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REVIEW ARTICLE

# "Polyphenolic-food" Effects on Brain Health (Human Data review)

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## Abstract

Preventive strategies and nutritional interventions seem to be promising approaches to delay neurocognitive decline and reduce the risk of neurodegenerative diseases. Among the various nutritional protocols, numerous studies confirm: the Mediterranean diet is the best food style to preserve the decay of our brain and live long. The elderly who constantly follow this type of diet would have a brain less "consumed" than those who follow a different food style. But what are the magic molecules present in fruits, vegetables, olive oil, legumes, able to protect us from aging and degenerative phenomena? The polyphenols: phytochemicals that fight cellular aging by counteracting the action of free radicals. These substances are able to stimulate cell repair systems, to amplify the endogenous antioxidant defenses, to specifically inhibit the action of inflammatory molecules. The trigger of this defensive response is linked to the peculiar ability of the polyphenols to modulate specific signaling mechanisms and transcription factors.

Here we review the role of some "polyphenolic-food" of Mediterranean diet for the maintenance of cognitive performance, focusing specifically on human studies and the beneficial effects associated with overall diet composition, rather than single nutrient supplementations, for the prevention or the delay of neurodegenerative diseases.

**Keywords:** antioxidants, brain, Mediterranean diet, neurodegeneration, nutrition, polyphenols

## Abbreviations:

| | |
|---|---|
| CBVD | CereBroVascular Disease |
| CNS | Central Nervous System |
| CVD | CardioVascular Diseases |
| EVOO | Extra Virgin Olive Oil |
| HD | Huntington's Disease |
| MedDiet | Mediterranean Diet |
| ND | Neurodegenerative Diseases |
| PD | Parkinson's Disease |
| RNS | Reactive Nitrogen Species |
| ROS | Reactive Oxygen Species |

## Introduction

Neurodegenerative diseases represent a major threat to human health. These age-dependent disorders are becoming increasingly prevalent, in part because the elderly population has increased in recent years[1-3]. While genetic factors play an important role in age-related memory decline, such nongenetic lifestyle factors as diet and exercise contribute as well[4-6]. Several clinical trials of antioxidant use in subjects with normal aging or Alzheimer's disease suggest memory benefits[7,8], while others yielded negative results[9-13].

Many fruits are rich in various antioxidants, including ascorbic acid, carotenoids, and phenolics, commonly consumed fruits show large differences in antioxidant capacity, as determined by the ferric reducing/antioxidant power (FRAP) assay[14]. In particular, there is special interest in the polyphenols, which have been studied extensively in animal models of Alzheimer's disease[15,16]. For example, emerging data on pomegranate fruits and their inherent polyphenols suggest positive benefits ranging from neuroprotective effects to staving off effects of senescent neurodegeneration in animal models of Alzheimer's disease[17-20].

Therefore, many potential approaches are currently under investigation worldwide. One of the most intriguing and appealing lines of investigation is the association between lifestyle habits such as diet and dietary compounds and the occurrence of neurodegenerative diseases and a common factor recognized in many neurodegenerative diseases and age-related degenerative processes is oxidative stress: the brain is particularly susceptible to oxidative stress due to the high consumption of oxygen[21-31].

## Search Methodology

Literature searches used for this article include PubMed, and Google Scholar database ranging from the year 1970 to January 2019. Data relating to human trials have been included.

## Brain and Natural antioxidants

In recent years, neurodegenerative diseases are increasing exponentially in industrialized countries, and also in developing countries. The latest data presented by the Alzheimer

Association speak of a triplication of Alzheimer's cases from today at 2050, and for that date it is expected that in the Western world one in three elderly will be affected by Alzheimer.

These are huge numbers, unsustainable for any health system[32]. In this context, find substances that increase the natural defenses of the brain, slowing death of neurons and preventing the onset of cognitive diseases, is increasingly a socio-health emergency[33].

Among the environmental variables, the diet is certainly the one most able to influence our state of health and the quality of aging, and this seems to be true also for the brain.

Recently the World Dementia Council has asked the Alzheimer Association to evaluate and develop a consensus document on modifiable risk factors for cognitive decline and dementia. The Alzheimer Association concluded that in addition to regular physical activity, factor control of cardiovascular risk and continuous mental "training", a critical element in reducing risk to develop cognitive deficits and dementia during aging, is played by the diet, identifying specifically the Mediterranean diet as the best nutritional strategy to maintain correct brain function[34]. Numerous epidemiological, observational studies and, recently, also solid studies of intervention emphasized the importance of some compounds contained in food in supporting a correct cerebral physiology and in conditioning the cognitive processes and the tone of the humor[35]. The role of essential nutrients, non-essential compounds and even non-nutrients derived from diet and use of nutraceutical substances capable of positively interfering with inflammation and stress are, therefore, increasingly seen as a potential preventive strategy against neurodegenerative diseases and of brain aging in general[36].

Many antioxidant compounds derived from natural products have demonstrated neuroprotective activity in either in vitro or in vivo models of neuronal cell death, but studies that examine possible brain mechanisms of polyphenol treatment in humans are limited.

The greatest part of molecules with antioxidant action is present in food, and particularly in plant foods. Plants are immobile and cannot escape from adverse environmental effects as easily as other organisms such as animals. For this reason, plant systems have adapted to survive in extreme conditions, e.g., illumination, high temperature, draught, and freezing, which could lead to oxidative damage due to excessive production of free radicals. These developed antioxidative mechanisms involve a wide array of compounds, which includes superoxide dismutase, catalase, and important antioxidant metabolites such as ascorbate, glutathione, tocopherol, carotenoids and phenolic compounds such as flavonoids and anthocyanins. These natural substances help to delay or prevent certain types of damage to the cell. They play an instrumental role in protecting fats, enzymes, and vitamins.

Studies have shown that antioxidants may help to counteract the unstable molecules that comprise free radicals, counteracting the negative effects of oxidative stress. Recent studies discovered that antioxidants may reverse some of the symptoms of aging (such as memory loss). Free radical attack on brain cells results in memory loss. The brain is particularly susceptible to oxidative stress because of its high demand for oxygen[28]. Due to neurons' high cellular respiration rate, and low antioxidant defense system they are also highly vulnerable to oxidative stress

particularly in an aging brain[37]. This makes the brain more susceptible to free radical attack than just about any other area of the body.
Antioxidants are essential to scavenge free radicals and not only protect the central nervous system from further degradation but potentially reverse some of the damage that has already been done. It has been suggested that one of the main mechanisms of neurodegeneration is from the increased and long-term effects of oxidative stress[37-40].

The efficacy of antioxidants comes from their chemical structure, composed of one or more aromatic rings with several hydroxyl groups attached. These hydroxyl groups trap excess electrons balancing ROS/RNS[41]. Certain antioxidants based on their chemical structure, i.e., the number of rings and the chemical element that binds them together, may be better at trapping excess electrons and be a stronger antioxidant. The structure also plays a role when getting through the blood-brain barrier, which depends on a number of factors such as size and lipophilicity.
Brightly colored fruits and vegetables, such as the typical foods of the Mediterranean diet, are a great source of antioxidants. In general, the concentration of antioxidants is directly proportional to the fruit brightness.

## NUTRITION AND LONGEVITY: MEDITERRANEAN DIET

Several studies have attempted to define the factors responsible for the extreme longevity; longevity is explained by both genetic and environmental factors although in different proportions[42,43]. Several studies involving dietary patterns have shown that specific dietary patterns are potentially associated with longevity although the results are complex and difficult to define[42-44].

In the 1960s, the results of an epidemiological study developed by Ancel Keys, in which the dietary aspects and lifestyle of the people were analyzed, showed that the population living in the vicinity of the Mediterranean Sea had a lower incidence of cardiovascular diseases (CVD), which was correlated with diet, the concept of the Mediterranean diet was born from that moment[45,46] . The term "Mediterranean diet" refers essentially to a diet based on the intake, in large quantities and clearly prevalent, of vegetables, fruit, legumes, nuts, cereals and whole foods, together with olive oil (as the main source of fats) and fish, while meat, especially red meat and its derivatives (sausages and various cold cuts), is consumed in moderate quantities; accompanying meals with spices and wine intake a moderate amount[46-49].

Subsequently, the diets of 5 populations with extraordinarily high longevity have been recently described and labeled "Blue Zones"50 Populations of Okinawa, Japan; Sardinia, Italy; Loma Linda, California; the Nicoya Peninsula, Costa Rica and Ikaria, Greece seem to have a high prevalence of centenarians and a preferential attitude toward a plant baseddiet[50].

Although the scientific literature regarding diet and life span is complex and with different opinions, there are qualified studies like the previous quoted Seven Countries Study on Mediterranean diet and the Dietary Approaches to Stop Hypertension[51] that have evaluated the effect of diet on the development and the progression of some diseases. In fact, regardless of the diversity in scientific approach, evidence has supported the view that diets rich in vegetables and fruits, containing a high quantity of phytonutrients and antioxidants, but with reduced amounts of

meat, refined grains, saturated fat, sugar, salt, and full-fat dairy products, are associated with reduced risk of CVD, some cancers, diabetes, Alzheimer disease, and several other chronic diseases[43,51,52] .

In 2006, in a northern Manhattan cohort, findings on overall diet and cognition suggest that high adherence to the Mediterranean diet decreases the risk of cognitive decline and AD in a not demented elderly population[53] and decreases the risk of mortality in AD patients[54]. More recently in the same cohort, higher adherence to the MedDiet was associated with a trend for reduced risk of developing mild cognitive impairment (MCI) and with reduced risk of MCI conversion to AD[55]. In a subsample of 1410 subjects included in the E3C Bordeaux cohort[56] with 5 year follow-up after a 24-hour dietary recall, higher adherence to MedDiet was not associated with the risk for incident dementia but was associated with a slower cognitive decline. In an associated editorial, Knopman[57] suggests that the MedDiet may act on cognition through cerebrovascular mechanisms or by affecting the metabolism of the β-amyloid or the tau protein and that effects may be brought about by some components of the MedDiet.

Two multicenter, randomized, controlled trials, the so-called PREvención con DIeta MEDiterránea (PREDIMED) and PREDIMED-NAVARRA studies have been carried out in Spain on people at high cardiovascular risk. The PREDIMED study was a primary prevention trial originally designed to test the long-term effects of the MedDiet on the incidence of CVD in people with high cardiovascular risk. The cohort was also evaluated for cognitive performance, after adjustment for several potentially interfering factors. It emerged that an intervention with a MedDiet enriched in extra virgin olive oil (EVOO) (better than with wine or nuts) significantly improved cognition, and that EVOO phenolic content was the main factor responsible for this result[58-60].

On the other hand, a low adherence to the Mediterranean diet has been linked to a greater predisposition to suffer mild cognitive deterioration and AD[43,61]. In a cross-sectional study, the association between adherence to a MedDiet and risk for Alzheimer's disease and mild cognitive impairment in a large, elderly, Australian cohort subjects was evaluated. It was demonstrated that Australian cohort, AD and mild cognitive impairment participants had a lower adherence to the MedDiet than healthy controls participants[61], reason why it is established that this diet could have a neuroprotective role due to its anti-inflammatory effect, the decrease in oxidative stress and the cardiovascular protection it generates[62].

On November 16, 2010, UNESCO included the Mediterranean diet in the Heritage List Intangible Cultural Heritage of Humanity. The Mediterranean diet is a food model that characterizes not only a lifestyle, but also a culture and has been reported as a means to improve health, quality of life and life span itself (expectation of life).

The Mediterranean diet can be considered a nutritional pool comprising different nutraceuticals (bioactive components present and conveyed by food) able to favorably influence the health[43]. Therefore, MedDiet seems to have a positive effect on the onset of neurodegenerative diseases as, by way of example, Alzheimer's disease: the greater consumption of foods that constitute the "backbone" of this diet (vegetables, fruit, legumes, cereals, fish, dried fruit and monounsaturated fatty acids [MUFA] such as olive oil at the expense of lower consumption of meat, dairy products and alcohol) seems to constitute a factor of protection against these pathologies[47]. Recent studies

have also associated with this nutritional approach is the recognition of a greater length of telomeres, one of the biomarkers of aging[63], then in general individuals who they follow this dietary regime have a longer life expectancy. The low content of animal proteins and the low glycemic index of MedDiet directly modulate the mTOR and IGF-1 levels, known to be involved in the process of aging and longevity.

In addition to the diet, it is established that physical activity on a regular basis causes an increase in blood flow, improves oxygenation and glucose intake at the brain level, in addition to activating growth factors that promote an increase in cerebral capillary density[64]. The stimulation of brain and intellectual activity through games, puzzles, crosswords and the promotion of reading would also have a favorable role in protecting against the development of AD[65,66].

In 2006, a prospective study was conducted seeking to relate the consumption of the Mediterranean diet with the risk of developing AD, obtaining as a relationship a decrease between 9 to 10% of the risk. Like this study, there are others who managed to relate diet and AD in some way, however, not all studies have been conclusive in achieving correlations. This could be due to the difficulty of standardizing the studies, since the geographic, cultural, socio-demographic and environmental conditions cannot be controlled and could interfere with the results obtained[67].

But what are the magic molecules present in fruits, vegetables, olive oil, legumes, able to protect us from aging and degenerative phenomena? Polyphenols, which have nutritional interest as micronutrients, are particularly abundant in several foods (vegetables, fruits), oils (argan and olive oils) and beverages (red wines) associated with in the Mediterranean diet[68]. Despite their wide distribution, studies on the beneficial effects they have on human health began only in the mid 1990s. For this reason, one of the most intriguing and appealing evidence of the recent literature is the association between lifestyle habits such as diet and dietary compounds and the occurrence of neurodegenerative disease. In this review, we will focus on studies that investigated the association between nutrition and neurodegenerative disease, with our attention on the role of "polyphenolc-food" tipycal of Mediterranean-like diet.

## What are polyphenols? Nomenclature, classifications and occurrence in foods

Polyphenols are a wide group of bioactive compounds naturally occurring in plants as secondary metabolites. These molecules share a common phenolic structure composed of hydroxyl groups on an aromatic ring. According to the number and arrangement of the phenol rings, polyphenols can be divided into different classes. There are currently about 8000 different polyphenols, divided into at least 10 different classes based on their chemical structure. Phenolic compounds have at least one aromatic ring with one or more hydroxyl groups attached and are classified as flavonoids and nonflavonoids. They are classified as:

(1) flavonoids including flavanols, isoflavones, flavanones, flavonones, and anthocyanidins;

(2) nonflavonoids such as phenolic acids (groups of compounds derived from benzoic and hydroxycinnamic acids), stilbenes, and lignans; tannins are flavonoid polymers (Fig. 1)

The most abundant classes present in fruits and fruit-derived beverages are phenolic acids, phenolic alcohols, flavonoids, stilbenes and lignans. Within these classes phenolic acids and flavonoids represent 30 and 60%, respectively, of total PP intake with the Mediterranean diet.

Polyphenols are the most abundant antioxidants in our diet and are widespread constituents of fruits, vegetables, cereals, olive, dry legumes, chocolate and beverages, such as tea, coffee and wine. Despite their wide distribution, the health effects of dietary polyphenols have come to the attention of nutritionists only in the last years. The main factor responsible for the delayed research on polyphenols is the variety and the complexity of their chemical structure They tend to donate an electron or a hydrogen atom to a free radical and convert it into an inoffensive molecule. Therefore, phenolics have relevant in vitro and in vivo antioxidant activities. Phenolic compounds occur in free and conjugated forms with sugars, acids, and other biomolecules as water-soluble (phenolic acids, flavonoids and quinones) or water-insoluble compounds (condensed tannins). Processed foods and beverages, such as black tea, matured red wine, coffee, and cocoa, may contain phenolic transformation products that are best described as derived polyphenols[68-73].

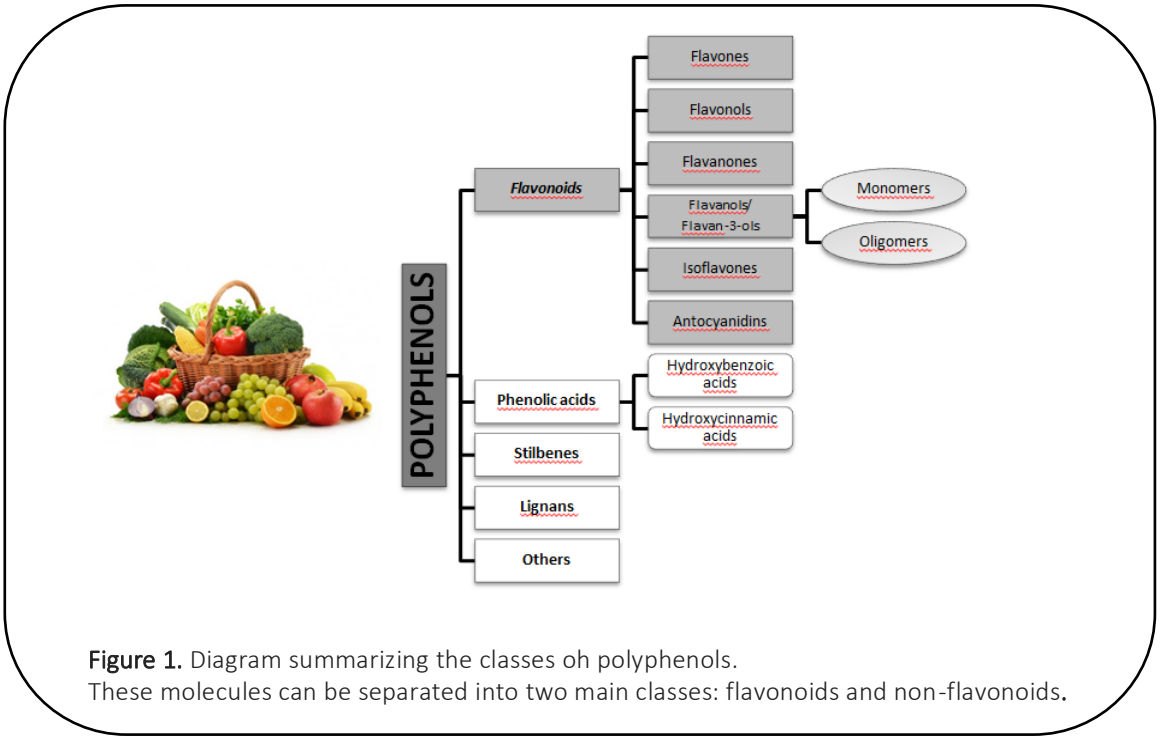


**Figure 1.** Diagram summarizing the classes oh polyphenols.
These molecules can be separated into two main classes: flavonoids and non-flavonoids.

## Biological effects of Polyphenols

Historically, polyphenols were mostly of interest to plant scientists as they play many roles in plants and form part of the class of secondary metabolites or phytochemicals. In planta, they protect against stresses such as UV light, deter attacks from pests and provide colour to attract certain insects. In the 1930s, one of the flavonoids, hesperidin, was proposed to be classified as a vitamin, vitamin P, and although this did not lead to an accepted classification, it was followed by numerous papers in the 1950s showing protective effects on the vascular system Polyphenols are botanical nutraceuticals which have antioxidant properties. This characteristic is what makes polyphenols important to neuroprotective studies. Along with their antioxidant properties against ROS, polyphenols are known to have other health benefits such as anti-inflammatory, anti-cancer, anti-ulcer, and anti-infective properties[74-81]. Polyphenols may also have indirect peripheral effects[81], such as improving cardiovascular health resulting in

increased blood flow to the brain[82,83]. Some antioxidants are found in the body naturally while others need to be obtained in the diet[84].

The wide and increasingly recognized beneficial properties of plant polyphenols have led to proposing them as *nutraceuticals* and the aliments containing them as functional foods. The latter are defined as "Natural or processed foods that contain known or unknown biologically-active compounds; these foods, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic diseases"[26]. There are a number of studies that have indicated that the consumption of polyphenols-rich plant foods and extracts may also be capable of inducing improvements in cognitive performance. A combination of preclinical and epidemiological studies suggests that polyphenols may be effective in reversing neurodegenerative pathology and age-related declines in neurocognitive performance, although at present, a direct association between polyphenol consumption and improvement in neurological health has not been made. The potential of polyphenols to improve neurological health appears to be related to a number of mechanisms, including their ability to interact with intracellular neuronal and glial signaling, to influence the peripheral and cerebrovascular blood flow, and to reduce neuronal damage and losses induced by neurotoxins and neuroinflammation[85-92].

Research on the neuroprotective effects of diet polyphenols has developed considerably in recent years. Furthermore, it is believed that the mechanism of action of the polyphenols goes beyond the antioxidant activity only to the attenuation of oxidative stress.

Flavonoids are naturally occurring phytochemicals found in a variety of fruits and vegetables and offer color, flavor, aroma, nutritional and health benefits. Flavonoids have been found to play a neuroprotective role by inhibiting and/or modifying the self-assembly of the amyloid-β (Aβ) peptide into oligomers and fibrils, which are linked to the pathogenesis of Alzheimer's disease. The neuroprotective efficacy of flavonoids has been found to strongly depend on their structure and functional groups. Flavonoids may exist in monomeric, as well as di-, tri-, tetra- or polymeric form through C-C or C-O-C linkages. It has been shown that flavonoids containing two or more units, e.g., biflavonoids, exert greater biological activity than their respective monoflavonoids. For instance, biflavonoids have the ability to distinctly alter Aβ aggregation and more effectively reduce the toxicity of Aβ oligomers compared to the monoflavonoid moieties. Although the molecular mechanisms remain to be elucidated, flavonoids have been shown to alter the Aβ aggregation pathway to yield non-toxic, unstructured Aβ aggregates, as well as directly exerting a neuroprotective effect to cells. In this chapter, we review biflavonoid-mediated Aβ aggregation and toxicity, and highlight the beneficial roles biflavonoids can potentially play in the prevention and treatment of Alzheimer's disease[93].

Polyphenols have been associated with a reduced risk of developing dementia, an improved cognitive performance in normal aging and an improved cognitive evolution. Letenneur et al.[94] performed a prospective cohort study over a 10-year period among subjects aged 65 years or older to investigate the relation among antioxidants, cognitive decline, and dementia. A total of 1,640 subjects free from dementia at baseline in 1990 and with reliable dietary assessments were re-examined four times over a 10-year period. Cognitive functioning was assessed through three psychometric tests. Information on flavonoid intake was collected at baseline. After adjustment

for age, sex, and educational level, flavonoid intake was associated with better cognitive performance at baseline and with a better evolution of the performance over time. Subjects included in the two highest quartiles of flavonoid intake had better cognitive evolution than subjects in the lowest quartile. After 10 years' follow-up, subjects with the lowest flavonoid intake had significantly worse performance on psychometric tests, even after adjustment for several other potential confounders[94,95]. In a cross-sectional study, Nurk et al.[96] examined the relation between the intake of three common foodstuffs that contain flavonoids (chocolate, wine, and tea) and cognitive performance. More than 2,000 participants (aged 70–74° years; 55 % women) recruited from the population-based Hordaland Health Study in Norway underwent cognitive testing. Participants who consumed chocolate, wine, or tea had significantly better mean test scores and a lower prevalence of poor cognitive performance than those who did not. Participants who consumed all three studied items had the best test scores and the lowest risks of poor test performance. The associations between the intake of these foodstuffs and cognition were dose dependent, with maximum effect at intakes of 10 g/day for chocolate and 75–100 mL/day for wine, but were approximately linear for tea. The effect was most pronounced for wine and modestly weaker for chocolate intake. Therefore, in the elderly, a diet high in some flavonoid-rich foods is associated with better performance in several cognitive abilities in a dose-dependent manner[95,96].

The neuroprotective actions of dietary polyphenols involve a number of effects within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning, and cognitive function. While many of the mechanisms underpinning their beneficial effects remain to be elucidated, it has become clear that they partly involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling, and may also involve hormetic effects to protect neurons against oxidative and inflammatory stressors.

Emerging evidence suggests that dietary-derived flavonoids have the potential to improve human memory and neurocognitive performance by their ability to protect vulnerable neurons, enhance existing neuronal function, and stimulate neuronal regeneration[97]. Long-term potentiation is widely considered to be one of the major mechanisms underlying memory acquisition, consolidation and storage in the brain, and is known to be controlled at the molecular level by the activation of a number of neuronal signaling pathways. These pathways include the phosphatidylinositol-3 kinase/protein kinase B/Akt (Akt), protein kinase C, protein kinase A, calcium–calmodulin kinase and mitogen-activated protein kinase pathways. Growing evidence suggests that flavonoids exert effects on long-term potentiation, and consequently memory and cognitive performance, through their interactions with these signaling pathways[96]. Of particular interest is the ability of flavonoids to activate the extracellular signal-regulated kinase and the Akt signaling pathways, leading to the activation of the cyclic adenosine monophosphate response element binding protein, a transcription factor that increases the expression of a number of neurotrophins important in long-term potentiation and long-term memory. One such neurotrophin is Brain-Derived Neurotrophic Factor, which is known to be crucial in controlling synapse growth, promoting an increase in dendritic spine density, and enhancing synaptic receptor density[96].

A common molecular feature of amyloid neurodegenerative diseases is the unfolding/misfolding of specific proteins/peptides which consequently become prone to aggregate into toxic assemblies and deposits that are the key histopathological trait of these pathologies. Apart from the rare early-onset familiar forms, these neurodegenerative diseases are age-associated disorders whose symptoms appear in aged people after long incubation periods. This makes the therapeutic approach particularly compelling and boosts the search for both early diagnostic tools and preventive approaches. In this last respect, natural compounds commonly present in foods and beverages are considered promising molecules, at least on the bench side. The so-called *nutraceutical approach* suggests life-long healthy diets, particularly focusing on food molecules that are candidates to enter clinical trials as such or following a targeted molecular engineering. Natural phenols abundant in 'healthy' foods such as extra virgin olive oil, red wine, green tea, red berries and spices, appear particularly promising[98].

The focus of this min-review is on Mediterranean diet food as natural sources of neuroprotective phenolic compounds, identifying foods rich in phenolic compounds that are acknowledged to be *polyphenolic-foods* for the brain. The foods that comprise our categorization of "polyphenolic-foods" are red wine, olive oil berries and fruits. With the exception of olive oil and berries, the other "superfoods" have at least one well-studied polyphenol that they are abundant in, as resveratrol, epicathechins, quercetin, but will be discussed effects of polyphenol rich foods. This review will address these foods and their effects based on findings using the whole food or extracts thereof as a collective of mixed phenolics and it will reported only data related of human trials.

## MEDITERRANEAN DIET: A COCKTAIL OF POLYPHENOLS TO NOURISH THE BRAIN.

Olive oil, nuts, red wine, fruits, vegetables, key components of the MedDiet, are all polyphenol-rich foods and are believed to contribute to the beneficial effects of this diet. In this section, we aim to provide information on neuroprotective effects of MedDiet polyphenolic-food, focusing specifically on human studies.

### Beverage: Red Wine (resveratrol, quercetin, anthocyanins)

The Mediterranean Diet recognizes as positive the moderate and daily intake of wine during meals and, "the wine is exaltation of the therapeutic value of good food". Wine consumption has been popular worldwide for many centuries. Based on in vitro and in vivo studies, a certain amount of everyday wine consumption may prevent various chronic diseases. This is due, in part, to the presence and amount of important antioxidants in red wine, and, therefore, research has focused on them. Grape is one of the richest sources of polyphenols, with red varieties containing a substantially higher polyphenolic content than white (2.5g/L in red wine vs. 0.3g/L in white wine). Resveratrol, anthocyanins, and catechins have hight antioxidant power. Resveratrol is active in the prevention of cardiovascular diseases by neutralizing free oxygen radicals and reactive nitrogenous radicals; it penetrates the blood-brain barrier and, thus, protects the brain and nerve cells. It also reduces platelet aggregation and so counteracts the formation of blood clots or thrombi. Neuroprotective benefit has been attributed to a moderate consumption of wine, more specifically red wine[99].

A population-based prospective study in the Bordeaux region found that consuming three to four glasses of wine per day, which contains resveratrol, was associated with an 80% lower incidence

of dementia and Alzheimer's disease compared to non-drinkers[100]. Other epidemiologic evidence from the Copenhagen City Heart Study has shown that monthly or weekly red wine was associated with a reduced risk of neurodegenerative diseases, while the other alcoholic beverages studied, beer and spirits, were not[101].

Swada et al, conducted a randomized, double-blind, placebo-controlled phase II trial of resveratrol for subjects with mild to moderate AD. Resveratrol is detectable in the cerebrospinal fluid (at low nanomolar levels), is safe and well tolerated, alters the trajectories of the AD biomarkers, preserves the integrity of the blood-brain barrier and modulates the CNS immune response. However, scholars believe that further studies are needed to determine the safety and efficacy of resveratrol and the validity of this approach in the treatment and prevention of AD and other diseases of aging[102].

A clinical study, completed in 2014, included 119 patients with mild to moderate Alzheimer's disease. Participants took capsules containing placebo or resveratrol, starting with a dose of 500 mg per day and increasing up to 1 gram twice a day.

The researchers measured the blood levels of beta-amyloid-40 of the participants, a protein that typically decreases in the blood while Alzheimer's disease progresses. Patients treated with resveratrol showed little or no change in blood levels of beta-amyloid-40, while a decrease was observed in the placebo group. An analysis of 19 participants from each of the resveratrol and placebo groups also showed that resveratrol restores the integrity of the blood-brain barrier, the role of which is the restriction of the movement of molecules and cells between the blood system and the brain. Patients treated with resveratrol had lower levels in their cerebrospinal fluid (the fluid surrounding the brain and spinal cord) of a protein that breaks the blood-brain barrier at elevated levels[103].

The role of resveratrol in neurodegenerative diseases is still unclear, although some recent studies on red wine bioactive compounds suggest that resveratrol modulates multiple mechanisms of Alzheimer's disease pathology. Wine polyphenols could contribute to a better cognitive performance due to their protective effects against oxidative stress, which increases with age and is a risk factor for age-associated cognitive decline. Further possible neuroprotective mechanisms of polyphenols including resveratrol are reduced mitochondrial dysfunction, glucose toxicity, oxidative damage, and chronic inflammation, by improving glucose metabolism and vascular functions and by activating so-called longevity genes including the sirtuins[99,104].

## FRUITS

The *Pomegranate* (Punica granatum) is a rich source of bioactive compounds with antioxidant capacity. In recent years, studies have shown that this fruit has numerous benefits to human health, which has increased interest in studying its therapeutic properties[105,106]. In mouse models of Alzheimer's disease, the consumption of a diet rich in pomegranate pulp or the direct consumption of the fruit's juice increased behavioral performance and reduced amyloid plaque deposition in the hippocampus by 50%[107]. The function of pomegranate pulp has been attributed to its antioxidant capacity given by phenolics, such as gallic acid, punicalagin α and punicalagin β, of which the latter two polyphenolics are unique to the pomegranate. Punicalagin is hydrolysable

tannin (ellagitannin) with recognized antioxidant, anti-inflammatory and antiproliferative activities. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents[105,106].

Bookheimer et al[108] performed a preliminary, placebo-controlled randomized trial of pomegranate juice in older subjects with age-associated memory complaints using memory testing and functional brain activation (fMRI) as outcome measures. Thirty-two subjects were randomly assigned to drink 8 ounces of either pomegranate juice or a flavor-matched placebo drink. Subjects received memory testing, fMRI scans during cognitive tasks, and blood draws for peripheral biomarkers before and after the intervention. After 4 weeks, only the pomegranate group showed a significant improvement in the Buschke selective reminding test of verbal memory and a significant increase in plasma antioxidant capacity. Furthermore, the pomegranate group had increased fMRI activity during verbal and visual memory tasks. These results suggest a role for pomegranate juice in augmenting memory function through task-related increases in functional brain activity. The presence of polyphenol metabolites validated compliance with the experimental regimen and efficacy of pomegranate juice in releasing polyphenols. Although the duration of this study was short, there is evidence in the animal literature suggesting that antioxidant use can affect cerebral blood flow, including task-related cerebral blood flow, acutely and over short time intervals as in the present study Future studies are needed to validate these results within larger samples and determine the long-term effects of pomegranate juice on a range of comprehensive cognitive functions.

The *Apples* have long held a terrific reputation for keeping the doctor away, some specific studies on their brain-boosting benefits are worth noting. An apple a day may supply major bioactive compounds, which may play an important role in reducing the risk of neurodegenerative disorders. A University of Massachusetts-Lowell study led by Shea et al. showed that apples and apple juice helped mice with an Ahlzheimer's-like defect improve memory tasks and quercetin was found to protect rat brain cells from oxidative stress[109].
Not all apples are the same also in terms of quantity of antioxidant and anti-inflammatory polyphenols; the Annurca variety, the MedDiet apple, contains a number of higher polyphenolic molecules and possesses remarkable properties[110-113].

Preclinical studies demonstrate that apple juice exerts multiple beneficial effects including reduction of central nervous system oxidative damage, suppression of Alzheimer's disease hallmarks, improved cognitive performance, and organized synaptic signaling. Rubio-Perez et al have[114] tested whether daily consumption of a beverage with high antioxidant power combining extracts of green tea and apple over a period of eight months could affect biomarkers of inflammation in AD patients in initial phase, moderate phase and a control group. Administration of the antioxidant beverage to the three groups did not produce a significant change in serum levels of the anti-inflammatory cytokines interleukin-4 and interleukin-10. In contrast, decreased serum levels of the pro-inflammatory cytokines interleukin-2, interferon-γ and tumor necrosis factor-α. AB was more effective against inflammation in the early period of AD, and could be used as a natural complementary therapy to alleviate or improve symptoms of inflammation in early stages of AD[114].
Remington et al, have initiated an open-label clinical trial in which 21 institutionalized individuals with moderate-to-severe AD consumed 2 4-oz glasses of apple juice daily for 1 month. Participants

demonstrated no change in the Dementia Rating Scale, and institutional caregivers reported no change in Alzheimer's Disease Cooperative Study - Activities of Daily Living in this brief study. However, caregivers reported an approximate 27% improvement in behavioral and psychotic symptoms associated with dementia as quantified by the Neuropsychiatric Inventory, with the largest changes in anxiety, agitation, and delusion. This pilot study suggests that apple juice may be a useful supplement, perhaps to augment pharmacological approaches, for attenuating the decline in mood that accompanies progression of AD, which may also reduce caregiver burden[115].

*Berries* are one of the best options for polyphenol related neuroprotective studies because they contain several different kinds of these compounds that can work together and have a synergistic effect in the central nervous system[116]. Blackberries, blueberries, currants, strawberries, small red fruits, raspberries, gooseberries are an extraordinary source of polyphenols: anthocyanins. Anthocyanins have been identified in several brain areas and have been associated with neuroregeneration and protection[117,118]. This is important, especially with regard to localization of a particular antioxidant in the brain[119], and for activating neuroprotective response pathways[120]. Berries are also very promising because they have more than one mechanism of action when it comes to neuroprotection: antioxidant thanks to the antocyanoside components and modulator of the synthesis of proteins actively involved in the structure and in the metabolism of nerve cells[120]. Antioxidants are not taken up equally into all brain areas either. For example, uptake of vitamin E, a potent antioxidant not found in berries, is lower in the striatum compared to other brain areas[119,121].

There is now substantial evidence suggesting that the ingestion of diets high in berries can have positive effects on the brain[122], it is still controversial whether this is due to direct or indirect effects on nervous system tissue[123]. Although most polyphenols that have been analyzed can be absorbed from the gastrointestinal tract and then distributed to blood and tissues, they additionally must be able to get across the blood-brain barrier in order to have a direct effect on the brain. Some research has demonstrated that dietary polyphenols can cross the blood-brain barrier and anthocyanins specifically have been detected in brain tissue after oral administration to rodents and pigs[121]. Estimates of specific anthocyanins in brain tissue are in the sub-nanomolar range (~0.2–0.25 nmol/g tissue), or even as low as the femtomolar range. It is also possible that polyphenolic compounds contained in extracts that are tested in vitro may not be the predominate forms that would actually enter the brain. Although anthocyanins arguably have good bioavailability, they do undergo significant metabolism, producing diverse metabolites. Some evidence suggests that certain polyphenolic compounds are maintained in their natural glycosylated form. Xenobiotic metabolism also likely contributes to the amounts and forms of polyphenols that cross the blood-brain barrier, as additional evidence has demonstrated that glucuronide forms of anthocyanins can be detected in the brain. It is also possible that metabolites of anthocyanins may compete for entry into the brain and therefore more well-designed studies on the ability of anthocyanins to cross the blood-brain barrier are necessary. These issues of bioavailability in the nervous system should be taken into consideration for in vivo and in vitro studies involving polyphenols in berries[121]. A clinical study conducted in 2010 investigated the effects of daily wild blueberry juice consumption for 12 weeks in adults experiencing early memory decline[124]. Regarding list recall and paired associate learning, the group administered the berry juice performed exceptionally better than the placebo group. The findings of this preliminary study suggest that moderate-term blueberry supplementation can confer neurocognitive benefit and

establish a basis for more comprehensive human trials to study preventive potential and neuronal mechanisms. Even though these preliminary results are encouraging, the study is highly debatable however as the sample size was only nine[121].

A recent study, 13 men and 24 women, between the ages of 60 and 75 years, were recruited into a randomized placebo-controlled trial in which they consumed either freeze-dried blueberry (24 g/day, equivalent to 1 cup of fresh blueberries) or a blueberry placebo for 90 days. Participants completed a battery of balance, gait, and cognitive tests at baseline and again at 45 and 90 days of intervention. This study showed more convincingly that a diet high in blueberries can improve cognitive abilities in older adults[122].

There is now ample evidence of the benefit of berry-derived polyphenols for neurodegeneration and the brain as a whole. However studies in vivo point out the importance of understanding bioavailability. For example, how much fruit would need to be consumed daily to provide beneficial effects against brain aging or neurodegenerative disease is not known. Also, it is not known how long the beneficial effects of a diet rich in berries lasts after the berries have been consumed. Further development of nutraceuticals containing extracts from fruits and leaves may be desirable. However, further investigation is needed to determine the appropriate 'dose' for health benefits or treatment of a particular disease, without resulting in toxicity.

Walnuts, hazelnuts, almonds, pistachios: a coffin of health molecules. On 100 grams of walnuts, 57 are lipids, but are lipids of quality, similar to those of extra virgin olive oil, rich in a mix of monounsaturated and polyunsaturated fats Omega 6 and Omega 3 whose synergy produces beneficial health effects in general nervous system, cardiovascular and central, in particular; cholesterol is absent. On 100 gr of nuts, moreover, a good 25 grams are proteins with plenty of the amino acid arginine, precursor of nitric acid, a powerful vasodilator that contributes to the health of the arteries keeping them flexible and preventing the formation of plaques, in synergy with Vitamin Omega 3 and Edi which also contains walnuts and walnuts. The dried fruit also contains a fair amount of proanthocyanidins whose chemopreventive activity is known, the ability to maintain vascular function and to inhibit platelet aggregation. The synergy of polyphenols, vitamin E and polyunsaturated fatty acids (Omega 3) has been linked to a decrease in the risk of cognitive deficits associated with aging.

There is a particular focus on the three types of nuts, including almonds, hazelnuts and walnuts in the manuscripts of traditional Persian medicine as preventive agents against cerebrospathies and memory loss. Almonds, hazelnuts and walnuts provide macronutrients, micronutrients and phytochemicals that influence different pathways in AD pathogenesis such as amyloidogenesis, tau phosphorylation, oxidative stress, cholinergic pathways and some non-target mechanisms including lowering cholesterol and anti-inflammatory properties, as well as effect on neurogenesis. These nuts are recommended in neurodegenerative diseases for their protective activity of the brain and in particular for the inversion of cerebral atrophy in the case of hazelnut. The therapeutic claims of the researchers mentioned in their books are based on their clinical observations with the support of a long history of experiences. Studies conducted on cellular and animal models suggest that hazelnut, as a food supplement, improves healthy aging and could be a beneficial diet for the treatment of AD, but in humans, there is a paucity of clinical trials exploring

the effects of fruits with shell on neuropsychological function in different types of neurodegenerative diseases[125].

Data related to "The Walnuts and Healthy Aging Study (WAHA)" are still being processed. The primary aim of WAHA is to examine the effects of ingesting walnuts daily for 2 years on cognitive function and retinal health, assessed with a battery of neuropsychological tests and optical coherence tomography, respectively. All participants followed their habitual diet, adding walnuts at 15% of energy (≈30–60 g/day) (walnut group) or abstaining from walnuts (control group). The results of WAHA might provide high-level evidence of the benefit of regular walnut consumption in delaying the onset of age-related cognitive impairment and retinal pathology. The findings should translate into public health policy and sound recommendations to the general population[126].

## Condiment: Extra Virgin Olive Oil

The high content in plant polyphenols, one of the main features underlying the beneficial effects of the MD, is provided mainly by the use of EVOO, the main source of alimentary lipids. More than 200 different chemical compounds have been detected in olive oil including sterols, carotenoids, triterpenic alcohols and phenolic compounds. Phenolic compounds are also the main antioxidants found in virgin olive oil[127-130]. The main phenolic subclasses present in olive oil are phenolic alcohols, phenolic acids, flavonoids, lignans, and secoiridoids. The main secoiridoids in olive oil are oleuropein and ligstroside, their aglycones result constituted by elenolic acid esterified to hydroxytyrosol or tyrosol respectively Other secoiridoids, derived from oleuropein and ligstroside, are oleacein and oleocanthal, the dialdehydic form of decarboxymethyl elenolic acid bound to hydroxytyrosol or tyrosol respectively[127-130].

After olive oil consumption its polyphenols are quickly metabolized and absorbed. Through the gastro intestinal tract, secoiridoid aglycones such as oleuropein and ligstroside are mainly hydrolyzed in elenolic acid plus hydroxytyrosol and tyrosol respectively. Hydroxytyrosol and tyrosol are absorbed in a dose-dependent manner, their peak plasma levels are found 1 h after ingestion. However, when administered as aqueous solution their bioavailability is particularly low, highlighting how the vehicle is important to determine hydroxytyrosol and tyrosol bioavailability[128-131].

To date many reports demonstrated that phenolics from Olea europaea L., found also in extra virgin olive oil, exert strong antioxidant properties and are able to counteract oxidative stress in brain tissue. A study evaluating the association between the traditional MD and the incidence of mortality from cerebrovascular disease (CBVD), showed that increased adherence to the MD was inversely associated with CBVD incidence[132]. These inverse trends were mostly evident among women and with respect to ischemic rather than hemorrhagic CBVD and were largely driven by consumption of vegetables, legumes, and olive oil.

Berr et al, in the "Three-City Study", have examined the association between olive oil use, cognitive deficit and cognitive decline in a large elderly population. The present report shows in a large non-demented elderly population that olive oil consumption habits are significantly associated with selective cognitive deficit and cognitive decline, independently of other dietary intakes and after

adjusting for potential confounders. Intensive use of olive oil in diet is associated with lower odds of cognitive deficit in visual memory and verbal fluency and decline in visual memory, however the relationship is not significant when assessing global cognitive functioning with the Mini-Mental-State-Examination used as an index of global cognitive performance 6,947 subjects with a brief baseline food frequency questionnaire and repeated cognitive tests were followed. Olive oil intake was categorized as none, moderate and intensive. Associations between olive oil and cognitive outcomes were examined taking into account socio-economic factors, health behaviors, health measures and other dietary intakes. Participants with moderate or intensive use of olive oil compared to those who never used olive oil showed lower odds of cognitive deficit for verbal fluency and visual memory. For cognitive decline during the 4-year follow-up, the association with intensive use was significant for visual memory but not for verbal fluency in multivariate analysis[133].

## FUTURE PERSPECTIVE AND CONCLUSIONS

The Mediterranean diet would be the best in the world: this is what emerges from the world ranking of the diets elaborated by the U.S. News & World Report, known globally for the preparation of rankings and advice for consumers. Among 41 diets examined by health experts, the Mediterranean Diet ranked #1 in Best Diets Overall, thanks to the positive effects on longevity and health benefits [https://health.usnews.com/best-diet/mediterranean-diet].

The MedDiet has been shown to exert positive effects on cognitive functions during aging and based on animal research it has been postulated that specific nutrients could exert even more directly protective effects on the aging brain, e.g., considering amyloid-beta metabolism[134]. The MedDiet has been considered for the prevention of cardiovascular and other chronic degenerative diseases focusing on the impact of a holistic dietary approach rather than on single nutrients. MedDiet is a complex eating pattern and a multitude of single components could cause beneficial effects[135,136]. Understanding these mechanisms and eventually develop preventive and therapeutic strategies based on those insights, are important issues for future research.

There is now ample evidence, in our view, of the benefit of polyphenols for neurodegeneration and the brain as a whole. However, several of the latter studies discussed in vivo point out the importance of understanding bioavailability. For example, how much fruit would need to be consumed daily to provide beneficial effects against brain aging or neurodegenerative disease is not known. Also, it is not known how long the beneficial effects of a diet rich in berries lasts after the berries have been consumed. Further development of nutraceuticals containing extracts from fruits and leaves may be desirable. However, further investigation is needed to determine the appropriate 'dose' for health benefits or treatment of a particular disease, without resulting in toxicity. Studies in vitro need to use appropriate concentrations of polyphenols that are predicted to enter the brain and reach target cells. A lot of laboratory group are further pursuing studies *in vitro* and *in vivo* so that it may have a greater understanding of the mechanisms by which polyphenols produce their beneficial effects on the nervous system (Figure 2).

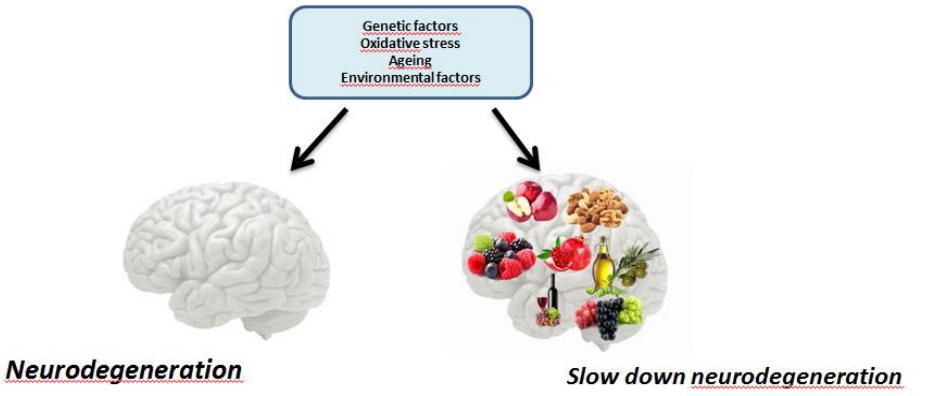


Figure 2. Polyphenolic-food intake actions on neurodegenerative damages

To circumvent the drawback of poor biodisponibility, new delivery systems, such as the encapsulation of bioactive molecules in lipid nanocapsules appear to provide a promising frontier that could pave the way for the development of brain-targeted nutraceutical products. However, administration of nanoparticle preparations for prolonged periods may give rise to toxicity of the carriers with which the active compounds are complexed

In the last years, the search is directed towards the polyphenols's effect on functional lymphatic drainage in the brain. Brain lymphatic drainage helps maintain water and ion balance of the interstitial fluid, waste clearance, and reabsorption of macromolecular solutes. The impairment and dysfunction of the brain lymphatic systemhas crucial roles in age-related changes of brain function and the pathogenesis of neurovascular, neurodegenerative, and neuroinflammatory diseases, as well as brain injury and tumors. Malfunction of the meningeal lymphatic vessels could be a root cause of a variety of neurological disorders in which altered immunity is a fundamental player such as multiple sclerosis, Alzheimer's disease, and some forms of primary lymphedema that are associated with neurological disorders. Understanding how the brain tackles the waste problem is crucial. In every organ, the elimination of waste is as important as the delivery of nutrients. In the brain it is a particularly interesting topic, because essentially all neurodegenerative diseases involve an accumulation of protein waste that eventually suffocates and kills the brain's neural network. If the glinfathic system fails to purify the brain as it should, both as a result of normal aging, and in response to a brain injury, waste may begin to accumulate in the brain. This may be what happens with beta-amyloid deposits in Alzheimer's The key component elements (regions, cells, and water transporters) of the brain lymphatic system and their regulators as potential therapeutic targets in the treatment of neurologic diseases and their resulting complications the polyphenols could act on this drainage system[137,138].

Many attempts are currently being made in order to delay the progression of AD by reducing inflammatory mechanisms underlying the disease. Several studies support a relationship among neuroinflammation and nutrients, foods or dietary patterns, taking into account the synergistic or antagonistic biochemical interactions among nutrients as well as the different food sources of the same nutrient. Natural antioxidant and anti-inflammatory compounds found in plant foods, such

as fruits, particularly berries (such as strawberry, blueberry, blackcurrant, blackberry, blueberry and mulberry) have been shown to exert neuroprotective activity. It is still unclear whether the dietary bioactive compounds enter the blood brain barrier playing a direct antiinflammatory or pro-inflammatory effect on microglia and/or other Central Nervous System cells.

Another hypothesis is that they may trigger a peripheral reaction that induce indirectly a CNS' response.

In the future, dietary prophylactic therapies to neurodegeneration may be based on concomitant use of polyphenolic-food to synergistically target multiple pathological mechanisms. Rational and well-validated design of novel delivery systems or other approaches to enhance bioavailability is imperative to produce more pronounced nutraceutical and/or therapeutic effects associated with food-polyphenolic dietary.

Moreover, comprehensive knowledge on the reciprocal interactions between dietary polyphenols and human gut microbiota will allow us to better interpret the fate of polyphenols and guide us to develop strategies to augment systemic exposure and bioefficacy of polyphenols by altering the microenvironment of the lower gut. These complimentary approaches represent exciting frontiers of science in which multidisciplinary fields, especially genetics, biochemistry, microbiology, pharmacognosy, epidemiology, nutrition and phytochemistry, begin to merge to address complex challenges stemming from the accelerated aging of populations. Once the low-bioavailability issue is properly addressed, the amounts of polyphenol-rich botanicals required to achieve the biological effects in the brain or other target tissues may be lowered, thus reducing chances of any side effect caused by pharmaceutical dosage. Although therapies involving polyphenols-rich botanicals are currently not regarded as mainstream therapeutic options, these botanicals including polyphenols-rich products, as polyphenolic-food, will play an increasingly essential part in the context of deceleration systemic senescence and the promotion of healthy aging.

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