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Effects of Polyphenols on Brain Ageing and Alzheimer's Disease: Focus on Mitochondria

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Abstract The global trend of the phenomenon of population ageing has dramatic consequences on public health and the incidence of neurodegenerative diseases. Physiological changes that occur during normal ageing of the brain may exacerbate and initiate pathological processes that may lead to neurodegenerative disorders, especially Alzheimer's disease (AD). Hence, the risk of AD rises exponentially with age. While there is no cure currently available, sufficient intake of certain micronutrients and secondary plant metabolites may prevent disease onset. Polyphenols are highly abundant in the human diet, and several experimental and epidemiological evidences indicate that these secondary plant products have beneficial effects on AD risks. This study reviews current knowledge on the potential of polyphenols and selected polyphenol-rich diets on memory and cognition in human subjects, focusing on recent data showing *in vivo* efficacy of polyphenols in preventing neurodegenerative events during brain ageing and in dementia. Concentrations of polyphenols in animal brains following oral administration have been consistently reported to be very low, thus eliciting controversial discussion on their neuroprotective effects and potential mechanisms. Whether polyphenols exert any direct antioxidant effects in the brain or rather act by evoking alterations in regulatory systems of the brain or even the body periphery is still unclear. To understand the mechanisms behind the protective abilities of polyphenol-rich foods, an overall understanding of the biotransformation of polyphenols and identification of the various metabolites arising in the human body is also urgently needed.

Keywords Polyphenols · Brain ageing · Alzheimer's disease · Mitochondria

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Introduction

In 1936, the group of Szent-Györgyi (Nobel prize in 1937) reported the isolation of the so-called 'vitamin P', which showed capillary resistance-increasing properties in humans [1]. The activity of 'vitamin P' has later been attributed to the presence of various polyphenols, mainly flavonoids such as flavones, flavanones and flavonols [2].

In the 75 years since the description of 'vitamin P', a plethora of studies focused on polyphenols as plant food constituents with possible health-beneficial effects, especially on age-related, chronic diseases such as Alzheimer's disease (AD) and other dementias, cancer, as well as cardiovascular disease (CVD) [3–6].

In the human diet, polyphenols are highly abundant and several hundreds of different compounds have been identified [7]. Polyphenols can be divided into several groups based on the number of phenol rings and the structural elements binding these rings to one another (Fig. 1) [8]. Flavonoids are the most abundant group among dietary

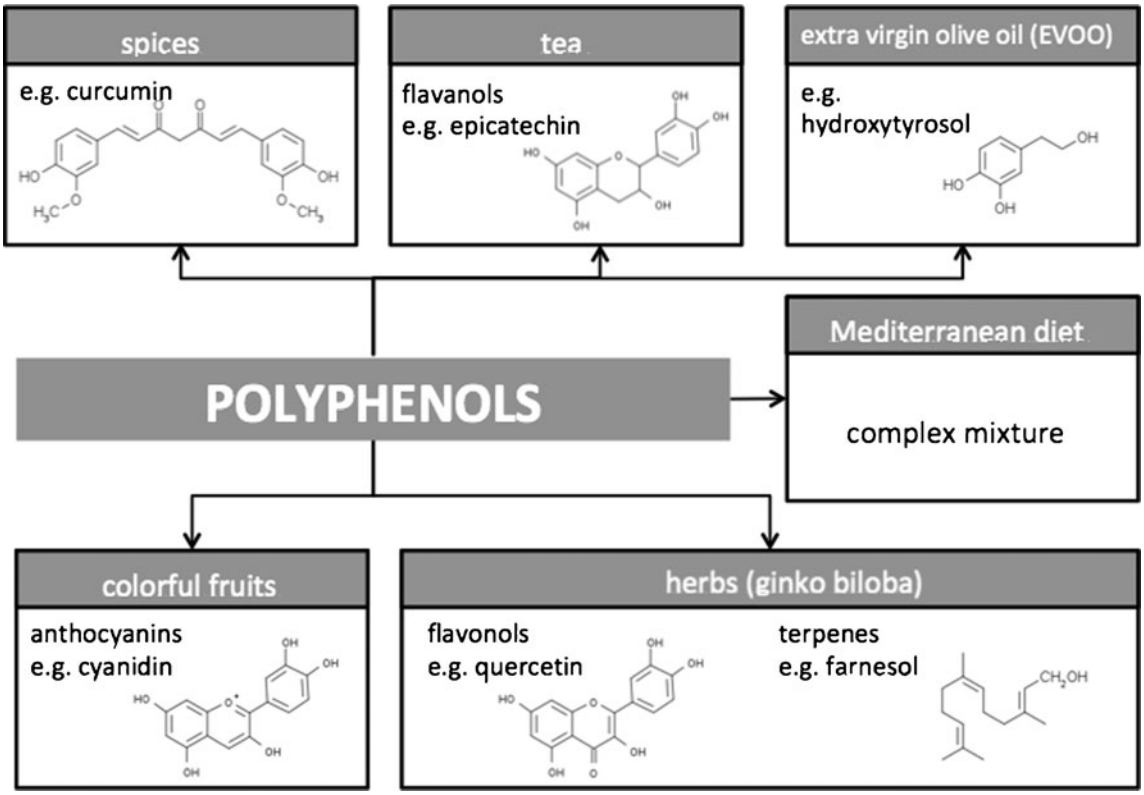

Fig. 1 Polyphenol-rich diets with neuroprotective potentials and their main polyphenolic compounds. In spices, tea, oils, fruits and herbs, polyphenols have a great abundance in the human diet and several hundreds of different compounds have been identified in food. As a function of their number of phenol rings and of the structural elements binding these rings to one another, these molecules can be divided into several groups. Flavonoids are the most abundant group among dietary polyphenols. The common structure of flavonoids consists of two aromatic rings bound together by three carbon atoms forming an oxygenated heterocycle. Flavonoids themselves can be divided into six subclasses: flavonols, flavones, isoflavones, flavanones, anthocyanidins and flavanols (catechins and pro-anthocyanidins)

polyphenols [9]. Flavonoids commonly consist of two aromatic rings bound together by three carbon atoms, forming an oxygenated heterocycle. Flavonoids can further be divided into six subclasses: flavonols, flavones, isoflavones, flavanones, anthocyanidins and flavanols (catechins and proanthocyanidins) [8]. With the exception of the rarely glycosylated flavanols, flavonoids are generally present in glycosylated forms in plants [10].

The majority of studies reporting biological activities and targets of polyphenols have used cell culture experiments which are prone to artefacts. For example, the addition of the green tea flavanol, epigallocatechin-3-gallate (EGCG; but also of other redox-active compounds such as vitamin C), at concentrations of 0.05–1 mM to cell culture media generates hydrogen peroxide in the low to high micromolar range in various types of cell culture media [11,12]. Depending on its concentration, hydrogen peroxide acts as a potent second messenger or cell stressor [13,14]. Both effects may significantly confound the interpretation of cell culture data. Similarly underappreciated is the problem of nutrient depletion (e.g. of pyruvate) in cell culture media due to test compound-induced hydrogen peroxide production [15]. In addition, it is often difficult to extrapolate *in vitro* data to *in vivo* conditions [5]. Thus, our review will focus on recent advances in the understanding of the *in vivo* efficacy of polyphenols in preventing neurodegenerative events during brain ageing and in dementia.

Mitochondria, Brain Ageing and Alzheimer's Disease

Mitochondria—Key Organelles for Energy Supply and Cell Death

Increasing evidence suggests that mitochondrial dysfunction plays an important role not only in brain ageing, but also in the pathogenesis of neurodegenerative diseases, including AD [16]. Mitochondria are complex, network-forming organelles, involved in different metabolic pathways, e.g. tricarboxylic acid cycle (TCA), energy transformation, amino acid metabolism and urea cycle [17]. Mitochondria consist of inner and outer membranes composed of phospholipid bilayers and proteins. The inner mitochondrial membrane harbours the proteins of the electron transfer

system (ETS), responsible for oxidative phosphorylation. The mitochondrial oxidative phosphorylation (OXPHOS) system is the final biochemical pathway that produces energy in form of ATP by consuming oxygen. Electrons are transferred through the complexes of the mitochondrial respiratory chain and simultaneously, an electrochemical proton gradient is built across the inner mitochondrial membrane, generating the proton-motive force that drives the production of ATP [18,19].

Alterations of mitochondrial efficiency and function are mainly related to alterations in mitochondrial mass, amount of respiratory enzymes or changes in enzyme activities [20–23]. A reduction in mitochondrial content or lowered ETS results in a general limitation of cellular energy production. Dysfunction of single complexes of the respiratory system are frequently accompanied by deleterious side effects, such as loss of mitochondrial membrane potential (MMP) and subsequently decreased ATP levels, but also production of reactive oxygen species (ROS) [24].

Apart from ROS enzymatically produced by NADPH oxidases, cytochrome P450-dependent oxygenases and xanthine dehydrogenases, mitochondria are regarded as the primary site of ROS production within cells. The ETS constantly generates ROS, which are usually kept in balance by various defence mechanisms, i.e. antioxidative molecules (e.g. glutathione (GSH) or vitamin E) and antioxidant enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase), as long as ROS levels are in the physiological range. Furthermore, slight uncoupling of the ETC, e.g. by uncoupling proteins, may also reduce ROS production. Functional failure of this system can lead to deleterious effects, which may exaggerate the consequences of mitochondrial dysfunction [25]. Mitochondria are often considered as both the initiator and the first target of oxidative stress. Insufficient defence mechanisms and excessive ROS production (e.g. as superoxide anions) can lead to cell damage. The major sources of superoxide anions are redox centres of complex I and III of the ETS, and different mitochondrial flavoproteins. Superoxide is a rather weak radical, but it is the precursor of various, potentially more toxic ROS [18,26,27]. Its transformation into hydrogen peroxide and hydroxyl radicals, as well as its participation in the formation of peroxynitrate, creates strong oxidants [28].

The proteins of the OXPHOS system and lipids are key targets of the deleterious effects of ROS, potentially leading to membrane depolarization and subsequently, impaired mitochondrial function [16,25]. For example, oxidative damage of omega-3 polyunsaturated fatty acids in the inner mitochondrial membrane has been shown to result in loss of MMP, representing one early hallmark of apoptosis [29]. Thus, mitochondria play an important role in producing energy, but also as major source of ROS. Therefore, efforts to increase mitochondrial function should be accompanied by equal efforts to limit deleterious ROS generation.

Mitochondria act as signal-integrating organelles in the onset of the intrinsic apoptotic pathway. Mitochondrial outer membrane permeabilization and permeability transition result both in the release of pro-apoptotic proteins, which in turn activate caspases and cell death mechanisms further downstream [30,31].

Dysfunction of single mitochondrial enzyme complexes, ROS production, mitochondrial permeability transition pore opening (mPTP), elevated apoptosis, as well as structural alterations and a diminished mitochondrial content, play a role in brain ageing, and are believed to be crucial for the onset and progression of neurodegenerative diseases [32–34].

Ageing—Still an Inevitable Physiological Process

Ageing affects the brain, manifested as decline in several physiological abilities, including sensory, motor and cognitive functions [35,36]. On the cellular level, impaired function of signalling mechanisms, altered gene expression and perturbed energy production have been reported. On the molecular level, oxidative stress is believed to cause accumulation of damaged proteins, lipids, carbohydrates and nucleic acids [37,38]. As previously mentioned, mitochondria have been suggested to play a major role in ageing in view of their central role in energy production, as major source of ROS and as critical regulators of apoptosis [16,39,40]. In mice, brain ageing is typically accompanied by substantial cognitive deficits, beginning in late adulthood at around 12 months of age [16,41]. Ageing has also been shown to affect the lipid composition of mitochondria from rodent brains. Interestingly, among phospholipids, only the cardiolipin fraction of non-synaptic mitochondria from brains of aged rats showed a significant decrease, which was linked to a decrease of linoleic acid [42]. At the same time, oxidative damage, for instance in the form of enhanced lipid peroxidation and reduced membrane fluidity in mitochondria, has been detected *ex vivo* [43,44]. Complexes I and IV of the mitochondrial respiratory chain show significantly decreased enzymatic activities in mitochondria isolated from brains of aged rodents [16,40,45–48]. Due to mitochondrial ROS production, mitochondrial proteins are particularly vulnerable to oxidation, and there is some evidence that mitochondrial DNA accumulates mutations with ageing [44,49–51].

Physiological changes that occur during the normal ageing of the brain may be exacerbated in vulnerable populations of neurons, initiating pathological processes that finally lead to neurodegenerative disorders [36]. Mitochondrial dysfunction has also been observed in the brain of female mice during reproductive senescence, together with

reduced mitochondrial bioenergetics, a shift to ketogenic profile, and a significant decline in mitochondrial complex IV activity and mitochondrial respiratory capacity [52].

Ageing—an Important Risk Factor for Neurodegeneration

To understand the onset and progression of neurodegenerative diseases is one of the major challenges of the twenty-first century. The United Nations estimate that the number of people suffering from age-related neurodegeneration, particularly from AD, will exponentially increase from 25.5 million in 2000 to an estimated 114 million in 2050 [53]. Several meta-analyses have consistently estimated the global prevalence of dementia in people aged over 60 at approximate 4 % [54]. The global annual incidence of dementia is estimated to be about 8 per 1,000 population [55], with no substantial variations across continents, except Africa [56]. The incidence rate of dementia increases exponentially, doubling approximately every 5 to 6 years with age and incidence rates across regions of dementia are quite similar [54,56,57]. The largest increase in absolute numbers of old persons will occur in developing countries [56]. Thus, the global trend in the phenomenon of population ageing has dramatic consequences on public health, healthcare financing and delivery systems in the world, especially in developing countries [56].

Alzheimer's Disease—a Devastating Neurodegenerative Disorder

The clinical symptoms of AD include a progressive loss of memory and impairment of cognitive abilities. Severe neurodegenerative alterations occur in AD brains, including loss of synapses and neurons, atrophy, and the selective depletion of neurotransmitter systems (e.g. acetylcholine) in the hippocampus and cerebral cortex—two brain regions involved in learning and memory [58]. Such defects are mainly observed in the later stage of the disease, and have also been partially demonstrated using transgenic animal models of AD [59,60].

AD is considered as a protein aggregation disorder, based on two key neuropathological hallmarks, namely the hyperphosphorylation of the tau protein, resulting in the formation of neurofibrillary tangles, and the increased formation and accumulation of amyloid-beta peptide (Aβ) oligomers and fibrils derived from amyloid precursor protein (APP) [61]. Although the exact underlying causes initiating the onset of AD are still unclear, an imbalance in oxidative and nitrosative stress, intimately linked to mitochondrial dysfunction, characterizes early stages of AD pathology [16].

Defective energy metabolism is a fundamental component of AD [62–65]. Increasing evidence suggests an important role of mitochondrial dysfunction and oxidative stress in AD [66–68]. Early defects in the expression of several subunits of respiratory chain complexes [69], decreased mitochondrial respiration (mainly mediated by a decline in complex I and complex IV function), and reduced MMP and ATP levels have been detected in several AD cell culture and animal models [68–71]. Direct effects of APP and Aβ on mitochondrial function may induce this early dysfunction. Accumulation of APP in mitochondria, which has been found in both transgenic cell lines and animals, correlates with mitochondrial dysfunction. This may provide one causal link explaining the impaired energy metabolism and subsequent rise in ROS/RNS in models of AD [72–74]. Aside from APP, Aβ itself has also been suggested to affect mitochondrial function. Data show that the presence of one of the key enzymes in Aβ release, namely γ-secretase, pinpoints to a direct production of Aβ in these organelles [75].

Recently, Leuner et al. showed that mitochondria-derived ROS are sufficient to trigger amyloidogenic APP processing *in vivo*, and that Aβ itself leads to mitochondrial dysfunction and increased ROS levels [71]. Finally, increasing evidence suggests that mitochondrial dysfunction in AD originates not only from the deleterious impact of APP/Aβ, but also from its interplay with hyperphosphorylated tau protein on the mitochondrial level [70].

Brain Ageing, Dementia and the Impact of Nutrition

The survival of any organism crucially depends on its nutrient intake, which provides all molecules for cell formation, maintenance and repair, either in the form of ready-made building blocks or precursors [76]. In the case of humans, the importance of nutrition becomes obvious in the form of distinct patterns of clinical symptoms caused by the inadequate intake of one of the macronutrients, vitamins or minerals [77]. The increase in life expectancy observed in the twentieth century in many populations throughout the world attests to the impact nutrition (in conjunction with better hygiene and medical practice) exerts on human health [78]. At the same time, however, human ageing beyond 50 years of age is typically accompanied by the occurrence of one, often more, chronic, age-related diseases, such as cancer, CVD and neurodegeneration [79,80]. Due to its physiological characteristics, the brain is particularly prone to damage induced by noxious changes or fluctuations in cellular homeodynamics [81,82]. Thus, the quest for primary prevention of neurodegeneration is imperative.

As stationary autotrophs, plants have evolved numerous pathways for the synthesis of secondary plant metabolites. These phytochemicals act, for example, as free radical scavengers or as defence against infectious microorganisms, with the aim of increasing a plant's chances for reproduction

and survival [83]. Of all secondary plant metabolites, the group of polyphenols attracted most interest as potential modulators of human health. The Paquid study, a large cohort study of cerebral ageing in France, is among the first nutritional investigations suggesting an inverse relation between the intake of polyphenols (here flavonoids) and a slower cognitive decline in subjects aged 65 years and older [84,85]. A recent publication based on the SU.VI.MAX studies seems to confirm some of the earlier results that indicated positive association between polyphenol intakes and better cognitive and memory performance. However, a more detailed analysis revealed that the polyphenol subgroups of catechins and flavonols exert both positive and negative effects in individual test paradigms [86].

Although overall encouraging, the neuroprotective property of polyphenol intake needs to be carefully assessed. In the following, we provide the reader with a comprehensive update of selected polyphenols and polyphenol-rich diets with regards to their potential in maintaining memory and cognition in human subjects (Fig. 1). In addition, we discuss some of the most promising mechanisms of action that could explain polyphenols' presumed health-beneficial effects.

Factors Affecting Polyphenol Brain Bioavailability

In order to reach the brain, orally ingested polyphenols must cross two barriers, i.e. the enterocytes in the intestine as well as the blood–brain barrier which separates the CNS from the body periphery [8,87]. With a few exceptions, only polyphenol aglycones can be absorbed in the small intestine [8,88]. Németh et al. identified polyphenol deglycosylation by small intestinal epithelial cell β-glucosidase as a crucial step in the absorption and metabolism of dietary flavonoids [89]. In addition, a sodium-dependent glucose transporter 1-dependent uptake of polyphenol glucosides has been suggested [90], but the extent of this mechanism is still unclear.

Most polyphenols, once they are released from the enterocytes into the lymph and subsequently blood, undergo substantial biotransformation in the form of methylation, glucuronidation, sulfation and thiol conjugation reactions [8,91]. These modifications typically alter the chemical properties of polyphenol metabolites, resulting in potentially new biological activities [8,92]. In addition, anthocyanins may be degraded due to their instability in neutral fluids [93].

Recently, the colonic microflora emerged as an important contributor to polyphenol bioavailability and metabolism [8]. For example, polyphenol metabolites of apple juice or green tea catechins formed by microbial metabolism in the small intestine of healthy ileostomy probands have been identified [94,95]. The microflora is able to extensively metabolize polyphenols, and their degradation products have been detected in human plasma and urine. Importantly, luminal microorganisms are not only affecting polyphenol breakdown; polyphenols can also significantly alter both composition and metabolism of the intestinal microbiota, possibly with subsequent effects on the host's health status [96–98].

Several publications indicate that orally administered polyphenols penetrate the blood–brain barrier (e.g. [99,100]) and reveal different pharmacokinetic profiles in blood plasma and brain homogenate [101]. However, brain bioavailability of polyphenols is still a matter of debate and a substantial number of publications have addressed this issue (reviewed in [102]). The amount of reliable data on this aspect is very limited due to the lack of important control procedures during data acquisition. In particular, the potentially confounding effect of residual cerebral microvessels and blood on the quantification of interstitially and intracellular located polyphenols (or drugs) is often overlooked [102,103]. Following the administration of *Hypericum performatum* or *Ginkgo biloba* extracts, for example, brain concentrations of the biflavone amentoflavone were below the lower limit of quantification (<0.01 nmol/g; LC-MS-MS) after performing the necessary correction for residual blood [104]. In agreement with these data, oral supplementation studies in exsanguinated and perfused animals consistently showed that polyphenol concentrations in animal brain were usually below 1 nmol/g tissue [105–108]. Although these data provide evidence that some polyphenols are able to penetrate into the animal brain at measurable levels, the detected concentrations do not support the concept of significant direct antioxidant effects of polyphenols in the CNS [102]. Hence, whether polyphenols exert any direct antioxidant effects in the brain or rather act by evoking alterations in regulatory systems of the brain or even the body periphery (which then signal to the brain) is still unclear.

In Vivo Effects of Selected Polyphenols and Polyphenol-Rich Diets on the Ageing Brain

Mediterranean Diets

After the seminal work of Ancel Keys and colleagues based on the Seven-Countries Study [109] which associated Mediterranean diets and improved cardiovascular health, the potential of these diets to attenuate the onset and progression of various chronic diseases has been the subject of many epidemiological, pre-clinical animal, as well as human, intervention studies.

In general, Mediterranean diets are characterized by a high intake of fruits, vegetables, legumes and cereals, a moderate intake of dairy products, fish and alcohol (mainly wine), and a comparatively low consumption of red meat

and poultry [110]. Here, it is important to keep in mind that 'the' Mediterranean diet does not exist [111]. Originally, the disease-preventing features of Mediterranean diets have been linked to the favourable ratio of unsaturated to saturated fatty acids [112]. In particular, a high alimentary intake of mono-unsaturated fatty acid-rich extra virgin olive oil (EVOO) has been suggested to account for the observed better health status of study subjects [113]. Studies conducted since the 1990s provide additional evidence that phenolic minor components, such as hydroxytyrosol, might also contribute to the cardiovascular health benefits of EVOO and Mediterranean diets in general (refer also to "Olive Oil Polyphenols" section) [114,115]. However, as people typically consume foods not in isolation but in combination [116], several research groups focused on assessing cognition, memory performance and AD risk in relation to differences in dietary patterns.

The prospective, community-based WHICAP study conducted by Scarmeas et al. suggests that a higher adherence to the Mediterranean diet is associated with a reduced risk for developing AD (hazard ratio=0.6 at the highest tertile of Mediterranean diet intake) [117]. However, the link between Mediterranean diet and AD risk seemed to be unrelated to vascular co-morbidity [117]. Interestingly, a subsequent study by the same authors further indicates that a higher adherence to the Mediterranean diet is not only associated with a reduced risk for developing mild cognitive impairment (MCI) but might also affect disease progression, evident by a lower risk for MCI conversion to AD [118]. Similarly, Tangney et al. concluded in the biracial Chicago Health and Ageing Project that adherence to a Mediterranean dietary pattern might slow down the age-associated rate of cognitive decline [119]. In a study population at high cardiovascular risk drawn from the PREDIMED cohort, increased consumption of polyphenol-rich Mediterranean foods was also associated with better cognitive performance [120].

In contrast, the prospective Three-City cohort study conducted in France, has shown for a sub-set of the participants that adherence to a higher Mediterranean diet is only associated with slightly slower MMSE decline, whereas three other cognitive tests were unaffected. Moreover, Mediterranean diet adherence did not alter the risk for incident dementia or AD during the 5 years of follow-up [121,122]. However, it is worth mentioning that the baseline analysis of the Three-City cohort study has indicated a significant association between daily fruits and vegetable consumption as well as weekly fish intake and a reduced risk for all-cause dementia and AD, respectively, in apolipoprotein E4 non-carriers [121]. A recent longitudinal investigation of more than 1,500 participants of the PATH study in Australia also found no protective effect of adherence to Mediterranean diet against cognitive decline [123].

Taken together, there is only equivocal evidence that adherence to a Mediterranean dietary pattern contributes significantly to the maintenance of memory and cognition in older people. The conflicting results can, at least partly, be attributed to differences in study design and assessment method of dietary adherence, as well as the control of confounding variables [111,124]. Recent meta-analyses and commentaries also highlight the difficulty in drawing final conclusions regarding the disease-preventing potential of Mediterranean diets. Whereas some authors suggest a 'significant and consistent protection provided by adherence to the Mediterranean diet in relation to the occurrence of major chronic diseases', others take a more measured position by concluding that 'for now, it is reasonable to nibble on these findings and savour them, but not to swallow them whole' [125,126].

Anthocyanins and Anthocyanin-Rich Fruits

Emerging evidence gained from animal intervention studies suggests a beneficial effect of colourful fruits on brain ageing, especially on age-related cognitive and motor decline. To date, research that has been done on blueberry, and also blackberry, strawberry, mulberry, Concord grape and pomegranate have shown them to be neuroprotective. The characteristic bright colour of these fruits is due to their high amount of anthocyanins, a flavonoid subgroup with high antioxidant potential *in vitro* and *in vivo* [127]. Early investigations of James Joseph and colleagues showed that feeding diets high in antioxidant activity might prevent and even reverse age-related deficits in motor and cognitive behaviour in Fischer 344 (F344) rats [128,129]. Diet supplementation with 1.86 % blueberry extract or 1.48 % strawberry extract for 8 weeks showed beneficial effects on cognitive performance in aged rats. Interestingly, although the different supplementations were based on equal antioxidant activity, only the blueberry-supplemented rats showed an improvement in motor performance (balance and coordination), a greater influence on receptor sensitivity (measured as oxotremorine enhancement of K^+-evoked dopamine release from striatal slices) as well as alterations in signal transduction events (measured as carbachol-stimulated GTP-ase activity). Additionally, striatal oxidative stress markers decreased modestly [129], suggesting that neuroprotection may not be attributed to simple antioxidant activity alone. There is increasing evidence that flavonoids, such as anthocyanins, do not exert their protective effects through direct ROS-scavenging (please refer to "Factors Affecting Polyphenol Brain Bioavailability" section.), but through indirect antioxidant activity. This assumption is also supported by the fact that the anthocyanin concentration in the human body seems to be very low. Often <0.1 % of ingested anthocyanins is recovered in the urine [130]. In rat

brain, anthocyanins were detected in a total concentration of about 0.25 nmol/g of tissue after 15 days of supplementation with blackberry extract [107]. Moreover, the anthocyanidin pelargonidin was found in a concentration of 0.16 nmol/g of rat brain tissue 2 h after oral administration of 50 mg/kg body weight. No pelargonidin was detected 18 h after administration [131]. This is in contrast to studies with blueberry-supplemented pigs, wherein anthocyanins were detected in the brain after a fasting period of 18–21 h [132,133]. In fasted pigs that received a diet supplemented with 1–4 % blueberries for 4 weeks, anthocyanin concentrations in the brain reached about 0.3–0.4 ng/g fresh weight. Interestingly, no anthocyanins were detected in the plasma or urine [133]. The data suggest that anthocyanins might be able to accumulate in animal brains and exert direct effects within the brain, but concentrations might be too low for direct ROS scavenging. However, anthocyanins might be able to alter signalling pathways, responsible for indirect antioxidant activities. Diet supplementation with 2 % blueberry extract for 4 months has been shown to significantly lower levels of protein transcription factor nuclear factor-kappa B (NF-κB), a highly responsive indicator of oxidative stress, in different brain regions of aged F344 rats. Normalized NF-κB levels further correlated negatively with object recognition memory [134]. Oral administration of 100 mg/kg purple sweet potato colour (PSPC) composed of a mixture of anthocyanins for 4 weeks has also been demonstrated to attenuate D-galactose-induced ageing-related changes in mouse brain. PSPC improved the spontaneous behaviour and cognitive performance, increased the activity of copper/zinc superoxide dismutase and catalase, and reduced the content of malondialdehyde as important indicator of oxidative damage in brain, as well as attenuated parameters connected to neuroinflammation (e.g. nuclear translocation of NF-κB) [135].

Besides the direct and indirect antioxidant activity, anthocyanins participate in interactions with target proteins of different signal transduction pathways. Orally administered PSPC (100 mg/kg for 4 weeks) has been shown to counteract the onset of neuronal apoptosis via survival mechanisms involving extracellular signal-regulated kinase (ERK 1/2), phosphoinositide 3-kinase (PI3K), Akt and c-Jun NH_2-terminal kinase (JNK) in D-galactose-treated old mice [136]. Rodent models of cerebral ischaemia support evidence for the involvement of survival mechanisms in neuroprotection of anthocyanins. Pretreatment with isolated anthocyanins (300 mg/kg p.o.) 24 h and 30 min before middle cerebral artery occlusion has been shown to reduce brain infarct volume along with blocking of the JNK and p53 signaling pathway in rats [137]. In mice, pretreatment with the anthocyanin cyanidin-3-*O*-glucoside (2 mg/kg p.o.) 24 h before induction of focal cerebral ischaemia attenuated the infarct volume and led to lower levels of brain superoxide [138]. Besides, a recent study investigated the effect of oral administration of PSPC (200 mg/kg for 4 weeks) on cognitive deficits induced by hippocampal mitochondrial dysfunction in mice that were treated with the neurotoxin domoic acid. The study indicates that PSPC might reverse the cognitive deficits by promoting oestrogen receptor-α-mediated mitochondrial biogenesis signalling, restoring mitochondrial dysfunction, decreasing ROS and protein carbonyl levels, and suppressing endoplasmic reticulum stress-induced apoptosis, which prevented neuron loss and restored the expression of memory-related proteins [139]. Additionally, supplementation with rabbit-eye blueberry extract in drinking water (2.6–3.2 mg anthocyanins/kg for 30 days) improved memory and behaviour in mice and decreased DNA damage in both hippocampal and cortical tissues *in vitro* [140]. Furthermore, there is evidence that the cognitive improvements in aged F344 rats fed with a 2 % blueberry extract supplemented diet are, at least partly, mediated by effects on hippocampal plasticity involving neurogenesis, neurotrophic factor insulin-like growth factor-1 (IGF-1) and its receptor, as well as mitogen-activated protein (MAP) kinase signal transduction cascades [141]. Neurogenesis was also observed in brains of 129 S1/SvImJ adult male mice fed a diet enriched in polyphenols and polyunsaturated fatty acids (9.27 % in diet for 40 days). Unfortunately, the composition of the diet was not described [142].

Anthocyanin-rich fruits have also been shown to exert promising effects in mouse models of AD. In mice transgenic for APP/Tg2576 and presenilin-1 (PS1) mutations, feed supplementation with 2 % blueberry extract from 4 months of age normalized behavioural impairment (assessed at 12 months of age) to values comparable to non-transgenic mice. Moreover, the study indicated that this prevention of behavioural deficits was probably due to enhancement of memory-associated neuronal signalling (e.g. ERK 1/2) and alterations in neutral sphingomyelin-specific phospholipase C activity. Interestingly, no alterations in Aβ burden were observed [143]. Conversely, pomegranate juice concentrate in drinking water (1:80 or 1:160 dilution) for 6.5 months [144] and 0.18 or 0.9 % mulberry extract supplemented diet for 3 months [145] reduced the accumulation of soluble $A\beta_{42}$ and amyloid deposition in the hippocampus of APP_{sw}/Tg2576 transgenic mice and the accumulation of Aβ in the brain of senescence-accelerated mouse prone 8 (SAMP8) mice, respectively. Mulberry extract-treated SAMP8 mice further displayed higher antioxidant enzyme activity and less lipid oxidation in the brain [145].

The different effects on Aβ in the AD mouse models may be explained by the different polyphenolic compositions of the tested fruits. Different effects on brain function were also detected in young rats that received either a 2 % blueberry or strawberry extract-supplemented diet for 8 weeks. After

whole-body exposure to high energy and charge (irradiation with 1.5 Gy of 1-GeV/n high-energy ^{56}Fe particles) producing deficits in neuronal functioning and behaviour similar to the adverse changes in ageing, the behaviour of rats in the Morris Water Maze suggested a region selectivity of the compounds in the berry extracts. The strawberry diet offered better protection against spatial deficits, as demonstrated by a better ability to retain place information, which is linked to a hippocampus-mediated behaviour. On the other hand, the blueberry diet seemed to improve reversal learning, a behaviour more dependent on intact striatal function [146].

Anthocyanins might also act differently depending on the concentration administered. Administration of 10 % Concord grape juice to aged F344 rats as sole source of liquid was able to improve receptor sensitivity, measured as oxotremorine enhancement of K^+-evoked release of dopamine from striatal slices, as well as cognitive performance. Administration of 50 % Concord grape juice (as sole source of liquid) improved motor function in the aged rats [147].

Interestingly, Concord grape juice and blueberry juice also showed beneficial effects on cognitive performance in preliminary investigations in humans. A randomized, placebo-controlled, double-blind trial with daily Concord grape juice supplementation (444–621mL/day, depending on body weight) over a period of 12 weeks led to a significant improvement in a measure of verbal learning and non-significant enhancement of verbal and spatial recall in 12 older adults with memory decline but not dementia [148]. In addition, daily consumption of wild blueberry juice (444–621mL, depending on body weight) in a sample of nine older adults with early memory changes improved paired associate learning and word list recall [149]. In a recent study, older adults with MCI consumed Concord grape juice (355–621mL, depending on body weight) or placebo for 16 weeks. Participants who consumed grape juice showed reduced semantic interference on memory tasks. Moreover, a relatively greater activation in anterior and posterior regions of the right hemisphere was detected using functional magnetic resonance imaging in the grape juice-treated subjects [150].

Tea polyphenols and Tea Consumption

Tea, made from the leaves of *Camellia sinensis*, is among the most frequently consumed beverages worldwide [151]. Depending on the degree of enzymatic oxidation by polyphenol oxidase, different tea products are obtained: green tea (non-fermented), oolong tea (half-fermented) and black tea (fermented). In addition to caffeine, minerals and amino acids, tea contains considerable amounts of polyphenolic flavanols called catechins. Whereas in green tea, 30–40 % of the leaf dry weight are polyphenols, most flavanols in black tea are converted to theaflavins and thearubigens in the course of the fermentation process [152,153].

In the early 1980s, the SAMP model was established to better facilitate the study of ageing and age-related diseases in mice [154]. From the different SAMP strains available, SAMP8 and SAMP10 mice drew particular attention due to their neuropathological changes and subsequent deficits in learning and memory [155]. SAMP8 mice treated from the age of 6 months with green tea as the sole drinking fluid for 16 weeks benefited from reduced brain oxidative damage and lower cognitive deficits compared to vehicle-treated animals [156]. Similarly, Unno et al. demonstrated in a series of experiments in SAMP10 mice supplemented with green tea catechins a suppressive effect on cognitive dysfunction, reduced brain oxidative damage to DNA and higher learning ability. Noteworthy, lifespan was unaffected by flavanol treatment suggesting that green tea polyphenols might exert healthy- but not anti-ageing effects [157–159].

In addition, the impact of the green tea polyphenol (−)-epigallocatechin-3-gallate (EGCG) on brain parameters of genetically modified AD mice has been investigated. The administration of EGCG (50 mg/kg body weight) in drinking water to an 8-month-old cohort of APPsw transgenic mice for a duration of 6 months, for example, resulted in reduced Aβ deposition and tau phosphorylation in the animals' brain as well as better performance in working memory tests [160]. In preseniline 2 mutant mice, EGCG (3 mg/kg body weight) administration in drinking water for 1 week increased not only the activity of brain α-secretase, but also led to enhanced memory function compared to unsupplemented animals [161]. Likewise, long-term intake of green tea catechins in rats prevented not only the age-related accumulation of oxidative stress biomarkers (here measured as protein carbonyls, levels of malondialdehyde and lipofuscin formation) in the brain, but also improved spatial learning and memory abilities of the animals [162]. Furthermore, green tea flavanol feeding has been shown to reduce the detrimental effects of Aβ infused into the cerebral ventricle of rats [163].

Based on these observations, it is tempting to speculate whether green tea polyphenols might be an effective prophylaxis against brain ageing and AD. However, caution regarding the validity of both the SAMP and transgenic mouse models has been advised by some authors. Although several contributions to a better understanding of fundamental mechanisms of age-related learning and memory deficits can be attributed to SAMP models [154], the question of whether SAMP mice represent a true (brain) ageing model or are maybe just sick is still a matter of debate [164]. Likewise, transgenic animal models have been paramount for developing new hypotheses of AD pathology [165].

Nonetheless, they need to be critically evaluated due to their shortcomings, for example in mirroring the temporal sequence of neuropathological events in human AD or in their morphological resemblance of the structure of Aβ deposits [166]. The striking discrepancy in the rate of successful intervention between AD animal models and human studies is likely an expression of this problem [167].

To date, only a few studies have assessed the association between tea intakes and cognitive health in later life. The results from cross-sectional studies are generally consistent and suggest that drinking tea is associated with a lower prevalence of cognitive impairment and better memory performance (reviewed in [152]). Prospective studies, in contrast, produced mixed results. Whereas data from the Singapore Longitudinal Ageing Studies suggest a reduced risk for cognitive decline in association with black and oolong tea (but not coffee) consumption [151]; Eskelinen et al. found the reverse association, i.e. coffee but not tea drinking in midlife was linked to a reduced risk of dementia in late life [168]. Interestingly, a recent longitudinal examination of people participating in the Chinese Longitudinal Healthy Longevity Survey indicates diverse health benefits for drinking tea in terms of reduced odds ratios for CVD, cognitive impairment and general disability in activities of daily living [169]. Although the outcome of these studies is promising, it is again important to keep in mind that so far, only associations between tea drinking and human health have been found, which do not allow drawing any conclusions referring to causality.

G. biloba

G. biloba (Coniferae) has been traditionally used for respiratory disorders in China and to improve memory loss associated with blood circulation abnormalities in Iran [170,171]. Nowadays, standardized extracts of *G. biloba*, particularly EGb761®, are available as herbal drug for the improvement of cognitive impairments, including dementia [172]. EGb761® contains 24 % flavonoids and 6 % terpenens [173,174]. While the terpene lactones are mainly responsible for the improvement of mitochondrial function by EGb761 (see the chapter by [175]), the flavonoid fraction seems to be mainly responsible for the free radical scavenging characteristics.

The flavonoid fraction, primarily composed of quercetin, kaempferol and isorhamnetin [176], is also mainly responsible for the inhibition of dopamine uptake by EGb761 (100 mg/kg b.w. p.o. for 14 days) in NMRI mice [177,178]. Ginkgo flavonols quercetin and kaempferol (50 mg/kg b.w. p.o.) fed for 4 months stimulated signalling pathways involving brain-derived neurotrophic factor (BDNF), phosphorylation of cyclic AMP response element binding protein (CREB) and postsynaptic density proteins (PSD95) in brains of (TgAPPsw/PS1e)-mice [179], confirming the effects of EGb761 in diet (100 mg/kg b.w. for 4 weeks) on BDNF and CREB levels in TgAPP/PS1mice [180]. Accordingly, a recent review concluded that EGb761® improves all aspects of impaired neuroplasticity including reduced long-term potentiation, reduced spine density, impaired neuritogenesis and even reduced neurogenesis [181].The clinical application of EGb761 in dementia has been reviewed in recent meta-analyses of short-term trials ([182,183]; for further detailed discussion of human trials with *G. biloba*, the reader is referred to Eckert et al. this issue [175])

Olive Oil Polyphenols

Potent antioxidative polyphenols are found in EVOO. Recent findings suggest that EVOO has beneficial effects on learning and memory deficits observed in ageing and diseases [184]. SAMP8 mice, an age-related learning/memory impairment model associated with increased brain oxidative damage, that received EVOO (75 μl/kg p.o. for 6 weeks) showed improvement in cognitive tests and novel object recognition [184]. *In vivo* and *ex vivo* studies provide evidence that phenolic minor components, such as hydroxytyrosol (HT), significantly contribute to the health benefits of EVOO [114,185,186]. HT is attracting distinct attention because of its ortho-diphenolic structure. HT is bioavailable and its metabolism has been elucidated in animals and humans [187–190]. One source of HT is olive mill waste water, currently discarded although rich in polyphenols that can be recovered by ad hoc techniques [191–193]. Recent data indicate neuroprotective effects of HT in animal feeding trials [185]. Acute treatment of mice with HT-rich extract (100 mg/kg p.o.) did not improve mitochondria-associated parameters, i.e. MMP and ATP levels in dissociated brain cells (DBC) *ex vivo* in response to oxidative stress [185]. In contrast, feeding of HT to mice (100 mg/kg p.o.) for 12 days induced a moderate, though statistically significant, hyper-polarization of mitochondria in unstressed DBC, an effect that has been associated with reduced rate of cell death [194]. Basal ATP levels, however, did not differ between study groups [185]. Feeding of HT-rich extract for 12 days did not ameliorate mitochondria-associated stress parameters in DBC, indicating that prolonged HT intake does not convey mitochondrial protection from severe oxidative and nitrosative stress. However, iron-stimulated lipid peroxidation *ex vivo* was reduced, providing first evidence of neuroprotective effects of oral HT intake [185].

Hormesis as Potential Mechanism—When and How It Matters

The term hormesis, coined by Southam and Ehrlich in the early 1940s, describes a process in which exposure to a low dose of an agent that is toxic at higher doses stimulates beneficial effects on the cell or organism [195,196]. Our knowledge about hormetic effects *in vivo* originates in large parts from ageing studies in the nematode *Caenorhabditis elegans* [197]. The extended lifespan of worms treated with the phenolics tannic acid and gallic acid, for example, has been explained by a hormetic mode of action [198]. However, not all polyphenols that have been shown to prolong *C. elegans* longevity do so by hormesis. Epicatechin, for instance, increases the lifespan of *C. elegans*, but treated worms are significantly smaller in body size, a trade-off phenomenon that argues against a hormetic mechanism [199]. Recently, the first direct evidence for hormesis induction in mammals has been reported. Following the induction of stroke, wild-type mice pre-treated with the polyphenol epicatechin showed significantly less detrimental symptoms in contrast to *nrf2* knock-out animals [200]. The transcription factor Nrf2 is one of the key regulators responsible for the upregulation of antioxidant and cell protective genes, such as heme oxygenase-1 and γ-glutamylcysteine sythetase, and Nrf2-regulated gene expression has been suggested as one of the key mechanisms for hormesis induction [201]. In order to modify the expression of cytoprotective proteins (phase 2 enzymes), Nrf2 needs to bind to the antioxidant response element (ARE) after translocation to the nucleus [202]. Many polyphenols and other phytochemicals (also called 'vitagenes') contain Michael acceptor functionalities which abolish the capacity of the protein Keap1 to repress Nrf2 in the cytoplasm [203]. The importance of Keap1 in this mechanism has been demonstrated in *keap1* knock-out mice. Presumably due to constitutive activation of Nrf2, neurons from these animals showed increased oxidative stress resistance and survival compared to those of wild-type mice [204]. Of note, the production of GSH, the most important antioxidant in the brain with intracellular concentrations in the millimolar range, is partly under control of the transcription factor Nrf2 via its effect on glutamate cysteine ligase, the rate-limiting enzyme in the de novo GSH synthesis [205–207]. Although GSH is exclusively synthesized in the cytosol, the uptake of GSH into mitochondria has been observed in various brain cell types and is particularly high in neurons, probably due to their increased requirements for antioxidant defence [208,209]. A beneficial effect of flavonoids in the form of liposomal quercetin (30 mg/kg body weight; i.p.) has been shown with regard to higher levels of cerebral GSH in striatum and cortex of ischemic rats [210]. Similarly, 7-month-old SAMP8 mice consuming a diet rich in phytochemical antioxidants for 10 months showed significantly higher GSH/glutathione disulfide (GSSG) ratios in brain mitochondria of both male and female animals [211]. Interestingly, Shenvi et al. recently suggested a novel, age-dependent switch in Nrf2 binding to ARE promoters as one key mechanism for the age-dependent reduction in GSH synthetic capacity (here in liver) of male Fisher rats [212]. In light of the promising impact flavonoids exert on GSH synthesis, one might speculate whether flavonoids (and other phytochemicals) increase the cellular GSH/GSSG ratio by direct or indirect interactions with the aforementioned switch in Nrf2-ARE promoter binding. In addition, other hormetic stressors, in particular exercise and dietary energy restriction, have been reported to increase the resistance of neurons to oxidative stress. Important neuronal signalling and repair pathways, including CREB, BDNF and APE1, might causally contribute to the observed hormetic response [213].

Recently, 'mitohormesis' (i.e. mitochondrially-mediated stress resistance) has been proposed as a framework for explaining how stress stimuli exert their health-beneficial effect on the cellular level [214]. The dynamic network and pool of mitochondria is constantly monitored and in the case of severe damage, dysfunctional mitochondria are separated, e.g. by the fission and fusion process, and then effectively eliminated by mitophagy [215]. The observed concomitant decline in mitochondrial mitogenesis and increase in mitochondrial heterogeneity likely contributes significantly to the functional decline in ageing and the onset of age-related diseases [215,216]. One mechanism for the activation of mitochondrial biogenesis is via stimulation of mitochondria by mild to moderate amounts of ROS. Increasing evidence suggests that physical exercise, caloric restriction, prooxidant phytochemicals (e.g. flavonoids and sulphoraphanes) and certain drugs (e.g. statins) activate mitohormesis, at least partly, by up-regulating the production of ROS, and by altering the cellular redox-balance and cell signalling [216,217]. As an example, resveratrol has been suggested to improve mitochondrial function and to protect against metabolic disease by activating SIRT1 and PGC-1alpha signalling [218].

However, the application of hormesis in practice faces several difficulties which have to be taken into consideration. Certain health conditions, such as stroke, are associated with alterations in the permeability of the blood–brain barrier which may change the penetration efficiency of nutrients or drugs into the brain [219], and subsequently lead to an improvement or worsening in the therapeutic outcome. Furthermore, there is evidence for a strong age-dependent effect on the hormetic response [220], suggesting that hormetic doses with established health-modifying effects in a population sub-set likely need to be adjusted across other population age- and health-groups. Finally, trade-offs (such as increased lifespan at the expense of

fecundity) need to carefully considered in the interpretation of the hormetic dose–response phenomena [221]. Thus, it may not come as a surprise that the public health implications of hormesis are controversially debated [222,223].

Conclusion and Future Perspective

Since Szent-Györgyi's discovery of 'vitamin P' in 1936, more than 10,000 articles have been published on the chemical nature and biological activities of flavonoids and other polyphenols (based on a PubMed search, March 2012). Today, there is little doubt that a balanced diet rich in fruits and vegetables helps to maintain human health by delaying or preventing the onset of chronic, age-related diseases [224,225]. However, similar to the vast number of polyphenols present in plant foods, a plethora of mechanisms have been proposed for explaining polyphenols' mode of action *in vivo*. One of the early and most popular paradigms, i.e. the direct antioxidant activity of polyphenols, is now heavily disputed and slowly replaced by other theories such as the induction of a hormetic dose response (Fig. 2) [102].

Concentrations of polyphenols in animal brains following oral administration have been consistently reported to be very low, thus eliciting controversial discussion on their

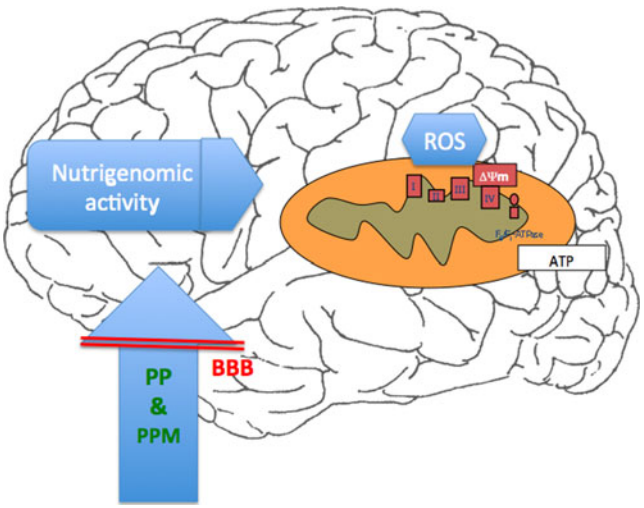

Fig. 2 Simplified model for the protective action of phytochemicals, especially polyphenols (*PPs*) and its metabolites (*PPM*) against mitochondrial dysfunction in brain ageing and Alzheimer's disease. Mitochondrial dysfunction is characterized by failure of the respiration complex activities (*I–V*), a drop in mitochondrial membrane potential ($\Delta\psi m$), enhanced levels of reactive oxidative species (*ROS*) and a drop in ATP-levels. Insufficient penetration of the blood brain barrier (*BBB*) is one problem of the preventive consumption of supplements or food enriched in secondary plant products. Nutrigenomic activity is mainly mediated by the antioxidant response element, which activates endogenous protective mechanisms such as antioxidant enzymes or proteins. Nutrigenomic activity is also responsible for induction of transcriptional co-activators such as PGC-1α and thus induces mitogenesis

neuroprotective effects and potential mechanisms. However, as mentioned above, polyphenols are subject to various biotransformation and degradation processes in the human body (refer to "Factors Affecting Polyphenol Brain Bioavailability" section). It is therefore possible that polyphenolic metabolites from the fermentation and biotransformation process reach the brain and contribute to neuroprotection, or might even be similarly or more effective than their parent compounds. For example, protocatechuic acid, a well-known metabolite of the anthocyanidin cyanidin, has been detected in the bloodstream of humans [226] and rats [227] after consumption of cyanidin-glucoside/cyanidin-glucoside-rich foods. In PC12 cells that have been widely used for neurobiological and neurochemical studies, protocatechuic acid has been shown to reduce mitochondrial dysfunction and apoptotic cell death induced by rotenone [228] and 1-methyl-4-phenylpyridinium ion [229]. Thus, phenolic acids and further metabolites may account, at least partly, for the beneficial effects of polyphenol-rich foods, such as colourful fruits, on brain function. An overall understanding of the biotransformation of polyphenols and identification of the various metabolites arising in the human body is therefore imperative in order to shed light on the mechanisms behind the protective activities of polyphenol-rich foods. Research on the effects of polyphenols on brain function must be based primarily on *in vivo* models, with artefact-free cell culture experiments being more suitable for investigating specific mechanisms [230]. Thus, animal models are indispensible until non-invasive imaging techniques emerge, allowing studies of mitochondrial function in the human brain.

Furthermore, the exposure to plant and animal foods is a lifelong event (in contrast to most drugs) and both the exclusion of potential confounders as well as the identification of robust biomarkers in human nutrition still pose a major challenge [77]. Moreover, bioavailability of polyphenol compounds has to be considered in nutrition-based and brain-directed strategies to improve mitochondrial function, and may include new formulations such as micro-encapsulation or liposomes [231,232]. Finally, future investigations also need to elucidate whether synergies between orally consumed polyphenols that are known to specifically modify metabolic and transport processes enhance polyphenols' bioavailability [233].

In conclusion, there is considerable evidence from animal and initial evidence from first human studies that suggest neuroprotective actions of polyphenols, promising the ability to prevent or even reverse changes in cognitive and motor functions in normal ageing and AD. Currently, it is not clear if the different compounds in plant based foods act in an independent, synergistic, additive or even antagonistic manner. However, recommendations of a daily intake of polyphenols need to consider functional active doses and

the issue of polyphenol bioavailability. Since mitochondrial dysfunction probably represents an early pathological event, human studies on the efficacy of polyphenols will likely need to be initiated early in the course of AD or even before the disease onset.

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