

Sarubbo F  
Miralles A  
Moranta D  
Esteban S

# DEMENTIA: ADVANCES AND TREATMENT

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# Dementia: Advances and Treatment

## Chapter 1

### Dietary polyphenols as promising molecules to prevent dementia

*Sarubbo F<sup>\*</sup>; 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, polyphenols have 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; I $\kappa$ B: 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- $\kappa$ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; NOX: NADPH oxidase; PI3K: Phosphoinositide 3-kinase pathway; ROS: Reactive Oxygen Species; SIRT1: Sirtuin 1;  $\tau$ Tau: protein; TNF- $\alpha$ : Tumor necrosis factor alpha

## 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 that every 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 their medical 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, and chelate 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 suggests that polyphenols may be promising molecules in the prevention of dementia.

## 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 dementia* (a 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 maintained at 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 in neurodegeneration 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- $\beta$  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  $\beta$ -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 involved 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  $\omega$ -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 called “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 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- $\kappa$ B [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-1 $\beta$ , TNF- $\alpha$ , interferons and prostaglandins [91,92]. There are several biomarkers of neuroinflammation implicated in dementia pathogenesis [104,105], for instance increased serum TNF- $\alpha$  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], among others. All together contributes with the onset and development of neurodegenerative diseases such as Alzheimer’s disease, 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, atherogenic adipokine 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,  $\beta$ -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, these subserve 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 antiinflammatory 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*, *lignans* and 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- $\kappa$ B [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- $\kappa$ B 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-1 $\alpha$  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-1 $\beta$  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- $\kappa$ B (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 deacetylate NF- $\kappa$ B, 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- $\kappa$ B, a critical subunit for activation of transcription of proinflammatory genes and therefore triggering an inflam-

matory processes [187]. This NF- $\kappa$ B 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- $\kappa$ B consists of a heterodimeric complex of p50/p52 and p65 proteins. In the cytoplasm, NF- $\kappa$ B heterodimer joins the inhibitory protein I $\kappa$ B and thus the entire complex is inactive [222]. ROS and other proinflammatory molecules activate protein kinase that phosphorylates I $\kappa$ B, 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- $\kappa$ B 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- $\kappa$ B 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- $\kappa$ B in aged skin of transgenic mice causes phenotypic rejuvenation of this tissue [217]. Similarly, genetic and pharmacological inhibition of NF- $\kappa$ B 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- $\kappa$ B subunit increases the duration and effectiveness of the NF- $\kappa$ B activation, generating increased inflammation [226]. The interaction between SIRT1 and NF- $\kappa$ B 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- $\kappa$ B. Additionally, other study reinforced the idea that SIRT1 deacetylate NF- $\kappa$ B since during HIV-1 studies [232] demonstrated that the viral protein Tat binds to SIRT1, inhibiting its activity, thereby preventing NF- $\kappa$ B 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- $\kappa$ B. Additionally, old rats fed diet rich in polyphenol also showed reduced expression of NF- $\kappa$ B 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- $\kappa$ B signaling [91,92]. Similar results have been shown in cancer studies, where resveratrol has been shown to exert antitumor actions through inhibiting NF- $\kappa$ B [234,235]. As it is schematized in figure 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- $\kappa$ B 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- $\beta$ -amyloid action and a potential in neutralizing abnormal folding of  $\tau$  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 disaggregation of  $A\beta$  fibril and protected from  $A\beta$  neurotoxicity by inhibiting inducible nitric oxide synthase inhibition [159] and decreasing cleavage of  $\beta$ -carboxyl terminal amyloid precursor protein [249]. This in turn prevents neuronal cell death by protecting neurons against  $\tau$  hyperphosphorylation induced by  $A\beta$ . The mechanism of  $A\beta$  inhibition is driven by: stimulating the  $\alpha$ -secretase; inhibiting the  $\beta$ -site amyloid precursor protein cleaving enzyme-1 (BACE1) and  $\gamma$ -protease pathways; and throughout hydrophobic interactions that involve  $\pi$ - $\pi$  bonding between the planar faces of the polyphenol structure and the aromatic residues of  $A\beta$ 42. Additionally, hydrogen bonding occurs between the peptide and the phenolic hydroxyl groups. Polyphenols intercede/impose between two  $\beta$ 42-amyloid aromatic residues preventing their  $\pi$ - $\pi$  stacking, blocking the amyloid self-assembly- $\beta$ -oligomer-sheet-fibril formation and gaining of toxic function[143]. In addition, resveratrol, curcumin, oleuropein, pentagalloylglucose inhibit  $\beta$ -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. Since there have been conducted clinical studies in humans, administering a single doses of 5 grams of oral resveratrol [252] or 150 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 treatments with 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  $A\beta$  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 A $\beta$  plaque deposits. Therefore, inhibitors of AChE prevent the aggregation of A $\beta$  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 A $\beta$  aggregation, indicating their potential in the treatment of age-related disorders such as Alzheimer's disease.

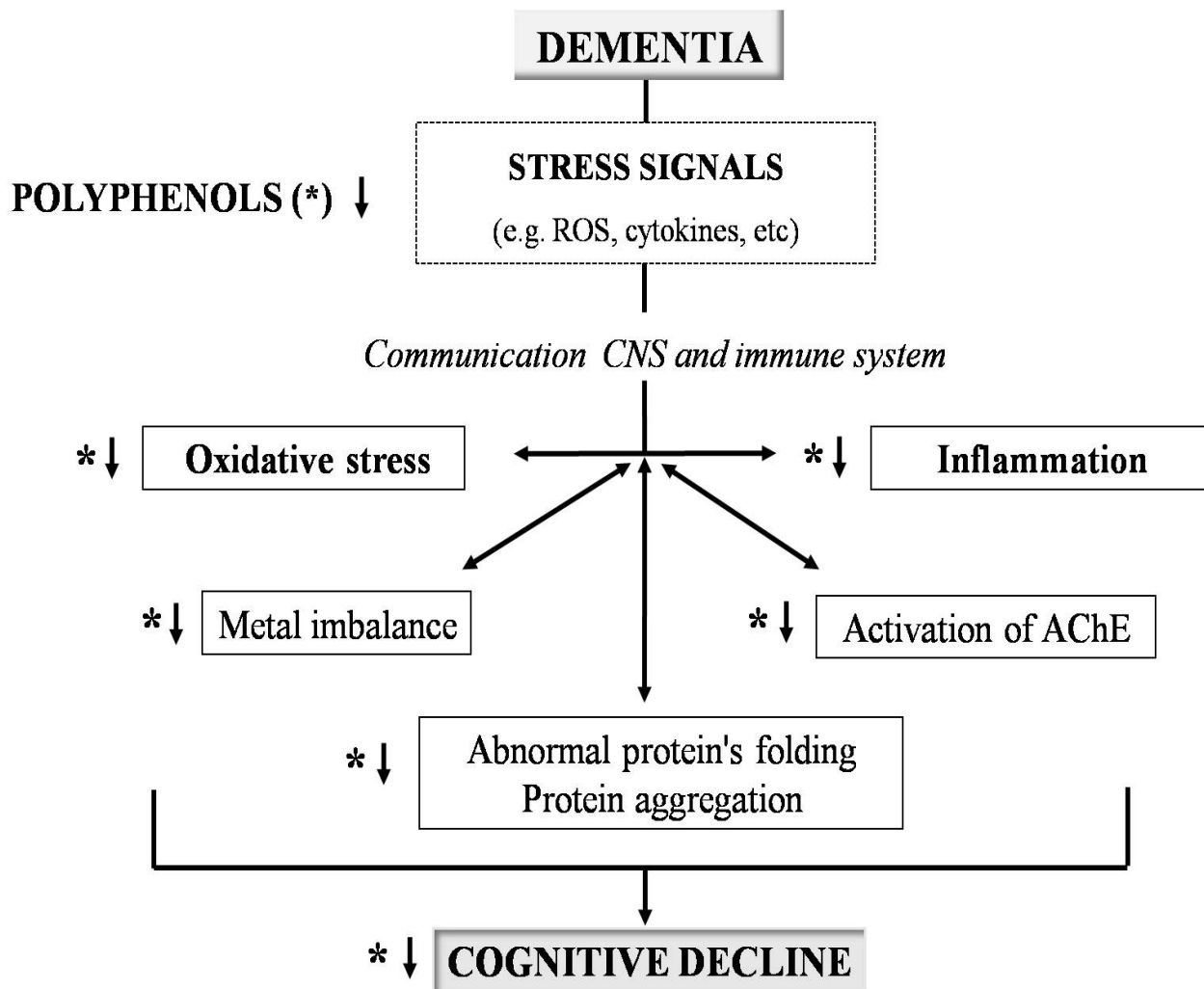
#### 4. Conclusion

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, protein aggregates, 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 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- $\kappa$ B signaling pathway. In addition, polyphenols can also avoid metal toxicity by inducing metal chelation, reducing the abnormal protein folding and protein aggregation, avoiding apoptosis, inhibiting AChE, and increasing the level of some neurotransmitters, which all together are characteristic 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 research will allow to know the most effective polyphenol's dosage and administration route for the treatment of dementia.

#### 5. Acknowledgements

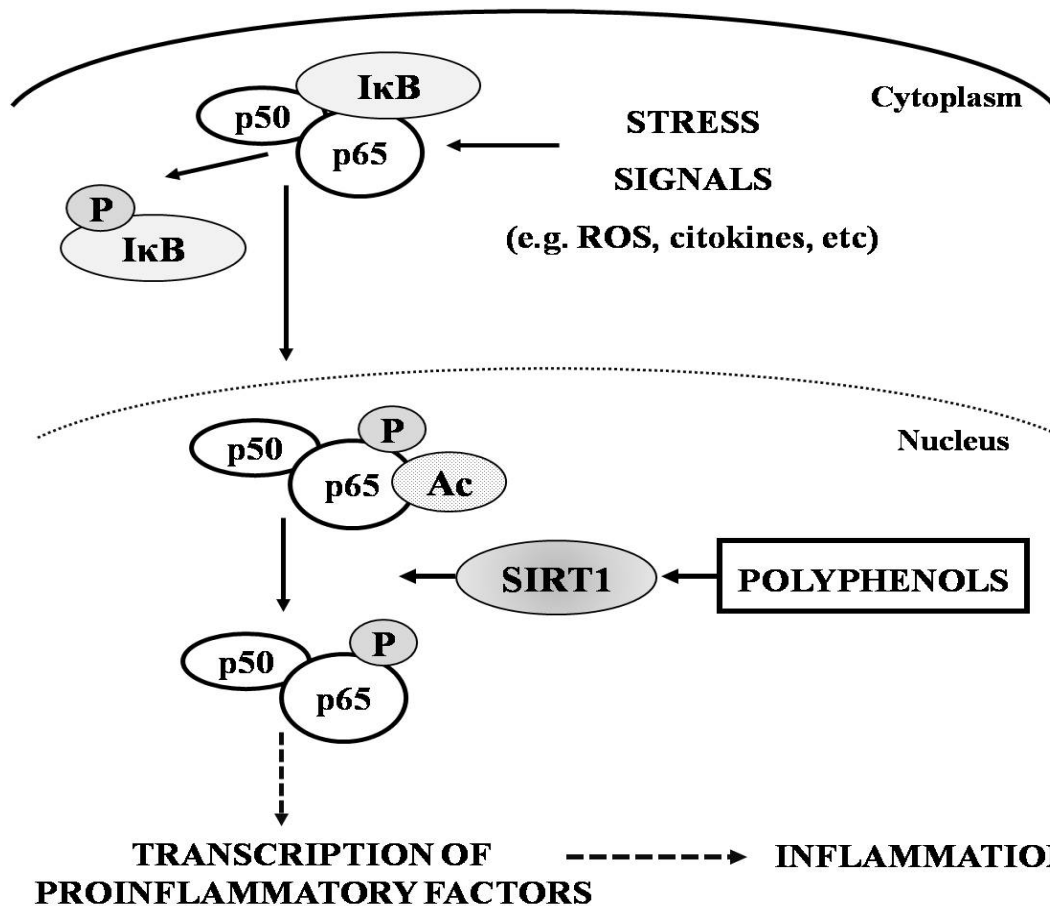
Financial contribution: Universitat de les Illes Balears (UIB), Govern Balear (ECT 025 09), Pont La Caixa-UIB Program (7/2014) and SAF2014-55903-R (MINECO, Madrid, Spain). F. Sarubbo was supported by a UIB contract.

## 6. Figures



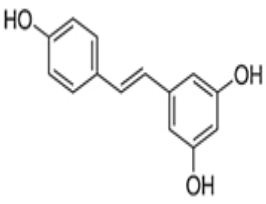
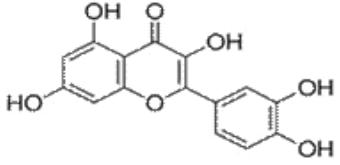
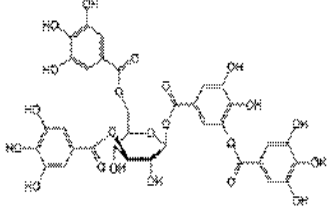
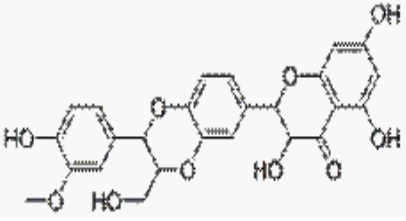
**Figure 1:** Effects of polyphenols(\*) in the attenuation on the main causes of dementia. The onset of neurodegenerative diseases such as dementia is produced by the increment of stress signals such as ROS or cytokines. Several mechanisms are triggered once the immune system, which is communicated 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 by avoiding 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 effects of polyphenols on SIRT1 and NF- $\kappa$ B signaling pathway involved in neuroinflammation. NF- $\kappa$ B consists of a heterodimeric complex of p50/p52 and p65 proteins. In the cytoplasm, NF- $\kappa$ B heterodimer joins the inhibitory protein I $\kappa$ B and thus the entire complex is inactive. ROS and other proinflammatory molecules such as cytokines activate protein kinase that phosphorylates I $\kappa$ B, 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- $\kappa$ B, which is modulated by post-transcriptional modifications such as phosphorylation (P) at serines (see paragraph 3.2 and 4.2) and acetylation (Ac) at lysines 310. The over activation of this NF- $\kappa$ B signaling pathway aggravates the inflammatory state. Polyphenols activate SIRT1, which deacetylates lysine 310 of p65 subunit of NF- $\kappa$ B, decreasing inflammation and neurodegeneration.

## 7. Table

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

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

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