Chapter 23
Nutritional Approaches for Healthy Aging of the Brain and the Prevention of Neurodegenerative Diseases

Heike Asseburg *, **Stephanie Hagl** *, **and Gunter P. Eckert**

1 Brain Aging: An Inevitable Physiological Process

The aging of the brain is characterized by a decline in several physiological abilities, including sensory, motor, and cognitive functions [78, 85, 87]. In mice, brain aging is typically accompanied by substantial cognitive deficits, beginning in late adulthood at around 12 months of age [90, 127]. Impaired function of signaling mechanisms, altered gene expression, and perturbed energy production are signs of aging on the cellular level. On the molecular level, oxidative stress results in the accumulation of damaged proteins, lipids, carbohydrates, and nucleic acids [33, 104]. Physiological changes that occur during normal aging of the brain may be exacerbated in vulnerable populations of neurons, initiating pathological processes that finally lead to neurodegenerative disorders [87].

2 Aging: 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 [143]. Several meta-analyses have consistently estimated the global prevalence of dementia in people aged over 60 to be approximately 4 % [101]. The global annual incidence of dementia is estimated to be about 8 per 1,000 population

*authors contributed equally

H. Asseburg • S. Hagl • G.P. Eckert (✉)
Nutritional Neuroscience Group, Department of Pharmacology, Goethe-University, Biocenter N260, R1.09, Max-von-Laue Str. 9, Frankfurt 60438, Germany
e-mail: gunter.eckert@nutritional-neuroscience.com

G. Folkerts and J. Garssen (eds.), *Pharma-Nutrition*, AAPS Advances in the Pharmaceutical Sciences Series 12, DOI 10.1007/978-3-319-06151-1_23,

[29], with no substantial variations across continents, except Africa [100]. The incidence rate of dementia increases exponentially, doubling approximately every 5–6 years with age and incidence rates of dementia are quite similar across regions [100, 101, 148]. The largest increase in absolute numbers of old persons will occur in developing countries [100]. Thus, the global trend in the phenomenon of population aging has dramatic consequences on public health, health-care financing, and health care delivery systems in the world [100].

3 Alzheimer's disease: A Devastating Neurodegenerative Disorder

The clinical symptoms of Alzheimer' disease (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 [6]. Such defects are mainly observed in the later stage of the disease and have also been partially demonstrated using transgenic animal models of AD [71, 118].

AD is considered as a protein aggregation disorder, based on two key neuropathological hallmarks. One hallmark is the hyperphosphorylation of the tau protein, resulting in the formation of neurofibrillary tangles (NFTs), and the second hallmark is the increased formation and accumulation of amyloid-beta peptide (Aβ) oligomers and fibrils derived from amyloid precursor protein (APP) [42]. 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 [90].

4 Mitochondrial Dysfunction: A Common Event in Brain Aging and Alzheimer's Disease

Increasing evidence suggests that mitochondrial dysfunction plays an important role in brain aging and in the pathogenesis of neurodegenerative diseases, including AD [24, 48, 78, 82, 83, 86, 116, 135, 141]. Mitochondria are complex, network-forming organelles, involved in different metabolic pathways, e.g., citric acid cycle (TCA), energy transformation, amino-acid metabolism, and urea cycle [95]. Mitochondria consist of inner and outer membranes composed of phospholipid bilayers and proteins. The inner mitochondrial membrane harbors 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 system 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 [13, 124].

Alterations of mitochondrial efficiency and function are mainly related to alterations in mitochondrial mass, amount of respiratory enzymes, or changes in enzyme activities [11, 34, 65, 98]. 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) [91].

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 defense mechanisms, i.e., anti-oxidative molecules (e.g., glutathione (GSH) or vitamin E) and antioxidant enzymes (e.g., superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione reductase), as long as ROS levels are in the physiological range. Furthermore, slight uncoupling of the ETS, e.g., by uncoupling proteins, may also reduce ROS production. Low levels of ROS are produced constantly which might have physiological functions as signaling molecules [38]. Functional failure of this system can lead to deleterious effects, which may exaggerate the consequences of mitochondrial dysfunction [46]. Insufficient defense mechanisms and excessive ROS production (e.g., as superoxide anions) can lead to cell damage. The major sources of superoxide anions are redox centers 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 [13, 69, 92]. Its transformation into hydrogen peroxide and hydroxyl radicals, as well as its participation in the formation of peroxynitrate, creates strong oxidants [31].

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 [46, 90]. 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.

Early defects in the expression of several subunits of respiratory system chain complexes [106], 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 [59, 73, 106, 141]. 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 [5, 37, 58]. Aside from APP, Aβ itself has also been suggested to affect mitochondrial function (Fig. 23.1). Data

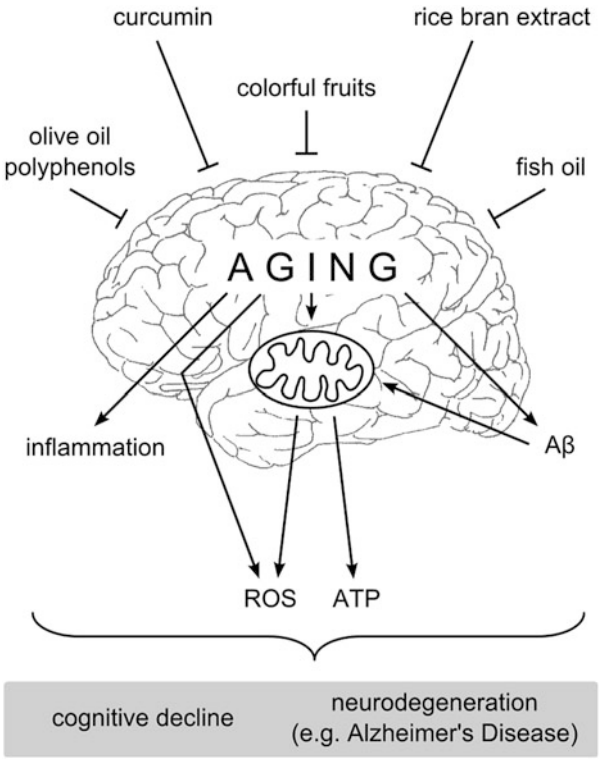


Fig. 23.1 Increasing evidence suggests that mitochondrial dysfunction plays an important role in brain aging and in the pathogenesis of neurodegenerative diseases. Dysfunction of single complexes of the respiratory system are frequently accompanied by deleterious side effects, such as decreased adenosine triphosphate (ATP) levels, but also production of reactive oxygen species (ROS). Direct effects of Aβ peptides on mitochondrial function may induce early mitochondrial dysfunction and explain the impaired energy metabolism in models of AD. Physiological changes that occur during the normal aging of the brain may be exacerbated in vulnerable populations of neurons, initiating pathological processes that finally lead to neurodegenerative disorders. Rice bran, curcumin, anthocyanin-rich fruits, and olive polyphenols represent promising nutraceuticals for modulating mitochondrial function in the brain

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 [45].

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 (Fig. 23.1) [73]. 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 hyper-phosphorylated Tau protein on the mitochondrial level [59].

5 Brain Aging, 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, in the form of either ready-made building blocks or precursors [55]. 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 [137]. 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 [97]. At the same time, however, human aging beyond 50 years of age is typically accompanied by the occurrence of one, often more, chronic, age-related diseases, such as cancer, cardio-vascular dieseases, and neurodegeneration [14, 32]. Due to its physiological characteristics, the brain is particularly prone to damage induced by noxious changes or fluctuations in cellular homeodynamics [103, 111]. 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 defense against infectious microorganisms, with the aim of increasing a plant's chances for reproduction and survival [60].

In the following sections we discuss rice bran, curcumin, anthocyanin-rich fruits, and olive polyphenols as promising nutraceuticals for modulating mitochondrial function in the brain (Fig. 23.1).

5.1 Rice Bran

With an annual worldwide production of over 600 tons in 2006, rice is one of the most important staple foods, especially in Asian countries. The outer layer of the rice grain is called rice bran and is removed during the rice milling process to produce white rice. As a by-product of the rice milling process, rice bran has an annual production rate of 40–70 million tons per year and usually is used as animal food [28, 53]. Since rice bran contains the enzyme lipase which quickly renders the bran rancid and inedible it has to be stabilized before using it as human aliment, for example in the form of oils and extracts as health food products [53].

Key components of the rice bran are tocopherols, tocotrienols (Fig. 23.2), and γ-oryzanol. Known beneficial health effects of rice bran include anti-inflammatory, cholesterol-lowering, antioxidant, and antidiabetic effects [3, 18, 57, 72]. We recently found that a stabilized rice bran extract (RBE) also improves brain mitochondrial function in guinea pigs by increasing mitochondrial content and resistance against oxidative and nitrosative stress [43]. Therefore, RBE might be a suitable substance for the prevention of mitochondrial dysfunction seen in brain aging and neurodegenerative diseases like AD.

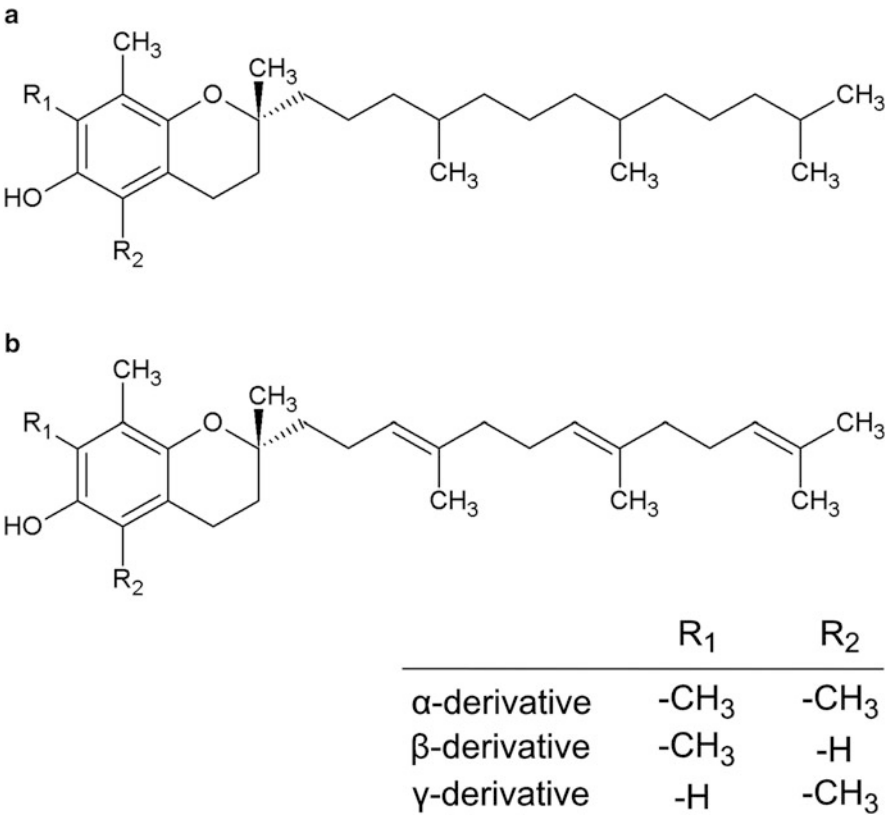


Fig. 23.2 Chemical structure of α-, β-, and γ-tocopherol (**a**) and tocotrienol (**b**)

Tocopherols and tocotrienols are ingredients of rice bran and very likely play an important role in mediating the above mentioned health-promoting effects [21, 30]. In micromolar concentrations, tocopherols as well as tocotrienols act as radical scavengers that react with free radicals to produce less reactive radicals, thus for example preventing lipid peroxidation in membranes and lipoproteins [96, 144]. At a concentration of 5 μM, a tocotrienol-rich fraction from palm oil was, for example, able to inhibit oxidative damage in lipids and proteins from rat brain mitochondria induced by ascorbate-Fe^{2+}, the free radical initiator azobis(2-amidopropane) dihydrochloride (AAPH) and photosensitization [54]. Supplementary vitamin E also prevented mitochondrial dysfunction in rat liver perfused with tert-butylhydroperoxide to induce lipid peroxidation by decreasing oxidative stress [44]. Altogether, tocotrienols seem to be better antioxidants than tocopherols, probably due to their faster recycling and better membrane distribution [113, 117]. Micromolar concentrations of tocopherols and tocotrienols that show antioxidative effects can usually not be reached in plasma and brain tissue by means of oral administration. On the other hand it has been reported that nanomolar

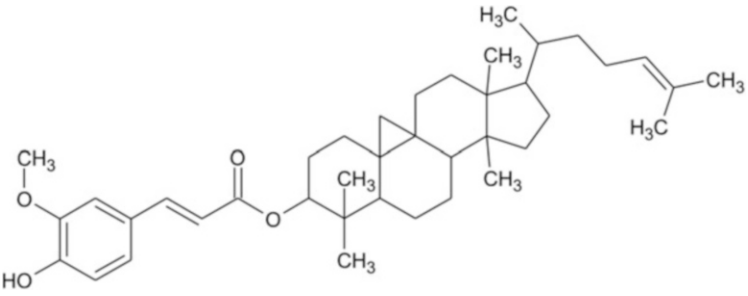


Fig. 23.3 Chemical structure of cycloartenyl ferulate, an exemplary member of the γ-oryzanol family which is a mix of ferulic acid esters of triterpene alcohol and phytosterols

concentrations of tocotrienols are sufficient to exert neuroprotective effects since they are able to modify several enzymes and signaling pathways in brain cells. Nanomolar concentrations of tocotrienols can be reached in human plasma after tocotrienol supplementation [30]. Among the cellular targets of tocotrienols are prenyl transferases [146], phospholipase A2 [61], 12-lipoxygenase [62], and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells) [35, 129].

Vitamin E has also been reported to directly interact with mitochondria [81], another possible mechanism for the neuroprotective potential of vitamin E. Dietary supplementation of rats with vitamin E (2.0 or 5.0 g/kg of food) for 3 months, for example, restored the age-dependent decrease in mitochondrial respiration and prevented an increase in oxidation products [93]. These effects are comparable to the increase in mitochondrial function seen in guinea pigs fed with RBE for 3 weeks [43], indicating that vitamin E at least partly accounts for the mitochondria-protective effects of RBE.

Another key ingredient of rice bran is γ-oryzanol, a mix of ferulic acid esters of triterpene alcohol and phytosterols (Fig. 23.3) [72]. Antitumoral as well as antioxidant properties (e.g., inhibition of lipid peroxidation) and the lowering of blood cholesterol levels are the main known biological effects of γ-oryzanol [3, 64, 99]. Since γ-oryzanol is not water-soluble, it has a very low bioavailability when orally administered [63]. It is largely de-ferulated in the gut [12], but no enhanced ferulic acid concentrations could be detected in plasma after oral administration of RBE to guinea pigs [43], confirming the low bioavailability.

We found that RBE enhances mitochondrial function by increasing mitochondrial content via activation of the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) [43]. One activator of PGC-1α is AMP-activated kinase (AMPK) which is, amongst others, induced by certain polyphenols, including resveratrol [77]. Therefore, it seems likely that RBE contains polyphenols or similar compounds able to activate PGC-1α. Identification of these compounds will have to be the subject of further upcoming studies.

Due to the observed beneficial effects of its main ingredients on neurons and the beneficial effects of RBE on mitochondrial function, rice bran appears to be a very

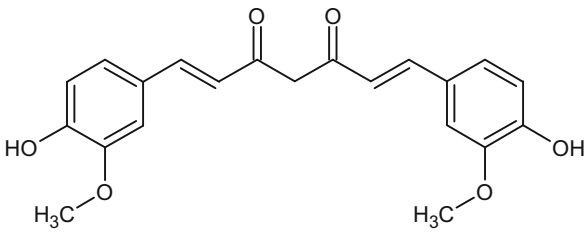


Fig. 23.4 Chemical structure of curcumin (keto form)

promising substance for the long-term prevention of neurodegeneration and the development of neurodegenerative diseases. Further studies need to be accomplished to examine the effects of rice bran administration in aging and neurodegenerative conditions.

5.2 Curcumin

Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are derived from the rhizome of the plant *curcuma longa* (Fig. 23.4). This plant has long been known as a spice, a dye, and a remedy especially in Asian countries before it became generally and worldwide common as main ingredient of curry powder. Apart from the use as spice, curcumin is also applied as food additive (E100) and a pigment in textile and cosmetic industry [27]. Curcumin has been associated with various beneficial health effects, among them antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, wound-healing, and anticancer properties [1, 40, 149]. Additionally curcumin has been shown to inhibit Aβ aggregation and reduce amyloid plaque burden in transgenic mouse models of AD [10, 75]. Taking all these effects into account, curcumin is assumed to have potential to act against various chronic diseases like diabetes, allergies, arthritis, and AD [1].

Epidemiologic evidence suggests that regular curry consumption decreases AD risk in elderly people. The Indo-US Study compared AD incidence rates in a rural, population-based cohort in India to those of a reference US population in Pennsylvania and found that AD incidence rates in India, where people consume curry spice on a daily basis, are much lower than those in the USA [16]. Ng and coworkers reported that regular curry consumption is correlated with better cognitive function in non-demented elderly Asians [94].

The antioxidative and anti-inflammatory effects of curcumin as well as its ability to inhibit protein aggregation seem to be the most important properties for the potential of curcumin against neurodegenerative diseases [22]. A lot of preclinical in vitro and in vivo studies have been accomplished to verify the beneficial effects of curcumin in neurotoxicity and AD. Apart from the reduction of amyloid plaque formation, curcumin also decreased oxidative injury, DNA damage, cytokine formation and memory deficits in mouse and rat models of AD [20, 22]. In a

homocysteine-induced rat neurotoxicity model, i.p. curcumin treatment (5 and 50 mg/kg body weight) for 10 days led to a significant decrease in malondialdehyde and superoxide anion levels, rescued hippocampal cells, and improved learning and memory [8]. In an Alzheimer transgenic APPsw mouse model (Tg2576), 6 month curcumin administration via a pelleted diet (160 and 5,000 ppm) decreased oxidized protein and interleukin-1β content in the brain. Insoluble and soluble Aβ concentrations as well as plaque burden were decreased in mouse brains by low-dose curcumin administration [75].

Curcumin has been shown to have beneficial effects on mitochondrial function, for example by inhibiting lipid peroxidation and protein oxidation in rat liver mitochondria [142]. It further counteracted *tert*-butyl hydroperoxide (t-BHP)-induced oxidative damage in rat cortical neurons by rescuing mitochondrial membrane potential, decreasing cytochrome c release and preventing apoptosis [147]. In the brains of streptozotocin-induced diabetic rats, activities of respiratory complexes I and IV were downregulated, and ATP levels were reduced. Curcumin administration to these rats (120 mg/kg bw p.o. for 4 weeks) rescued respiratory enzyme complex activities and restored ATP levels [102]. We recently showed that 5 month feeding of curcumin (500 mg curcumin per kg diet) was able to compensate mitochondrial dysfunction in a mouse model of accelerated aging. Thereby curcumin elevated the mitochondrial membrane potential, ATP levels, restored mitochondrial fusion processes, and elevated protein levels of PGC1α [25]. Since mitochondrial dysfunction plays a major role in aging as well as in the development of neurodegenerative diseases, this mechanism of action of curcumin might very well contribute to the observed beneficial effects of curcumin on neurodegeneration. Various in vitro and in vivo studies have also reported beneficial effects of curcuminoids in chemically induced cell culture and rodent models of Parkinson's Disease (summarized by [22]).

Molecular mechanisms of action of curcumin mainly comprise its activity as radical scavenger, its antioxidant and anti-inflammatory effects mediated through nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and NF-κB as well as epigenetic modulations. Due to its chemical structure, curcumin is a potent scavenger of free radicals [2, 133]. Additionally, curcumin also exerts antioxidant effects by activating Nrf2, a transcription factor that controls the expression of antioxidant and phase-II enzymes, for example heme oxygenase and glutathione synthesis enzymes [109, 145]. By diminishing ROS production via radical scavenging and upregulation of antioxidative enzymes, curcumin contributes to keeping oxidative stress in the cell low, thus amongst others protecting mitochondrial function [102, 125]. Curcumin inhibits NF-κB, a transcription factor controlling the expression of pro-inflammatory molecules (e.g., cytokines) [52, 56, 128]. In conditions of neurodegeneration or AD, microglia in the brain become activated and produce pro-inflammatory responses via NF-κB [84]. Curcumin is able to inhibit these inflammatory responses in microglia cells, thus contributing to the prevention of neurodegeneration and AD development [49, 139].

Despite these very promising in vitro and in vivo results, no clinical studies testing curucmin in MCI or AD patients have reported positive outcome so far. Two

24-week intervention studies with patients with possible/probable or mild to moderate AD receiving curcumin doses up to 4 g/day reported no changes in clinical or biomarker measures between the study groups [9, 107]. Probable reasons might be the choice of subjects or the low bioavailability of curcumin. The best time for prevention in sporadic AD is the preclinical stage when neurodegeneration has already started but no clinical symptoms have yet occurred [136]. Therefore, neurodegeneration might have been too far advanced in the subjects included in these studies to be able to detect positive curcumin effects. Phase I clinical trials have proven that curcumin is well tolerated even in high doses (up to 12 g), but oral bioavailability is very low (plasma levels often below 1 μM) [27]. Curcumin concentrations in the brains of mice were in the low ng/g tissue range 45 min after oral administration of 120 mg curcumin/kg body weight (unpublished data). Probable reasons for the low bioavailability are poor absorption, rapid metabolism, and rapid systemic elimination of curcumin [4, 17].

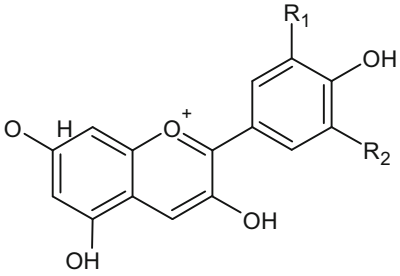
To increase curcumin bioavailability, several different approaches have been pursued. One is the simultaneous administration of other secondary plant compounds like piperine which inhibit hepatic and intestinal metabolism of curcumin and are able to increase curcumin bioavailability significantly [120]. Other approaches comprise the production of curcumin nanoparticles or liposome-encapsulated curcumin [70, 130]. We recently showed that administration of curcumin micelles (AquaNova, Darmstadt, Germany) for 45 min increased curcumin plasma concentrations 50-fold in C57BL/6 mice, curcumin brain concentrations were increased sixfold (unpublished data).

Altogether, curcumin appears to be a promising food ingredient to help in the prevention of neurodegeneration seen in aging and, for example, in Alzheimer's Disease. To display its protective effects, data from clinical and epidemiological studies suggest that curcumin might have to be administered over an extended period of time starting before the onset of clinical symptoms of neurodegeneration. This long-term preventive effect of curcumin will have to be proven in upcoming clinical trials.

5.3 Anthocyanin-Rich Fruits

In the last decade, colorful fruits have emerged as potential neuroprotective food components. Many animal intervention studies with blueberry, blackberry, strawberry, mulberry, Concord grape, and pomegranate provide evidence of the beneficial effects of colorful fruits on aging (especially on age-related cognitive and motor decline) and neurodegeneration. Anthocyanins, a flavonoid subgroup (Fig. 23.5) with high antioxidant potential, are responsible for the characteristic bright colors in these fruits and may also account at least in part for their neuroprotective activity [110, 140].

In the late nineties, James Joseph and colleagues showed that feeding diets with high antioxidant potential might prevent and even reverse age-related deficits in motor and cognitive behavior in Fischer 344 (F344) rats. However, although based



	R_1	R_2
pelargonidin	H	H
cyanidin	OH	H
peonidin	OCH_3	H
delphinidin	OH	OH
petunidin	OCH_3	OH
malvidin	OCH_3	OCH_3

Fig. 23.5 Basic structure of anthocyanin aglycone and substituents of the 6 main structures found in food. In plant material anthocyanins are usually present as 3-glycoside and 3′ 5-glycoside [19]

on equal antioxidant activity, the supplementations with blueberry and strawberry did not lead to the same improvement in behavioral performance. Blueberry supplementation ameliorated both motor and cognitive performance, whereas strawberry supplementation only led to an improvement in motor performance suggesting that simple antioxidant activity is not the sole explanation for the neuroprotective activity [51]. To date, the theory that flavonoids like anthocyanins exert their effects by direct scavenging of reactive-oxygen-species (ROS) is more and more replaced by the assumption that they act by indirect antioxidant activity and activation of signaling pathways [7, 112]. Supporting evidence for this theory comes from bioavailability studies that often report <0.1 % recovery of ingested anthocyanins in the urine [88, 110]. Like all polyphenols, anthocyanins are subject to various degradation and biotransformation processes leading to a variety of metabolites in the human body. Moreover, to exert direct effects in the brain anthocyanins also have to cross the blood–brain barrier (BBB) separating the CNS from the body periphery. Feeding studies with rodents and pigs have been shown that anthocyanins are able to cross the BBB. After 15 days of supplementation with blackberry extract [131] and 2 h of administration of the anthocyanidin pelargonidin (50 mg/body weight) [26], 0.25 nmol anthocyanins/g and 0.16 nmol pelargonidin/g tissue, respectively, were detected in rat brain. Moreover, data from pigs suggest that anthocyanins may accumulate in brain tissue. After a feeding period with 1–4 % blueberries for 4 weeks, fasted pigs showed anthocyanin concentration of about 0.3–0.4 ng/g tissue in the brain but not in plasma or urine. However, there is a lack of data concerning the presence of anthocyanin metabolites which are suggested to account at least in part for the in vivo effects of anthocyanin-rich fruits [110].

Regarding neuroprotection, the most extensively studied anthocyanin-rich diet in rodents is the 2 % blueberry-supplemented diet which led to improvements in cognitive and motor performance of aged rats or models of increased oxidative stress or inflammation [15, 23, 36, 105, 122]. The recent work by Rendeiro and colleagues strengthens the theory that the containing flavonoids represent causal

neuroprotective agents in the blueberry diet. Purified blueberry anthocyanins in equivalent doses to the whole blueberry extract led to the same improvement of spatial working memory performance as whole blueberry-diet [105]. Several other anthocyanin-rich fruits have shown to have a beneficial impact on behavioral performance of rodents. However, there seem to be differences in the activity that might be fruit or flavonoid specific as well as concentration-dependent. For example, Concord grape juice in a concentration of 10 % in drinking water improved cognitive performance in aged F344 rats whereas a concentration of 50 % of the juice ameliorated motor function [121]. 2 % blueberry and 2 % strawberry extract diets protected differently from ^{56}Fe particle irradiation which induces oxidative stress, inflammation and behavioral deficits similar to those seen in aging. Strawberry-supplemented rats had a better ability to retain place information (reduced spatial deficits) linked to hippocampus-mediated behavior, blueberry-supplemented rats, in contrast, showed improved reversal learning which is more dependent on intact striatal function [122]. Nevertheless, a recent study showed that ^{56}Fe particle irradiation causes downregulation of genes involved in protective stress signaling which could be ameliorated by blueberry- or strawberry-supplemented diets to a similar extent [123].

A great deal of research has concentrated on the impact of berry fruits and flavonoids on signaling cascades (reviewed in [89, 126]). In this regard, studies on the mechanism of cognitive effects of blueberry diet in rats revealed an involvement of neurogenesis, neurotrophic factor insulin-like growth factor-1 (IGF-1) and its receptor, as well as mitogen-activated protein (MAP) kinase signal transduction [15]. Grape powder in drinking water of rats (15 g/L) prevented the L-buthionine-(S,R)-sulfoximine induced oxidative stress and cognitive impairment as well as prevented the activation of brain extracellular signal-regulated kinase-1/2 (ERK-1/2) and decrease of glyoxalase-1 (GLO-1), glutathione reductase-1 (GSR-1), calcium/calmodulin-dependent protein kinase type IV (CAMK-IV), cAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF) levels [150]. Research also concentrated on the effects of purple sweet potato color (PSPC) which is composed of a mixture of anthocyanins. PSPC (100 mg/kg) attenuated D-galactose-induced aging related changes in mouse brain after oral administration for 4 weeks. The improvement of behavioral performance was accompanied by an enhanced activity of the antioxidant enzymes copper/zinc superoxide dismutase and catalase, less oxidative brain damage measured as malondialdehyde, and diminished parameters related to neuroinflammation (e.g., nuclear translocation of NF-κB) [118]. Further studies using this model also revealed the ability of PSPC to counteract the onset of neuronal apoptosis by promoting survival mechanisms which involves ERK 1/2, phosphoinositide 3-kinase (PI3K), Akt, and c-Jun NH2-terminal kinase (JNK) [80]. Recently, PSPC (200 mg/kg for 4 weeks) has also been tested in a mouse model of cognitive impairment induced by hippocampal mitochondrial dysfunction in mice that were treated with the neurotoxin domoic acid. The study results suggest that better cognitive performance involved estrogen receptor-α-mediated mitochondrial biogenesis signaling, restored mitochondrial dysfunction, decreased ROS and

protein carbonyl levels, and suppressed endoplasmic reticulum stress-induced apoptosis [79]. Further evidence for the amelioration of mitochondrial dysfunction is provided by a study with anthocyanins from grape skin in rats with transient memory impairment and mitochondrial dysfunction induced by scopolamine. The i.p. treatment with 200 mg/kg grape skin anthocyanins reversed the impairment of memory and restored ATP levels in hippocampus and cerebral cortex [41]. Mitochondrial dysfunction has also been investigated in cell cultures treated with protocatechuic acid, a well-known metabolite of the anthocyanidin cyanidin, which has been detected in the bloodstream of humans [138] and rats [134] after consumption of cyanidin glucoside/cyanidin-glucoside-rich foods. Protocatechuic acid was effective to decrease mitochondrial dysfunction and apoptotic cell death induced by rotenone [39] and 1-methyl-4-phenylpyridinium ion [76] in the neuronal-like cell line PC 12. Moreover, treatment of human neuroblastoma SK-N-MC cells with metabolites obtained from in vitro digestion of wild blackberry extract was effective in diminishing ROS, modulating GSH and maintaining high mMP at levels approaching concentrations that are described for human plasma [132].

Mitochondrial dysfunction, oxidative stress, and inflammation occur not only in aging but also in age-related neurodegenerative changes (Fig. 23.1). Slowing down or even preventing aging processes in the brain by nutritional approaches might therefore as well contribute to the prevention of neurodegenerative diseases like Alzheimer's disease. Anthocyanin-rich fruits have a beneficial in mouse models of AD. In amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice diet supplementation with 2 % blueberry extract from 4 months of age prevented behavioral deficits assessed at 12 months of age as well as enhanced memory-associated neuronal signaling. No changes in Aβ burden were observed [50]. However, less accumulation of soluble Aβ42 and amyloid deposition was observed in the hippocampus of APP transgenic mice after the treatment with pomegranate juice concentrate in drinking water (1:80 or 1:160 dilution) for 6.5 months [47]. In APP/PS1 transgenic mice drinking water supplemented with pomegranate extract (6.25 mL/L) for 3 months led to improved spatial learning and memory, decreased Aβ plaque load, reduced microgliosis as well as lowered tumor necrosis factor a (TNF-α) concentrations and nuclear factor of activated T-cell (NFAT) transcriptional activity [108]. Additionally, 0.18 or 0.9 % mulberry extract supplemented diet for 3 months led to a decreased accumulation of Aβ as well as higher antioxidant enzyme activity and less lipid oxidation in the brain of senescence-accelerated mouse prone 8 (SAMP8) mice [119].

Importantly, preliminary studies in older adults with mild cognitive impairment (MCI) show beneficial effects of Concord grape and blueberry juice [66–68]. MCI is the first clinical appearance of neurodegeneration accompanied by increased risk for dementia. In many individuals MCI progresses to AD. The consumption of wild blueberry juice (6 and 9 mL/kg) for 12 weeks improved paired associate learning in the Verbal Paired Associate Learning Test (V-PAL) and word list recall in the California Verbal Learning Test (CVLT) in 9 older adults with MCI [68]. In a similar study 12 older adults with MCI showed improved verbal learning in CVLT

and a trend toward improved performance with respect to delayed verbal recall and spatial memory after the consumption of Concord grape juice (6 and 9 mL/kg) for a period of 12 weeks [67]. Recently, Concord juice treatment of MCI individuals for 16 weeks reduced semantic interference on memory tasks and led to a relatively greater activation in anterior and posterior regions of the right hemisphere detected using functional magnetic resonance imaging [66].

5.4 Olive Oil Polyphenols

Olive oil is a typical component of Mediterranean diets which have been related to many health beneficial effects including the improvement of cognitive decline. Interestingly, the health benefits of extra virgin olive oil (EVOO) seem to be not only due to its high amount of mono-unsaturated fatty acids but also due to phenolic minor components such as hydroxytyrosol [110]. The phenols present in the native olive fruit differ from those in EVOO. Olives mainly contain the glycosides oleuropein and ligstroside that are degraded to their aglycones and various derivates during ripening. The aglycones and derivates are the most abundant phenols in olive oil. Hydroxytyrosol and tyrosol are the end products of the hydrolysis of those aglycones in olive oil (Fig. 23.6) [154].

Recently, EVOO showed beneficial effects in SAMP8 mice, a model of age-related learning/memory impairment associated with increased amyloid-β protein and brain oxidative damage [151]. The oral administration of EVOO (75 μL/kg body weight) for 6 weeks improved cognitive function and oxidative brain damage in aged SAMP8 mice. Interestingly, mice that received EVOO with enhanced amount of olive oil polyphenols showed a greater improvement in both cognitive function and oxidative damage than mice that received regular EVOO [151]. Additionally, mice treated with EVOO (10 % wt/wt dry diet) rich in phenols (6 mg/kg polyphenols/day) from middle age to senescence had improved contextual memory in the step-down test and a better performance in motor coordination in the rotarod test [152].

Data from human and animal studies indicate that olive oil phenols are well absorbed and underlie biotransformation processes common for polyphenols in general [154]. As *ortho*-diphenol, hydroxytyrosol contributes significantly to the oxidation stability of olive oil and is attracting particular attention as antioxidant [154, 110]. However, the intake of phenols in the amounts provided by dietary olive oil is suggested to be too low for direct antioxidant activity in the human body [154]. Several studies therefore concentrated on hydroxytyrosol-rich extracts. Importantly, conjugated hydroxytyrosol was detected in brain tissue of rats (50 nmol/g) after a single dose of a phenolic extract of olive cake (3 g/kg body weight) [153]. An interesting source of hydroxytyrosol is olive mill water waste which is currently discarded. Olive mill water waste is very rich in polyphenols that can be recovered by ad hoc techniques [110]. Hydroxytyrosol-rich extract, prepared from olive mill water waste administrated to mice (100 mg/kg) for 12 days led to a

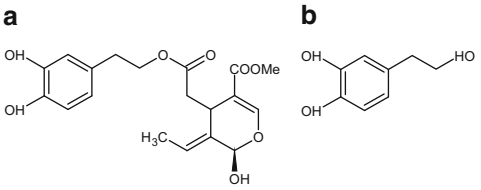


Fig. 23.6 Olive oil phenols (**a**) Oleuropein aglycone (**b**) Hydroxytyrosol

moderate, although statistically significant hyperpolarization of mitochondria in dissociated mouse brain cells [115] which is an effect that has been related to a decreased rate of cell death [74]. Moreover, hydroxytyrosol-rich extract was effective to reduce iron-stimulated lipid peroxidation ex vivo, suggesting a neuroprotective effect of hydroxytyrosol intake [115]. Recent in vitro data mainly confirm our previous observation of promising cytoprotection of brain cells by HT-rich olive mill waste water extract in different stressor paradigms [114]. Furthermore, correlation analyses revealed that the observed cytoprotective effects in PC12 cells are likely due to HT present in the extract.

In summary, aging of the brain is characterized by a decline in several physiological abilities, including sensory, motor, and cognitive functions. Physiological changes that occur during normal aging of the brain may be exacerbated in vulnerable populations of neurons, initiating pathological processes that finally lead to neurodegenerative disorders, especially to AD. The incidence rate of AD increases exponentially, doubling approximately every 5–6 years with age. The global trend in the phenomenon of population aging has dramatic consequences on public health, health-care financing, and health care delivery system in the world, especially in developing countries. Increasing evidence suggests that mitochondrial dysfunction plays an important role in brain aging and in the pathogenesis of neurodegenerative diseases. 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. Rice bran, curcumin, anthocyanin-rich fruits, and olive polyphenols are promising nutraceuticals for modulating mitochondrial function in the brain and might contribute to the prevention of AD.

References

1. Aggarwal BB, Sundaram C, Malani N, Ichikawa H (2007) Curcumin: the Indian solid gold. Adv Exp Med Biol 595:1–75
2. Ak T, Gülçin İ (2008) Antioxidant and radical scavenging properties of curcumin. Chem Biol Intera 174:27–37
3. Akihisa T, Yasukawa K, Yamaura M, Ukiya M, Kimura Y, Shimizu N, Arai K (2000) Triterpene alcohol and sterol ferulates from rice bran and their anti-inflammatory effects. J Agri Food Chem 48:2313–2319

4. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB (2007) Bioavailability of curcumin: problems and promises. Mol Pharma 4:807–818
5. Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG (2003) Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. J Cell Biol 161:41–54
6. Arendt T (2009) Synaptic degeneration in Alzheimer's disease. Acta Neuropathol 118:167–179
7. Arumugam TV, Gleichmann M, Tang SC, Mattson MP (2006) Hormesis/preconditioning mechanisms, the nervous system and aging. Aging Res Rev 5:165–178
8. Ataie A, Sabetkasaei M, Haghparast A, Moghaddam AH, Ataee R, Moghaddam SN (2010) Curcumin exerts neuroprotective effects against homocysteine intracerebroventricular injection-induced cognitive impairment and oxidative stress in rat brain. J Med Food 13:821–826
9. Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J, Lam L, Leung V, Hui E, Ng C, Woo J, Chiu HF, Goggins WB, Zee BC, Cheng KF, Fong CY, Wong A, Mok H, Chow MS, Ho PC, Ip SP, Ho CS, Yu XW, Lai CY, Chan MH, Szeto S, Chan IH, Mok V (2008) Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. J Clin Psychopharm 28:110–113
10. Begum AN, Jones MR, Lim GP, Morihara T, Kim P, Heath DD, Rock CL, Pruitt MA, Yang F, Hudspeth B, Hu S, Faull KF, Teter B, Cole GM, Frautschy SA (2008) Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. J Pharmacol Exp Ther 326:196–208
11. Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK, Perry RH, Jaros E, Hersheson JS, Betts J, Klopstock T, Taylor RW, Turnbull DM (2006) High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nat Genet 38:515–517
12. Berger A, Rein D, Schafer A, Monnard I, Gremaud G, Lambelet P, Bertoli C (2005) Similar cholesterol-lowering properties of rice bran oil, with varied gamma-oryzanol, in mildly hypercholesterolemic men. Eur J Nutr 44:163–173
13. Brand MD, Affourtit C, Esteves TC, Green K, Lambert AJ, Miwa S, Pakay JL, Parker N (2004) Mitochondrial superoxide: production, biological effects, and activation of uncoupling proteins. Free Radic Biol Med 37:755–767
14. Brody JA, Schneider EL (1986) Diseases and disorders of aging: an hypothesis. J Chronic Dis 39:871–876
15. Casadesus G, Shukitt-Hale B, Stellwagen HM, Zhu X, Lee H-G, Smith MA, Joseph JA (2004) Modulation of hippocampal plasticity and cognitive behavior by short-term blueberry supplementation in aged rats. Nutr Neurosci 7:309–316
16. Chandra V, Pandav R, Dodge HH, Johnston JM, Belle SH, DeKosky ST, Ganguli M (2001) Incidence of Alzheimer's disease in a rural community in India: the Indo-US study. Neurol 57:985–989
17. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, Ko JY, Lin JT, Lin BR, Ming-Shiang W, Yu HS, Jee SH, Chen GS, Chen TM, Chen CA, Lai MK, Pu YS, Pan MH, Wang YJ, Tsai CC, Hsieh CY (2001) Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 21:2895–2900
18. Cicero AF, Derosa G (2005) Rice bran and its main components: potential role in the management of coronary risk factors. Curr Top Neutraceutical Res 3:29–46
19. Clifford MN (2000) Anthocyanins – nature, occurrence and dietary burden. J Sci Food Agri 80:1063–1072
20. Cole GM, Teter B, Frautschy SA (2007) Neuroprotective effects of curcumin. Adv Exp Med Biol 595:197–212
21. Colombo ML (2010) An update on vitamin E, tocopherol and tocotrienol-perspectives. Molecules 15:2103–2113

22. Darvesh AS, Carroll RT, Bishayee A, Novotny NA, Geldenhuys WJ, van der Schyf CJ (2012) Curcumin and neurodegenerative diseases: a perspective. Exp Opin Investig Drugs 21:1123–1140
23. Duffy KB, Spangler EL, Devan BD, Guo Z, Bowker JL, Janas AM, Hagepanos A, Minor RK, DeCabo R, Mouton PR, Shukitt-Hale B, Joseph JA, Ingram DK (2008) A blueberry-enriched diet provides cellular protection against oxidative stress and reduces a kainate-induced learning impairment in rats. Neurobiol Aging 29:1680–1689
24. Eckert GP, Renner K, Eckert SH, Eckmann J, Hagl S, Abdel-Kader RM, Kurz C, Leuner K, Muller WE (2012) Mitochondrial dysfunction – a pharmacological target in Alzheimer's disease. Mol Neurobiol 46:136–150
25. Eckert GP, Schiborr C, Hagl S, Abdel-Kader R, Muller WE, Rimbach G, Frank J (2013) Curcumin prevents mitochondrial dysfunction in the brain of the senescence-accelerated mouse - prone 8. Neurochem Int 62:595–602
26. El Mohsen MA, Marks J, Kuhnle G, Moore K, Debnam E, Kaila Srai S, Rice-Evans C, Spencer JP (2006) Absorption, tissue distribution and excretion of pelargonidin and its metabolites following oral administration to rats. Br J Nutr 95:51–58
27. Esatbeyoglu T, Huebbe P, Ernst IMA, Chin D, Wagner AE, Rimbach G (2012) Curcumin – from molecule to biological function. Angew Chem Int Ed Engl 51:5308–5332
28. Farrell DJ (1994) Utilization of rice bran in diets for domestic fowl and ducklings. World Poul Sci J 50:115–131
29. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M (2005) Global prevalence of dementia: a Delphi consensus study. Lancet 366:2112–2117
30. Frank J, Chin XW, Schrader C, Eckert GP, Rimbach G (2012) Do tocotrienols have potential as neuroprotective dietary factors? Aging Res Rev 11:163–180
31. Fukai T, Ushio-Fukai M (2011) Superoxide dismutases: role in redox signaling, vascular function, and diseases. Antiox Redox Sign 15:1583–1606
32. Fulop T, Larbi A, Witkowski JM, McElhaney J, Loeb M, Mitnitski A, Pawelec G (2010) Aging, frailty and age-related diseases. Biogeront 11:547–563
33. Genova ML, Pich MM, Bernacchia A, Bianchi C, Biondi A, Bovina C, Falasca AI, Formiggini G, Castelli GP, Lenaz G (2004) The mitochondrial production of reactive oxygen species in relation to aging and pathology. Ann NY Acad Sci 1011:86–100
34. Gimenez-Roqueplo AP, Favier J, Rustin P, Mourad JJ, Plouin PF, Corvol P, Rotig A, Jeunemaitre X (2001) The R22X mutation of the SDHD gene in hereditary paraganglioma abolishes the enzymatic activity of complex II in the mitochondrial respiratory chain and activates the hypoxia pathway. Am J Hum Gen 69:1186–1197
35. Glauert HP (2007) Vitamin E and NF-kappaB activation: a review. Vitam Horm 76:135–153
36. Goyarzu P, Malin DH, Lau FC, Taglialatela G, Moon WD, Jennings R, Moy E, Moy D, Lippold S, Shukitt-Hale B, Joseph JA (2004) Blueberry supplemented diet: effects on object recognition memory and nuclear factor-kappa B levels in aged rats. Nutr Neurosci 7:75–83
37. Grant SM, Shankar SL, Chalmers-Redman RM, Tatton WG, Szyf M, Cuello AC (1999) Mitochondrial abnormalities in neuroectodermal cells stably expressing human amyloid precursor protein (hAPP751). Neuroreport 10:41–46
38. Gruber J, Schaffer S, Halliwell B (2008) The mitochondrial free radical theory of aging – where do we stand? Front Biosci 13:6554–6579
39. Guan S, Jiang B, Bao YM, An LJ (2006) Protocatechuic acid suppresses MPP+-induced mitochondrial dysfunction and apoptotic cell death in PC12 cells. Food Chem Tox 44:1659–1666
40. Gupta SC, Prasad S, Kim JH, Patchva S, Webb LJ, Priyadarsini IK, Aggarwal BB (2011) Multitargeting by curcumin as revealed by molecular interaction studies. Nat Prod Rep 28:1937–1955
41. Gutierres JM, Carvalho FB, Schetinger MRC, Rodrigues MV, Schmatz R, Pimentel VC, Vieira JM, Rosa MM, Marisco P, Ribeiro DA, Leal C, Rubin MA, Mazzanti CM, Spanevello

R (2012) Protective effects of anthocyanins on the ectonucleotidase activity in the impairment of memory induced by scopolamine in adult rats. Life Sci 91:1221–1228
42. Haass C, Selkoe DJ (2007) Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol 8:101–112
43. Hagl S, Kocher A, Schiborr C, Eckert SH, Ciobanu I, Birringer M, El-Askary H, Helal A, Khayyal MT, Frank J, Muller WE, Eckert GP (2013) Rice bran extract protects from mitochondrial dysfunction in guinea pig brains. Pharmacol Res 76C:17–27
44. Ham AJ, Liebler DC (1997) Antioxidant reactions of vitamin E in the perfused rat liver: product distribution and effect of dietary vitamin E supplementation. Arch Biochem Biophys 339:157–164
45. Hansson CA, Frykman S, Farmery MR, Tjernberg LO, Nilsberth C, Pursglove SE, Ito A, Winblad B, Cowburn RF, Thyberg J, Ankarcrona M (2004) Nicastrin, presenilin, APH-1, and PEN-2 form active gamma-secretase complexes in mitochondria. J Biol Chem 279:51654–51660
46. Harper ME, Bevilacqua L, Hagopian K, Weindruch R, Ramsey JJ (2004) Aging, oxidative stress, and mitochondrial uncoupling. Acta Physiol Scand 182:321–331
47. Hartman RE, Shah A, Fagan AM, Schwetye KE, Parsadanian M, Schulman RN, Finn MB, Holtzman DM (2006) Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiol Dis 24:506–515
48. Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Vinters HV, Tabaton M, Shimohama S, Cash AD, Siedlak SL, Harris PL, Jones PK, Petersen RB, Perry G, Smith MA (2001) Mitochondrial abnormalities in Alzheimer's disease. J Neurosci 21:3017–3023
49. Jin C-Y, Lee J-D, Park C, Choi Y-H, Kim G-Y (2007) Curcumin attenuates the release of pro-inflammatory cytokines in lipopolysaccharide-stimulated BV2 microglia. Acta Pharma Sin 28:1645–1651
50. Joseph JA, Arendash G, Gordon M, Diamond D, Shukitt-Hale B, Morgan D, Denisova NA (2003) Blueberry supplementation enhances signaling and prevents behavioral deficits in an Alzheimer disease model. Nutr Neurosci 6:153–162
51. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC (1999) Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci 19:8114–8121
52. Jurenka JS (2009) Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev 14:141–153
53. Kahlon TS (2009) Rice bran: production, composition, functionality and food applications, physiological benefits. CRC Press, Boca Raton
54. Kamat JP, Devasagayam TP (1995) Tocotrienols from palm oil as potent inhibitors of lipid peroxidation and protein oxidation in rat brain mitochondria. Neurosci Lett 195:179–182
55. Kamphuis PJ, Scheltens P (2010) Can nutrients prevent or delay onset of Alzheimer's disease? J Alzheimers Dis 20:65–75
56. Kang G, Kong P-J, Yuh Y-J, Lim S-Y, Yim S-V, Chun W, Kim S-S (2004) Curcumin suppresses lipopolysaccharide-induced cyclooxygenase-2 expression by inhibiting activator protein 1 and nuclear factor kappab bindings in BV2 microglial cells. J Pharmcol Sci 94:325–328
57. Kaup RM, Khayyal MT, Verspohl EJ (2013) Antidiabetic effects of a standardized Egyptian rice bran extract. Phytother Res 27:264–271
58. Keil U, Bonert A, Marques CA, Scherping I, Weyermann J, Strosznajder JB, Muller-Spahn F, Haass C, Czech C, Pradier L, Muller WE, Eckert A (2004) Amyloid beta-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis. J Biol Chem 279:50310–50320

59. Keil U, Hauptmann S, Bonert A, Scherping I, Eckert A, Muller WE (2006) Mitochondrial dysfunction induced by disease relevant AbetaPP and tau protein mutations. J Alzheimer Dis 9:139–146
60. Kennedy DO, Wightman EL (2011) Herbal extracts and phytochemicals: plant secondary metabolites and the enhancement of human brain function. Adv Nutr 2:32–50
61. Khanna S, Parinandi NL, Kotha SR, Roy S, Rink C, Bibus D, Sen CK (2010) Nanomolar vitamin E alpha-tocotrienol inhibits glutamate-induced activation of phospholipase A2 and causes neuroprotection. J Neurochem 112:1249–1260
62. Khanna S, Roy S, Ryu H, Bahadduri P, Swaan PW, Ratan RR, Sen CK (2003) Molecular basis of vitamin E action: tocotrienol modulates 12-lipoxygenase, a key mediator of glutamate-induced neurodegeneration. J Biol Chem 278:43508–43515
63. Kim JS, Lee J-S, Chang P-S, Lee HG (2010) Optimization, in vitro release and bioavailability of gamma-oryzanol-loaded calcium pectinate microparticles reinforced with chitosan. New Biotech 27:368–373
64. Kim SP, Kang MY, Nam SH, Friedman M (2012) Dietary rice bran component gamma-oryzanol inhibits tumor growth in tumor-bearing mice. Mol Nutr Food Res 56:935–944
65. Kraytsberg Y, Kudryavtseva E, McKee AC, Geula C, Kowall NW, Khrapko K (2006) Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. Nat Genet 38:518–520
66. Krikorian R, Boespflug EL, Fleck DE, Stein AL, Wightman JD, Shidler MD, Sadat-Hossieny S (2012) Concord grape juice supplementation and neurocognitive function in human aging. J Agri Food Chem 60:5736–5742
67. Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA (2010) Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. Br J Nutr 103:730–734
68. Krikorian R, Shidler MD, Nash TA, Kalt W, Vinqvist-Tymchuk MR, Shukitt-Hale B, Joseph JA (2010) Blueberry supplementation improves memory in older adults. J Agrid Food Chem 58:3996–4000
69. Kudin AP, Bimpong-Buta NY, Vielhaber S, Elger CE, Kunz WS (2004) Characterization of superoxide-producing sites in isolated brain mitochondria. J Biol Chem 279:4127–4135
70. Kundu P, Mohanty C, Sahoo SK (2012) Antiglioma activity of curcumin-loaded lipid nanoparticles and its enhanced bioavailability in brain tissue for effective glioblastoma therapy. Acta Biomater 8:2670–2687
71. Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M, Viola KL, Klein WL (2007) Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. J Neurosci 27:796–807
72. Laokuldilok T, Shoemaker CF, Jongkaewwattana S, Tulyathan V (2011) Antioxidants and antioxidant activity of several pigmented rice brans. J Agri Food Chem 59:193–199
73. Leuner K, Schutt T, Kurz C, Eckert SH, Schiller C, Occhipinti A, Mai S, Jendrach M, Eckert GP, Kruse SE, Palmiter RD, Brandt U, Drose S, Wittig I, Willem M, Haass C, Reichert AS, Mueller WE (2012) Mitochondria-derived ROS lead to enhanced amyloid beta formation. Antioxid Redox Signal 16:1421–1433
74. Liang BC, Miller L, Weller A (1999) Ethyl-nitrosourea transformed astrocytes exhibit mitochondrial membrane hyperpolarization and constrained apoptosis. Apoptosis 4:89–97
75. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM (2001) The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 21:8370–8377
76. Liu Y-M, Jiang B, Bao Y-M, An L-J (2008) Protocatechuic acid inhibits apoptosis by mitochondrial dysfunction in rotenone-induced PC12 cells. Toxicol In Vitro 22:430–437
77. López-Lluch G, Irusta PM, Navas P, Cabo R (2008) Mitochondrial biogenesis and healthy aging. Exper Gerontol 43:813–819

78. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153:1194–1217
79. Lu J, Wu D-M, Zheng Y-l, Hu B, Cheng W, Zhang Z-F (2012) Purple sweet potato color attenuates domoic acid-induced cognitive deficits by promoting estrogen receptor–αmediated mitochondrial biogenesis signaling in mice. Free Rad Biol Med 52:646–659
80. Lu J, Wu DM, Zheng YL, Hu B, Zhang ZF (2010) Purple sweet potato color alleviates D-galactose-induced brain aging in old mice by promoting survival of neurons via PI3K pathway and inhibiting cytochrome C-mediated apoptosis. Brain Pathol 20:598–612
81. Majima HJ, Indo HP, Suenaga S, Matsui H, Yen H-C, Ozawa T (2011) Mitochondria as possible pharmaceutical targets for the effects of vitamin E and its homologues in oxidative stress-related diseases. Curr Pharm Des 17:2190–2195
82. Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH (2006) Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum Mol Gen 15:1437–1449
83. Manczak M, Park BS, Jung Y, Reddy PH (2004) Differential expression of oxidative phosphorylation genes in patients with Alzheimer's disease: implications for early mitochondrial dysfunction and oxidative damage. Neuromol Med 5:147–162
84. Mattson MP, Camandola S (2001) NF-kappaB in neuronal plasticity and neurodegenerative disorders. J Clin Invest 107:247–254
85. Mattson MP, Chan SL, Duan W (2002) Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. Physiol Rev 82:637–672
86. Mattson MP, Gleichmann M, Cheng A (2008) Mitochondria in neuroplasticity and neurological disorders. Neuron 60:748–766
87. Mattson MP, Magnus T (2006) Aging and neuronal vulnerability. Nat Rev Neurosci 7:278–294
88. McGhie TK, Walton MC (2007) The bioavailability and absorption of anthocyanins: towards a better understanding. Mol Nutr Food Res 51:702–713
89. Miller MG, Shukitt-Hale B (2012) Berry fruit enhances beneficial signaling in the brain. J Agri Food Chem 60:5709–5715
90. Muller WE, Eckert A, Kurz C, Eckert GP, Leuner K (2010) Mitochondrial dysfunction: common final pathway in brain aging and Alzheimer's disease – therapeutic aspects. Mol Neurobiol 41:159–171
91. Murphy MP (2009) How mitochondria produce reactive oxygen species. Biochem J 417:1–13
92. Murphy MP (2009) Mitochondria – a neglected drug target. Curr Opin Investig Drugs 10:1022–1024
93. Navarro A, Bandez MJ, Lopez-Cepero JM, Gomez C, Boveris A (2011) High doses of vitamin E improve mitochondrial dysfunction in rat hippocampus and frontal cortex upon aging. Am J Physiol Regul Integr Comp Physiol 300:R827–R834
94. Ng T-P, Chiam P-C, Lee T, Chua H-C, Lim L, Kua E-H (2006) Curry consumption and cognitive function in the elderly. Am J Epidemiol 164:898–906
95. Nijtmans LGJ, Ugallde C, van den Heuvel LP, Smeitink JAM (2004) Function and dysfunction of the oxidative phospharylation system. In: Koehler C, Bauer MF (eds) Mitochondrial function and biogenetics. Springer Inc., Heidelberg, pp 149–167
96. Niki E, Traber MG (2012) A history of vitamin E. Ann Nutrit Metabol 61:207–212
97. Oeppen J, Vaupel JW (2002) Demography. Broken limits to life expectancy. Science 296:1029–1031
98. Pagliarini DJ, Calvo SE, Chang B, Sheth SA, Vafai SB, Ong SE, Walford GA, Sugiana C, Boneh A, Chen WK, Hill DE, Vidal M, Evans JG, Thorburn DR, Carr SA, Mootha VK (2008) A mitochondrial protein compendium elucidates complex I disease biology. Cell 134:112–123

99. Parrado J, Miramontes E, Jover M, Marquez JC, Mejias MA, de Teran LC, Absi E, Bautista J (2003) Prevention of brain protein and lipid oxidation elicited by a water-soluble oryzanol enzymatic extract derived from rice bran. Eur J Nutr 42:307–314
100. Qiu C, De Ronchi D, Fratiglioni L (2007) The epidemiology of the dementias: an update. Curr Opin Psychiatry 20:380–385
101. Qiu C, Kivipelto M, von Strauss E (2009) Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dial Clin Neurosci 11:111–128
102. Rastogi M, Ojha RP, Rajamanickam GV, Agrawal A, Aggarwal A, Dubey GP (2008) Curcuminoids modulates oxidative damage and mitochondrial dysfunction in diabetic rat brain. Free Radic Res 42:999–1005
103. Rattan SI (2006) Theories of biological aging: genes, proteins, and free radicals. Free Radic Res 40:1230–1238
104. Reddy PH, Reddy TP (2011) Mitochondria as a therapeutic target for aging and neurodegenerative diseases. Curr Alz Res 8:393–409
105. Rendeiro C, Vauzour D, Rattray M, Waffo-Téguo P, Mérillon JM, Butler LT, Williams CM, Spencer JPE (2013) Dietary levels of pure flavonoids improve spatial memory performance and increase hippocampal brain-derived neurotrophic factor. PLoS One 8:e63535
106. Rhein V, Song X, Wiesner A, Ittner LM, Baysang G, Meier F, Ozmen L, Bluethmann H, Drose S, Brandt U, Savaskan E, Czech C, Gotz J, Eckert A (2009) Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. Proc Natl Acad Sci U S A 106:20057–20062
107. Ringman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Beigi M, Gylys KH, Badmaev V, Heath DD, Apostolova LG, Porter V, Vanek Z, Marshall GA, Hellemann G, Sugar C, Masterman DL, Montine TJ, Cummings JL, Cole GM (2012) Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. Alz Res Ther 4:43
108. Rojanathammanee L, Puig KL, Combs CK (2013) Pomegranate polyphenols and extract inhibit nuclear factor of activated T-cell activity and microglial activation in vitro and in a transgenic mouse model of alzheimer disease. J Nutr 143:597–605
109. Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A, Calabrese V (2006) Curcumin activates defensive genes and protects neurons against oxidative stress. Antiox Redox Sign 8:395–403
110. Schaffer S, Asseburg H, Kuntz S, Muller W, Eckert G (2012) Effects of polyphenols on brain aging and Alzheimer's disease: focus on mitochondria. Mol Neurobiol 46:161–178
111. Schaffer S, Eckert GP, Schmitt-Schillig S, Muller WE (2006) Plant foods and brain aging: a critical appraisal. Forum Nutr 59:86–115
112. Schaffer S, Halliwell B (2012) Do polyphenols enter the brain and does it matter? Some theoretical and practical considerations. Genes Nutr 7:99–109
113. Schaffer S, Muller WE, Eckert GP (2005) Tocotrienols: constitutional effects in aging and disease. J Nutr 135:151–154
114. Schaffer S, Muller WE, Eckert GP (2010) Cytoprotective effects of olive mill wastewater extract and its main constituent hydroxytyrosol in PC12 cells. Pharmacol Res 62:322–327
115. Schaffer S, Podstawa M, Visioli F, Bogani P, Müller WE, Eckert GP (2007) Hydroxytyrosol-rich olive mill wastewater extract protects brain cells in vitro and ex vivo. J Agric Food Chem 55:5043–5049
116. Schioth HB, Craft S, Brooks SJ, Frey WH 2nd, Benedict C (2012) Brain insulin signaling and Alzheimer's disease: current evidence and future directions. Mol Neurobiol 46:4–10
117. Serbinova E, Kagan V, Han D, Packer L (1991) Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. Free Rad Biol Med 10:263–275
118. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ (2008)

Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med 14:837–842
119. Shih P-H, Chan Y-C, Liao J-W, Wang M-F, Yen G-C (2010) Antioxidant and cognitive promotion effects of anthocyanin-rich mulberry (Morus atropurpurea L.) on senescence-accelerated mice and prevention of Alzheimer's disease. J Nutr Biochem 21:598–605
120. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 64:353–356
121. Shukitt-Hale B, Carey A, Simon L, Mark DA, Joseph JA (2006) Effects of Concord grape juice on cognitive and motor deficits in aging. Nutrition 22:295–302
122. Shukitt-Hale B, Carey AN, Jenkins D, Rabin BM, Joseph JA (2007) Beneficial effects of fruit extracts on neuronal function and behavior in a rodent model of accelerated aging. Neurobiol Aging 28:1187–1194
123. Shukitt-Hale B, Lau FC, Cheng V, Luskin K, Carey AN, Carrihill-Knoll K, Rabin BM, Joseph JA (2013) Changes in gene expression in the rat hippocampus following exposure to (56)Fe particles and protection by berry diets. Cent Nerv Syst Agents Med Chem 13:36–42
124. Smeitink J, van den Heuvel L, DiMauro S (2001) The genetics and pathology of oxidative phosphorylation. Nat Rev Gen 2:342–352
125. Sood PK, Nahar U, Nehru B (2011) Curcumin attenuates aluminum-induced oxidative stress and mitochondrial dysfunction in rat brain. Neurotox Res 20:351–361
126. Spencer JPE (2010) The impact of fruit flavonoids on memory and cognition. Br J Nutr 104: S40–S47
127. Stoll S, Scheuer K, Pohl O, Muller WE (1996) Ginkgo biloba extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse. Pharmacopsychiatry 29:144–149
128. Surh Y-J, Han SS, Keum Y-S, Seo H-J, Lee SS (2000) Inhibitory effects of curcumin and capsaicin on phorbol ester-induced activation of eukaryotic transcription factors, NF-\kappaB and AP-1. Biofactors 12:107–112
129. Suzuki YJ, Packer L (1993) Inhibition of NF-kappa B activation by vitamin E derivatives. Biochem Biophys Res Commun 193:277–283
130. Takahashi M, Uechi S, Takara K, Asikin Y, Wada K (2009) Evaluation of an oral carrier system in rats: bioavailability and antioxidant properties of liposome-encapsulated curcumin. J Agri Food Chem 57:9141–9146
131. Talavera S, Felgines C, Texier O, Besson C, Gil-Izquierdo A, Lamaison J-L, Remesy C (2005) Anthocyanin metabolism in rats and their distribution to digestive area, kidney, and brain. J Agri Food Chem 53:3902–3908
132. Tavares L, Alves PM, Ferreira RB, Santos CN (2011) Comparison of different methods for DNA-free RNA isolation from SK-N-MC neuroblastoma. BMC Res Notes 4:3
133. Tennesen HH, Greenhill JV (1992) Studies on curcumin and curcuminoids XXII: curcumin as a reducing agent and as a radical scavenger. Int J Pharma 87:79–87
134. Tsuda T, Horio F, Osawa T (1999) Absorption and metabolism of cyanidin 3-O-β-D-glucoside in rats. FEBS Lett 449:179–182
135. Valla J, Berndt JD, Gonzalez-Lima F (2001) Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration. J Neurosci 21:4923–4930
136. Vanitallie TB (2013) Preclinical sporadic Alzheimer's disease: target for personalized diagnosis and preventive intervention. Metabol Clin Exp 62(Suppl 1):S30–S33
137. Visioli F (2012) Can experimental pharmacology be always applied to human nutrition? Int J Food Sci Nutr 63:10–13
138. Vitaglione P, Donnarumma G, Napolitano A, Galvano F, Gallo A, Scalfi L, Fogliano V (2007) Protocatechuic acid is the major human metabolite of cyanidin-glucosides. J Nutr 137:2043–2048

139. Wang H-M, Zhao Y-X, Zhang S, Liu G-D, Kang W-Y, Tang H-D, Ding J-Q, Chen S-D (2010) PPARgamma agonist curcumin reduces the amyloid-beta-stimulated inflammatory responses in primary astrocytes. J Alzheimers Dis 20:1189–1199
140. Wang L-S, Stoner GD (2008) Anthocyanins and their role in cancer prevention. Cancer Lett 269:281–290
141. Wang X, Su B, Lee HG, Li X, Perry G, Smith MA, Zhu X (2009) Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. J Neurosci 29:9090–9103
142. Wei Q-Y, Chen W-F, Zhou B, Yang L, Liu Z-L (2006) Inhibition of lipid peroxidation and protein oxidation in rat liver mitochondria by curcumin and its analogues. Biochim Biophys Acta 1760:70–77
143. Wimo A, Winblad B, Aguero-Torres H, von Strauss E (2003) The magnitude of dementia occurrence in the world. Alzheimer Dis Assoc Disord 17:63–67
144. Wong RSY, Radhakrishnan AK (2012) Tocotrienol research: past into present. Nutr Rev 70:483–490
145. Yang C, Zhang X, Fan H, Liu Y (2009) Curcumin upregulates transcription factor Nrf2, HO-1 expression and protects rat brains against focal ischemia. Brain Res 1282:133–141
146. Yang Z, Xiao H, Jin H, Koo PT, Tsang DJ, Yang CS (2010) Synergistic actions of atorvastatin with gamma-tocotrienol and celecoxib against human colon cancer HT29 and HCT116 cells. Int J Cancer 126:852–863
147. Zhu YG, Chen XC, Chen ZZ, Zeng YQ, Shi GB, Su YH, Peng X (2004) Curcumin protects mitochondria from oxidative damage and attenuates apoptosis in cortical neurons. Acta Pharmacol Sin 25:1606–1612
148. Ziegler-Graham K, Brookmeyer R, Johnson E, Arrighi HM (2008) Worldwide variation in the doubling time of Alzheimer's disease incidence rates. J Alzheimer Assoc 4:316–323
149. Zingg J-M, Meydani M, Shishodia S (2013) Molecular mechanisms of curcumin action. Gene Expr Biof 39:37–55
150. Allam F, Dao AT, Chugh G, Bohat R, Jafri F, Patki G, Mowrey C, Asghar M, Alkadhi KA, Salim S (2013) Grape powder supplementation prevents oxidative stress-induced anxiety-like behavior, memory impairment, and high blood pressure in rats. J Nutr 143(6):835–842
151. Farr SA, Price TO, Dominguez LJ, Motisi A, Saiano F, Niehoff ML, Morley JE, Banks WA, Ercal N, Barbagallo M (2012) Extra virgin olive oil improves learning and memory in SAMP8 mice. J Alzheimer Dis 28(1):81–92
152. Pitozzi V, Jacomelli M, Catelan D, Servili M, Taticchi A, Biggeri A, Dolara P, Giovannelli L (2012) Long-term dietary extra-virgin olive oil rich in polyphenols reverses age-related dysfunctions in motor coordination and contextual memory in mice: role of oxidative stress. Rejuvenation Res 15(6):601–612
153. Serra A, Rubió L, Borràs X, Macià A, Romero M-P, Motilva M-J (2012) Distribution of olive oil phenolic compounds in rat tissues after administration of a phenolic extract from olive cake. Mol Nutr Food Res 56(3):486–496
154. Vissers MN, Zock PL, Katan MB (2004) Bioavailability and antioxidant effects of olive oil phenols in humans: a review. Eur J Clin Nutr 58(6):955–965