Dementia: Advances and Treatment

Chapter 1

Dietary polyphenols as promising molecules to prevent dementia

Sarubbo F*; Miralles A; Moranta D; Esteban S

[*]Laboratorio de Neurofisiología, Departamento de Biología, Instituto Universitario de Investigación en Ciencias de la Salud, Universidad de las Islas Baleares (UIB), Mallorca, Spain.

***Correspondence to: Sarubbo F,** Laboratorio de Neurofisiología, Departamento de Biología, Instituto Universitario de Investigación en Ciencias de la Salud, Universidad de las Islas Baleares (UIB), Mallorca, Spain.*

Email:fiorella.sarubbo@uib.es; Tel: +34 971 173145; Fax: +34 971 173184

Abstract

Due to the increased number of elderly people worldwide, nowadays one of the major medical and socio-economic challenges is to search strategies to combat the consequences of aging process, reducing the incidence of neurodegenerative diseases such as dementia. Dementia is a clinical syndrome of chronic and progressive symptoms characterized by multiple cognitive deficits associated with aging, which includes impairment in memory and in other cognitive functions to the extent that it interferes with daily function. In the last years oxidative stress and inflammation have been pointed out as the leading causes of brain aging and neurodegeneration. Therefore,an approach for preventing some brain age-related diseases, such as dementia, may be the consumption or administration of polyphenols,which are natural compounds present in edible plants. Due to their antioxidant and anti-inflammatory properties, polyphenolshave been suggested such as a beneficial strategy against the development of brain aging and neurodegeneration. This chapter summarizes the latest discoveries regarding how polyphenols exert positive effects combating the biochemical mechanisms that originate aging and dementia,such as oxidative stress, inflammation and the aggregation of abnormal folding proteins, among others.

Keywords: polyphenols; aging; antioxidant; anti-inflammatory; dementia; alzheimer's disease; neurodegenerative diseases.

Abbreviations

Akt: Protein kinase B; ALT: Alanine transaminase enzymes; AST: Aspartate transaminase enzymes; GPx: Glutathione peroxidase; HIV: Human Immunodeficiency Virus; IκB: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IL: Interleukin; MAO: Monoamine oxidase; MAPK: Mitogen-activated protein kinase signaling; MMSE: Mini Mental State Examination; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NOX: NADPH oxidase; PI3K: Phosphoinositide 3-kinasepathway; ROS: Reactive Oxygen Species; SIRT1: Sirtuin 1; τTau: protein; TNF-α: Tumor necrosis factor alfwa

1. Introduction

The term dementia derives from the Latin *demens* ("*de*": private, "*mens*": mind, intelligence, judgment),making reference to the cognitive decline that characterizes this disease.In this sense, the American Psychiatric Association defined dementia as any mental impairment, or global cognitive decline in a previously unimpaired person, characterized by a deterioration of cognitive, intellectual, emotional, and behavioral skills, severe enough to interfere with the daily life of its sufferers [1]. The incidence of this disease is growing up, since The World Health Organization estimates thatevery 4 seconds there is a new case of dementia worldwide, and in the world there are 47.5 million people with dementia (http://www.who.int/mediacentre/factsheets/fs362/en/; [2]). This disease is more prevalent in the elderly (95% of the reported cases involve people over 65 years-old). Therefore, with the growing elderly population, dementia has become a major cause of morbidity and mortality [3]. This also means an enormous economic impact worldwide [4], and illustrates the urgent need to design new therapies in order to prevent or reverse dementia and their consequences.The biochemical processes that favor some of these risk factors are oxidative stress, inflammation, deposition of abnormal protein aggregates in brain, metal deposition, and disturbances in cholinesterase [5].These processes are influenced only around 20–25% by genetics and around 75% by lifestyle, such as diet [2]. Therefore, given the lack of effective pharmaceutical treatment for common types of dementia, it is growing the interest in finding natural compounds that could avoid the clinical syndrome of dementia and theirmedical and socioeconomic consequences. In this sense, due to their antioxidant and anti-inflammatory properties, polyphenols, natural compound present in edible plants, has been pointed out as promising molecules to prevent dementia, because many processes that are associated with the pathophysiology of dementia can be reverted by polyphenols. Polyphenols combat oxidative stress and inflammation, also inhibit acetylcholinesterase activity, andchelate metal ions preventing free radical formation, among other effects [6]. Several studies about the effects of polyphenols in dementia have been underway in cell cultures, in animal models of dementia or Alzheimer's disease [7], and in some official systematic clinical trials (for one example of clinical trial in 2016 see: https://clinicaltrials.gov/ct2/show/study/NCT01504854), which suggeststhat polyphenols may be promising molecules in the prevention of dementia.

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2. Main Causes of Dementia

Dementia is a syndrome characterized for being a progressive and irreversible process, underpinned by a progressive pathology, which produce degeneration and neuronal death in several brain region, whereby it causes deterioration in the structure and function of the brain [8]. Moreover, it is considered to be predominantly a condition of later life, but not a part of the normal course of aging,as conditions with an underlying physical disease process [9]. The etiology of dementia is often multifactorial, but the most common causes include neurodegenerative diseases [10] which cause degenerative dementias. Therefore, different dementia types are usually classified according to the neurodegenerative disease that causes it, in this sense the two major degenerative causes of dementia are *Alzheimer's disease* and *vascular dementia* (i.e. dementia due to a series of small strokes). Other types of dementia includes: *Dementia with Lewy bodies* (cause by abnormal clumps of protein) [11,12], *mixed dementiaa* combination of Alzheimer's disease, vascular dementia and Lewy body dementia) [13,14,15], *Parkinson's disease* [16], *Frontotemporal dementia*(degeneration of nerve cells in the frontal and temporal lobes)[17], *Creutzfeldt-Jakob disease* (an abnormal form of a protein) [18], *Normal pressure hydrocephalus*[19], *Huntington's disease* (nerve cells in brain and spinal cord to waste away) [20], *Wernicke-Korsakoff Syndrome* [21,22]. However, not only neurodegenerative diseases cause dementia, there are also other multiple conditions that lead to nondegenerative dementias, such as infections (e.g. meningitis, neurosyphilis, prion diseases, herpes virus, HIV, toxoplasmosis, cryptococcus, cytomegalovirus, borrelia and cysticercosis) [23], head injury, brain tumors, subdural hematomas, simple and normal pressure hydrocephalus, hormone disorders, metabolic disorders, hypoxia, nutritional deficiencies, drug abuse, or chronic alcoholism and immunological causes [24,25,26,27]. Many of the nondegenerative dementias occur at an earlier age and often progress quickly compared to Alzheimer's disease and other degenerative dementias [27]. There are also risk factors that can eventually lead to dementia such as age, sexual hormones [28], and genetic factors (genetic polymorphisms) [29,30,31,32], environmental factors (chemical exposure, metals) [33]. The molecular mechanism of neuronal death and synaptic damage in dementia is not well understood and could differ among different types of neurodegenerative processes. However, the presence of some common factors, as oxidative stress, neuroinflammation and abnormal folding of proteins are common features of dementia. Therefore, below we describe the relationship between oxidative stress, neuroinflammation and abnormal folding of proteins with the onset of dementia.

2.1 Oxidative stress

Oxidative stress is one of the major harmful factors involved in the onset and progression of aging symptoms and in several neurodegenerative disorders that lead to dementia [34] [35,36], such as Alzheimer's disease [37,38,39], and Parkinson's disease [40,41]. The concept of oxidative stress has been defined by Helmut Sies in 1985, as a disturbance in the prooxi-

dant-antioxidant balance in favor of the former [42].The same author updated this definition in 2007 as an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage [43]. Oxidative stress is a normal phenomenon in the body. Under normal conditions, the intracellular levels of reactive oxygen species (ROS) are physiologically maintainedat low levels by various enzyme systems participating in the in vivo redox homeostasis. Therefore, oxidative stress can also be viewed as an imbalance between the prooxidants and antioxidants in the body [44]. During the aging process and in neurodegenerative diseases the rate of this damage increases while the efficiency of antioxidant and repair mechanisms decrease [45,46,47], which causes structural and functional impairment of cells by degrading lipids, proteins, and nucleic acids [48], and ultimately it results in cell death and consequently inneurodegeneration and dementia. Regarding this,it is founded the Free Radical Theory of Aging, which is one of the most accepted theories that tries to explain aging and diseases associated with degenerative aging, as a consequence of the accumulation of oxidative stress in cells throughout life [45]. The broad distribution in brain of the processes regulating oxidative stress and mediating neurotransmission may explain the wide range of disorders in which both have been implicated [49]. In this way, it has been associated oxidative stress with aging brain and several dementia types such as multiple sclerosis [50,51], amyotrophic lateral sclerosis [52,41], Parkinson's disease [40,41], and Alzheimer's disease [37,38,39], and vascular dementia [53]. In these dementia types there is a progressive imbalance between antioxidant defense and the concentration of intracellular ROS, increased level of ROS in the vasculature, reduced nitric oxide bioavailability, and endothelial dysfunction leading to vascular disease and associated with dementia [54]. Moreover, in Alzheimer's disease, an increased amount of amyloid-β peptide induces elevated ROS production thereby causing neuronal cell death and damage. The recent observation that increased atherosclerotic plaque formation is present in the main artery to the brain in Alzheimer's disease, coupled with the association of vascular risk factors with this disease, suggesting a link between vascular dementia and Alzheimer's disease. It was proposed that the majority of dementia cases share a vascular pathology and that oxidative stress is central to this common pathology [53]. Oxidative stress theory postulation has led to an increased research on the antioxidants role in the prevention of aging and dementia. One of the major enzymes involved in the process of oxidative stress is NADPH oxidase (NOX), whose overexpression is induced especially by microglial activation in the brain in both acute [55] and chronic conditions [56]. There is a direct relationship between the impairment of cognitive performance of Alzheimer's disease patients and the increase of NOX activity [57]. NOX seems to play a role in Alzheimer's disease, especially by the action of NOX2, which is upregulated in the brain of Alzheimer's disease patients [58]. NOX2 expression is induced by the presence of β-amyloid plaques that stimulate the activation of microglial NOX leading to superoxide production [59], which in turn leads to mitochondrial dysfunction [60], cleavage of nucleic acids [46], and proteolysis[61]. In this line, the cognitive decline associated with aging [62] and neurodegenerative diseases such as

dementia, correlates with a decrease in concentration of antioxidants in serum [63] and brain [64]. An antioxidant compound may be defined as any substance that retards, prevents, or eliminates oxidative damage caused by ROS in a target molecule [54]. An antioxidant enzyme involve in oxidative stress and cognitive decline is the Glutathione peroxidase (GPx), which is a free radical scavenger and a key-enzyme in the endogenous defensive mechanism against free radicals [65]. Their main role is to protect cells from ROS by inactivating hydrogen peroxides and lipid hydroperoxides originated during oxidative metabolism [66]. Accordingly, the decrease of GPx activity leads to tissue damage and cell death due to detrimental action of ROS in increased levels. GPx mechanism of action is based on the redox ability of thiol groups of glutathione and the catalytic reduction of peroxides, either inorganic (hydrogen peroxide) or organic (lipid peroxides). Their functioning is selenium-dependent [67], and a low dietary intake of this element alters GPx activity [66]. Although there is no consensus about the antioxidants effectiveness in vivo and much less about its mechanism of action during aging in the body; there are studies indicating that dietary antioxidants reduce cognitive impairment preventing oxidative damage in brain aging [68], but also they could suppress the expression of some genes related with brain aging in mice [69]. In this sense, several studies suggest that antioxidants such as vitamin B, E, the ω-3 fatty acids [70], and polyphenols, can prevent the cognitive decline; reducing the risk of neurodegenerative diseases as dementia [71,72,73,74,75]. Interestingly, in comparison with other antioxidants, polyphenols have the ability to exert numerous ROS-scavenging and anti-inflammatory independent actions (see section 3). The oxidative stress concept has gained weight and nowadays a new perspective is growing due to the discovery of the existence of the linkage of oxidative stress with inflammation and inflammatory responses [76,77], which are also another causes of dementia [78].

2.2 Neuroinflammation

Neuroinflammation has been identified as being a process closely linked with multiple neurodegenerative diseases [79,80,81]. The majority of the studies done with positron emission tomography imaging of the translocator protein microglial marker, found increased neuroinflammation in at least one neuroanatomical region in dementia patients, most usually Alzheimer's disease, relative to controls [82]. The term neuroinflammation is referred to the unchained response of immune system in front of pathogen invasion or tissue damage[83]. The immune system, specifically the microglia, defends the brain from pathogen invasion or tissue damage by producing factors (e.g. cytokines and interleukins (IL)) that influence surrounding astrocytes and neurons [84], thereby promoting an inflammatory response that further engages a self-limiting response through the immune system and initiates tissue repair[83]. However, the persistence of inflammatory stimuli or failure in normal resolution mechanisms prolonger the inflammatory state amplifying the disease's state [85]. Accordingly, specific inducers of inflammation associated with neurodegenerative diseases converge in mechanisms respon-

sible in the sensing, transduction and amplification of the inflammatory processes that result in the production of neurotoxic mediators, such as cytokines and IL [86,87]. These neurotoxic mediators are commonly linked to intracellular mechanisms such as the degradation of protein, the dysfunction of mitochondria, the defects of axonal transport and apoptosis [88,89]. In this regard, age-related inflammation, which is call "inflammaging", is closely related with the onset of dementia [90]. Inflammaging refers to an exaggerated response of the immune system against inflammatory stimuli in brain during aging, being postulated as one of the main characteristics of the brain aging process [91,92]. Neuroinflammation associated with aging can result from many causes; some of them are: the accumulation of damaged in tissues (due in part to oxidative damage) [93,94]; the exaggerated response of both the innate and adaptive immune system against pathogens and dysfunctional cells [95]; the tendency of senescent cells to secrete proinflammatory cytokines [91,92]; and deregulation of autophagy immune system, through over activation of the mammalian target of rapamycin (mTOR), which in turn generates defective proteins accumulation [96,97]. These alterations cause activation of the inflammasome and other proinflammatory signaling pathways such as the mitogen-activated protein kinase signaling (MAPK) [98,99,100,101], and the NF-κB [101]; but also the PI3K/Akt/mTOR pathway, which besides regulate autophagy, and interacts with the mentioned-proinflammatory pathways [102,103]. Once these pathways are activated cytokines production increases such as IL-1β, TNF-α, interferons and prostaglandins [91,92]. There are several biomarkers of neuroinflammation implicated in dementia pathogenesis[104,105], for instance increased serum TNF-α is strongly associated with dementia [106]. One study has suggested that IL-23 may be specific for frontotemporal dementia associated with while IL-17 may be specific for frontotemporal dementia associated with TDP-43 pathology [107]. The astrocytic and oligodendrocytic protein S100B is elevated in several dementia types (most notably in dementia related to prion diseases), but possibly also in mild/moderate Alzheimer's disease[108], where it is correlated with rate of brain atrophy [109]. Another protein, the glycoprotein YKL-40 produced by astrocytes or activated microglia, is increased in cerebrospinal fluid and serum in Alzheimer's disease and Frontotemporal dementia, favoring inflammation [110]. It was also pointed out that F2-Isoprostanes, markers of membrane lipid peroxidation and inflammation, are useful to predict conversion from mild-cognitive impairment to Alzheimer's disease [111]. All these alterations contribute significantly to cognitive (especially in memory) and motor decline in brain aging [112,94]. The prolongation of this state has many brain consequences such as structural changes in fronto-temporal areas [113,114], synaptic deterioration [115], and impaired synthesis of catecholamines and serotonin [116,117,118,119,74,119,75,73], amongothers. Alltogethercontributeswiththeonset and development of neurodegenerativediseasessuch as Alzheimer'sdisease, dementia [120], schizophrenia [121], Parkinson's disease, and multiple sclerosis, among others [122,123].Others major risk factors that contribute to inflammation and thus with dementia are cardiovascular, metabolic and adipose dysfunction, which in turn are usually present during aging. The micro- and macro-vascular complication

changes the brain's perfusion, leading to continuous oligodendrocyte death and the consecutive degeneration of myelinated fibers that increase low-grade inflammation amplification of the risk of stroke [124] and some types of dementia such as small vessel disease (SVD)-vascular dementia [125,126]. Dementia also appears after cardiovascular diseases such as strokes or atherosclerosis, which is an arterial disease that is characterized by vascular inflammation occasioned by the infiltration of monocytes into the injured vascular wall and an increase of IL-6 associated with future intracranial large artery stenosis progression after a stroke episode [127]. Moreover, adipose tissue dysfunction identified in obesity and hypertension, leads to secretion of a proinflammatory, atherogenicadipokine pattern, contributing to chronic and low-grade inflammation, and predisposing to cardiovascular diseases (e.g hypertension, atherosclerosis) [128,129] and dementia [130].

2.3 Abnormal protein's folding

Most of dementia types such as Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, and prion diseases are characterized by the accumulation of abnormal conformers of a host proteins in the central nervous system [131]. Multiple forms of misfolded proteins can be identified in the central nervous system from small oligomeric structures, β-pleated sheets, through to large amyloid deposits [132,133]. During protein synthesis and transport neurons permanently possesses a set of defense mechanisms that protects against abnormal protein's folding. These mechanisms include protein folding defense system and degrading system of defective proteins, which helps to eliminate the toxicity of misfolded proteins and their oligomeric or fibrillar states [88,134]. The protein folding defense systems are constitute by heat shock proteins or chaperones, and they stabilize new proteins to ensure correct folding or by helping to refold proteins that were damaged by cell stress [135]. The degrading system of defective proteins are constitute by ubiquitin-proteosome, and autophagy [136].A cell with an abnormal protein that has an intrinsic tendency to misfold and aggregate is more vulnerable to stress than normal counterparts. Furthermore, these abnormal proteins may precipitate even in the absence of stress and cause diseases named proteinopathies. It is possible that stress contributes to the pathogenesis of proteinopathies by promoting protein aggregation, even in cells that possess a normal chaperoning system [137,138]. Factors that usually converge during aging such as oxidative stress, inflammation and other exogenous and endogenous damaging situations leads to an abnormal protein's folding together with a dysfunction of the defense mechanisms contributing to the formation of protein deposits, which result in proteotoxic effects and loss of normal functionality, thesesubserve a cascade of events that favor the development of neurodegenerative diseases such as dementia [139,140,136]. Avoiding the formation of abnormal proteins and aggregates before the onset of neurodegeneration, and the clearance of deposited abnormal proteins from brain may be a therapeutic approach in patients who already display the neurodegenerative disease. Therefore, the dissection of the

kinetics of folding and deposition, the folding intermediates, and promoting factors such as oxidative stress or inflammation will be crucial for discovering new therapeutic targets [131].

In conclusion, although oxidative stress, inflammation and abnormal unfolding proteins are well differentiate processes, they are closely related, and affect each other. Therefore, future therapy of neurodegenerative disorders such as dementia, may be on track to prevent the causes that generate protein misfolding, aggregation, and deposition prior to clinical manifestation of the disease. In this line, polyphenols, which are natural compounds present in foods, due to their antioxidant and antiinflamatory properties have been pointed out as a promising treatment in dementia.

3. Promising Molecules to Prevent Dementia: Polyphenols

Dementia is one of the most common neurodegenerative disorders affecting the elderly. Therefore, the increase of life-expectancy is transforming dementia into a major health-care problem. The greatest risk factor for neurodegeneration and for the onset of dementia are aging and their causes such as oxidative stress and neuroinflammation, together with the abnormal folding and deposition of proteins [141]. It has been pointed out that genetics factors only contributes 20–25% to the onset of the causes of dementia, the 75% remaining are environmental factors such as lifestyle, exercise or diet [2]. Moreover,dementia is a progressive disease, whose causative origin starts long before the onset of symptoms. In fact, research focus on autosomal dominant Alzheimer's disease indicates that the disease process starts around 20 years prior to onset of dementia [142]. This illustrates the importance of therapeutic strategies focus on environmental factors in early stages of life. This strategies directed at preventing oxidative stress and neuroinflammation may be crucial for preventing the onset of dementia and neurodegeneration. Dietary components have a dynamic molecular impact on cellular functions, epigenetic alterations, mechanisms that control gene expression, oxidative stress and inflammation. In recent years it has been pointed out some dietary components as promising molecules to prevent aging and neurodegenerative diseases [2,143]. This is the case of dietary polyphenols (i.e., several hydroxyl groups on aromatic rings), which are natural compounds found in fruits, vegetables and edible plants, which possess antioxidant and anti-inflammatory properties [144]. It has been estimated that a balanced diet may provide around 1 g of polyphenols daily [145]. All plant phenolic compounds arise from a common intermediate, phenylalanine, or a close precursor, shikimic acid. Primarily they occur in conjugated forms with one or more sugar residues linked to hydroxyl groups, although direct linkages of the sugar (polysaccharide or monosaccharide) to an aromatic carbon also exist. Association with other compounds, like carboxylic and organic acids, amines, lipids, and connection with other phenol is also common [146]. Depending on the number of their phenol rings and the structural elements that bind these rings to one another, polyphenols are classified into the following groups: *stilbenes, flavonoids, phenolic acids, lignansand* others [147,148] (Table 1).

Polyphenols affect a wide range of mechanisms in the brain, that help to protect against aging, improving cognition, exploratory behavior, spatial learning and memory [149,150,75]. Therefore, polyphenols contribute to maintain mental health, as long as they reduce the risk of dementia [151] and prevent the onset from neurodegenerative diseases [152,153,154]. Much of the relevance of polyphenols in protecting the brain aging is due to its ability to cross the blood brain barrier, due to their lipophilic nature [155,156,157,158,159]. Polyphenols help to maintain the cerebral mass [160] and mitochondrial integrity as it was demonstrated after the long term oral administration of resveratrol [161]. It was also described that chronic treatment with polyphenols prevent the descent in the major neurotransmitters (serotonin, dopamine and noradrenalin), which occurs normally as a consequence of aging; this is the case of the polyphenol resveratrol [74,75]. Moreover, flavonoids like quercetin inhibit enzymes such as monoamine oxidase (MAO), having antidepressant effects [162], which is also important in dementia. Polyphenols also favor the activation of some anti-aging proteins, as it is the case of sirtuin 1 (SIRT1) [163], which affects synaptic plasticity and memory. The mechanism inside this set of brain effects can be related with the antioxidant and anti-inflammatory properties of polyphenols. As antioxidants, polyphenols protect lipids, proteins, carbohydrates and DNA from oxidative damage [164,165,166], and they also induce increased levels of antioxidant defense systems such as the enzyme GPx, ascorbic acid and, superoxide dismutase [167,168]. On the other hand, polyphenols also have the ability to suppress neuroinflammation [169]. It has been shown in a series of studies in vitro and in vivo, that polyphenols have potential to inhibit neuroinflammation through attenuating the activation of intracellular signaling pathways like MAPK and NF-κB [170,100]. Another characteristic feature of polyphenols is their interactions with peptides and proteins [2]. In summary, the positive effects of polyphenols are related to their preventive action in the main causes of dementia and aging, which are oxidative stress, inflammation and abnormal protein folding, among others. Polyphenols exert in each particular cause a set of particular effects, which altogether affects each other (Fig 1). Therefore, below we summarize the effects of polyphenols on: oxidative stress, neuroinflammation, abnormal protein folding and aggregation.

3.1 Effects of polyphenols on oxidative stress

Several studies have suggested that polyphenols, can prevent cognitive and motor decline; reducing the risk of neurodegenerative diseases such as dementia [71,72,75,74]. An antioxidant compound may be defined as any substance that retards, prevents, or eliminates oxidative damage caused by ROS in a target molecule [54]. In this sense, polyphenols can act as antioxidants by acting as direct scavengers of free radicals and clearing superoxide and hydroxyl radicals, directly inhibiting or quenching ROS due to the presence of benzene ring-bound hydroxyl groups that are capable of donating either one hydrogen atom or a single electron to the reactive species [171].A phenoxyl radical is generated which in turn can react

with a second radical, forming a stable quinone structure [172]. Besides, some polyphenols are also able to increase the level of antioxidant enzymes such as GPx(6), and to reduce or inhibit the major ROS-forming enzymes including MAO or xanthine oxidase, reducing ROS levels [171].Polyphenols have additional abilities, they can also chelate iron and copper ions rendering them inactive to participate in free radical generating reactions [173]; with important consequences on the prevention of neurodegenerative diseases such as Alzheimer's disease[174]. Regarding this, it has been found that polyphenols prevent metal deposition, regulate redox metal homeostasis, and prevent neurotoxicity, acting as potential therapeutic agents for dementia, Alzheimer's [7], and Parkinson's diseases[175].On the other hand, polyphenols can act as antioxidants indirectly, by modulating several signaling cascades including the Nrf2 and NF-κB or via modulation of the expression of microRNAs; leading to an induction of the expression of the antioxidant and detoxifying enzymes, but also elevating the intracellular GPx levels [176,177,178]. Moreover, alterations of mitochondrial functioning related to ROS production are characteristics in aging and in early stages of Alzheimer's disease, giving place to lipid peroxidation, nucleic acid damage, protein oxidation, and neuronal death [179]. Polyphenols are now recognized as molecules capable of modulating pathways that regulate mitochondrial biogenesis (i.e., inducing SIRT1), mitochondrial membrane potential (i.e., mitochondrial permeability transition pore opening and uncoupling effects), the components of mitochondrial electron transport chain (i.e., modulating complexes I to V activity) and ATP synthesis [171]. It has also been demonstrated that polyphenols modulate the intra-mitochondrial oxidative status (i.e., inhibiting/inducing ROS formation/removal enzymes), and ultimately mitochondrially-triggered cell death (i.e., modulating intrinsic-apoptosis)[171]. As example, the polyphenol resveratrol counteracts the production of mitochondrial ROS through two major mechanisms: on the one hand by efficiently scavenging hydroxyl, superoxide, and metal-induced radicals [180]; and on the other hand by increasing mitochondrial functioning and biogenesis through activating the SIRT1–PGC-1α pathway, thereby boosting mitochondrial bioenergetic efficiency [181,182,183].

3.2 Effects of polyphenols on inflammation

Localized inflammation and active microglia contribute to neurodegeneration and cognitive decline, leading to several shapes of dementia such as Alzheimer's disease[72]. Therefore, many of the anti-aging and anti-neurodegenerative strategies are oriented toward the prevention or attenuation of this proinflammatory state [171]. In this sense, it has been pointed out that polyphenols may modulate the brain immune system, exercising anti-inflammatory effects [101]. For example, diets enriched with resveratrol or flavonoids reduce neuroinflammation, by decreasing cytokines production (such as IL-1β in the hippocampus of older rodents) with a positive impact on cognitive processes [184,185,101,186]. In a mouse model of Alzheimer's disease,resveratrol improved cognitive functions [172,7]. In agreement, pteros-

tilbene, a resveratrol derivative, has shown promise in preclinical models of Alzheimer's disease, since the results have indicated that pterostilbene was effective reducing markers of cellular stress, inflammation [98], and modulate dopamine release in hippocampus reversing cognitive deficits in Alzheimer's disease [99]. It has also been found positive effects against oxidative stress and neuroinflammation by other polyphenols as rutin [172], oleuropein aglycone [101] and liquiritigenin [102]. These results open the door for the use of polyphenols for preventing oxidative stress and inflammation in aging-related disorders, like dementia [103,112,113]. Nowadays the research is focusing in insight the mechanism of action involved in these effects. Regarding this, the modulation of NF-κB (which in turn can be mediated by SIRT1, among other mechanisms) has been postulated as an important molecular mechanism in the prevention of aging effects by polyphenols [187,188].A major pathway appears to involve SIRT1, that seems to deacetylase NF-κB, a step that results in downstream blockade of microglia activation [189,94,96,97].SIRT1 is a histone and non-histone deacetylase enzyme responsible for regulating physiological and metabolic responses to stress signals; playing a critical role in cell survival [190,191,192], and conservation of the cellular glucose homeostasis [193,194,195], which altogether favors the longevity of the organism[196,197] and protect against aging and neurodegeneration [198,199]. Even more, SIRT1 directly protect against oxidative stress and modulates inflammatory responses preventing the onset of neurological diseases [200,201,202]. Moreover, it has been demonstrated that reduced SIRT1 levels in hippocampus is one of the characteristic causes of brain aging [203], progression of many inflammatory diseases [204] and cognitive impairment [205]; contributing to development of neurodegenerative diseases as several dementia types, such as the cases of Alzheimer's disease or Parkinson's disease [199,206,207]. Therefore, molecules that modulate the SIRT1 expression may represent a promise in preventing hallmarks of aging and therefore dementia[208]. The mechanisms responsible for the decline of SIRT1 associated with aging are still unknown, although one of the main cause could be oxidative damage [205]. Therefore, oxidative stress and inflammation are two process closely related in neurodegeneration. Polyphenols can activate SIRT1 through an allosteric mechanism common to chemically diverse SIRT1 activators, but this effect has been only demonstrated in vitro [209,210]. Polyphenols also induce SIRT1 overexpression contributing to protect cells against oxidative stress [211,212]. The reason why polyphenols increase SIRT1 level in vivo is not well known, but could be related to their antioxidant effect, since oxidative stress reduce SIRT1 mRNA level [213]. Cysteine residues from SIRT1 are also vulnerable to oxidation, which affects both the activity of SIRT1 and their degradation by the proteosomes [214,215].

Furthermore, SIRT1 overexpression is directly involved in the modulation of neuroinflammation in aging process by deacetylating non-histone proteins [216]. It has been demonstrated that SIRT1 deacetylated lysine 310 of RelA/p65 subunit of NF-κB, a critical subunit for activation of transcription of proinflammatory genes and therefore triggering an inflam-

matory processes [187]. This NF- κB signaling pathway is the prototypical one involved in inflammaging [217,187,92]. In the brain, this process is mainly related to glia cells, where promotes the expression of cytokines [218,219]; but also affects synaptic plasticity in neurons, contributing to memory process [220,221], one of the skill more affected in dementia. NF-κB consists of a heterodimeric complex of p50/p52 and p65 proteins. In the cytoplasm, NF-κB heterodimer joins the inhibitory protein IκB and thus the entire complex is inactive [222]. ROS and other proinflammatory molecules activate protein kinase that phosphorylates IκB, which releases the complex of p50/p65, allowing it to translocate to the nucleus where it can act such as a transcription factor by binding the DNA in specific promoter regions [223,224]. The transcriptional activation domain of NF-κB is in the p65 subunit [225,226]. This p65 subunit is also modulated by posttranslational modifications such as phosphorylation at serines [276,311,529,536] and acetylation at lysines 310 [226,187,122,123,218] and [221,227,228]. The over activation of this NF-κB signaling pathway is one of the transcriptional signs of aging process [229]. In this way it has been demonstrated that the conditional expression of an inhibitor of NF-κB in aged skin of transgenic mice causes phenotypic rejuvenation of this tissue [217]. Similarly, genetic and pharmacological inhibition of NF-κB signaling pathway prevents age associated characteristics in different models of accelerated aging mice [230,231]. It was also pointed out that the acetylation of lysine 310 of RelA/p65 NF-κB subunit increases the duration and effectiveness of the NF-κB activation, generating increased inflammation [226]. The interaction between SIRT1 and NF-κB is especially interesting in the regulation of aging studies [217,187], suggesting that SIRT1 could promote longevity and avoid neurodegeneration by inhibiting activation of NF-κB. Additionally, other study reinforced the idea that SIRT1 deacetylate NF-κB since during HIV-1 studies [232] demonstrated that the viral protein Tat binds to SIRT1, inhibiting its activity, thereby preventing NF-κB deacetylation; thus triggering the immune system activation. Together these observations support the idea that inflammatory responses and aging processes can be aggravated by enhancing the activation of NF-κB. Additionally, old rats fed diet rich in polyphenol also showed reduced expression of NF-κB in the hippocampus, striatum and frontal cortex together with an improvement in cognitive abilities [233]. In this regard, longevity factors, such as SIRT1 and their activators (i.e polyphenols), could regulate the efficiency of NF-κB signaling [91,92]. Similar results have been shown in cancer studies, where resveratrol has been shown to exert antitumor actions through inhibitingNF-κB [234,235]. As it is schematized infigure 2, polyphenols can activate SIRT1, since they may protect SIRT1 against oxidative stress actions, helping to avoid neurodegeneration and cognitive impairment associated with aging [236]. This is very important in the brain since it has been shown that SIRT1 regulates energy metabolism, axonal growth, dendrite formation, neuronal plasticity, neuronal survival against stress, and suppress inflammation by NF-κB modulation [237,101], as it has been pointed out in models of chronic inflammatory diseases [238,239,240]. Therefore, the activation of SIRT1 throughout treatments with polyphenols may be helpful for preventing brain aging.

3.3 Effects of polyphenols on folding and protein aggregation

In animal models of Alzheimer's disease, polyphenols have anti-β-amyloid action and a potential in neutralizing abnormal folding of τ proteins [241,242,243]. Moreover, for resveratrol [244], rutin, quercetin [245], the flavonoid fisetin [246], oleuropein aglycone [247], the flavonol morin [248], tannic acid [249], ferulic acid [250] and green tea polyphenols, where demonstrated their ability to inhibit formation, deposition and dissagreggation of Aβ fibril and protected from Aβ neurotoxicity by inhibiting inducible nitric oxide synthase inhibition [159] and decreasing cleavage of β-carboxyl terminal amyloid precursor protein [249]. This in turn prevents neuronal cell death by protecting neurons against τ hyperphosphorylation induced by Aβ. The mechanism of Aβ inhibition is driven by: stimulating the α-secretase; inhibiting the β-site amyloid precursor protein cleaving enzyme-1 (BACE1) and γ-protease pathways; and throughout hydrophobic interactions that involve π-π bonding between the planar faces of the polyphenol structure and the aromatic residues of Aβ42. Additionally, hydrogen bonding occurs between the peptide and the phenolic hydroxyl groups. Polyphenols intercede/impose between two β42-amyloid aromatic residues preventing their ϖ-ϖ stacking, blocking the amyloid self-assembly-β-oligomer-sheet-fibril formation and gaining of toxic function[143]. In addition, resveratrol, curcumin, oleuropein, pentagalloylglucose inhibit β-amyloid misfolding and aggregation by forming nontoxic complexes with the peptide [251].

Nowadays strategies for enhancing polyphenol bioavailability include encapsulation as phospholipid nanoparticles; incorporation with biodegradable polymers; use of bioactive analogues; modifications to improve pharmacokinetics, or use of adjuvants such as absorption enhancers [2]. Regarding this, tolerance is another important point. Sincethere have been conducted clinical studies in humans, administering a single doses of 5 grams of oral resveratrol [252] or150 mg of oral resveratrol six times a day for two days in healthy individual [253], observing good tolerance in both studies. Although, many questions regarding doses, safety, tolerance and efficacy of treatmentswith polyphenol in aging and neurodegenerative diseases need more clinical trials.

3.4 Other positive effects of polyphenols on dementia

On metal homeostasis: in neurodegenerative conditions and/or aging, metal homeostasis is impaired, leading to disease-promoting metal imbalance [254,255,256], which leads to a deposition of misfolded proteins, metal ion deregulation and exposure to oxidative stress [257,258]. Regarding this, copper, iron, zinc and aluminum are the deregulated metals founded in dementia [259]. All of them are able to alter Aβ metabolism and deposition [260]. Zinc deficiency increases neuroinflammation, affects BDNF maturation, and leads to mitochondrial failure, oxidative stress and cognitive decline [261,262]. In this way, resveratrol prevents the full development of zinc-dependent injurious mechanisms, reducing ROS production and neu-

roinflammatory response activation[263].

On acetylcholinesterase (AChE) (E.C. 3.1.1.7): cholinergic system impairment leads to the cognitive decline commonly associated with dementia.AChE, is one of the several proteins associated with Aβplaque deposits. Therefore, inhibitors of AChE prevent the aggregation of Aβ fibrils in Alzheimer's disease [264].Resveratrol [265] and polyphenols of green and white tea extracts [266] have been pointed out as AChE inhibitors blocking Aβ aggregation, indicating their potential in the treatment of age-related disorders such as Alzheimer's disease.

4. Conclusion

Today, more than 45 million people live with dementia, a neurodegenerative chronic disease linked with aging process. Therefore, one of the major medical and socio-economic challenges of modern societies is to find solutions for treating this invalidating disease. In the last decade, scientific studies suggested that neurodegenerative diseases are accompanied by oxidative stress, inflammation, proteinaggregates, metal accumulation, and mitochondrial dysfunctions, among others, which can be prevented or mitigated with the administration of dietary compounds. This is the case of polyphenols, natural antioxidant and anti-inflammatory molecules that exert multiple beneficial effects on health, especially in the prevention of brain aging and neurodegenerative diseases, such as dementia. The key to their beneficial effects it is founded in their antioxidant and anti-inflammatory properties, together with their ability to cross the blood brain barrier. The latest research pointed out that polyphenols can avoid oxidative stress and inflammation, by modulating the anti-aging protein SIRT1 and the inflammatory NF-κB signaling pathway. In addition, polyphenols can also avoid metal toxicity by inducing metal chelation, reducingthe abnormal protein folding and protein aggregation, avoiding apoptosis, inhibitingAChE, and increasing the level of some neurotransmitters, which all together arecharacteristic disturbances of dementia. This set of effects point to dietary polyphenols as promising molecules to prevent dementia, turning them into key molecules to improve memory and the cognitive abilities that are usually affected by this disease. The discovery of these molecules opens a promising outlook, where future researchwill allow to know the most effective polyphenol's dosage and administration route for the treatment of dementia.

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6. Figures

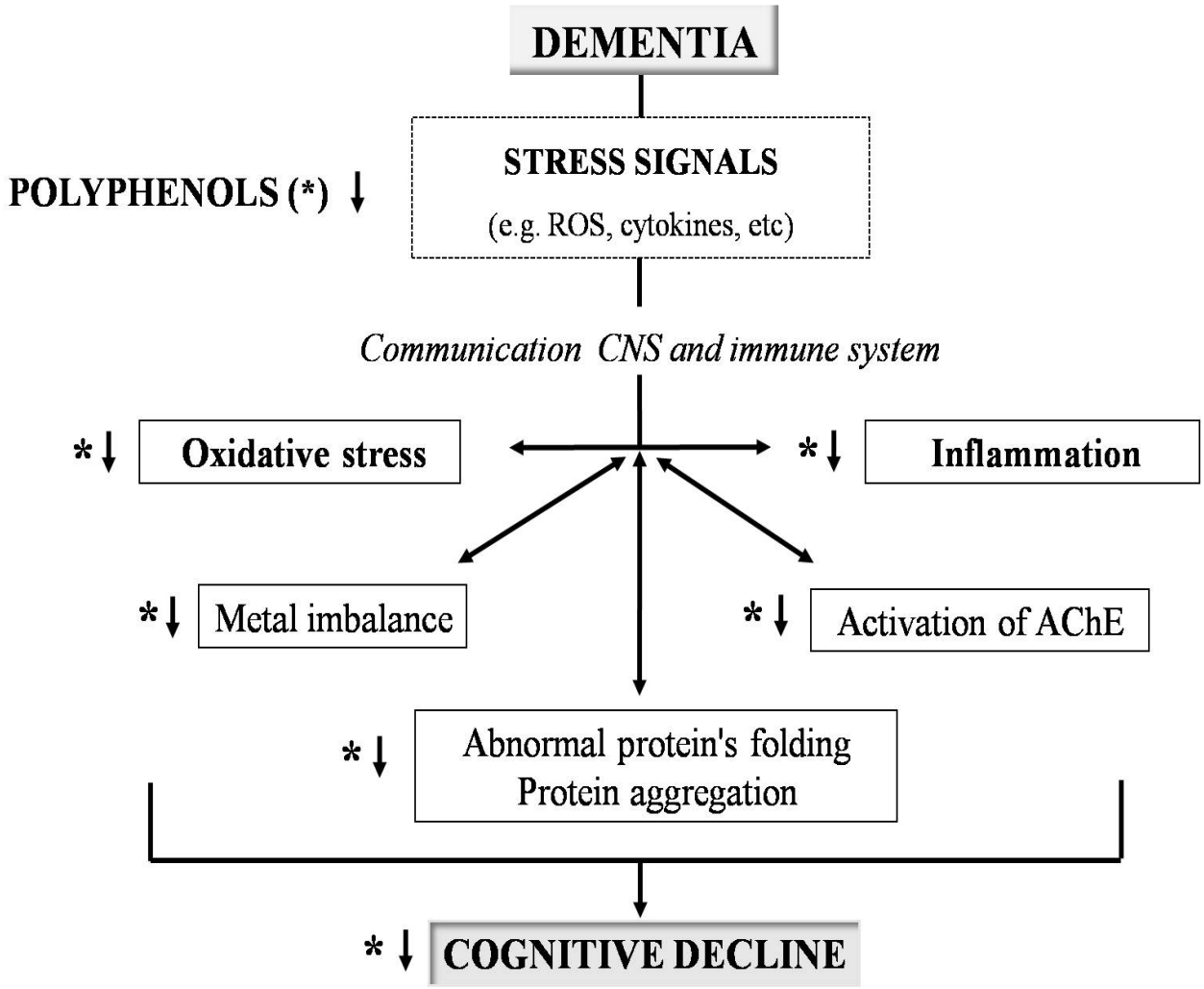


Figure 1: Effects of polyphenols(*) in the attenuation on the main causes of dementia. The onset of neurodegenerative diseases such as dementia is produced by the increment of stress signals such as ROS or cytokines.Several mechanisms are trigger once the immune system, which is communicated with the central nervous system (CNS), is activated by stress signals, contributing to oxidative stress and inflammation, abnormal protein folding, protein aggregation, metal imbalance and activation of acetylcholinesterase (AChE), leading to cognitive decline. All these mechanisms influence each other, but oxidative stress and inflammation have been pointed out as the leading causes of neurodegeneration. Therefore, polyphenols byavoiding oxidative stress, inflammation, abnormal protein folding, protein aggregation, and metal imbalance and by inhibiting acetylcholinesterase (AChE), prevent the cognitive decline by acting on the leading causes of dementia.

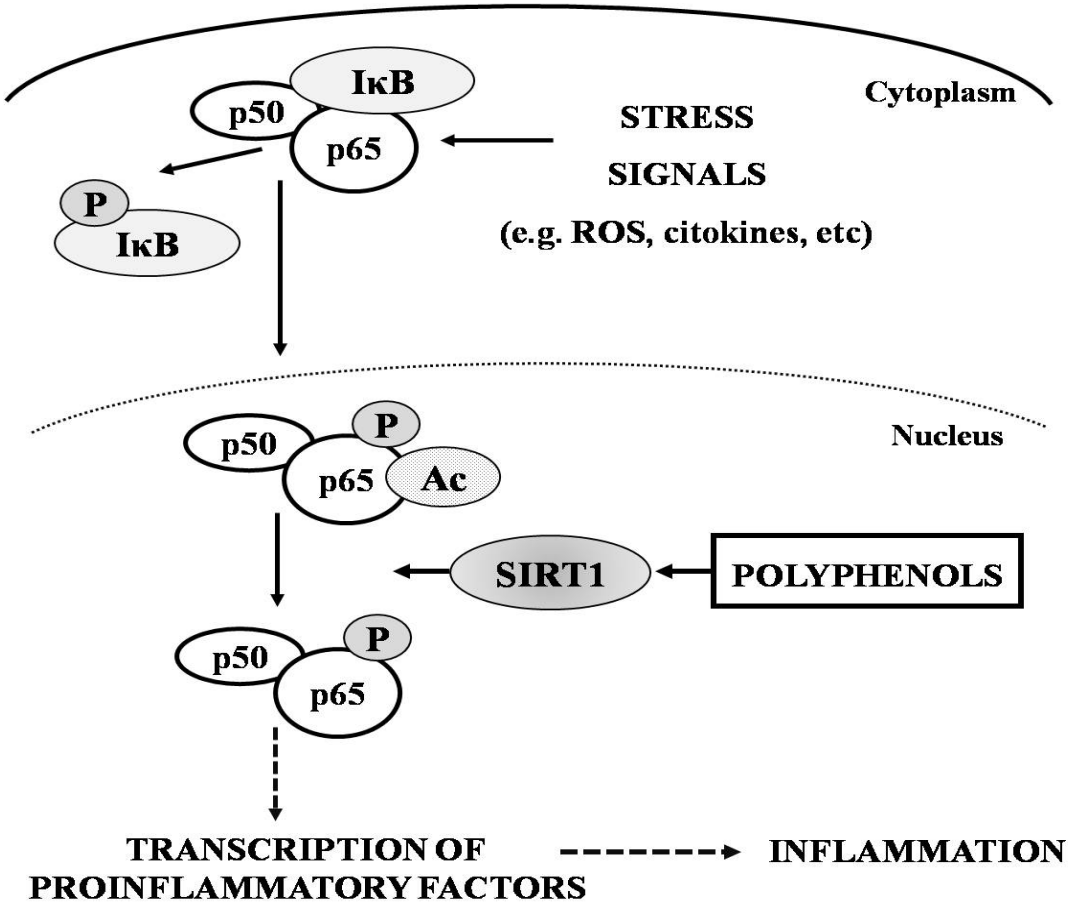


Figure 2: Scheme of the effectsof polyphenols on SIRT1 and NF-κB signaling pathway involved in neuroinflammation. NF-κB consists of a heterodimeric complex of p50/p52 and p65 proteins. In the cytoplasm, NF-κB heterodimer joins the inhibitory protein IκB and thus the entire complex is inactive. ROS and other proinflammatory molecules such as cytokines activate protein kinase that phosphorylates IκB, which releases the complex of p50/p65, allowing it to translocate to the nucleus where it can act as a transcription factor by binding the DNA in specific promoter regions. The subunit p65 is the transcriptional activation domain of NF-κB, whichis modulated by post-transcriptional modifications such as phosphorylation (P) at serines (*see paragraph 3.2and 4.2*) and acetylation (Ac) at lysines 310. The over activation of this NF-κB signaling pathway aggravates the inflammatory state. Polyphenols activate SIRT1, which deacetylate lysine 310 of p65 subunit of NF-κB, decreasing inflammation and neurodegeneration.

7. Table

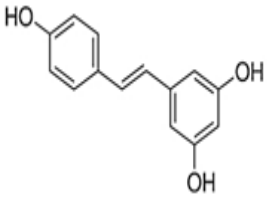
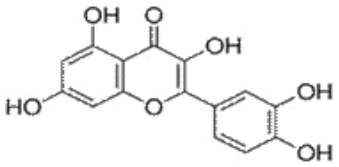
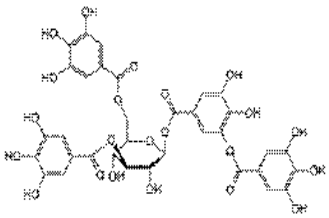
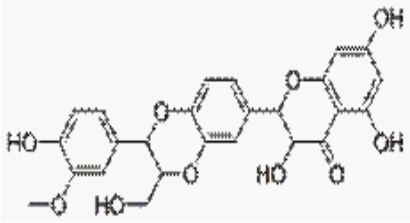
GROUPS OF POLYPHENOLS	EXAMPLES	CHEMICAL STRUCTURE
STILBENES	Resveratrol Pterostilbene	 **e.g. resveratrol**
FLAVONOIDS	Quercetin Naringenin Fisetin Rutin Morin Liquiritigenin Green tea polyphenols: Catechin Epicatechin	 **e.g. quercetin**
PHENOLIC ACIDS	Tannic acid Ferulic acid	 **e.g. tannic acid**
LIGNANS	Silymarin	 **e.g. silymarin**

Table 1: Classification of the main groups of polyphenols. Examples of polyphenols with effects on dementia cited in the text, and chemical structure.

5. References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Diagnostic Stat Man Ment Disord 4th Ed TR. 2013;280.

2. Hügel H, Jackson N. Polyphenols for the prevention and treatment of dementia diseases. Neural Regen Res. 2015;10(11):1756–1758.

3. Fadil H, Borazanci A, Ait Ben Haddou E, Yahyaoui M, Korniychuk E, Jaffe SL, et al. Early onset dementia.. International review of neurobiology. 2009. p 245-62.

4. Wimo A, Jönsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. Alzheimer's Dement. 2013;9(1):1–11.

5. Choi DY, Lee YJ, Hong JT, Lee HJ. Antioxidant properties of natural polyphenols and their therapeutic potentials for Alzheimer's disease. Brain Res Bull. 2012;87(2–3):144–53.

6. Desai A. Dietary Polyphenols as Potential Remedy for Dementia. Adv Neurobiol. 2016;12:41–56.

7. Lakey-Beitia J, Berrocal R, Rao KS, Durant AA. Polyphenols as Therapeutic Molecules in Alzheimer's Disease Through Modulating Amyloid Pathways. Mol Neurobiol. 2015;51(2):466–79.

8. Annear MJ, Toye C, McInerney F, Eccleston C, Tranter B, Elliott K-E, et al. What should we know about dementia in the 21st century? A Delphi consensus study. BMC Geriatr. 2015;15(1):5.

9. Vemuri P, Simon G, Kantarci K, Whitwell JL, Senjem ML, Przybelski SA, et al. Antemortem differential diagnosis of dementia pathology using structural MRI: Differential-STAND. Neuroimage. 2011;55(2):522–31.

10. Foguem C, Kamsu-Foguem B. Neurodegeneration in tauopathies and synucleinopathies. Rev Neurol. 2016;172(11):709–14.

11. McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, et al. Dementia with Lewy bodies. Lancet Neurol. 2004;3(1):19–28.

12. Mayo MC, Bordelon Y. Dementia with lewy bodies. Semin Neurol. 2014;34(2):182–8.

13. O'Brien JT, Thomas A. Vascular dementia. Lancet. 2015;386(10004):1698–706.

14. Foster NL, Larson EB, Ad LD. Mixed Dementia. Jama J Am Med Assoc. 2004;292(23):2901–8.

15. Jellinger KA. The enigma of mixed dementia. Alzheimer's and Dementia. 2007. p. 40–53.

16. Anang J, Nomura T, Romenets S, Nakashima K, Gagnon J, Postuma R. Dementia Predictors in Parkinson Disease: A Validation Study. J Park Dis. 2016; Epub ahead of print.

17. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015;386(10004):1672–82.

18. De Villemeur TB. Creutzfeldt-Jakob disease. Handb Clin Neurol. 2013;112:1191–3.

19. Picascia M, Minafra B, Zangaglia R, Gracardi L, Pozzi N, Sinforiani E, et al. Spectrum of cognitive disorders in idiopathic normal pressure hydrocephalus. Funct Neurol. 2016;31(3):143–7.

20. Eddy C, Parkinson E, Rickards H. Changes in mental state and behaviour in Huntington's disease. Lancet Psychiatry. 3(11):1079–86.

21. Reed LJ, Lasserson D, Marsden P, Stanhope N, Stevens T, Bello F, et al. FDG-PET findings in the Wernicke-Korsakoff syndrome. Cortex. 2003;39(4–5):1027–45.

22. Cunningham E. Dementia. Ulster Med J. 2015;84(2):79–87.

23. lmeida OP, Lautenschlager NT. Dementia associated with infectious diseases. Int Psychogeriatr. 2005;17 Suppl 1(S1):S65-77.

24. Koliatsos V. A Clinical Approach to Cognitive Impairment. Clin Neuropsychiatry. 2016;14(4):437–47.

25. Fleming K, Andrea M, Adams C, Petersen R. Dementia: Diagnosis and Evaluation. Mayo Clin Proc. 1995;70(11):1093–

1107.

26. Harvey R, Skelton-Robinson M, Rossor M. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry. 2003;74:1206–9.

27. Ghosh A. Endocrine, metabolic, nutritional, and toxic disorders leading to dementia. Ann Indian Acad Neurol. 2010;13(Suppl 2):S63-8.

28. Barron AM, Pike CJ. Sex hormones, aging, and Alzheimer's disease. Front Biosci (Elite Ed). 2012;4:976–97.

29. Chou P, Wu M, Chou M, Chien I, Yang Y. Angiotensin-converting enzyme insertion/deletion polymorphism and the longitudinal progression of Alzheimer's disease. Geriatr Gerontol Int. 2016; Epub ahead of print.

30. Jamal S, Goyal S, Shanker A, Grover A. Computational Screening and Exploration of Disease-Associated Genes in Alzheimer's Disease. J Cell Biochem. 2016; Epub ahead of print.

31. Kanatsu K, Tomita T. Molecular mechanisms of the genetic risk factors in pathogenesis of Alzheimer disease. Front Biosci (Landmark Ed). 2017;22:180–92.

32. Loy CT, Schofield PR, Turner AM, Kwok JBJ. Genetics of dementia. The Lancet. 2014. p. 828–40.

33. Uchoa M, Moser V, Pike C. Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors. Front Neuroendocr. 2016;43:60–82.

34. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of aging. Nature. 2000;408(6809):239–47.

35. Santos J, Gois A, Mendonça D, Freire M. Nutritional status, oxidative stress and dementia: the role of selenium in Alzheimer's disease. Front Aging Neurosci. 2016;6(206).

36. Polidori MC, Scholtes M. Beyond and behind the fingerprints of oxidative stress in age-related diseases: Secrets of successful aging. Arch Biochem Biophys. 2016;595:50–3.

37. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med. 1997;23(1):134–47.

38. Praticò D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. Trends in Pharmacological Sciences. 2008. p. 609–15.

39. Zhao Y, Zhao B. Oxidative stress and the pathogenesis of alzheimer's disease. Oxidative Medicine and Cellular Longevity. 2013. 13(4):223-50.

40. Freire M, Santos J. Parkinson's disease: general features, effects of levodopa treatment and future directions. Front Neuroanat. 2010;4:146.

41. Dias V, Junn E, Mouradian MM. The role of oxidative stress in parkinson's disease. Journal of Parkinson's Disease. 2013. p. 461–91.

42. Sies H. Introductory remarks. Oxidative stress. 1985. p. 1–8.

43. Sies H, Jones D. Oxidative Stress. Encyclopedia of Stress (Second Edition). 2007. p. 45–8.

44. Rahal A, Kumar A, Singh V, Yadav B, Tiwari R, Chakraborty S, et al. Oxidative stress, prooxidants, and antioxidants: The interplay. BioMed Research International. 2014. 63:187-94

45. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956;11(3):298–300.

46. Nunomura A, Moreira PI, Castellani RJ, Lee HG, Zhu X, Smith MA, et al. Oxidative damage to RNA in aging and neurodegenerative disorders. Neurotoxicity Research. 2012. p. 231–48.

47. Padurariu M, Ciobica A, Lefter R, Serban IL, Stefanescu C, Chirita R. The oxidative stress hypothesis in Alzheimer's disease. Psychiatria Danubina. 2013. p. 401–9.

48. Reynolds A, Laurie C, Lee Mosley R, Gendelman HE. Oxidative Stress and the Pathogenesis of Neurodegenerative Disorders. International Review of Neurobiology. 2007. p. 297–325.

49. Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. Science. 1993;262(5134):689–95.

50. Clausen J, Jensen GE, Nielsen SA. Selenium in chronic neurologic diseases - Multiple sclerosis and Batten's disease. Biol Trace Elem Res. 1988;15(1):179–203.

51. Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy 3. JNeurol. 2004;251(0340–5354):261–8.

52. Baillet A, Chanteperdrix V, Trocmé C, Casez P, Garrel C, Besson G. The role of oxidative stress in amyotrophic lateral sclerosis and Parkinson's disease. Neurochem Res. 2010;35(10):1530–7.

53. Bennett S, Grant MM, Aldred S. Oxidative stress in vascular dementia and alzheimer's disease: A common pathology. Journal of Alzheimer's Disease. 2009. p. 245–57.

54. Halliwell B, Zentella A, Gomez E, Kershenobich D. Antioxidants and human disease: A general introduction. Nutr Rev. 1997;55(1):S44–9.

55. Block ML, Zecca L, Hong J-S. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007;8(1):57–69.

56. Wu D, Teismann P, Tieu K, Vila M, Jackson-Lewis V, Ischiropoulos H, et al. NADPH oxidase mediates oxidative stress in the 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine model of Parkinson's disease. Proc Natl Acad Sci U S A. 2003;100(10):6145–50.

57. Ansari MA, Scheff SW. NADPH-oxidase activation and cognition in Alzheimer disease progression. Free Radic Biol Med. 2011;51(1):171–8.

58. Zekry D, Epperson TK, Krause KH. A role for NOX NADPH oxidases in Alzheimer's disease and other types of dementia? IUBMB Life. 2003;55(6):307–13.

59. Wilkinson BL, Cramer PE, Varvel NH, Reed-Geaghan E, Jiang Q, Szabo A, et al. Ibuprofen attenuates oxidative damage through NOX2 inhibition in Alzheimer's disease. Neurobiol Aging. 2012;33(1).

60. Guimaraes JS, Freire MA, Lima RR, Souza-Rodrigues RD, Costa AM, dos Santos CD, et al. Mechanisms of secondary degeneration in the central nervous system during acute neural disorders and white matter damage. Rev Neurol. 2009;48(6):304–10.

61. Esler WP, Wolfe MS. A portrait of Alzheimer secretases--new features and familiar faces. Science. 2001;293(5534):1449–54.

62. López-Otín C, Blasco M, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6).

63. Reiter R. Oxidative damage in the central nervous system: Protection by melatonin. Prog Neurobiol. 1998;56(3):359–84.

64. Rinaldi P, Polidori M, Metastasio A, Mariani E, Mattioli P, Cherubini A, et al. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. Neurobiol Aging. 2003;24:915–9.

65. Chen J, Berry MJ. Selenium and selenoproteins in the brain and brain diseases. Journal of Neurochemistry. 2003. p. 1–12.

66. Arthur JR. The glutathione peroxidases. Cell Mol Life Sci. 2000;57(13–14):1825–35.

67. Ceballos-Picot I, Merad-Boudia M, Nicole A, Thevenin M, Hellier G, Legrain S, et al. Peripheral antioxidant enzyme activities and selenium in elderly subjects and in dementia of Alzheimer's type - Place of the extracellular glutathione peroxidase. Free Radical Biology and Medicine. 1996. p. 579–87.

68. Lau F, Shukitt-Hale B, Joseph J. The beneficial effects of fruit polyphenols on brain aging. Neurobiol Aging. 2005;26(SUPPL.):128–32.

69. Liu J, Killilea D, Ames B. Age-associated mitochondrial oxidative decay: improvement of carnitine acetyltransferase substrate-binding affinity and activity in brain by feeding old rats acetyl-L- carnitine and/or R.-alpha -lipoic acid. Proc Natl Acad. 2002;(99):1876–1881.

70. Coley N, Vaurs C, Andrieu S. Nutrition and Cognition in Aging Adults. Clin Geriatr Med. 2015;3:453–64.

71. Corredor C. Antioxidantes. In: Patiño Restrepo JF, editor. Metabolismo, nutrición y shock. cuarta. Bogotá: Editorial médica panamericana; 2006. p. 293.

72. Joseph J, Cole G, Head E, Ingram D. Nutrition, brain aging, and neurodegeneration. J Neurosci. 2009;29(41):12795–801.

73. Ramis M, Sarubbo F, Terrasa J, Moranta D, Aparicio S, Miralles A, et al. Chronic α-tocopherol increases central monoamines synthesis and improves cognitive and motor abilities in old rats. Rejuvenation Res. 2016; 19(2):159-71

74. Sarubbo F, Ramis M, Aparicio S, Ruiz L, Esteban S, Miralles A, et al. Improving effect of chronic resveratrol treatment on central monoamine synthesis and cognition in aged rats. Age (Omaha). 2015;37(37):9777.

75. Sarubbo F. Estrategias neuroprotectoras en el envejecimiento cerebral. Mecanismos neuroquímicos y moleculares y su correlación con los efectos sobre las capacidades cognitivas [Doctoral thesis].University of the Balearic Islands, Palma de Mallorca, Spain; 2016.

76. Sies H. Oxidative stress: A concept in redox biology and medicine. Redox Biol. 2015;4:180–3.

77. Bennett SJ. Oxidative Stress Biomarkers in Dementia. The University of Birmingham; 2010.

78. Lee YJ, Han SB, Nam SY, Oh KW, Hong JT. Inflammation and Alzheimer's disease. Archives of Pharmacal Research. 2010. p. 1539–56.

79. Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep. 2016;13(4):3391–6.

80. O'Callaghan JP, Sriram K, Miller DB. Defining "neuroinflammation". Ann N Y Acad Sci. 2008;1139:318–30.

81. Allison DJ, Ditor DS. The common inflammatory etiology of depression and cognitive impairment: a therapeutic target. J Neuroinflammation. 2014;11:151.

82. Stefaniak J, O'Brien J. Imaging of neuroinflammation in dementia: a review. J Neurol Neurosurg Psychiatry. 2015;21–8.

83. Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease - A double-edged sword. Neuron. 2002. p. 419–32.

84. Sofroniew M, Vinters H. Astrocytes: biology and pathology. Acta Neuropathol. 2010;119(1):7–35.

85. Das Sarma J. Microglia-mediated neuroinflammation is an amplifier of virus-induced neuropathology. Journal of NeuroVirology. 2014. p. 122–36.

86. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms Underlying Inflammation in Neurodegenera-

tion. Cell. 2010. p. 918–34.

87. Teeling JL, Perry VH. Systemic infection and inflammation in acute CNS injury and chronic neurodegeneration: Underlying mechanisms. Neuroscience. 2009. p. 1062–73.

88. Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease. Science. 2002;296(5575):1991–5.

89. Chen H, Chan DC. Mitochondrial dynamics-fusion, fission, movement, and mitophagy-in neurodegenerative diseases. Hum Mol Genet. 2009;18(R2).

90. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.

91. Salminen A, Kauppinen A, Suuronen T, Kaarniranta K. SIRT1 longevity factor suppresses NF-κB-driven immune responses: Regulation of aging via NF-κB acetylation? BioEssays. 2008;30(10):939–42.

92. Salminen A, Ojala J, Huuskonen J, Kauppinen A, Suuronen T, Kaarniranta K. Interaction of aging-associated signaling cascades: Inhibition of NF-κB signaling by longevity factors FoxOs and SIRT1. Cell Mol Life Sci. 2008;65(7–8-):1049–58.

93. Martinon F. Signaling by ROS drives inflammasome activation. European Journal of Immunology. 2010. p. 616–9.

94. Barrientos RMR, Kitt MM, Watkins LRL, Maier SFS. Neuroinflammation in the normal aging hippocampus. Neuroscience. 2015;309:1–15.

95. Deeks SG. HIV Infection, Inflammation, Immunosenescence and Aging. Annu Rev Med. 2011;62:141–55.

96. Pallauf K, Rimbach G. Autophagy, polyphenols and healthy aging. Aging Research Reviews. 2013. p. 237–52.

97. Yang F, Chu X, Yin M, Liu X, Yuan H, Niu Y, et al. MTOR and autophagy in normal brain aging and caloric restriction ameliorating age-related cognition deficits. Behav Brain Res. 2014;264:82–90.

98. Bhat N, Zhang P, Lee J, Hogan E. Extracellular signal-regulated kinase and p38 subgroups of mitogen-activated protein kinases regulate inducible nitric oxide synthase and tumor necrosis factor-alpha gene expression in endotoxin-stimulated primary glial cultures. J Neurosci. 1998;18:1633–1641.

99. Culbert A, Skaper S, Howlett D, Evans N, Facci L, Soden P, et al. MAPK-activated protein kinase 2 deficiency in microglia inhibits pro-inflammatory mediator release and resultant neurotoxicity. Relevance to neuroinflammation in a transgenic mouse model of Alzheimer disease. J Biol Chem. 2006;281:23658–23667.

100. Spencer J. Flavonoids and brain health: Multiple effects underpinned by common mechanisms. Genes Nutr. 2009;4(4):243–50.

101. Spencer J, Vafeiadou K, Williams R, Vauzour D, Spencer J, Vafeiadou K, et al. Neuroinflammation: Modulation by flavonoids and mechanisms of action. Mol Aspects Med. 2012;33:83–97.

102. Song K, Wang H, Krebs T, Danielpour D. Novel roles of Akt and mTOR in suppressing TGF-β/ALK5-mediated Smad3 activation. EMBO J. 2005;25(1):58–69.

103. Han S, Yun Y. NF-κB/STAT3/PI3K signaling crosstalk in iMycEμ B lymphoma. Mol Cancer. 2010;9(97).

104. Schott JM, Revesz T. Inflammation in Alzheimer's disease: insights from immunotherapy. Brain. 2013. p. 2654–6.

105. Ahmed RM, Paterson RW, Warren JD, Zetterberg H, O'Brien JT, Fox NC, et al. Biomarkers in dementia: clinical utility and new directions. J Neurol Neurosurg Psychiatry. 2014;85(12):1426–34.

106. Miller ZA, Rankin KP, Graff-Radford NR, Takada LT, Sturm VE, Cleveland CM, et al. TDP-43 frontotemporal

lobar degeneration and autoimmune disease. J Neurol Neurosurg Psychiatry. 2013;84(9):956–62.

107. Hales CM, Hu WT. From frontotemporal lobar degeneration pathology to frontotemporal lobar degeneration biomarkers. Int Rev Psychiatry. 2013;25(2):210–20.

108. Peskind ER, Griffin WST, Akama KT, Raskind MA, Van Eldik LJ. Cerebrospinal fluid S100B is elevated in the earlier stages of Alzheimer's disease. Neurochem Int. 2001;39(5–6):409–13.

109. Petzold A, Jenkins R, Watt HC, Green AJE, Thompson EJ, Keir G, et al. Cerebrospinal fluid S100B correlates with brain atrophy in Alzheimer's disease. Neurosci Lett. 2003;336(3):167–70.

110. Craig-Schapiro R, Perrin R, Roe C. YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease. Biol Psychiatry. 2010;68:903–12.

111. Brys M, Pirraglia E, Rich K, Rolstad S, Mosconi L, Switalski R, et al. Prediction and longitudinal study of CSF biomarkers in mild cognitive impairment. Neurobiol Aging. 2009;30(5):682–90.

112. Kreutzberg GW. Microglia: a sensor for pathological events in the CNS. Trends Neurosci. 1996;19:312–8.

113. Ownby R. Neuroinflammation and cognitive aging. Curr Psychiatry Rep. 2010;12(1):39–45.

114. Barrientos R, Frank M, Watkins L, Maier S. Aging-related changes in neuroimmune-endocrine function: Implications for hippocampal-dependent cognition. Horm Behav. 2012;62(3):219–27.

115. Bliss T, Collingridge G. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993;361(6407):31–9.

116. García-Bueno A, Leza J. Mecanismos inflamatorios/antiinflamatorios en el cerebro tras la exposición a estrés. Rev Neurol. 2008;46(11):675–83.

117. Esteban S, Garau C, Aparicio S, Moranta D, Barceló P, Ramis M, et al. Improving effects of long-term growth hormone treatment on monoaminergic neurotransmission and related behavioral tests in aged rats. Rejuvenation Res. 2010;13(6):707–16.

118. Esteban S, Garau C, Aparicio S, Moranta D, Barceló P, Fiol M, et al. Chronic melatonin treatment and its precursor L-tryptophan improve the monoaminergic neurotransmission and related behavior in the aged rat brain. J Pineal Res. 2010;48(170–177):170–7.

119. Moranta D, Barceló P, Aparicio S, Garau C, Sarubbo F, Ramis M, et al. Intake of melatonin increases tryptophan hydroxylase type 1 activity in aged rats: Preliminary study. Exp Gerontol. 2014;49(1):1–4.

120. Liu L, Chan C. The role of inflammasome in Alzheimer's disease. Aging Res Rev. 2014;15:6–15.

121. Wonodi I, Schwarcz R. Cortical kynurenine pathway metabolism: A novel target for cognitive enhancement in schizophrenia. Schizophr Bull. 2010;36(2):211–8.

122. Simi A, Lerouet D, Pinteaux E, Brough D. Mechanismsofregu- lationforinterleukin-1β in neurodegenerativedisease. Neuropharmacology. 2007;(52):1563–1569.

123. Van Eldik L, Thompson W, Ranaivo H, Behanna H, Martin Watterson D. Glia Proinflammatory Cytokine Upregulation as a Therapeutic Target for Neurodegenerative Diseases: Function-Based and Target-Based Discovery Approaches. Int Rev Neurobiol. 2007;82:277–96.

124. Shimizu M, Ishikawa J, Yano Y, Hoshide S, Shimada K, Kario K. The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events. Atherosclerosis. 2011;219(1):316–21.

125. de Leeuw F-E, de Groot JC, Oudkerk M, Witteman JCM, Hofman A, van Gijn J, et al. Hypertension and cerebral

white matter lesions in a prospective cohort study. Brain. 2002;125(Pt 4):765–72.

126. Schiffrin E. Inflammation, immunity and development of essential hypertension. J Hypertens. 2014;32(2):228–9.

127. Tousoulis D, Kampoli A-M, Papageorgiou N, Androulakis E, Antoniades C, Toutouzas K, et al. Pathophysiology of atherosclerosis: the role of inflammation. Curr Pharm Des. 2011;17(37):4089–110.

128. Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. Physiol Behav. 2008;94(2):206–18.

129. Goossens GH, Bizzarri A, Venteclef N, Essers Y, Cleutjens JP, Konings E, et al. Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation. Circulation. 2011;124(1):67–76.

130. Blüher M. Adipose tissue dysfunction in obesity. Experimental and Clinical Endocrinology and Diabetes. 2009. p. 241–50.

131. Diack AB, Alibhai JD, Barron R, Bradford B, Piccardo P, Manson JC. Insights into mechanisms of chronic neurodegeneration. International Journal of Molecular Sciences. 2016. 17(1).

132. Kayed R, Glabe CG. Conformation-Dependent Anti-Amyloid Oligomer Antibodies. Methods in Enzymology. 2006. p. 326–44.

133. Piccardo P, Manson JC, King D, Ghetti B, Barron RM. Accumulation of prion protein in the brain that is not associated with transmissible disease. Proc Natl Acad Sci U S A. 2007;104(11):4712–7.

134. Hershko A, Ciechanover A. The ubiquitin system. Annu Rev Biochem. 1998;67:425–79.

135. Pratt W, Morishima Y, Peng H, Osawa Y. Proposal for a role of the Hsp90/Hsp70-based chaperone machinery in making triage decisions when proteins undergo oxidative and toxic damage. Exp Biol Med. 2010;235(3):278–89.

136. Pajares M, Jiménez-Moreno N, Dias IHK, Debelec B, Vucetic M, Fladmark KE, et al. Redox control of protein degradation. Redox Biology. 2015. p. 409–20.

137. Macario AJL, Conway de Macario E. Stress and molecular chaperones in disease. International Journal of Clinical and Laboratory Research. 2000. p. 49–66.

138. Macario AJL, Conway de Macario E. Sick chaperones, cellular stress, and disease. N Engl J Med. 2005;353(14):1489–501.

139. Eisenberg D, Jucker M. The amyloid state of proteins in human diseases. Cell. 2012. p. 1188–203.

140. ellinger KA. Basic mechanisms of neurodegeneration: A critical update. J Cell Mol Med. 2010;14(3):457–87.

141. Agostinho P, Cunha RA, Oliveira C. Neuroinflammation, Oxidative Stress and the Pathogenesis of Alzheimer's Disease. Curr Pharm Des. 2010;16:2766–78.

142. Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012;367(9):795–804.

143. Hügel HM. Brain food for alzheimer-free aging: Focus on herbal medicines. Adv Exp Med Biol. 2015;863:95–116.

144. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;(79):727–47.

145. Scalbert A, Williamson G. Dietary Intake and Bioavailability of Polyphenols. J Med Food. 2000;3(2):121–5.

146. Kondratyuk TP, Pezzuto JM. Natural Product Polyphenols of Relevance to Human Health. Arch Physiol Biochem. 2004;42(s1):46–63.

147. Spencer J, Abd El Mohsen M, Minihane A, Mathers J. Biomarkers of the intake of dietary polyphenols: strengths, limitations and application in nutrition research. Br J Nutr. 2008;99:12–22.

148. Beckman CH. Phenolic-storing cells: keys to programmed cell death and periderm formation in wilt disease resistance and in general defence responses in plants? Physiol Mol Plant Pathol. 2000;57(3):101–10.

149. Liu J, Yu H, Ning X. Effect of quercetin on chronic enhancement of spatial learning and memory of mice. Sci China C Life Sci. 2006;49(6):583–90.

150. Ansari M, Abdul H, Joshi G, Opii W, Butterfield D. Protective effect of quercetin in primary neurons against Abeta (1-42): relevance to Alzheimer's disease. J Nutr Biochem. 2009;20:269–75.

151. Truelsen T, Thudium D, Grønbaek M, Copenhagen T, Heart C. Amount and type of alcohol and risk of dementia: the Copenhagen City Heart Study. Neurology. 2002;59(9):1313–9.

152. Gomez-Pinilla F, Nguyen T. Natural mood foods: The actions of polyphenols against psychiatric and cognitive disorders. Nutr Neurosci. 2012;15(3):127–33.

153. Scalbert A, Manach C, Morand C, Rémésy C, Jiménez L. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr. 2005;45(4):287–306.

154. Scalbert A, Johnson I, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr J. 2005;81(1):215S–217S.

155. Abbott N, Patabendige A, Dolman D, Yusof S, Begley D. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37(1):13–25.

156. Abbott N. Blood-brain barrier structure and function and the challenges for CNS drug delivery. J Inherit Metab Dis. 2013;36(3):437–49.

157. Moriya J, Chen R, Yamakawa J, Sasaki K, Ishigaki Y, Takahashi T. Resveratrol improves hippocampal atrophy in chronic fatigue mice by enhancing neurogenesis and inhibiting apoptosis of granular cells. Biol Pharm Bull. 2011;34(3):354–9.

158. Narita K, Hisamoto M, Okuda T, Takeda S. Differential neuroprotective activity of two different grape seed extracts. PLoS One. 2011;6(1):1–10.

159. Liu Z, Zhuang C, Sheng S, Shao L, Zhao W, Zhao S. Overexpression of a resveratrol synthase gene (PcRS) from Polygonum cuspidatum in transgenic Arabidopsis causes the accumulation of trans-piceid with antifungal activity. Plant Cell Rep. 2011;(30):2027–2036.

160. Smoliga J, Baur J, Hausenblas H. Resveratrol and health--a comprehensive review of human clinical trials. Mol Nutr Food Res. 2011;55(8):1129–41.

161. Yang T, Wang L, Zhu M, Zhang L, Yan L. Properties and molecular mechanisms of resveratrol: a review. Pharmazie. 2015;70(8):501–6.

162. Bandaruk Y, Mukai R, Kawamura T, Nemoto H, Terao J. Evaluation of the inhibitory effects of quercetin-related flavonoids and tea catechins on the monoamine oxidase-A reaction in mouse brain mitochondria. J Agric Food Chem. 2012;60(41):10270–7.

163. Davis J, Murphy E, Carmichael M. Effects of the dietary flavonoid quercetin upon performance and health. Curr Sports Med Rep. 2009;8(4):206–13.

164. Khurana S, Venkataraman K, Hollingsworth A, Piche M, Tai T. Polyphenols: Benefits to the Cardiovascular System

in Health and in Aging. Nutrients. 2013;5:3779–827.

165. Cirillo G, Curcio M, Vittorio O, Iemma F, Restuccia D, Spizzirri U, et al. Polyphenol conjugates and human health: perspective review. Crit Rev Food Sci Nutr. 2014;(2014):37–41.

166. Karimi G, Vahabzadeh M, Lari P, Rashedinia M, Moshiri M. Silymarin, a promising pharmacological agent for treatment of diseases. Iran J Basic Med Sci. 2011;14(4):308–17.

167. De Groot H, Rauen U. Tissue injury by reactive oxygen species and the protective effects of flavonoids. Fundam Clin Pharmacol. 1998;12(3):249–55.

168. Nencini C, Giorgi G, Micheli L. Protective effect of silymarin on oxidative stress in rat brain. Phytomedicine. 2007;14(2–3):129–35.

169. Venigalla M, Gyengesi E, Sharman M, Münch G. Novel promising therapeutics against chronic neuroinflammation and neurodegeneration in Alzheimer's disease. Neurochem Int. 2015;95:63-74.

170. Spencer J. The impact of fruit flavonoids on memory and cognition. Br J Nutr. 2010;104 Suppl:S40–7.

171. Sandoval-Acuña C, Ferreira J, Speisky H. Polyphenols and mitochondria: An update on their increasingly emerging ROS-scavenging independent actions. Arch Biochem Biophys. 2014;559:75–90.

172. Hollman PCH, Cassidy A, Comte B, Heinonen M, Richelle M, Richling E, et al. The biological relevance of direct antioxidant effects of polyphenols for cardiovascular health in humans is not established. J Nutr. 2011;141:989S–1009S.

173. Pandey K, Rizv S. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009;2(5):270–8.

174. Chan S, Kantham S, Rao VM, Palanivelu MK, Pham HL, Shaw PN, et al. Metal chelation, radical scavenging and inhibition of Aβ42 fibrillation by food constituents in relation to Alzheimer's disease. Food Chem. 2016;199:14–24.

175. Schapira AH. Etiology of Parkinson's disease. Neurology. 2006;66(10 Suppl 4):S10-23.

176. Bohn T. Dietary factors affecting polyphenol bioavailability. Nutr Rev. 2014;72(7):429–52.

177. Curti V, Capelli E, Boschi F, Nabavi SF, Bongiorno AI, Habtemariam S, et al. Modulation of human miR-17-3p expression by methyl 3-O-methyl gallate as explanation of its in vivo protective activities. Mol Nutr Food Res. 2014;58(9):1776–84.

178. Tsuji P, Stephenson K, Wade K, Liu H, Fahey J. Structure-Activity Analysis of Flavonoids: Direct and Indirect Antioxidant, and Antiinflammatory Potencies and Toxicities. Nutr Cancer. 2013;(October):37–41.

179. Wang X, Wang W, Li L, Perry G, Lee H, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta - Mol Basis Dis. 2014;1842(8):1240–7.

180. Leonard SS, Xia C, Jiang BH, Stinefelt B, Klandorf H, Harris GK, et al. Resveratrol scavenges reactive oxygen species and effects radical-induced cellular responses. Biochem Biophys Res Commun. 2003;309(4):1017–26.

181. Khan M, Khan M, Khan A. Naringenin ameliorates Alzheimer's disease (AD)-type neurodegeneration with cognitive impairment (AD-TNDCI) caused by the intracerebroventricular- streptozotocin in rat model. Neurochem Int. 2012;61:1081–1093.

182. Choi KM, Lee HL, Kwon YY, Kang MS, Lee SK, Lee CK. Enhancement of mitochondrial function correlates with the extension of lifespan by caloric restriction and caloric restriction mimetics in yeast. Biochem Biophys Res Commun. 2013;441(1):236–42.

183. Desquiret-Dumas V, Gueguen N, Leman G, Baron S, Nivet-Antoine V, Chupin S. Resveratrol induces a mitochon-

drial complex I-dependent increase in NADH oxidation responsible for sirtuin activation in liver cells. J Biol Chem. 2013;288:36662–36675.

184. Williams C, El Mohsen M, Vauzour D, Rendeiro C, Butler L, Ellis J, et al. Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels. Free Radic Biol Med. 2008;45(3):295–305.

185. Abraham J, Johnson R. Consuming a diet supplemented with resveratrol reduced infection-related neuroinflammation and deficits in working memory in aged mice. Rejuvenation Res. 2009;12(6):445–53.

186. Flowers A, Lee J, Acosta S, Hudson B, Small C, Sanberg, et al. NT-020 treatment reduces inflammation and augments Nrf-2 and Wnt signaling in aged rats. J Neuroinflammation. 2015;12(1):174.

187. Yeung F, Hoberg J, Ramsey C, Keller M, Jones D, Frye R, et al. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 2004;23(12):2369–80.

188. Wenzel U. Nutrition, sirtuins and aging. Genes Nutr. 2006;1(2):85–93.

189. Shahidi F, Naczk M. Food Phenolics: Sources, Chemistry, Effects, Applications. Food Chem. 1996;57(3):481–2.

190. Brunet A, Sweeney L, Sturgill J, Chua K, Greer P, Lin Y, et al. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science (80-). 2004;303(5666):2011–5.

191. Yamamoto H, Schoonjans K, Auwerx J. Sirtuin functions in health and disease. Mol Endocrinol. 2007;21(8):1745–55.

192. Horio Y, Hayashi T, Kuno A, Kunimoto R. Cellular and molecular effects of sirtuins in health and disease. Clin Sci. 2011;121(5):191–203.

193. Kawahara T, Michishita E, Adler A, Damian M, Berber E, Lin M, et al. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. Cell. 2009;136(1):62–74.

194. Kanfi Y, Peshti V, Gil R, Naiman S, Nahum L, Levin E, et al. SIRT6 protects against pathological damage caused by diet-induced obesity. Aging Cell. 2010;9(2):162–73.

195. Zhong L, D'Urso A, Toiber D, Sebastian C, Henry R, Vadysirisack D, et al. The Histone Deacetylase Sirt6 Regulates Glucose Homeostasis via Hif1α. Cell. 2010;140(2):280–93.

196. Chung S, Yao H, Caito S, Hwang J, Arunachalam G, Rahman I. Regulation of SIRT1 in cellular functions: Role of polyphenols. Arch Biochem Biophys. 2010;501(1):79–90.

197. Duan W. Sirtuins: from metabolic regulation to brain aging. Front Aging Neurosci. 2013;5(36):5:36.

198. Qin W, Yang T, Ho L, Zhao Z, Wang J, Chen L, et al. Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. J Biol Chem. 2006;281(31):21745–54.

199. Jiang M, Wang J, Fu J, Du L, Jeong H, West T, et al. Neuroprotective role of Sirt1 in mammalian models of Huntington's disease through activation of multiple Sirt1 targets. Nat Med. 2012;18(1):153–8.

200. Zhang F, Wang S, Gan L, Vosler P, Gao Y, Zigmond M, et al. Protective effects and mechanisms of sirtuins in the nervous system. Prog Neurobiol. 2011;95(3):373–95.

201. Zhang H, Li L, Gao P, Chen H, Zhang R, Wei Y, et al. Involvement of the p65/RelA subunit of NF-κB in TNF-α-induced SIRT1 expression in vascular smooth muscle cells. Biochem Biophys Res Commun. 2010;397:569–75.

202. Yao H, Chung S, Hwang J, Rajendrasozhan S, Sundar I, Dean D, et al. SIRT1 protects against emphysema via FOXO3-mediated reduction of premature senescence in mice. J Clin Invest. 2012;122(6):2032–45.

203. Quintas A, De Solis AJ, Diez-Guerra FJ, Carrascosa JM, Bogonez E. Age-associated decrease of SIRT1 expression in rat hippocampus. Prevention by late onset caloric restriction. Exp Gerontol. 2012;47(2):198–201.

204. Michán S, Li Y, Chou M, Parrella E, Ge H, Long J, et al. SIRT1 is essential for normal cognitive function and synaptic plasticity. J Neurosci. 2010;30(29):9695–9707.

205. Wu A, Ying Z, Gomez-Pinilla F. Oxidative stress modulates Sir2alpha in rat hippocampus and cerebral cortex. Eur J Neurosci. 2006;23(10):2573–80.

206. Herskovits A, Guarente L. SIRT1 in Neurodevelopment and Brain Senescence. Neuron. 2014;81(3):471–83.

207. Herskovits A, Guarente L. Sirtuin deacetylases in neurodegenerative diseases of aging. Cell Res. 2013;23(6):746–58.

208. Hall J, Dominy J, Lee Y, Puigserver P. The sirtuin family's role in aging and age-associated pathologies. J Clin Invest. 2013;123(3):973–9.

209. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, et al. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature. 2003;425(6954):191–6.

210. Hubbard BP, Gomes a. P, Dai H, Li J, Case a. W, Considine T, et al. Evidence for a Common Mechanism of SIRT1 Regulation by Allosteric Activators. Science (80-). 2013;339(6124):1216–9.

211. Mannari C, Bertelli E, Stiaccini G, Giovannini L. Wine, sirtuins and nephroprotection: not only resveratrol. Med Hypotheses. 2010;75(6):636–8.

212. Bhullar K, Hubbard B. Lifespan and healthspan extension by resveratrol. Biochim Biophys Acta. 2015;1852:1209–18.

213. Yamakuchi M, Ferlito M, Lowenstein C. miR-34a repression of SIRT1 regulates apoptosis. Proc Natl Acad Sci USA. 2008;105:13421–13426.

214. Cai W, Ramdas M, Zhu L, Chen X, Striker G., Vlassara H. Oral advanced glycation endproducts (AGEs) promote insulin resistance and diabetes by depleting the antioxidant defenses AGE receptor-1 and sirtuin 1. Proc Natl Acad Sci USA. 2012;109:15888–15893.

215. Furukawa A, Tada-Oikawa S, Kawanishi S, Oikawa S. H2O2 accelerates cellular senescence by accumulation of acetylated p53 via decrease in the function of SIRT1 by NAD+ depletion. Cell Physiol Biochem. 2007;20:45–54.

216. Xie J, Zhang X, Zhang L. Negative regulation of inflammation by SIRT1. Pharmacol Res. 2013;67(1):60–7.

217. Adler A, Sinha S, Kawahara T, Zhang J, Segal E, Chang H. Motif module map reveals enforcement of aging by continual NF-κB activity. Genes Dev. 2007;21(24):3244–57.

218. Kaltschmidt C, Kaltschmidt I, Neumann H, Wekerle H, Baeuerle P. Constitutive NF-KB Activity in Neurons. Mol Cell Biol. 1994;14(6).

219. Meberg P, Kinney W, Valcourt E, Routtenberg A. Gene expression of the transcription factor NF-kB in hippocampus: regulation by synaptic activity. Mol Brain Res. 1996;38:179– 190.

220. Jana M, Dasgupta S, Liu X, Pahan K. Regulation of tumor necrosis factor-alpha expression by CD40 ligation in BV-2 microglial cells. J Neurochem. 2002;80(1):197–206.

221. Nakajima K, Matsushita Y, Tohyama Y, Kohsaka S, Kurihara T. Differential suppression of endotoxin-inducible inflammatory cytokines by nuclear factor kappa B (NFkappaB) inhibitor in rat microglia. Neurosci Lett. 2006;401(3):199–202.

222. Baldwin A. The NF-kB and IkB proteins: New discoveries and insights. Annu Rev Immunol. 1996;(14):649–81.

223. Siebenlist U, Franzoso G, Brown K. Structure, regulation and function of NF-κB. Annu Rev Cell Biol. 1994;10:405–455.

224. Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol. 2009;1(4):1–14.

225. Kaltschmidt B, Widera D, Kaltschmidt C. Signaling via NF-kB in the nervous system. Biochim Biophys Acta - Mol Cell Res. 2005;1745(3):287–99.

226. Chen L-F, Greene WC. Regulation of distinct biological activities of the NF-kappaB transcription factor complex by acetylation. J Mol Med (Berl). 2003;81(9):549–57.

227. Schmitz M, Mattioli I, Buss H, Kracht M. NF-κB: a multifaceted transcription factor regulated at several levels. Chembiochem. 2004;5(10):1348–58.

228. Perkins N. Integrating cell-signalling pathways with NF-κB and IKK function. Nat Rev Mol Cell Biol. 2007;8(1):49–62.

229. Quivy V, Van Lint C. Regulation at multiple levels of NF-κB-mediated transactivation by protein acetylation. Biochem Pharmacol. 2004;68(6):1221–9.

230. Osorio F, Bárcena C, Soria-Valles C, Ramsay A, de Carlos F, Cobo J, et al. Nuclear lamina defects cause ATM-dependent NF-κB activation and link accelerated aging to a systemic inflammatory response. Genes Dev. 2012;26(20):2311–24.

231. Tilstra J, Robinson A, Wang J, Gregg S, Clauson C, Reay D, et al. NF-κB inhibition delays DNA damage-induced senescence and aging in mice. J Clin Invest. 2012;122(7):2601–12.

232. Kwon H, Brent M, Getachew R, Jayakumar P, Chen D, Schnolzer M, et al. Human immunodeficiency virus type 1 Tat protein inhibits the SIRT1 deacetylase and induces T cell hyperactivation. Cell Host Microbe. 2008;3(3):158–67.

233. Goyarzu P, Malin DH, Lau FC, Taglialatela G, Moon WD, Jennings R, et al. Blueberry supplemented diet: effects on object recognition memory and nuclear factor-kappa B levels in aged rats. Nutr Neurosci. 2004;7(2):75–83.

234. Holmes-McNary M, Baldwin S. Chemopreventive properties of trans-resveratrol are associated with inhibition of activation of the IκB kinase. Cancer Res. 2000;60:3477–83.

235. Manna S, Mukhopadhyay A, Aggarwal B. Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation. J Immunol. 2000;164(12):6509–19.

236. Ng F, Wijaya L, Tang B. SIRT1 in the brain-connections with aging-associated disorders and lifespan. Front Cell Neurosci. 2015;9(March):64.

237. Labinskyy N, Csiszar A, Veress G, Stef G, Pacher P, Oroszi G, et al. Vascular dysfunction in aging: potential effects of resveratrol, an anti-inflammatory phytoestrogen. Curr Med Chem. 2006;13(9):989–96.

238. Birrell M, McCluskie K, Wong S, Donnelly L, Barnes P, Belvisi M. Resveratrol, an extract of red wine, inhibits lipopolysaccharide induced airway neutrophilia and inflammatory mediators through an NF-κB-independent mechanism. FASEB J. 2005;19(7):840–1.

239. Milne J, Lambert P, Schenk S, Carney D, Smith J, Gagne D, et al. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature. 2007;450(7170):712–6.

240. Rajendrasozhan S, Yang S, Edirisinghe I, Yao H, Adenuga D, Rahman I. Deacetylases and NF-kappaB in redox regulation of cigarette smoke-induced lung inflammation: epigenetics in pathogenesis of COPD. Antioxid Redox Signal. 2008;10(4):799–811.

241. Wang T, Gu J, Wu PF, Wang F, Xiong Z, Yang YJ, et al. Protection by tetrahydroxystilbene glucoside against cerebral ischemia: involvement of JNK, SIRT1, and NF-κB pathways and inhibition of intracellular ROS/RNS generation. Free Radic Biol Med. 2009;47(3):229–40.

242. Thomas P, Wang YJ, Zhong JH, Kosaraju S, O'Callaghan NJ, Zhou XF, et al. Grape seed polyphenols and curcumin reduce genomic instability events in a transgenic mouse model for Alzheimer's disease. Mutat Res - Fundam Mol Mech Mutagen. 2009;661(1–2):25–34.

243. Ksiezak-Reding H, Ho L, Santa-Maria I, Diaz-Ruiz C, Wang J, Pasinetti GM. Ultrastructural alterations of Alzheimer's disease paired helical filaments by grape seed-derived polyphenols. Neurobiol Aging. 2012;33(7):1427–39.

244. Feng Y, Wang X ping, Yang S gao, Wang Y jiong, Zhang X, Du X ting, et al. Resveratrol inhibits beta-amyloid oligomeric cytotoxicity but does not prevent oligomer formation. Neurotoxicology. 2009;30(6):986–95.

245. Jimenez-Aliaga K, Bermejo-Bescs P, Benedi J, Mart??n-Aragon S. Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects in vitro and potent antioxidant activity in APPswe cells. Life Sci. 2011;89(25–26):939–45.

246. Ushikubo H, Watanabe S, Tanimoto Y, Abe K, Hiza A, Ogawa T, et al. 3,3',4',5,5'-Pentahydroxyflavone is a potent inhibitor of amyloid β fibril formation. Neurosci Lett. 2012;513(1):51–6.

247. Martorell M, Forman K, Castro N, Capó X, Tejada S, Sureda A. Potential Therapeutic Effects of Oleuropein Aglycone in Alzheimer's disease. Curr Pharm Biotechnol. 2016;17(11):994–1001.

248. Gong EJ, Park HR, Kim ME, Piao S, Lee E, Jo DG, et al. Morin attenuates tau hyperphosphorylation by inhibiting GSK3β. Neurobiol Dis. 2011;44(2):223–30.

249. Mori T, Rezai-Zadeh K, Koyama N, Arendash GW, Yamaguchi H, Kakuda N, et al. Tannic acid is a natural β-secretase inhibitor that prevents cognitive impairment and mitigates Alzheimer-like pathology in transgenic mice. J Biol Chem. 2012;287(9):6912–27.

250. Jagota S, Rajadas J. Effect of phenolic compounds against Aβ aggregation and Aβ-induced toxicity in transgenic C. elegans. Neurochem Res. 2012;37(1):40–8.

251. Ehrnhoefer DE, Bieschke J, Boeddrich A, Herbst M, Masino L, Lurz R, et al. EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers. Nat Struct Mol Biol. 2008;15(6):558–66.

252. Boocock DJ, Faust GES, Patel KR, Schinas AM, Brown V a, Ducharme MP, et al. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol Biomarkers Prev. 2007;16:1246–52.

253. Almeida L, Vaz-da-Silva M, Falcão A, Soares E, Costa R, Loureiro AI, et al. Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple-dose study in healthy volunteers. Mol Nutr Food Res. 2009;53(S1):S7–15.

254. Bolognin S, Messori L, Zatta P. Metal ion physiopathology in neurodegenerative disorders. NeuroMolecular Med. 2009;11(4):223–38.

255. Breydo L, Uversky V. Role of metal ions in aggregation of intrinsically disordered proteins in neurodegenerative diseases. Metallomics. 2011;3(11):1163–80.

256. Jellinger KA. The Relevance of Metals in the Pathophysiology of Neurodegeneration, Pathological Considerations. Int Rev Neurobiol. 2013;110:1–47.

257. Duce JA, Tsatsanis A, Cater MA, James SA, Robb E, Wikhe K, et al. Iron-Export Ferroxidase Activity of β-Amyloid Precursor Protein is Inhibited by Zinc in Alzheimer's Disease. Cell. 2010;142(6):857–67.

258. Boillée S, Vande Velde C, Cleveland DW. ALS: A Disease of Motor Neurons and Their Nonneuronal Neighbors.

Neuron. 2006;52(1):39–59.

259. Brewer GJ. Copper excess, zinc deficiency, and cognition loss in Alzheimer's disease. BioFactors. 2012;38(2):107–13.

260. Bolognin S, Messori L, Drago D, Gabbiani C, Cendron L, Zatta P. Aluminum, copper, iron and zinc differentially alter amyloid-Abeta (1–42) aggregation and toxicity. J Biochem Cell Biol. 2011;43:877–885.

261. Zatta P, Lucchini R, Van Rensburg SJ, Taylor A. The role of metals in neurodegenerative processes: Aluminum, manganese, and zinc. Brain Res Bull. 2003;62(1):15–28.

262. Duce JA, Bush AI. Biological metals and Alzheimer's disease: Implications for therapeutics and diagnostics. Prog Neurobiol. 2010;92(1):1–18.

263. Zaky A, Mohammad B, Moftah M, Kandeel K, Bassiouny A. Apurinic/apyrimidinic endonuclease 1 is a key modulator of aluminum-induced neuroinflammation. BMC Neurosci. 2013;14:26.

264. Inestrosa NC, Alvarez A, Dinamarca MC, Pérez-Acle T, Colombres M. Acetylcholinesterase-amyloid-beta-peptide interaction: effect of Congo Red and the role of the Wnt pathway. Curr Alzheimer Res. 2005;2(3):301–6.

265. Jang M, Piao X, Kim J, Kwon S, Park J. Inhibition of cholinesterase and amyloid-beta aggregation by resveratrol oligomers from Vitis amurensis. Phytother Res. 2008;22:544–9.

266. Okello EJ, Leylabi R, McDougall GJ. Inhibition of acetylcholinesterase by green and white tea and their simulated intestinal metabolites. Food Funct. 2012;3(6):651–61.