49]. Current treatments only partly alleviate symptoms but cannot stop or reverse the progression of the disease. Due to their favorable safety profile and availability, dietary approaches, in particular using polyphenol-enriched diets [56–58], are drawing attention as tools to prevent AD development [59–64]. The use of cheap and widely available compounds, like polyphenols, as nutraceutical or pharmaceutical tools in brain disorders such as AD

may provide new strategies for the prevention or delay of cognitive decline.

3.2.2. Parkinson's disease

Parkinson's disease (PD) is a degenerative disorder of the central nervous system with no known cause, and is more common in older people, with most cases occurring after the age of 50 [65]. Dopamine-innervated brain structures, namely in the basal ganglia, are the most seriously affected brain areas in PD [66]. The clinical expression of PD mostly affects motor capacity, but patients often presents neuropsychiatric symptoms including depression, apathy, anxiety, hallucinations and cognitive dysfunction, reaching a prevalence of about 30 to 40% at advanced stages of the disease [67, 68]. Previous observations suggest that the neuropsychological profiles of PD and AD are different, with PD subjects being better at recall but worse at praxis than those with AD [69]. PD patients also display impairments in verbal fluency, visual perception and performance tasks [69, 70], suggesting impairments in the executive and visuospatial domains [71]. Many risk and protective factors for PD have been investigated. An increased risk of PD is associated with exposure to certain pesticides, insecticides and heavy metals [72–74], in contrast with a lower risk in tobacco smokers [74], coffee consumers [75] and individuals treated with anti-inflammatory drugs [74]. Although modern treatments are effective at managing the early motor symptoms of the disease [76], and surgery and deep-brain stimulation can be of use when drugs do not suffice to control symptoms [77], as there is currently no cure for PD. Interestingly, a diet enriched in polyphenol compounds has shown some efficacy in alleviating the symptoms of PD [78]. For example, in MPTP-injected mice, a toxin known to induce neuronal death, resveratrol was able to prevent MPTP-induced depletion of striatal dopamine, and to maintain striatal tyrosine hydroxylase protein levels, two neuropathological markers observed in PD patients [78, 79].

4. The effects of berries on age-related cognitive decline

Most studies of berries and age-related cognitive decline focus on specific berries high in antioxidants such as blueberries, strawberries or grapes. Blueberries, which contain large amounts of polyphenols, exert a greater antioxidant capacity than most

other fruits and vegetables [80]. A number of studies suggest that the consumption of blueberries delays age-related physiological and functional deficits. For example, the daily consumption of blueberry juice for 12 weeks improves episodic memory performance in older adults (mean age: 76.2 years) [13]. Consistent with these results, work carried out in aged rats has shown the beneficial effects of blueberries on memory and motor performance, resulting in the attenuation of memory decline as evaluated in object recognition and spatial working memory tasks [9, 81]. From a mechanistic point of view, a blueberry-enriched diet administered to very old rats (24 months old) compared to younger rats normalizes the level of NMDA-receptor-dependent long-term potentiation (LTP) in their hippocampus. LTP is widely recognized as a cellular correlate of memory formation, and this result suggests the normalization of synaptic plasticity by diet [82]. A more recent study in a senescence-accelerated mouse model also suggests that the beneficial effects of blueberry on cognitive decline could be due to an increase in the expression of phosphorylated extracellular signal-regulated kinases (ERKs). The authors of this study proposed that this promnesic effect of blueberry polyphenols may be due to their antioxidant activity, their capacity to activate superoxide dismutase (SOD) and to reduce malondialdehyde content [83]. However, it is currently admitted that the effects of blueberry extracts on cognitive functions involve more than their antioxidant actions. Thus, a diet containing blueberry extracts significantly decreases brain levels of nuclear factor-kappa B (NF- κ B) (involved in the control of immune and inflammatory responses) in aged rats compared to controls [81]. These brain levels of NF- κ B are significantly higher in aged rats than younger ones [84]. These results are in accordance with the known effect of flavonoids on cellular signaling, especially on NF- κ B activity [85, 86]. Studies on strawberries highlight the high antioxidant and anti-inflammatory activities of these fruits, which may prevent the appearance of neurochemical and behavioral alterations with aging. Animal studies show that a strawberry supplement prevents the effects of aging on neuronal signal transduction and improves memory processes in aged rats [84, 87] and in a rodent model of accelerating aging [88]. The grape is particularly rich in flavonoids including catechins, epicatechins and quercetins as well as anthocyanins and PAs, all known to have potent antioxidant capacities. The "French Paradox" has sparked a renewed interest in grape polyphenols with respect to their

potential benefits to human health, including brain health. Indeed, the strikingly lower incidence of coronary disease in France compared with other western countries has opened up a field of questions, and the hypothesis of the protective role of the oxidation of polyphenols contained in red wines has emerged and has been widely studied since. *De facto*, the nutritional properties of grapes as the source of wine polyphenols are also the subject of numerous studies. Similar to results obtained with blueberry juice, Concord grape juice consumption for 12 weeks leads to an improvement of memory performance evaluated by the Californian learning test in older humans [14]. A similar effect has been observed in aged rats with Concord grape juice consumption [89]. Specific extracts of the berries (e.g. grape seed extracts, GSEs) are more commonly used for nutritional intervention because they are highly enriched in polyphenols, in particular in flavanols, anthocyanins and resveratrol. These extracts are suitable for nutritional supplementation, as they contain a higher concentration of polyphenols than fruits or juices, and this facilitates the identification of their functional and behavioral effects and the study of the underlying neurobiological mechanisms. More recently, the beneficial effects of blackberries and mulberries on age-related memory deficits as well as on motor behavior have been shown in aged rats [90] and in senescence-accelerated mice [91].

Together, these data argue in favor of the use of berry extracts as dietary supplements to target memory performance, and to better understand the mechanisms underlying their beneficial effects.

5. Flavanols

5.1. Effects on age-related cognitive decline

A recent study has provided detailed information on habitual dietary intake of flavanols, in particular flavan-3-ol monomers, PAs and theaflavins, in humans aged 18–64 years in the European Union. This study demonstrates that dietary intake amounts for flavan-3-ol monomers, PAs and theaflavins vary significantly across European countries (181 mg/d to 793 mg/d). Moreover, the average habitual intake of flavan-3-ols is considerably below the amounts used in most dietary intervention studies [92]. Several studies have shown the beneficial effects of flavanols on cognitive performance. Their molecular impact

has also been investigated *in vitro* and *in vivo*. Some studies have evaluated the benefits of supplementation with flavanols from GSEs. Indeed, GSEs are a rich source of monomeric phenolic compounds such as catechin, epicatechin and dimeric, trimeric and tetrameric PAs. Supplementation with GSE significantly improved the memory performance of aged rats evaluated using a brightness-discrimination task in a T-maze. This beneficial effect might be explained by reduced blood glucose levels and decreased oxidative stress in the hippocampus [93, 94]. Indeed, the promnesic effects of GSEs are due to the stimulation of antioxidant defense mechanisms, attenuating lipid peroxidation and protein oxidation. A positive effect on the cholinergic system, which also underlies the beneficial activity of GSEs on memory, has also been observed in adult and middle-aged rats [93, 95]. A recent study has also evaluated the impact of pure flavanols on memory and the underlying molecular mechanisms in 18-month-old male rats. A significant improvement in spatial working memory was observed in rats receiving pure flavanols (catechin and epicatechin) at levels similar to that found in blueberries (2% w/w) for 6 weeks. Interestingly, this behavioral effect was linked with an increase in hippocampal brain-derived neurotrophic factor (BDNF), thus confirming the therapeutic value of polyphenol extracts in memory processes [96]. Epicatechin, administered for 6 weeks, combined with physical exercise, enhances spatial learning and reference memory, increases angiogenesis and neuronal spine density in the hippocampal dentate gyrus (DG) of mice, and upregulates hippocampal genes associated with learning concomitant with the decreased expression of inflammation and cell death genes. In the absence of physical exercise, epicatechin still has an effect, but to a lower extent, on spatial memory retention and angiogenesis in the DG as well as on gene expression [97]. The flavanols (-)-epicatechin and 3-O-methyl(-)-epicatechin, one of its metabolites, exerted a stimulatory effect on ERK1/2 and on the downstream transcription factor C-AMP Response Element-Binding protein (CREB). Moreover, these flavanols protected neurons against oxidative damage via a mechanism involving the suppression of c-Jun N-terminal kinase (JNK), and its downstream partners, c-Jun and pro-caspase-3 [98, 99]. In addition, it has been shown *in vitro*, in glial cells, that catechin from green tea protects cells from oxidative stress-induced DNA damage and decreases cell death by reducing NF- κ B and p53 activity [100]. Moreover, physiologically relevant concentrations of epicate-

chin and catechin inhibit TNF- α , which is released by primary glial cells, suggesting that flavanols may also have the potential to exert anti-inflammatory effects in the central nervous system [101].

5.2. Therapeutic potential in neurodegenerative diseases

Data gathered in various models of neurodegenerative diseases provide arguments for the use of flavanols in neuroprotection. For example, various flavanol-rich cocoa extracts inhibit the oligomerization of A β fragments 40 and 42 in the mouse hippocampal region, while one extract, Lavado, also rescues the LTP response after damage by A β fragments [102]. Along these lines, oral administration of flavanol epicatechin prevents defects in spatial learning and memory performance observed after the injection of A β fragments 25–35 directly into the CA1 subregion of the hippocampus of rats [103]. Epicatechins also inhibit damage due to reactive oxygen species (ROS) generated by A β fragments [103]. Similarly, Wistar rats fed catechins for 21 days prior to intracerebroventricular injections of streptozotocin (STZ), used to model sporadic AD, present a dose-dependent amelioration of both path length and latency in the Morris Water Maze task [104]. More interestingly, Desideri et al. have tested the effect of cocoa flavanols on humans suffering from mild cognitive impairment and found that, on average, greater daily oral doses of flavanols over a period of 8 weeks are associated with an enhancement of cognitive function [105]. These studies support the potential of flavanols in preventing memory loss, cognitive impairment and oxidative stress induced by A β fragments, all prominent features of AD.

Moreover, several studies have provided evidence of the neuroprotective activity of flavanols in both cellular and animal models of PD. For example, the intragastric administration of catechins in mice protects, in a dose-dependent manner, *substantia nigra* dopaminergic neurons from the neurodegenerative effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injections [106]. In a similar experiment, SH-SY5Y cells exposed to the 1-methyl-4-phenylpyridinium ion (MPP⁺) showed greater viability, as well as decreased ROS production when pretreated with catechins [107]. However, the neuroprotective activity of catechins may result not only from their free-radical scavenger properties but also from their implication in several

cellular signaling pathways involving JNK or GSK-3 β [106]. Furthermore, in the 6-hydroxydopamine (6-OHDA) rat model of PD, intraperitoneal treatment with catechins prevents working memory deficits and mesencephalic dopamine loss as well as motor impairments [108]. Taken together, these findings suggest that flavanols may have therapeutic potential in neurodegenerative diseases, particularly in the PD field. Further investigations are required to elucidate the molecular mechanisms underlying the neuroprotective effects of flavanols.

6. Anthocyanins

6.1. Effects on age-related cognitive decline

Most studies performed in order to assess the potential effects of anthocyanins on health have been carried out using fruit extracts rich in anthocyanins, but some have used metabolites of anthocyanins. Anthocyanins are major dietary components especially in those who routinely eat berries or derivatives such as juices or red wine [28]. Unlike other flavonoids which are absorbed and excreted, anthocyanins do not appear to undergo extensive metabolism to glucuronide and sulfate derivatives, and their excretion is low. In interventional studies in humans, the typical recovery of anthocyanins in the urine is <0.1% of intake [109]. For instance, Wu et al. [110] have reported the total urinary excretion of anthocyanins from blueberries consumed by elderly women to be 0.004% of intake. These low recovery levels could be a consequence of anthocyanins undergoing structural rearrangements in response to pH changes. Such rearrangements are likely to occur *in vivo* as anthocyanins pass from a low pH in the stomach to the more basic conditions of the small intestine.

In rodent studies, the consumption of foods rich in anthocyanins prevents memory deficits [89, 111–113]. Thus, a 3-month supplementation with a blueberry-enriched diet improves spatial working memory performance of aged rats [9]. The activation of CREB and ERK1/2, an increase in the levels of both BDNF and pro-BDNF as well as of CaMKII, CaMKIV, PKA, Akt, mTOR and Arc/Arg3 in the hippocampus seems to underlie these behavioral effects. Similar effects have been shown using both pure anthocyanins and extracts. Thus, a 6-week supplementation with pure anthocyanins in 18-month-old

rats induces significant improvements in spatial memory linked with an increase in hippocampal BDNF levels [96]. A purple sweet potato color extract administered for 4 weeks by gavage in a mouse model of accelerated aging induced by D-galactose (D-gal), attenuates D-gal-induced cognitive impairment, partly via the improvement of antioxidant and anti-inflammatory responses [114]. In the same manner, in SAMP8 mice, a model of accelerated aging, 12 weeks of supplementation with a mulberry extract rich in anthocyanins improves learning and memory abilities and displays hepatoprotective effects through the regulation of mitogen-activated protein kinases (MAPKs, e.g. JNK, p38, ERK) and the activation of Nrf2 [91]. Likewise, it has recently been shown that 8 weeks of supplementation with cyanidin-3-O-galactoside from blueberries improves learning and memory in the same animal model. The recovery of cognitive and behavioral functions in aged animals could be explained by an improvement of oxidative status via the activation of SOD and a reduction in the malondialdehyde content of brain tissue and plasma. Furthermore, an increase in phosphorylated ERK in the hippocampus, an inhibition of damage to the pyramidal cell layer and more generally, an improvement of hippocampal neuron survival, have all been observed [83]. Interestingly, these beneficial effects of anthocyanins on cognitive function have also been reported in young mice (3–4 months old) and rats (10 weeks and 12 months old), in which they improve learning and memory performances. At the molecular level, these studies have reported reduced oxidative DNA damage in brain tissue, a lower level of lipid peroxidation, higher brain levels of ascorbic acid and glutathione, and a decrease in acetylcholinesterase activity, following treatment with anthocyanins. Moreover, the modulation of ERK1/2 activation and the increase of CREB, BDNF and pro-BDNF levels in the hippocampus have also been reported [111, 113, 115, 116]. More recently, an important effect on hippocampal synaptic plasticity has been evidenced in young rats (8 weeks old) fed for a short period (3 weeks) with blueberries by gavage. In addition to improved spatial memory acquisition and consolidation, increased levels of the polysialylated form of the neural cell adhesion molecule (PSA-NCAM), a marker of neuronal plasticity, in the DG, accompanied by an increase in hippocampal NR2B-containing NMDA receptors, have been observed in rats fed by gavage with blueberries [117]. It has also been suggested that polyphenols could act on the

inflammatory process. The exposure of microglial cells to an anthocyanin-rich blueberry extract induces the significant suppression of the expression of both the iNOS and COX-2 genes, known to be involved in the inflammatory process [118]. However, in another study, when activated microglia were exposed to the pure anthocyanins, cyanidin and pelargonidin, no effects on iNOS expression or TNF- α release were observed [101].

6.2. Therapeutic potential in neurodegenerative diseases

Besides their abovementioned properties in aging, anthocyanins may alter specific pathophysiological processes related to various neurodegenerative disorders. For instance, Tarozzi et al. have shown that the anthocyanin cyanidin-3-O-glucoside (C3G) protects SH-S5Y5 human cells against the neurotoxicity induced by A β oligomers, probably by preventing them from binding to the cell membrane [119]. In addition, a recent *in silico* simulation has revealed that anthocyanins could induce conformational changes that activate FKBP52 [120], a protein complex known to inhibit the aggregation of tau [121]. In animal models, anthocyanin gavage for one week prior to an intracerebral injection of STZ prevents memory deficits in Wistar rats [122]. In a similar study, intraperitoneal treatment with anthocyanins also protected against the memory impairment elicited by injections of scopolamine, used to elicit memory impairment [123]. These studies support the potential of anthocyanins or their metabolites to prevent AD or slow its progression.

There is also evidence of the neuroprotective activity of anthocyanins in models of PD. For example, in primary cultures of midbrain cells, a series of anthocyanins isolated from blackcurrants, including delphinidin-3-O-glucoside and C3G, reduces dopaminergic cell death induced by rotenone [124], an insecticide known to cause nigral neurodegeneration *in vivo*. Anthocyanins display inhibitory effects on monoamine oxidase B (MAOB), an action similar albeit smaller than that of drugs currently used to treat early PD [125]. Together, these investigations highlight the therapeutic potential of anthocyanins in neurodegenerative diseases. However, more pre-clinical and clinical studies investigating the effects of pure anthocyanins and their derivatives are required to determine their potential benefits in AD or PD.

7. Stilbenes: Resveratrol

7.1. Effects on age-related cognitive decline

Resveratrol is a polyphenol found mainly in grapes and red wine. It possesses diverse biological activities that confer protection against oxidative stress, inflammation, cardiovascular disease, and cancer [126–130]. As mentioned previously, resveratrol also exerts beneficial effects on age-related cognitive impairment. Indeed, resveratrol can, for example, improve working memory, spatial learning and memory and spontaneous locomotor activity in various animal models such as healthy non-human primates (*Microcebus murinus*) or aged mice with LPS-induced deficits [25, 131, 132]. Recently, a significant enhancement of angiogenesis and neurogenesis has been observed in the DG of these mice [25]. One of the main hypotheses to explain how resveratrol induces these beneficial health effects *in vivo* is the modulation of sirtuin 1 (SIRT1), one of seven proteins belonging to the sirtuin family and an energy sensor involved in longevity. Many studies have evaluated this mechanism, seeking to determine if the interaction between SIRT1 and resveratrol is direct or indirect, a question still under debate. On the one hand, there are much data to support the hypothesis that SIRT1 is directly activated by resveratrol [126, 133–144]. On the other hand, resveratrol also indirectly inhibits the PI3K/mTOR/S6K pathway [145–149]. SIRT1 and mTOR could be members of the same sirtuin/mTOR network [150], and it is likely that mTOR (pro-aging pathway) and sirtuins (anti-aging pathway) antagonize each other [151]. Han et al. have investigated the possible existence of specific polyphenol-binding sites at the cell membrane level in the rat brain [152]. Their results suggest that the neuroprotective action of various polyphenols and resveratrol analogs could be mediated by the activation of common “receptor” binding sites that are particularly enriched at the level of the cell membrane.

In addition to the above pathways, resveratrol could act through the cyclooxygenase (COX) and 5-lipoxygenase cascades, thereby modulating the production of pro-inflammatory molecules [153]. Inhibitors of these enzymes are commonly used as anti-inflammatory drugs. Because resveratrol is an effective *in vivo* inhibitor of COX activity [154–156], its anti-inflammatory properties have been investigated. Intravenously administered resveratrol decreases neuroinflammation induced by

ischemia/reperfusion [157]. The anti-inflammatory effects of resveratrol in aged mice could also be linked to its ability to inhibit factors involved in gene transcription such as MAPKs, AP-1 and NF- κ B [133, 158–161]. The link between SIRT1 and NF- κ B signaling is particularly interesting because, according to a number of authors, SIRT1 can prolong the lifespan by inhibiting NF- κ B signaling to an extent sufficient to reverse gene expression changes associated with aging in mice [160, 162, 163]. Moreover, a reduction in the levels of inflammatory markers such as interleukin-1 β has been observed in resveratrol-supplemented mice in both the plasma and hippocampus. The *in vitro* analysis of its impact on microglial cells has confirmed that resveratrol potently inhibits LPS-induced interleukin-1 β production [131]. Thus, resveratrol could present an attractive alternative to current treatments against chronic inflammation. Resveratrol also has considerable antioxidant activity, although it is unclear if this is the result of a direct scavenging effect or the activation of pathways that upregulate natural cellular antioxidant defenses. Resveratrol can inhibit the production of ROS by neutrophils, monocytes, and macrophages [164–168]. In spontaneously hypertensive rats, which are prone to stroke, resveratrol significantly reduces markers of oxidative stress in the serum and urine [169]. Furthermore, in guinea pigs, resveratrol decreases the concentration of ROS generated by menadione [170]. These data indicate that resveratrol can suppress pathological increases in the peroxidation of lipids and other macromolecules *in vivo*, but whether the mechanism is direct, indirect or both has yet to be determined. There are other data in support of these protective effects. For instance, resveratrol can dramatically increase mitochondrial manganese SOD expression and activity in MRC-5 cells, as well as in mouse brain tissue [171]. Despite all these arguments, it is important to emphasize that, even if the scientific literature widely credit resveratrol with being responsible for the protective effects of red wine [172, 173], it is certainly not the only cause. Indeed, stilbene concentrations in red wine are so low that a human being would have to consume more than 60 liters daily to reach the levels required to increase longevity and provide the same protective effects as those observed in animal models [174]. Resveratrol is thus a minor component of the human diet, and its potential therapeutic use would only be probably possible at pharmacological doses.

A naturally dimethylated analog of resveratrol, pterostilbene, exhibits similar biological activities

including an antioxidant activity [175]. However, pterostilbene has been shown to display a higher *in vivo* bioavailability, possibly due to increased lipophilicity induced by the substitution of a methoxy rather than a hydroxyl group [176]. Pterostilbene is a molecule found in blueberries [177] and grapes [178]. Unfortunately, there are no reported estimates regarding pterostilbene intake in humans. Joseph et al. [179] have reported that dietary pterostilbene is effective in reversing cognitive deficits in aged rats with a correlation with hippocampal pterostilbene levels. Quite recently, it has been shown that, at equivalent and diet-achievable doses, pterostilbene is a more potent modulator of cognition and cellular stress than resveratrol, likely driven by increased peroxisome proliferator-activated receptor alpha (PPAR- α) expression and the aforementioned methoxy moiety [180].

7.2. Therapeutic potential in neurodegenerative diseases

The evidence of a neuroprotective action of resveratrol *in vitro* and *in vivo* has generated a lot of interest pertaining to its use in preventing neurodegenerative diseases [181]. For example, in transgenic animal models of AD-like neuropathology, chronic resveratrol administration promotes neuronal survival in the hippocampus [182], prevents learning deficits [182] and reduces A β plaque pathology by 50 to 90% depending on the brain region studied [183]. The potential therapeutic activity of resveratrol in AD has also been reported by Marambaud et al. who tested the neuroprotective activity of various polyphenols such as resveratrol, quercetin and catechin in series of cell lines. Resveratrol was particularly effective in reducing, in a dose-dependent manner, the production of intracellular A β peptides via a proteasome-dependent mechanism [184]. In animals, oral administration of a grape-seed polyphenol extract containing resveratrol significantly attenuates the development of tau neuropathology in a mouse model of AD [185]. Treatment with a standardized grape polyphenol preparation containing resveratrol leads to the improvement of cognitive function and greatly reduces total amyloid content in the brain of J20 AD mice, an animal model of A β pathology [186]. According to a recent report, chronic resveratrol administration leads to decreases in the ratio of soluble A β 42/A β 40 (–42%) and in the concentration of insoluble human tau (–93%) in the parietotemporal cortex of 18-month-old mice in a triple-transgenic

model of AD [187]. More importantly, because this study used an end wash-out study design, it showed that these effects of resveratrol on the A β 42/A β 40 ratio and insoluble tau lasted for at least 3 months after the end of treatment, consistent with the disease-modifying effects of resveratrol.

In the PD field, a dose-dependent protective role of resveratrol on dopaminergic neurons in midbrain slice cultures from Wistar rats exposed to cytotoxic drugs, MPP⁺ or thrombin has been reported, highlighting the possible antioxidant effect of resveratrol [188]. Studies carried out in mice show that resveratrol administration protects mice from MPTP-induced hydroxyl radical overloading and dopaminergic neuron loss [79, 189]. This action has been attributed to the resveratrol-induced activation of SIRT1, as the protective effect is lost in the presence of a SIRT1 inhibitor [190]. Overall, although the modulating effect on oxidative stress remains an essential element in the neuroprotective effect of resveratrol, it is becoming clear that other cellular mechanisms also underlie such effects of polyphenols and their metabolites in AD and PD [191]. The consumption of resveratrol-rich foods, such as berries, cocoa and grapes [64], throughout life holds strong potential to limit or delay neurodegeneration and to prevent or reverse the age-dependent deterioration in cognitive performance.

8. Brain bioavailability

In order to understand whether polyphenols and their metabolic derivatives are capable of directly inducing neuroprotective effects, it is important to know whether they can access the central nervous system. To enter the brain, absorbed polyphenols or their active metabolites must first cross the blood brain barrier (BBB). Some studies have reported that polyphenols can be found in brain tissue after oral ingestion. For instance, some flavanols, such as metabolites of catechin and epicatechin, can be found in the rat brain following oral intake [9, 97, 192–194]. Some flavonoids, including dietary anthocyanins such as cyanidin-3-rutinoside and pelargonidin-3-glucoside, are also able to cross the BBB in relevant *in vitro* and *in situ* models [195]. Moreover, anthocyanins have also been detected in different regions of the brain of rats [196] and pigs fed blueberries [197, 198], and at trace levels in brains of rats fed a blueberry extract-enriched diet containing anthocyanins for 10 weeks [10]. Similarly, in pigs given a 4-week supplement

of blueberry extract containing anthocyanins (undefined amounts), 300 pg/g of anthocyanins have been detected in the cerebellar tissue and 700 pg/g in the eye tissue [197]. In a much shorter time frame, 18 h after the administration of pelargonidin by gavage (50 mg/kg of body weight), unmetabolized anthocyanin has been detected in the rat brain at a concentration of 0.2 nmol/g (wet weight) [199]. In contrast, in another study, there were no detectable anthocyanins in the brain of rats 24 h after acute administration by gavage of 2.8 ml of raspberry juice, which is a nutritionally-relevant dose equivalent to 700 ml of juice for a 70 kg human [200]. However, several reports have confirmed that orally administered resveratrol after being absorbed by the organism, crosses the BBB and is incorporated into the brain [201–204]. Despite the brain functional effect of polyphenols evidenced in human, there is a lack of information concerning their brain bioavailability.

How polyphenols cross the BBB is still under debate. To gain access to the brain, a polyphenol must be highly lipid-soluble, or subject to transport processes [195, 205]. In addition, polyphenols are regarded as xenobiotics by the body, and their bioavailability can be severely affected by ABC transporter efflux pumps which are present at the BBB. These pumps reject xenobiotics across the BBB, from the brain to the blood [195, 205, 206]. However, certain polyphenols are known to inhibit these transporters, thereby facilitating the accumulation of other substrates into the brain, increasing their central bioavailability [207, 208]. In addition, most studies have been performed in animals with metabolic rates and levels of transporter expression, which differs from humans. Thus, the conclusion of these studies must be interpreted carefully pertaining to BBB transport and biodistribution occurring in a human setting.

Finally, whether the concentrations of polyphenols or their metabolites found in cerebral tissue are sufficient to exert pharmacological actions remain to be determined. However, the accumulating data at least suggest that the brain is not completely impermeable to these families of compounds.

9. Conclusion

The constantly increasing number of elderly people is dramatically linked with an increase in the prevalence of neurodegenerative diseases. This is one of the major medical and socio-economic challenges of modern societies. Various mechanisms

leading to memory deficiency with aging have been described. Among these, inflammation, the modification of oxidative status and DNA damage can all have a strong impact on memory processes, reducing cerebral plasticity and leading to the loss of neurons and the diminution of synaptic connectivity. The development of functional foods with “anti-aging” activity is thus of overwhelming interest to both the general public and scientific communities. As discussed in this review, it appears that berries, which are rich in phenolic compounds, exert beneficial effects by attenuating age-related cognitive decline and, possibly as well, on the development of neurodegenerative diseases. Both berries and well-characterized polyphenols such as flavanols, anthocyanins and resveratrol can have beneficial effects on the brain, and more broadly, have been shown to display important biological properties. To better understand their neuroprotective effects, it is essential to identify their active ingredients and their mechanisms of action. Polyphenols are ubiquitous in plant foods and beverages and can therefore be consumed daily in the diet. They have often been generically referred to as “antioxidants”, but a number of different mechanisms underlie the potential of polyphenols to improve neurological health, including their ability to interact with neuronal and glial signaling, to reduce neuronal damage and loss induced by neurotoxins or neuroinflammation, to alter ROS production as well as to attenuate the accumulation of neuropathological markers, such as A β . However, the majority of the data used to support this neuroprotective effect comes from studies dealing with a complex mix of compounds with high polyphenol contents. Furthermore, the effects of the structural changes undergone by polyphenols during metabolism and their interaction with the BBB have not yet been adequately studied to draw clear conclusions on their cerebral bioavailability. Moreover, most of these studies have been performed in animals, and it is now important to develop clinical studies to validate the data gathered so far. Indeed, nutritional intervention studies must be carried out to confirm that polyphenols could be a valuable asset in strategies aimed at delaying or preventing age-related cognitive decline and the development of neurodegenerative diseases in human. Since there are much evidences in the literature in favor of the preventive and therapeutic benefits of polyphenols, to understand their mechanisms, the timing and scope of administration of these compounds in aging and disease processes is an achievable goal. Further investigations are now

needed to expand our understanding of the dynamic role these dietary compounds play in the alleviation of age-associated risk factors in the brain.

Acknowledgments

We thank the Aquitaine regional council for its financial support.

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