antioxidants

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*Review*

# Oxidative Stress and Cognitive Decline: The Neuroprotective Role of Antioxidants

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**Abstract:** Free- radicals (Oxygen and Nitrogen species) are formed in mitochondria during the oxidative phosphorylation. Their high reactivity, due to not-engaged electrons, leads to an increase of the oxidative stress. This condition affects above all the brain, that usually needs a large oxygen amount and in which there is the major possibility to accumulate "Reacting Species". Antioxidant molecules are fundamental in limiting free-radical damage, in particular in the central nervous system: the oxidative stress, in fact, seems to worsen the course of neurodegenerative diseases.

The aim of this review is to sum up antioxidant molecules with the greatest neuroprotective properties and the role of physical activity against free radical genesis, understanding their relationship with the Central Nervous System.

**Keywords:** oxidative stress; cognitive decline; antioxidants.

## 1. Introduction

Oxidative stress is known to be involved in the pathogenesis of several diseases: in particular, a strict connection between a free-radical increase and the onset of neurodegenerative disorders has been widely demonstrated [1].

Free radicals are atoms or molecules characterized by one or more electrons not engaged in chemical bonds, which, remaining unpaired, tend to accept electrons from other molecules: this reaction causes their oxidation [2, 3]. An oxidation–reduction imbalance in living organisms leads to an excess of reactive oxygen and nitrogen species (RONS) with a consequent oxidative stress status [2, 4] that is classified as basal, low, intermediate and high according to its intensity [5,6].

The oxidative stress is known to be involved in the genesis of several diseases such as atherosclerosis, diabetes, cardiovascular and neurodegenerative disorders [7].

There are a large number of antioxidant defensive mechanisms against RONS. The antioxidant molecules are divided into two groups: enzymatic and non-enzymatic compounds. The enzymatic group includes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR). SOD, one of the main protective mechanisms against ROS, catalyzes the conversion of O2- to $H_2O_2$ and $O_2$ [8], while CAT converts the generated $H_2O_2$ into water and $O_2$ [9]. The non-enzymatic group involves glutathione (GSH), abundant in brain cells, thioredoxin (Trx), vitamins A, E and C, selenium, retinoic acid, carotenoids and flavonoids. GSH reacts with ROS to generate glutathione disulfide (GSSG) and enters a cycle together with GPx and GR [10].

All these systems are essential to protect us against a possible free radical damage.

Since the brain consumes a large amount of oxygen (about 20% more than other parts of the body), if antioxidant defenses are insufficient and levels of polyunsaturated lipids are high there will be the possibility of an accumulation of biomolecules damaged by RONS [11]. So, neuronal cells are particularly vulnerable to oxidative damage because of their high oxygen consumption, the weak antioxidant defense [12] and high content of polyunsaturated fatty acids in their membranes: in fact, the lipids of the neuronal membrane are rich in chains side polyunsaturated fatty acids (PUFA). PUFAs composed of eicosapentaenoic (C20:5) and decosahexanoic (C22:6) acids are particularly vulnerable to free radicals attack due to the double bonds that allow RONS to remove hydrogen ions [13].

In particular, RONS overproduction in brain cells reacts with cell membrane PUFAs causing their peroxidation [14]. More specifically, lipid peroxidation generates a heterogeneous group of relatively stable products such as malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), acrolein and isoprostane [15].

As a result, membrane fluidity decreases causing a greater permeability. This facilitates a massive entry of substances into the intracellular system, (eg K +, Ca2 +, etc.) that could alter membrane proteins, enzymes and receptors [16].

Carbohydrates are also influenced by RONS with the formation of advanced glycation products (AGE) [17], involved in the development of neurodegenerative disorders [18].

In addition, RONS alter DNA and RNA heterocyclic bases, in particular guanine: these alterations occur in Parkinson's disease affected brains. Instead, Alzheimer's Disease affected brains, are characterized by elevated carbonylation and nitration, that respectively introduce in proteins carbon monoxide or one or more $NO_2$ groups derived from nitric acid [17, 19].

All neurodegenerative disorders share several common characteristics, such as an abnormally aggregated protein accumulation and mitochondrial dysfunction that demonstrate an oxidative stress status [20]. In particular, neurodegeneration-involved reactive species are hydrogen peroxide ($H_2O_2$), superoxide anion ($O_2^-$) and highly reactive hydroxyl radical (HO •) [21]. They are able to preclude the protein reduction, cause translation errors in vivo altering protein structure, and function [22].

The risk of developing neurodegenerative disorders is also related to some lifestyle factors, such as obesity, sedentary lifestyle and unbalanced diet, because of their role in RONS genesis [23, 24].

Therefore, considering the fact that oxidative stress is one of the most important risk factors involved in the onset, maintenance and progression of neurodegenerative diseases, both enzymatic and non-enzymatic antioxidants, in association with a healthy lifestyle, could have a fundamental protective role against them [25-28]. The oxidative stress theory and its consequences at cellular level is shown in Figure 1.

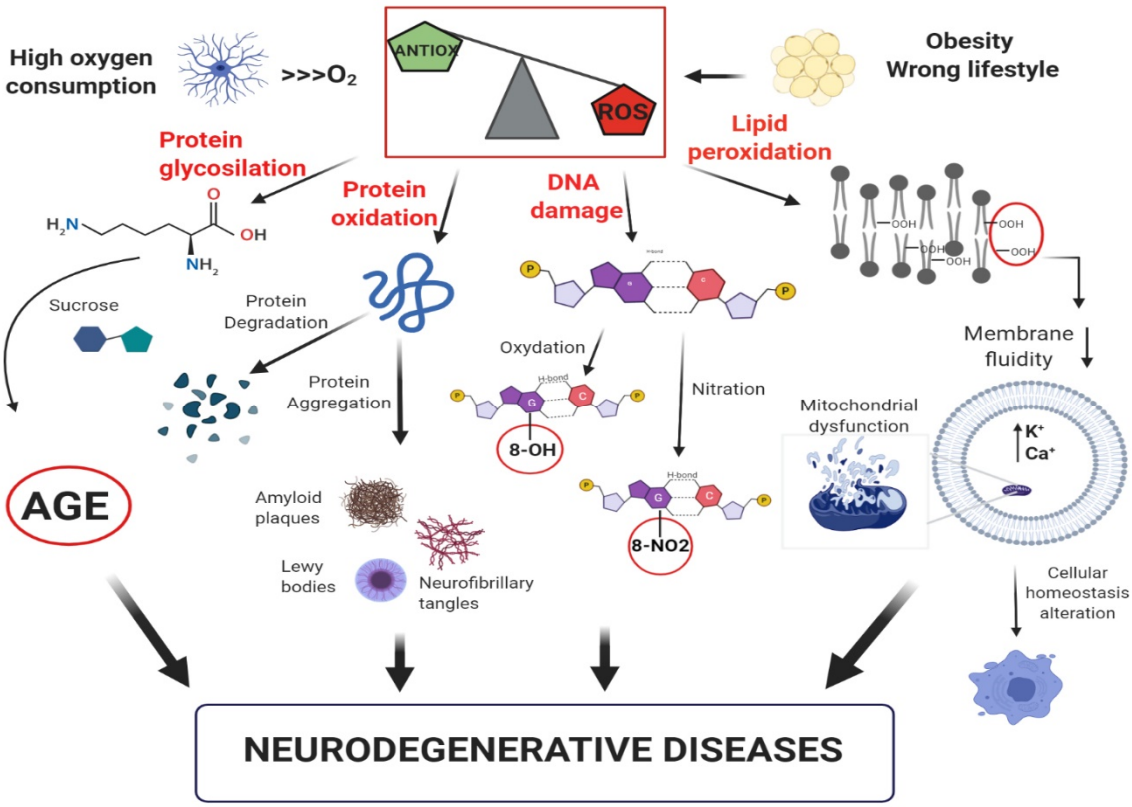


**Figure 1** Model of free-radical formation and its consequences at a cellular level. The intense oxygen consumption in the brain induces the formation of reactive oxygen species (ROS). Their high reactivity leads to an increase of the oxidative stress, which promotes: i) glycosylation and oxidation of proteins, leading to the formation of advanced glycation products (AGE) or loss of protein function; ii) DNA damage with oxidation or nitration of guanine bases; iii) lipid peroxidation with reduction of membrane fluidity and increase in cell permeability, resulting in alteration of cellular homeostasis. All these factors can contribute to the development of neurodegenerative disorders.

## 2. Vitamin C and E

A diet characterized by vegetables and fruits, is positively associated with cognitive efficiency and reduced the risk of dementia in the elderly because usually rich in Vitamin C, carotenoids and Vitamin E.

Considering the chemical point of view, Vitamin C is defined as Ascorbic Acid (AA). It has six-carbon compound that contain two acid-ionizing groups [29]. In human body, brain is the region with the highest concentration of AA [30]. This high concentration, attests to the fundamental involvement of AA in brain function. Indeed, many studies suggest that AA has a neuroprotective role thanks to an antioxidant activity modulation [31, 32]. This modulation is related to the buffering of the oxidizing species induced by methamphetamine [33], homocysteine [34], ethanol [35] and other molecules [36, 37].

It is interesting to note that the AA activity is quite vast, considering also the interaction with Vit.E. their association is remarkable in the protection of membranes and other hydrophobic compartments [38, 39].

In particular, a clinical study has highlighted the association between vitamin E and C intake and a delayed AD onset in a group of elderly subjects [40], similar results were also obtained by Shen and colleagues in 2012 [41]. In fact, it has been shown that a supplementation of these vitamins and so their greater concentration in cerebrospinal fluids can prevent lipid oxidation in AD patients [42].

Vitamin E is a lipophilic molecule that could be found in plants and in many mediterranean diet food [43]. Vit. E is referred to compounds called tocopherols and tocotrienols [44]. These usually include 8 molecules ($\alpha$-, β-, $\gamma$-,δ-tocopherols and $\alpha$-, β-, $\gamma$-,δ -tocotrienols), with great antioxidant capacity [45].

The presence of an electrophilic hydroxyl group on the chroman ring, allows Vitamin E to be a strong antioxidant. To understand Vitamin E role as a protective factor in neurodegenerative disorders, it has to be considered what happens if it is deficient. For example, it is demonstrated that Vitamin E deficit is related to an impairment of cerebellar Purkinje neurons that are the main integrators of cerebellar neural circuits [46] As far as Parkinson's disease, evidence suggests that a Vitamin E supplementation can improve symptoms, functional capabilities and the inflammatory state of affected patients [47].

In addition, Khanna et al. (2003) showed a fundamental role of Vitamin E against glutamate- induced neurotoxicity [48]. In a later study, it is observed that the co-treatment with vitamin E analogs is able to block NO or O2• donor-induced cell death in rat striatal cultures [49].

It is clear that, the use of vitamins E and C as antioxidant supplements is fundamental to delay the onset of neurodegenerative disorders and their complications (Figure 2).

## 3. Fatty Acids

Recently, it has grown an interest in polyunsaturated fatty acids (PUFAs) and their beneficial effects on health, due to their strong antioxidant properties [50,51]. PUFAs (omega-3 and omega-6 fatty acids) usually have two or more double bonds in the carbon chain structure. Omega-6 fatty acids include linoleic acid (LA), γ-linolenic acid (GLA) and arachidonic acid (AA). Omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Their intake is important since their limited synthesis in humans [50,52].

Cell-membrane PUFAs composition could be modified with dietary supplementation but it depends on age and probably also on the quantity PUFAs integration [53]. High fatty acid diet increases their percentage in inflammatory cell membranes of inflammatory cell and reduces AA levels, a stress-related biomarker and an inflammatory process trigger (through pro-inflammatory eicosanoids production) [54, 55].

PUFAs, in particular EPA and DHA, are interesting because of their beneficial effects in preventing cognitive decline through neuroprotective properties such as increasing nerve membrane neuroplasticity, promoting synaptogenesis, modulating signal transduction pathways in neuronal cells and attenuating inflammatory processes [50, 52, 56] (Figure 2).

Furthermore, DHA, produced by the desaturation and elongation of α-linolenic acid (ALA), is able to influence a certain number of membrane proteins, such as receptors, ion channels and enzymes. Furthermore, DHA can modulate dopaminergic, serotonergic and cholinergic neurotransmission, thus regulating signal transduction pathways [57]. DHA is also considered important for neurogenesis regulation, neural synapses increase and neuronal damage protection [58].

In fact, Omega-3 DHA is directly absorbed into cell membranes: it composes at least 30% of brain matter (in general, fats are more than 50% of the brain) [57]. DHA level decreases significantly both in the blood plasma and in the brain, in physiological aging, above all in AD patients [59] because of its lower exogenous intake and its greater oxidation [60]. However, several studies suggest that Omega-3 fatty acid integration is beneficial only in the early stages of cognitive decline [57].

Indeed, there are discrepancies about fatty acid effectiveness on cognitive functioning [61-64]. That because of multiple variables such as PUFA amount to administer (both omega-3 and omega-6), the type and quality of their source (such as fish oil and / or vegetable oil or other), differences among tests to investigate cognitive efficiency, sample homogeneity in terms of age and functioning and/or cognitive impairment [65]. A recent double-blind randomized study investigated the effectiveness of fatty acid intake (omega-3 and omega-6) combined with other antioxidant vitamins in a group of older people with MCI. Neuroaspis PLP10®, a nutraceutical containing omega-3 (EPA (810 mg) / DHA (4140 mg)), omega-6 (GLA (1800 mg) / LA (3150 mg)) (1: 1 w / w), vitamin A (0.6 mg) and vitamin E (22 mg as α-tocopherol plus 760 mg as pure γ-tocopherol) was administered to the experimental group subjects for 6 months [65].

In this study [65], both tests investigating overall cognitive function (ACE-R and MMSE) showed a significant improvement in the experimental group compared to the control group, regarding memory, language (fluency) and visual-spatial skills (ACE-R). An attentional functionality improvement was evidenced too (specifically, in a symbol cancellation test and in the Stroop test, in particular in the word and color subtests but not in the test in which the interference inhibition capacity is investigated). Besides, from a functional point of view, the experimental group obtained high scores in tests investigating muscle strength, endurance, power and balance. These physical performance parameters are important since they refer to the most demanding daily activities [66]. In parallel, an increase in the quality of life, sleep and perceived fatigue was demonstrated.

The results of this study are similar to what described by Bo et al. [67]. They showed that 6-month intake of DHA (480 mg/die) and EPA (720 mg/die) could improve the perceptual speed, spatial imagery efficiency, and working memory in MCI elderly. Sinn et al. [68] has also shown that 6-month intake of fish oils (1.55 g of DHA and 0.40 g of EPA per day) improves cognitive functions and in particular executive efficiency. The same results have not been obtained on patients with known neurodegenerative diseases such as AD, to indicate that greater benefit is drawn from taking PUFA in the early stages of cognitive impairment [69, 70].

## 4. Coenzyme Q10

Coenzyme Q10 (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) is a fat-soluble compound also known as CoQ10, vitamin Q10, ubidecarenone or ubiquinone. An endogenous substance is produced by mitochondria in doses of about 3-5 mg per day. It is one of the main elements involved in mitochondrial oxidative phosphorylation and also acts as an antioxidant [70, 71]. In vitro studies have shown that CoQ10 easily crosses the blood brain barrier.

Thanks to its oxidizing and antioxidant properties, it is a cellular redox state modulator.

CoQ10 is located in the internal mitochondrial membrane and protects cells from apoptosis at a morphological and at a molecular level [72]. Furthermore, as a lipophilic antioxidant, it can eliminate radicals from membranes, cytosol and plasma.

It plays an important role in Parkinson's disease (PD). In fact, CoQ10 levels are significantly lower than normal in neuron and platelet mitochondria of PD patients. In vitro studies on fibroblasts of PD patients have shown that CoQ10 intake restores the electron transport chain activity. The first clinical studies on the CoQ10 neuroprotective effects were reported in 1994 by Beal et al. [73]: this study demonstrated the association between 16-month CoQ10 intake (1200 mg per day) and a reduced functional decline (44%) in PD patients. Muller et al. [74] confirmed these data: 28 PD patients showed moderate symptom improvement thanks to CoQ10 oral administration (360 mg per day).

The antioxidant potential of CoQ10 was further evaluated in a pilot study [75] on 11 patients with Rett Syndrome, a severe neurodevelopmental disorder in which hypoxia-induced oxidative stress

associates with the pathogenesis and the disease progression [76,78]. After 12-month CoQ10 intake (300 mg / day), there was a significant improvement in red blood cells' energy status, suggesting an attenuation of the oxidative stress [75,76].

Promising results were also observed in a double-blind randomized clinical trial involving patients with remitting-intermittent multiple sclerosis [78]. The experimental group took 500 mg of CoQ10 for 12 weeks, and showed a significant reduction in inflammatory markers, such as tumor necrosis factor $\alpha$ (TNF-$\alpha$), interleukin 6 (IL-6) and matrix metalloproteinase 9 (MMP-9).

## 5. Nigella Sativa

Nigella sativa L. (N. sativa), also known as black cumin, is a plant grown in the Mediterranean countries, in the south and south-west Asia, characterized by its high bioactive-compound content seed (e.g. Tocopherols, vitamin A and C, β-carotene, etc.) and its anti-inflammatory, antioxidant, immunomodulating and anticancer properties [79, 80]. N. sativa contains fixed oil (22-38%), volatile oil (0.40-1.5%), proteins (21–31%), carbohydrates (25–40%), minerals (3.7 –7%), vitamins (1-4%), saponins (0.013%) and alkaloids (0.01%) [81], in particular, its biological activity is associated with its thymoquinone content (TQ) [82].

Bordoni et al. [83] revealed the association between the anti-inflammatory and antioxidant properties of N. Sativa oil (grown in the Marche region of Italy) and its conservation. Therefore, the Stored Extracted Oil (SEO) and the Fresh Extracted Oil (FEO) were obtained from the same cultivation in order to analyze their thymoquinone content. The cultivated oil showed a higher content of thymoquinone (7,200 mg / mL) compared to other crops [84,85] and it was higher in FEO while decreased with storage time.

In murine models, it has been demonstrated that thymoquinone is useful to obtain a delayed onset of the microglia degeneration caused by the oxidative stress [86].

In addition, TQ is able to improve and regenerate antioxidants enzymes such as glutathione peroxidase and glutathione reductase previously repressed by Beta-amyloid in differentiated cell lines of rats affected by Alzheimer disease [87] (Figure 2).

## 6. Chlorogenic Acids

Chlorogenic acid (CA), the main phenolic coffee component, is another polyphenolic substance with an excellent antioxidant activity. It belongs to the chlorogenic acid family (CGA) that are phenolic acids derived from cinnamic acid esterification, such as caffeic, ferulic and p-coumaric acids. CGA are also widely present in drinks based on herbs, fruits and vegetables.

Chlorogenic acids have antibacterial, antioxidant and anti-inflammatory activities [88]. Several *in vitro* and in vivo studies have highlighted their ability to counteract neurodegenerative events. Although a preclinical study on AD transgenic mice reported that caffeine reduces brain beta-amyloid (Aβ) levels [89-91], it is still unknown which element is specifically related to AD. Currently, few studies have analyzed CGA effects on human cognitive impairment. Epidemiological studies have found that coffee drinking habits reduce cognitive impairment and the risk of developing neurodegenerative diseases such as AD [92,93].

In particular, Kim et al. [94] investigated the association between coffee intake and AD neuropathological markers in vivo (411 healthy elderly subjects).

The results showed that the coffee intake ( ≥2 cups / day) was associated with lower levels of Aβ brain deposition compared to its less intake (<2 cups/ day), suggesting that a moderate daily coffee intake helps to reduce amyloid pathological deposition in the brain [94].

Eskelinen et al. [95] obtained similar results observing that coffee intake in middle age reduces the risk of developing AD in elderly.

Recently, Kato et al. [96] conducted a pilot study and described cognitive function changes after 6-months CGA intake (330 mg /die) in elderly with subjective memory loss.

In particular, significantly higher scores emerged in tests investigating attentional, executive and mnesic functionality. In the same study, there was a significant reduction in A$\beta$42, A$\beta$42 / A$\beta$40 plasma levels and a significant increase in DHEA-S levels after CGA intake (Figure 2).

Previous studies have shown that CGAs improve blood pressure and vascular endothelial functions, both associated with dementia onset [97-99]: in fact, hypertension, in middle age, is a risk factor for dementia and cognitive impairment in old age and continuous CGA consumption may delay its onset [100].

Saitou et al. [101] investigated CGA effects on healthy subjects with subjective memory loss.

In this randomized controlled double-blind study, experimental group took a compound based on CGA (caffeoylquinic acids (CQA), feruloylquinic acids (FQA) and dicaffeoylquinic acids (diCQA) for 16 weeks, CQA - FQA total amount was 300 mg, obtained by extraction from green coffee beans.

Participants underwent a neuropsychological examination (MMSE and RBANS) at baseline, after 8 weeks and after 16 weeks. At the end of the treatment, significant differences between CGA intake group and the placebo one was evidenced: in particular, elevated scores were recorded in tests investigating motor speed, psychomotor speed and executive functions. Serum concentration of cognitive impairment-linked biomarkers revealed an increase in apolipoprotein A1 (ApoA1) and Transthyretin (TTR) levels in the experimental group at 16 weeks.

Considering these results, CGA intake may improve not only motor activity, but also the cognitive functions that control its execution and monitor its efficiency.

These results confirm what was described previously by the same authors in a pilot study [95].

## 7. Selenium

Selenium is an essential micronutrient with a very narrow recommended dietary range. The RDA for selenium is around 55 lg / day and it can be integrated with a specific dietary intake. Selenium, in the form of selenocysteine, is a component of 25 selenoprotein classes, including GPx, selenoproteins P, W and R and thioredoxins (TrxR). As an antioxidant, it provides protection from ROS-induced cellular damage [102-104] (Figure 2).

Its brain concentration changes in Alzheimer's disease patients and Multiple Sclerosis ones; therefore, this element may have an important role in the protection from neurodegeneration [105-108]. Considering that old people are more exposed to selenium deficiency due to metabolic changes, lower bioavailability and diet changes [109-111], several studies have hypothesized the possibility of its exogenous assumption in order to prevent aging-related diseases.

Selenoproteins, such as glutathione peroxidases (GPx), play an important role in antioxidant defenses. The main brain selenoproteins are P and GPx: the first one has been identified in senile plaques and neurofibrillary tangles, suggesting its important role against oxidative damage [112, 113], GPx, which neutralizes peroxides, is expressed by neurons and glial cells [114,115]. The biosynthesis of selenoproteins depends on selenium availability. Therefore, an adequate selenium intake may be particularly important for maintaining brain function [116].

Brazil nut (Bertholletia excelsa) is the richest dietary selenium source and its intake improves selenium status [117, 118]. Although some studies have reported that selenium stet is important for maintaining cognitive efficiency [119-121], only few studies have evaluated its real clinical efficacy Cardoso et al. [119] analyzed the effects of Brazil nut consumption on cognitive function in a group of older people with MCI. The experimental group took a 5-gram Brazil nut per day, containing approximately 288.75 μg of selenium (more than the recommended levels - 55 μg / day - but not exceeding the tolerable upper intake level - 400 μg / day) [119]. Selenium plasma and erythrocyte concentrations, Gpx activity in erythrocytes, ability to absorb oxygen radicals and MDA, and lipid peroxidation genotoxic product were recorded at baseline and after 6 months. The CERAD neuropsychological battery assessed cognitive functions. After 6 months, no selenium deficiency was observed in the treated group, while control subjects had a level below the cut-off (> 84–100 μg / L). Furthermore, an increase in plasma and erythrocyte selenium concentrations was observed in the experimental group, there was also a significant improvement in erythrocyte GPX activity. Although no intergroup changes emerged in overall cognitive performance, assessed with the CERAD total score, subtests investigating constructive praxis and verbal fluency showed higher scores in the treated group.

## 7. Probiotics

Probiotics refer to a group of live nonpathogenic microorganisms, which, when administered in adequate amounts, are able to establish the microbial balance, particularly in the gastrointestinal tract [122]. Their importance is also related to their antioxidant properties: they act as metal-ion chelators, have their own antioxidant enzymatic systems (SOD and CAT), can produce various metabolites (GSH, butyrate and folate) and mediate Antioxidant Signaling Pathways [122]

According to the theory of the "gut-brain axes", the gut microbiota can have significant effects on cognitive alterations and these alterations can be partially reversed by colonization of the gut [123]. Bagga et al. [124] showed that Probiotic administration for 4 weeks was associated with changes in several brain activation pathways regarding emotional memory and emotional decision-making abilities.

Therefore, a rational manipulation of intestinal microbiota through probiotics, could affect positively Central Nervous System-associated disorders. Bonfili at al. showed that a probiotic formulation (namely SLAB51) counteracted brain oxidative damages associated with Alzheimer's disease (AD) [125]. A clinical trial by Kobayashi et al. investigated the effects of oral administration of Bifidobacterium breve strain A1 (B. breve A1) on behavior and physiological processes in Alzheimer's disease (AD) model mice. The consumption of B. breve A1 suppressed the hippocampal expressions of inflammation and immune-reactive genes that are induced by amyloid-β suggesting that B. breve A1 has therapeutic potential for preventing cognitive impairment in AD [126].

Michael et al. investigated the neuroprotective role of two bacterial consortia, known as Lab4 and Lab4b, using the established SH-SY5Y neuronal cell model. Both consortia were equally able to attenuate intracellular reactive oxygen species accumulation in SH-SY5Y cells [127].

Another clinical trial showed that heat-killed L. buchneri KU200793 has an important antioxidant activity mediated by its ability to increase levels of BDNF and so its intake can be considered useful in PD prevention [128]. Therefore, in accordance with the above, thanks to their antioxidant properties, probiotics seems to be fundamental to delay the progression of these neurodegenerative disorders (Figure 2).

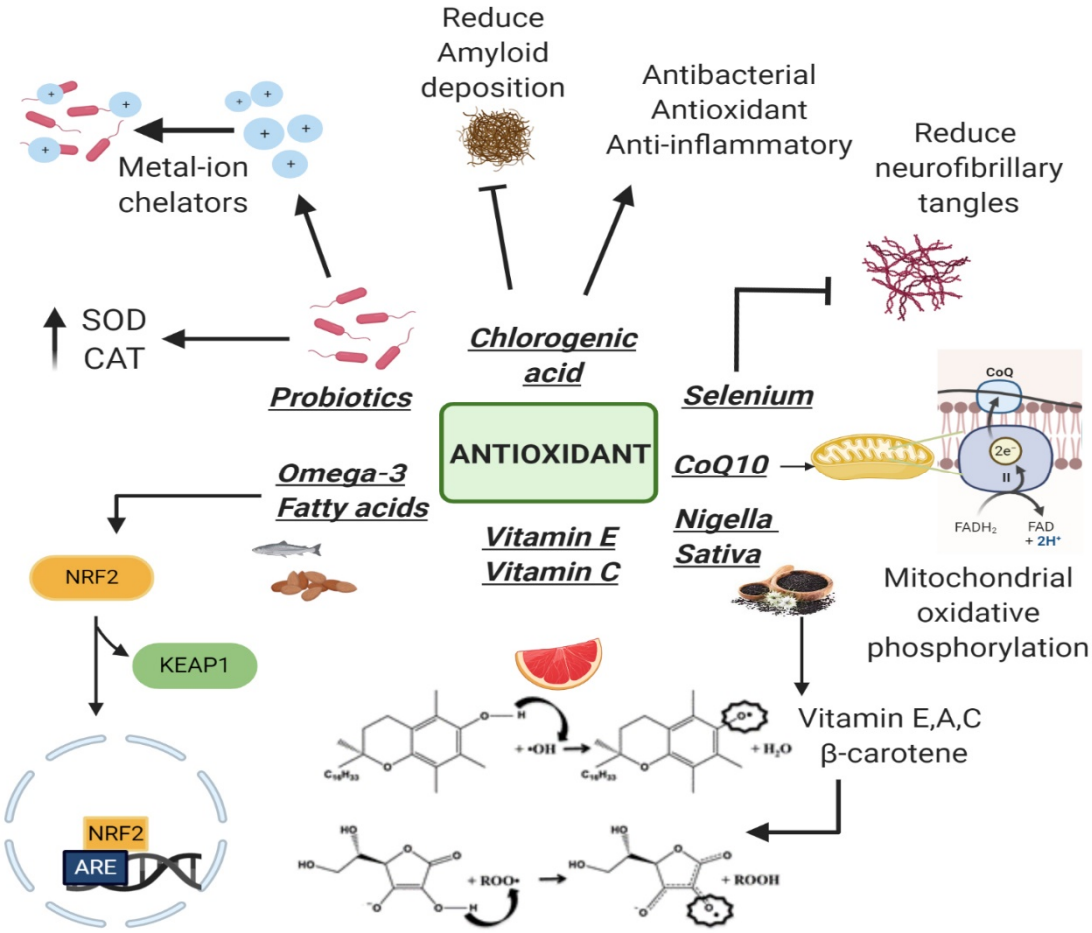


**Figure 2** Antioxidants with neuroprotective properties. Following the detachment of Keap1 subunit, Omega-3 increases the antioxidant genes expression. Vitamins E, C and Nigella Sativa (rich in vitamins) neutralize free radicals thanks to the presence of an electrophilic hydroxyl group on the chromane ring. Coenzyme Q10 (CoQ10) plays a fundamental role in the electron transport chain protecting cells from apoptosis at a morphological and molecular level. Selenium is able to reduce neurofibrillary tangle formation while chlorogenic acid reduces amyloid deposition. Probiotics act as metal ion chelators and as antioxidants using their antioxidant enzyme systems: superoxide dismutase and catalase (SOD and CAT).

## 8. Physical Activity as an antioxidant system

Regular physical exercise is able to induce a lot of adaptations on human organisms: in particular, it promotes neoangiogenesis and an antioxidant defense increase. The beneficial effects of physical activity are summarized in Figure 3. As far as the brain concerns, regular exercise leads to remarkable modifications, such as the enhancement of neuroplasticity and growth factor expression, the decrease of inflammatory states; it also acts as a buffer against the oxidative stress [129].

Brain is vulnerable to the oxidative damage due to its high O2-dependent mitochondrial activity. During exercise we observed an increased oxygen uptake and cerebral blood flow (40–70%) in order to sustain energy demands [130]. These adaptations lead to enhance mitochondrial activity and ROS.

The repeated stimulus induced by a constant and regular physical activity promotes the improvement in the antioxidant defense system, thus defining the physical activity paradox called also "hormetic effect". The term "hormetic" means just a biphasic dose-response effect related to the exercise stimulus [131].

It is interesting to note that both endurance and resistance training exercise of sufficient intensity and duration increase oxidative modification of proteins, nucleic acids and lipids. The main adaptive responses to this kind of exercises are related to their upregulation of endogenous antioxidants, such as glutathione peroxidase (GSH), superoxide dismutase [132] and Catalase (CAT). Indeed, as described by Mee-inta et al. (2019), glutathione peroxidase (L-γ-glutamyl-L-cysteinyl-glycine) plays a crucial role in astrocytes and microglia because it controls the redox balance and anti-inflammatory mediators [133].

In addition to increasing main antioxidant enzyme levels, it was also observed that regular physical activity in middle-aged rats could up-regulate peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α). The activation of PGC-1 α leads to an enhancement of antioxidant enzymes including GPX and Mn-SOD with a simultaneous decrease in the oxidative stress status. In addition, PGC-1 α activation promotes mitochondrial biogenesis, resulting in an increased ATP availability and a decrease in oxidizing species [134]. Thanks to this antioxidant response, resistance training is able to affect positively cognition functions. For example, Lachman et al. (2006) showed a memory improvement in older adults with disability, thanks to home-based Strong for Life program [135]. Moreover, it has been demonstrated an improved ability to remember actions in the future after a single strength exercise session in healthy youths [136].

More generally, studies have shown that resistance training can contribute significantly to the prevention of neurodegenerative diseases [137, 138, 140]. As well as to the maintenance, development and brain recovery through specific neurochemical adaptations induced by this kind of training [139]: in particular, low levels of ROS, which are produced intermittently for a short period of time during a training protocol program, activate intracellular signaling pathways that promote cellular adaptations, leading to an increase in capacity against subsequent stress. Conversely, moderate levels of ROS generation over a long period, or high generation due to high intensity exercise, induce structural and functional damage [141].

It has been suggested that maybe there could be a link between muscle and brain. This because resistance training could act on rapamycin (mTOR), a serine/threonine kinase, fundamental for brain survival, and on an intracellular protein called cAMP-response element-binding protein (CREB), essential in dopaminergic neurons [142]. This theory was later confirmed by Lloyd et al. (2017), who observed how resistance training enhanced mTOR and CREB signalling in brain tissues [143].

The influence of exercise on brain redox systems has been widely reported in scientific literature: in fact, it is able to reduce OS, maintain brain redox balance and increase levels of Brain-derived Neurotrophic Factor (BDNF) [144-150].

In particular, BDNF leads to the activation nuclear factor erythroid 2-related factor 2 (Nrf2, a cellular regulator of antioxidant defense systems) [151], which regulates the expression of enzymes and detoxification antioxidants to protect brain cells from oxidants, electrophiles and inflammatory agents [152] and to maintain mitochondrial function, cellular redox and protein homeostasis [153-156].

Currently, several training protocols are able to improve antioxidant defenses. High Intensity Interval Training (HIIT) is one of them. HIIT is a kind of training in which exercises are performed in intermittent aerobic intervals. The volume and the intensity of HIIT is usually 90% of VO2max and the training session lasts about 45 minutes [157]. Because of these features, HIIT induces a remarkable positive adaptation on body composition and cardiorespiratory fitness [158]. Although several studies have also shown an important correlation between HIIT and antioxidant defenses enhancement [159,160,161], the actual HIIT effects on memory and other cognitive capacities remain to be elucidated.

Analyzing literature data, it is still not clear what could happen if strenuous physical activity is performed. A typical strenuous physical activity is for example, the ultra-endurance race (UE). Studies have shown that UE causes a physiological impairment on cardiac remodelling, marked muscle damage and hepatic dysfunction [162]. In addition, UE also leads to an increased oxidative damage on the central nervous systems [163]. In a recent study, de Souza et al. (2020) showed that a high-volume training, just like UE, provoked cerebellar lipid peroxidation, and unbalanced enzymatic antioxidant resources in rodents [162].

It is so possible to assume that the neuroprotective role of physical activity as an antioxidant system is more evident if a regular and constant exercise is considered, while a strenuous exercise could affect negatively brain cells.

Moreover, physical activity (endurance training, HIIT or resistance training) is able to induce structural changes in several brain areas, with a consequent improvement in brain function. These modifications consist in an increased total branch length of Purkinje cells [164], cerebellar angiogenesis [165] and plasticity in the motor cortex [166]. Finally, a moderate exercise acts positively on brain cell apoptotic signals through the inhibition of RONS [167].

In summary, it seems evident that physical activity, performed in a regular way, is able to induce brain adaptations mediated by its capacity of decreasing oxidizing species and increasing antioxidant defenses with a remarkable effect on cortex, hippocampal and cerebellum function, neoangiogenesis and the reduction of neuro-inflammation [168].

Unfortunately, the relationship between physical exercise and adaptation response is very complex, because of lots of variables such as intensity, volume, frequency, exercise choice, exercise order and inter-set rest intervals [169]. Their presence determines different effects on brain adaptation in terms of antioxidant defenses and oxidative stress status.

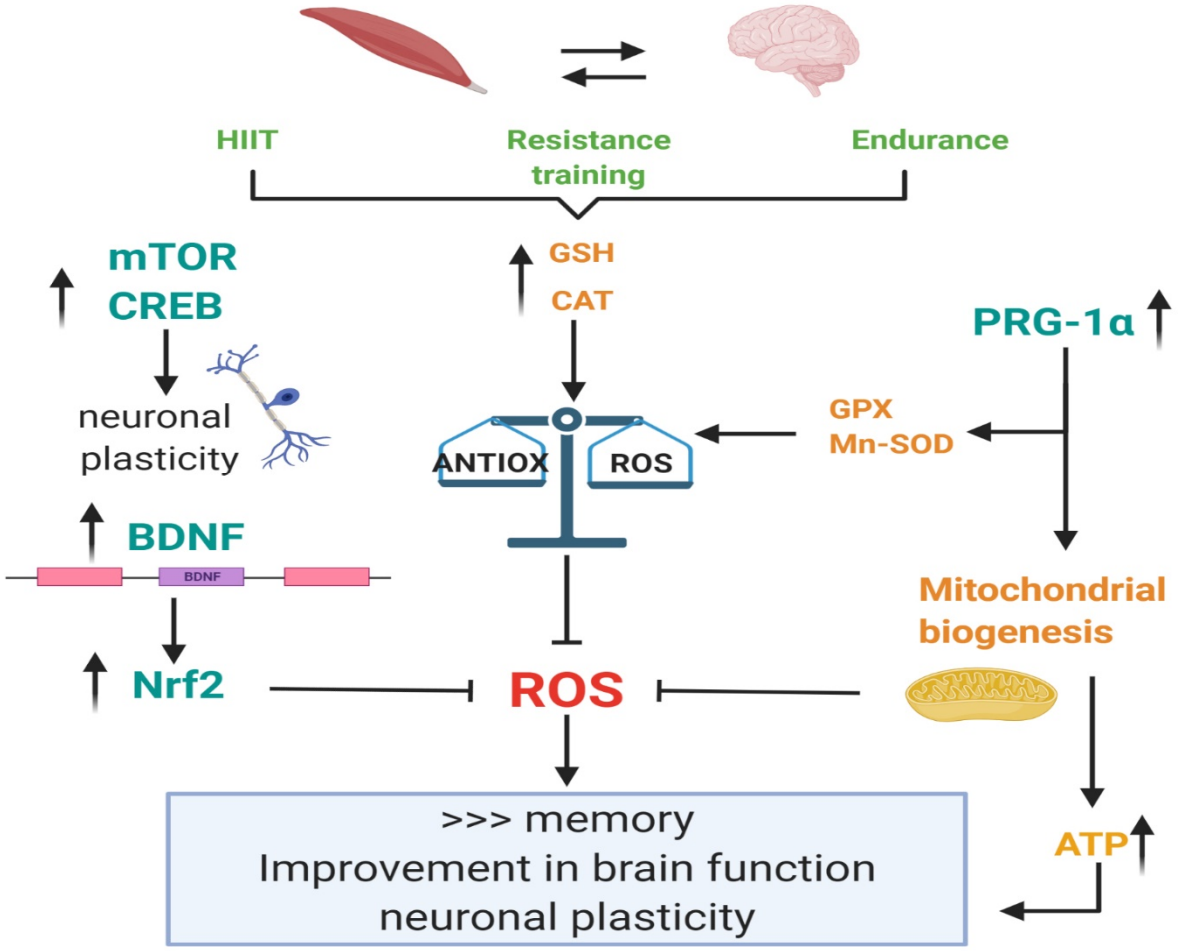


**Figure 3** Beneficial effects of physical activity. Physical activity is able to induce cerebral adaptations by decreasing the levels of oxidant species and by increasing the antioxidant defenses. After regular exercise, upregulation of endogenous antioxidants is achieved, such as glutathione peroxidase (GSH) and catalase (CAT); the mammalian target of rapamycin (mTOR) pathway is activated and Brain-derived Neurotrophic Factor (BDNF) gene expression increases leading to the activation of nuclear factor erythroid 2-related factor 2 (Nrf2). Following exercise, up-regulation of the peroxisome proliferator-activated receptor- $\gamma$ coactivator 1 $\alpha$ (PGC-1 $\alpha$) is also obtained. All these pathways lead to a reduction of ROS, an increase in memory and cognitive functions, as well as neuronal plasticity.

## 9. Conclusions

In the light of the above, antioxidant molecules seem to be protective against free radical damage that affects brain cells. It is possible to assume that, their intake could be fundamental to delay a potential onset of neurodegenerative diseases and improve cognitive functions. Moreover, physical activity, because of its neuroprotective role against the oxidative stress, should be performed just to amplify the effect of the antioxidant intake in patients affected by these disorders.

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