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Antioxidant Activity of Wine Polyphenols for Alzheimer Prevention

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ABSTRACT

Increasing evidence demonstrates that oxidative stress causes damage to cell function with aging and is involved in a number of age related disorders including atherosclerosis, arthritis, and neurodegenerative disorders. Cellular changes show that oxidative stress is an event that precedes the appearance of the hallmark pathologies of the disease, neurofibrillary tangles and senile plaques. Although excessive consumption of ethanol in alcoholic beverages causes multi-organ damage, moderate consumption, particularly of red wine, is protective against all-cause mortality. There is currently much interest in phytochemicals as bioactive compounds of wine. Wine intake is associated with a lower incidence of AD (Alzheimer disease) since wine is enriched in antioxidant compounds with potential neuroprotective activities. The findings that red wine presented more health-promotion activity than beer or spirits caused research attention to focus on phenolic compounds. Several studies have been undertaken to differentiate the effects of phenolic and other non-alcohol components of wine from those due to alcohol. From polyphenolics resveratrol and flavanols can be underlined. Resveratrol is a potential therapeutic agent to amilorate age-related neurodegenerative disorders. Catechins, the most abundant phenolics in wine, could influence on the development of AD. This manuscript summarizes recent studies on the possible mechanisms of action, potential therapeutic uses, and bioavailability of the nonalcoholic constituents of wine.

Keywords: Alzheimer disease, antioxidant, antocyanins, flavan 3-ols, oxidative stress, polyphenols, resveratrol, wine
Abbreviations: Aβ, Amiloid-β peptides; **AD**, Alzheimer disease; **Apo E**, apolipoprotein E; **APP**, amyloid precursor protein; **BACE**, enzyme beta-secretase; **EGCG**, (-)-epigallocatechin-3-gallate; **fAβ**, beta-amyloid fibrils; **HNE**, 4-hydroxynonenal; **HMW**, high molecular weight; **LAD**, late stage Alzheimer disease; **MCI**, mild cognitive impairment; **mtDNA**, mitochondrial DNA; **NF-κB**, nuclear factor kappa-light-chain-enhancer of activated B cells; **OHA**, 8-hydroxyadenine; 8-**OHdG**, 8-hydroxydeoxyguanosine; **8-OHG**, 8-hydroxyguanine; **8-OHU**, 8-hydroxyuracil; **SOD**, superoxide dismutase; **tfR**, transferrin receptor

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ALZHEIMER DISEASE

Progressive mental deterioration in old age has been recognized and described throughout history. However, it was not until 1906 that a German physician, Dr. Alois Alzheimer, specifically identified a collection of brain cell abnormalities as a disease. One of Dr. Alzheimer's patients died after years of severe memory problems, confusion and difficulty understanding questions. Upon her death, while performing a brain autopsy, the doctor noted dense deposits surrounding the nerve cells (neuritic plaques). Inside the nerve cells he observed twisted bands of fibers (neurofibrillary tangles). Today, this degenerative brain disorder bears his name, and when found during an autopsy, these plaques and tangles mean a definite diagnosis of Alzheimer's disease (AD).

AD is the main cause of dementia in elderly people. The prevalence of AD is expected to quadruple by the year 2047. The disorder is a growing public-health concern with potentially devastating effect. There are no known cures or preventions for AD. Even delaying the onset by a few years would decrease its prevalence and burden on public-health systems (Luschinger 2004). Despite continued efforts, the development of an effective treatment for AD remains elusive (Ballenger 2006).

AD is no longer the condition described in texts written

Received: 25 October, 2010. Accepted: 21 May, 2011.

Invited Review

some 10 years ago, i.e., a pathology caused by quite mysterious phenomena (Christen 2000). Research in the fields of genetics and molecular biology has produced many findings about this common neurodegenerative disease. Many genes involved with the disease have been identified. Some of these genes are involved in early-onset forms of the disease and have a direct causal effect: the amyloid precursor protein (APP) gene located on chromosome 21 and presenilin genes 1 (PS1) and 2 (PS2) located on chromosomes 14 and 1, respectively. The apolipoprotein E (apo E) gene (located on chromosome 19), the α_2-macroglobulin gene located on chromosome 12, and other unidentified genes may determine susceptibility in late-onset forms and sporadic cases (Christen 2000).

Genetic research along these lines, together with research in molecular biology investigating the main components of the 2 principal hallmarks of AD, i.e., senile plaques (typically bearing β-amyloid) and neurofibrillary tangles (mainly composed of tau protein), have helped produce hypotheses about the pathogenesis of AD that no doubt come close to reflecting the real situation. In particular, it appears that a cascade of events may occur that leads to amyloidogenesis and, more specifically, to the formation and deposition of a long β-amyloid peptide (of 42 or 43 amino acids; the shorter form of 40 amino acids has no pathologic effect). Various mutations that have been identified on the APP, PS1, or PS2 gene all feature increased production of this peptide. Various complementary factors, including cytokines, transforming growth factor β1, and interleukin 1, seem to be involved in triggering the process of amyloidogenesis (Younkin *et al*. 1998; Zhu 2007).

There is increasing consensus that the production and accumulation of amyloid-β (Aβ) peptides is central to the pathogenesis of AD. Deposition of Aβ peptides into insoluble fibrous aggregates known as amyloid plaques in the brain is a major hallmark of AD neuropathology. Moreover, increasing evidence suggests that cognitive decline in AD may be directly caused by accumulation of soluble high molecular weight (HMW) oligomeric Aβ species in the brain that are generated by aggregation of Aβ peptides (Lesne *et al*. 2006; Castellani *et al.* 2007). Although neurofibrillary tangles can occur independently, and cause neuronal death in frontotemporal dementia, the presence of both lesions in the neocortex is essential to the diagnosis of AD (Hardy 2002). Thus, major efforts from both academia and industry are presently focused on developing pharmacologic strategies that could delay the initiation and/or slow the oligomerization/aggregation of amyloid peptide.

In addition to age and genetic factors there are another potential contributing factors such as:

- Cardiovascular disease: Risk factors associated with heart disease and stroke, such as high blood pressure and high cholesterol, may also increase one's risk of developing AD. High blood pressure may damage blood vessels in the brain, disrupting regions that are important in decision-making, memory and verbal skills. This could contribute to the progression of the disease (Launer 2000). High cholesterol may inhibit the ability of the blood to clear protein from the brain (Pfrieger 2002).
- Type 2 diabetes: There is growing evidence of a link between AD and type 2 diabetes (Kim *et al*. 2010). In Type 2 diabetes insulin does not work effectively to convert blood sugar into energy. This inefficiency results in production of higher levels of insulin and blood sugar which may harm the brain and contribute to the progression of AD (Kroner 2009).
- Inflammation: Inflammation is a natural, but sometimes harmful, healing bodily function in which immune cells rid themselves of dead cells and other waste products. As protein plaques develop, inflammation results, but it is not known whether this process is damaging and a cause of AD, or part of an immune response attempting to contain the disease.
- Other possible risk Factors: Some studies have implicated prior traumatic head injury, lower education level and female gender as possible risk factors. AD may also be associated with an immune system reaction or a virus (Lesne *et al.* 2006).
- Oxidative damage: Free radicals are unstable molecules that sometimes result from chemical reactions within cells. These molecules seek stability by attacking other molecules, which can harm cells and tissue and may contribute to the neuronal brain cell damage caused by AD (http://www.ahaf.org/alzheimers/about/risk/).

Alzheimer disease and oxidative stress

The fact that age is a key risk factor in AD provides considerable support for the free radical hypothesis because effects of the attacks by free radicals, particularly those produced by reactive oxygen species (ROS), can accumulate over the years. Other identified risk factors, such as brain trauma, are also likely to be involved in the production of free radicals. The free radical hypothesis can account for the vastly heterogeneous nature of AD and the fact that both genetic and nongenetic causes are involved. Such general considerations suggest that free radicals are involved in many age-related pathologies, specifically in AD and all neurodegenerative diseases (Benzi and Moretti 1995; Cooper 1997).

Within any functional, aerobic cell, the processes involved in respiration inevitably generate ROS (Petersen *et al.* 2007). In particular, the oxidation-reduction reactions necessary for the generation of ATP produce free radical intermediates as electrons are transferred from one molecule to another. Despite the resident sequestration mechanisms present within the cell that prevent the potentially harmful dispersion of the free radical intermediates, a substantial amount of ROS manage to escape daily, free to wreak havoc on macromolecules. In fact, in a specialized cell with high metabolic activity, such as a neuron, the number of such free radicals produced is estimated by some to be 10^{11} ROS/cell/day (Petersen *et al.* 2007).

Advances in our understanding of the etiologies and pathogenesis of AD highlight a role for free radical-mediated injury to brain regions from early stages of this illness (Sonnen *et al.* 2008). Oxidative stress in broadly defined as a perturbation of cellular homeostasis, such that the rate of ROS production exceeds that of their neutralization. If homeostasis is not re-established, oxidative stress may progress toward the initiation of apoptotic cell death and tissue degeneration (Blomgren and Hagnerg 2006). In order to cope with an excess of free radicals produced, human bodies have developed sophisticated mechanisms for maintaining redox homeostasis. These protective mechanisms include scavenging or detoxification of ROS, blocking ROS production, sequestration of transition metals, as well as enzymatic and non-enzymatic antioxidant defenses produced in the body, that is endogenous and others supplied with the diet, namely exogenous ones. Among them, dietary polyphenols have been widely studied for their strong antioxidant capacities and other properties by which cell functions are regulated (Hartman *et al.* 2006)

Several evidences indicate that increase in ROS, an antioxidant systems deficit, decreased repair DNA mechanisms, proteolysis and the loss of immune system regulation are contributing factors to an increased oxidative stress. All those processes ultimately lead to a progressive neuronal death and damage.

Free radicals are in fact potent deleterious agents causing cell death or other forms of irreversible damage, e.g., free radicals appear to modify ≈10000 DNA base pairs every day. Neurons appear to be particularly vulnerable to attack by free radicals for the following reasons:

- Their glutathione (GSH) content, an important natural antioxidant, is low.
- Their membranes contain a high proportion of polyunsaturated fatty acids.
- Brain metabolism requires substantial quantities of oxy-

gen.

The involvement of free radicals in the pathogenesis of AD is, however, now widely accepted for the following reasons:

- Neurons are particularly sensitive to free radicals (Finch and Runkun 2001).
- Aging is the principal AD risk factor and is itself related to accumulated free radical attacks (Christen 2000).
- Examinations of the brains of AD patients show many signs of free radical attacks, i.e., damage to mitochondrial and nuclear DNA, protein oxidation, lipid peroxidation, and AGEs (Mecocci *et al.* 1994; Hartman 1995; Opazo 2005).
- Traces of substances have been found in the brains of AD patients that indicate the presence of metals (iron, copper, zinc, and aluminum) capable of catalyzing reactions that produce free radicals (Deibel *et al.* 1997).
- Free radical scavengers reduce the toxicity of β-amyloid (Yatin *et al.* 2000).
- β-Amyloid is sensitive to the action of free radicals, contributing to aggregation and itself producing peptides in free radical form (Friedlich 1994).
- Apo E is subject to free radical attacks and a correlation exists between apo E peroxidation and AD; it can also act as an isoform-dependent free radical scavenger. The oxidative status of the brain is related to the apo E genotype (Huebbe *et al.* 2007).
- AD is related to mitochondrial anomalies, particularly for cytochrome-c oxidase, and these anomalies may explain the abnormal production of free radicals (Beal 1995).
- The use of many free radical scavengers (vitamin E, selegiline, and *Ginkgo biloba* extract EGb 761) has produced positive therapeutic results, as has the use of anti-inflammatory drugs, estrogens, and the iron-chelating agent desferrioxamine, which inhibits the catalytic action of iron (Kanowski *et al.* 1996; Sano *et al.* 1997; Yatin *et al.* 2000).

Oxidative damage can be found in membranes (lipid peroxidation), proteins (nitrosylation and others post-translational changes) and nucleic acids. Increasing evidence supports a role for oxidative DNA damage in aging and several neurodegenerative diseases including AD (Galasko and Montine 2010). Wang *et al.* (2005) found that levels of multiple oxidized bases in AD brain specimens were significantly higher in frontal, parietal, and temporal lobes compared to control subjects and that mitochondrial DNA had approximately 10-fold higher levels of oxidized bases than nuclear DNA. These data suggest that oxidative damage to mitochondrial DNA may contribute to the neurodegeneration of AD.

Under normal circumstances, the brain is protected from such damage by a careful balance between pro-oxidant and antioxidant mechanisms which include antioxidant enzymes and free-radical-scavenging chemicals such as ascorbate, vitamin E and protein sulphydryls. In AD, this balance appears to be disturbed, with pathological studies of biopsy and post-mortem cerebral tissue reporting excess DNA oxidation, protein oxidation and lipid peroxidation, and increased activity of the antioxidant enzyme superoxide dismutase (SOD) (Lovell *et al.* 1995).

Furthermore, reduced metabolic activity, deemed the result of oxidative damage to vital mitochondrial components, has been demonstrated in AD (Hirai *et al.* 2001).

Oxidative stress can induce neuronal damages, modulate intracellular signaling, ultimately leading to neuronal death by apoptosis or necrosis. Thus antioxidants have been studied for their effectiveness in reducing these deleterious effects and neuronal death in many *in vitro* and *in vivo* studies. Increasing number of studies demonstrated the efficacy of polyphenolic antioxidants from fruits and vegetables to reduce or to block neuronal death occurring in the pathophysiology of these disorders (Ramassamy 2006). Ramesh *et al.* (2010) observed that diets rich in saturated fatty acids and alcohol, and deficient in antioxidants and vitamins appear to promote the onset of the disease, while diets rich in unsaturated fatty acids, vitamins, antioxidants, and wine likely suppress its onset. In addition, evidence suggests that diets rich in polyphenols and some spices suppress the onset of AD by scavenging free radicals and preventing oxidative damage.

The oxidative stress is at the forefront of AD. While its implications in the characteristic neurodegeneration of AD are vast, the most important aspect is that it seems increasingly apparent that oxidative stress is in fact a primary progenitor of the AD, and not merely an epiphenomenon. The evidence indicates that a period of gradual oxidative damage accumulation precedes and actually leads to the seemingly sudden appearance of clinical and pathological AD symptoms (Bonda *et al.* 2010).

Jo *et al*. (2010) observed that the enzyme Beta-secretase (BACE1), an enzyme responsible for the production of amyloid beta-peptide (Aβ), is increased by oxidative stress and is elevated in the brains of patients with sporadic AD. Levels of gamma- and beta-secretase activities were greater in brain tissue samples from AD patients compared to non-demented control subjects.

Lovell and Markerbery (2007) showed elevations of 8-hydroxyguanine (8-OHG), 8-hydroxyadenine (8-OHA), 5-hydroxycytosine (5-OHC), and 5-hydroxyuracil, (8-OHU) a chemical degradation product of cytosine, in both nuclear and mitochondrial DNA isolated from vulnerable regions of LAD brain (late-stage Alzheimer disease) compared to age-matched normal control subjects.

Bradley *et al.* (2010) demonstrate increased levels of 4-hydroxynonenal (HNE) and acrolein in vulnerable brain regions of subjects with mild cognitive impairment (MCI) and late-stage Alzheimer disease (LAD). But not significant differences in levels of protein carbonyls were observed.

Alzheimer disease and metals

Metal ions are known to catalyze the production of free radicals and induce mental retardation or dementia, and several studies have also identified metals such as Pb, Fe, Al, Cu, and Zn in AD pathogenesis.

Iron is involved in the formation of the free hydroxyl radical, which has recognized deleterious effects, as described in Fenton's and Haber-Weiss' classical reactions as well as the formation of advanced products glycation end products (Castellani *et al.* 2001). Many observations provide proof that the metabolism of iron is involved in AD. The concentration of iron in the brains of AD patients is elevated. Iron, transferrin, and ferritin have been found in senile plaques (Beal 1995; Beal *et al.* 1997). An *in situ* iron detection method revealed a significant association of redox-active iron with both tumor necrosis factor and senile plaques in AD.

Aluminum has been suggested as a causal factor in AD, in part because of reports showing the toxicity of aluminum, the elevation of aluminum concentrations in the brains of patients with AD, and an association between aluminum concentrations in water and the prevalence of AD (Kennard *et al.* 1996).

The possible involvement of copper in neurodegeneration is also suggested by the fact that this metal is essential for many enzyme activities, including cytochrome-C oxidase and Cu/Zn SOD (Linder *et al.* 1996).

Histochemical studies have demonstrated that the direct detection of redox activity in AD lesions is inhibited by prior exposure of tissue sections to copper and iron selective chelators. Re-exposure of the chelator-treated sections to either copper or iron salts can reinstate activity, suggesting that redox imbalance in AD is dependent on these metals. It is therefore probable that accumulation of iron and copper is a major source of the production of ROS, which are in turn responsible for the more global oxidative stress parameters observed in AD (Patterson *et al.* 1999).

While specific metal chelators have been tested for therapy, they have not been very successful, probably due to

their late administration, i.e., after brain damage has been triggered. Since several dietary polyphenols are known to chelate metals, their routine use may also be protective against the onset of AD.

Alzheimer disease and inflammation

Inflammation of brain tissue is an important component in the pathogenesis of AD, involving the activation of both microglia and astrocytes. Recent histological studies have revealed the presence of activated microglia and reactive astrocytes in and around extraneuronal Aβ plaques in brains from AD patients. These activated microglia and reactive astrocytes are believed to facilitate the clearing of Aβ deposits from the brain parenchyma. However, now there is increasing evidence to suggest that the chronic activation of microglia, presumably via the secretion of cytokines and reactive molecules may exacerbate Aβ plaque pathology as well as enhance the hyperphosphorylation of tau and the formation of NFTs (Oddo *et al.* 2006). Activation of microglial NADPH oxidase in the brain also generates ROS and results in significant neuronal death (Park *et al.* 2009). Thus, the suppression of microglial activity in the AD brain has been considered a possible therapeutic strategy to treat AD patients. Suppressive anti-inflammatory drugs, particularly nonsteroidal anti-inflammatory drugs, have been found to lessen the effects of Aβ in transgenic mice (Gasparini *et al.* 2004).

The increase in the activity of NF-κB protects neurons against β-amyloid toxicity. Many data suggest that NF-κB plays an important role in neurodegenerative disorders. Goodman and Mattson (1996) showed that activation of NF-κB may constitute a cytoprotective signaling pathway that induces expression of protective gene products such as calbindin and antioxidant enzymes. In fact, exposure of cells to oxidative stress results in activation of NF-κB and high constitutive NF-κB activity mediates resistance to oxidative stress in neuronal cells.

In addition to the oxidative stress the inflammation is an important feature of the brain pathology of AD. ROS alter nuclear histone acetylation and deacetylation (chromatin remodeling) leading to increased NF-κB-dependent gene expression of proinflammatory mediators. Naturally occurring dietary polyphenols can directly scavenge ROS and modulate signaling pathways mediated via NF-κB and MAP kinase pathways, and upregulate GSH biosynthesis gene via Nrf2 activation. They also downregulate expression of proinflammatory mediators, matrix metalloproteinases, adhesion molecules, and growth factor receptor genes by inhibiting histone acetyltransferase activity and activating histone deacetylase/sirtuins. Thus, these polyphenolic compounds have therapeutic value as antioxidant and anti-inflammatory therapy against chronic inflammatory epigenetically regulated diseases (Rahman 2008).

All observations suggesting the involvement of ROS in the pathogenesis of AD raise the possibility of the therapeutic use of free radical scavengers and antioxidants. The hypothesis is particularly attractive because many free radical scavengers are known and many (e.g., vitamins E and C, *Ginkgo biloba* extract EGb 761, melatonin, flavonoids, resveratrol and carotenoids) have no major side effects. This hypothesis has been tested with a reasonable degree of success under both experimental and clinical conditions. Many experimental studies showed that free radical scavenging substances inhibit the toxic effect of β-amyloid or hydrogen superoxide on cell cultures and organotypic hippocampal cultures (Bastianetto *et al.* 1998; Christen 2000).

Behl and Sagara (1997) showed that this β-amyloid toxicity on PC12 cell lines is prevented by vitamin E and by antioxidants in general. Moreover they showed that hydrogen peroxide mediates this β-amyloid toxicity, which explains why catalase, which degrades hydrogen peroxide, protects the cells from β-amyloid toxicity.

Regular consumption of antioxidants in the diet may have a beneficial effect in humans. Cognitive impairment has been associated with lower vitamin C intakes. Fruit and vegetables could also have protective effects against stroke and vascular dementia. Epidemiologic studies to confirm the beneficial effects of antioxidants in AD are needed (Chadman *et al.* 1997).

Genetic factors are important risk factors for AD, especially for early-onset AD cases. Despite a relatively lower penetrance of genetic factors among late-onset sporadic AD cases, genetic factors remained to be highly relevant for the vast majority of late-onset sporadic AD cases, which is the most common form of AD. Non-genetic factors, including modifiable lifestyle dietary regimens such as moderate consumption of certain alcoholic beverages, are receiving increasing attention in AD research, especially in light of recent epidemiological studies indicating that moderate wine consumption may reduce the relative risk for AD clinical dementia (Cummings 1995; Luchsinger 2005). No specific environmental risk factor has been definitively identified as being associated with AD. However, the potentially important role for diet in the causation or prevention of AD is supported by several observations. For instance (Luchsinger and Mayeux 2004) is evidence that homocysteine-related vitamins, fats, and red wine consumption have a role in the pathogenesis of AD.

WINE POLYPHENOLS AND ALZHEIMER DISEASE

Polyphenols are abundant micronutrients in our diet, and evidence for their role in the prevention of degenerative diseases such as cancer and cardiovascular diseases is emerging. The health effects of polyphenols depend on the amount consumed and on their bioavailability (Manach *et al.* 2004).

Several epidemiological studies indicate that moderate consumption of red wine is associated with a lower incidence of dementia and AD. Red wine contains a complex mixture of bioactive compounds that are predominantly phenolic in nature. These include flavonols such as myricetin, kaempferol and the predominant quercetin, the flavan-3-ol monomers catechin and epicatechin, the oligomeric and polymeric flavan-3-ols or proanthocyanidins, various highly coloured anthocyanins, various phenolic acids (gallic acid, caftaric acid, caffeic acid, *p*-coumaric acid) and the stilbene resveratrol. These compounds occur in red wine but many of them are virtually absent from white wine because the skins and seeds are present during the fermentation of red wine but not of white wine. Red wine is one of the richest sources of polyphenols in human diets. Highly tannic red wines can contain up to 3 grams of total polyphenols per litre, and moderate red wine drinkers will consume polyphenols at levels well above the population average (Waterhouse 2002).

The first study, published in 1997, reported that moderate to mild wine consumption was associated with a low risk of AD (Orgogozo *et al.* 1997). Later, a nested case-control study (Truelsen *et al.* 2002) and a cohort study (Luchsinger *et al.* 2004) of individuals aged 65 years and older confirmed that intake of wine, but not other alcoholic drinks, was associated with a low risk of dementia, including AD. Furthermore, a prospective analysis of risk factors for AD in the Canadian population determined that wine consumption was the most protective variable against AD by reducing the risk of AD by 50% (Lindsay *et al.* 2002). Interestingly, wine intake in this population was found to be even more protective than the use of nonsteroidal anti-inflammatory drugs (Lindsay *et al.* 2002). Nevertheless, it should be noted that the notion that wine intake – and more specifically red wine intake – lowers AD risk is still controversial and remains to be addressed.

Previous studies have suggested that some polyphenolic compounds could reduce brain amyloid neuropathology and improve cognitive function by promoting nonamyloidogenic α-secretase activity (Marambaud *et al.* 2005; Rezai-Zadeh *et al.* 2005; Wang *et al.* 2006). They also reported that resveratrol, a natural polyphenol mainly found in grape

and red wine, could reduce Aβ by promoting intracellular Aβ degradation *in vitro.* Another study also suggested that a few select grape-derived polyphenolics could reduce aggregations of synthetic Aβ peptides *in vitro* (Porat *et al.* 2006).

Wang *et al.* (2006) found that Cabernet Sauvignon significantly attenuated AD-type deterioration of spatial memory function and Aβ neuropathology in Tg2576 mice relative to control Tg2576 mice that were treated with either a comparable amount of ethanol or water alone. These authors suggest that Cabernet Sauvignon exerts a beneficial effect by promoting nonamyloidogenic processing of APP, which ultimately prevents the generation of Aβ peptides. This study supports epidemiological evidence indicating that moderate wine consumption, within the range recommended by the FDA dietary guidelines of one drink per day for women and two for men, may help reduce the relative risk for AD clinical dementia.

Ono *et al.* (2008) showed that a commercially available grape seed polyphenolic extract, MegaNatural-AZ, significantly attenuated AD-type cognitive deterioration and reduced cerebral amyloid deposition.

Similarly, Wang *et al.* (2008) found that a naturally derived grape seed polyphenolic extract can significantly inhibit amyloid β-protein aggregation into high-molecular-weight oligomers *in vitro*. When orally administered to Tg2576 mice, this polyphenolic preparation significantly attenuates AD-type cognitive deterioration coincidentally with reduced HMW soluble oligomeric Aβ in the brain. They suggested that grape seed-derived polyphenolics may be useful agents to prevent or treat AD.

Ho *et al.* (2009) found that moderate consumption of two unrelated red wines generate from different grape species, a Cabernet Sauvignon and a Muscadine wine that were characterized by distinct component composition of polyphenolic compounds, significantly attenuated the development of AD-type brain pathology and memory deterioration in a transgenic AD mouse model. They found that treatment with Cabernet Sauvignon reduced the generation of AD-type amyloid-β (Aβ) peptides and the Muscadine treatment attenuates Aβ neuropathology and Aβ-related cognitive deterioration in Tg2576 mice by interfering with the oligomerization of Aβ molecules to soluble HMW Aβ oligomer species that are responsible for initiating a cascade of cellular events resulting in cognitive decline. They suggested the possibility of developing a "combination" of dietary polyphenolic compounds for AD prevention and/or therapy by modulating multiple Aβ-related mechanisms.

The different polyphenols and their relation with AD development haven been analysed in the present review. A summary is shown in **Tables 1** and **2**.

ANTHOCYANINS

The wine anthocyanins are monoglucosides of five anthocyanidins, namely delphinidin, cyanidin, petunidin, peonidin and malvidin. The acylated anthocyanins are esters of the glucose moiety of the free anthocyanins with acetic, *p*-coumaric or caffeic acids (**Table 1A**). The amount of anthocyanins in young red wine varies between 90-400 mg/L (Guerrero *et al.* 2009b).

It seems that anthocyanins are absorbed very rapidly but rather inefficiently. However, the bioavailability of anthocyanins could have been underestimated due either to inaccurate methodology or to the different chemical forms that anthocyanins can take depending on pH. This could possibly explain why any therapeutic effects that anthocyanins have contingent on sufficient bioavailability, in terms of exposure at the level of cells and at the level of the organism as a whole through the diet (Guerrero *et al*. 2009a).

Shih *et al.* (2007) observed the effects of the anthocyanins in the contributions to activation of phase II antioxidant and detoxifying enzymes, chemopreventive potency, and involved transcriptional regulation and showed that treatment of anthocyanins leads to positive effects on elevating the antioxidant capacity, including activated expression of glutathione-related enzymes (glutathione reductase, glutathione peroxidase, and glutathione *S*-transferase) and recruited GSH content. They suggest that natural anthocyanins are recommended as chemopreventive phytochemicals and could stimulate the antioxidant system to resist oxidant-induced injury. More important, the promoting effect of anthocyanins on ARE-regulated phase II enzyme expression seems to be a critical point in modulating the defence system against oxidative stress.

Heo and Lee (2005) showed that strawberry phenolic compounds significantly reduced oxidative stress-induced neurotoxicity. Strawberry showed the highest cell protective effects compared with banana and orange. The protective effects appeared to be due to the higher phenolic contents including anthocyanins, and anthocyanins in strawberries seemed to be the major contributors.

To our knowledge, there is no study of wine anthocyanins and their relationship with AD. However, as anthocyanins of strawberry are quite similar to these from wine, it can be suggested that the protective effect may be similar. Further studies are required.

FLAVONOLS

Flavonols are found in wines as myricetin, quercetin, kaempferol, isorhamnetin, syringetin and laricitrin (**Table 1B**) (Guerrero *et al.* 2009b). Its concentration in wine ranges from 50 to 100 mg/L (Zafrilla *et al.* 2003).

With respect to its bioavailability, quercetin is absorbed in humans and can reach high concentrations that are sufficient to increase plasma antioxidant capacity. Moreover, quercetin glucosides are among the polyphenols most readily absorbed in humans (Guerrero *et al.* 2009a).

Ono *et al.* (2003) examined the effects of wine-related polyphenols (myricetin, morin, quercetin, kaempferol (+)-catechin and (-)-epicatechin) on the formation, extension, and destabilization of β-amyloid fibrils (fAβ). They showed that all examined polyphenols dose-dependently inhibited formation of fAβ from fresh Aβ, as well as their extension. Moreover, these polyphenols dose-dependently destabilized preformed fAβ. However, the mechanisms by which these polyphenols inhibit fAβ formation and destabilize preformed fAβ *in vitro* are still unclear, polyphenols could be a key molecule for the development of preventives and therapeutics for AD.

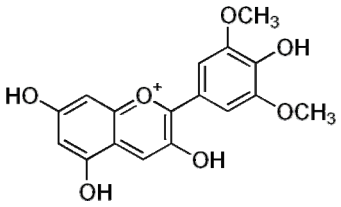
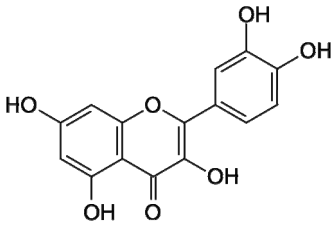
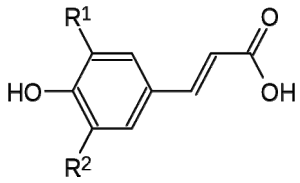
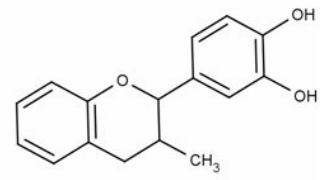
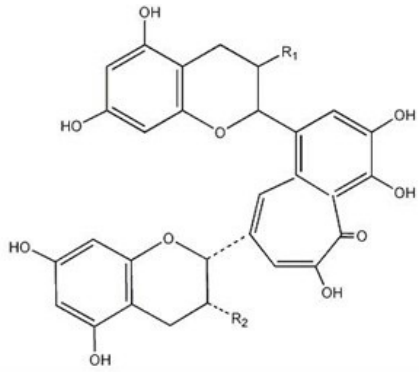
Quercetin, has antioxidant properties, increases GSH levels and antioxidant enzyme function. Considerable attention has been focused on increasing the intracellular GSH levels in many diseases, including AD. Pretreatment of primary hippocampal cultures with quercetin significantly attenuated Abeta(1-42)-induced cytotoxicity, protein oxidation, lipid peroxidation and apoptosis. A dose-response study suggested that quercetin showed protective effects against Abeta (1-42) toxicity by modulating oxidative stress at lower doses, but higher doses not only were non-neuroprotective, but were toxic. These findings provide motivation to test the hypothesis, that quercetin may provide a promising approach for the treatment of AD and other oxidative stress-related neurodegenerative diseases (Ansari *et al.* 2009).

In the same line, *in vitro* assays with kaempferol on PC12 cell showed it had protective effects against oxidative stress-induced. Moreover, administration of kaempferol reversed amyloid AB peptide-induced impaired performance in Y-maze test (Kim *et al.* 2010).

HDROXYCINNAMIC ACID DERIVATIVES

Hydroxycinnamic acid derivatives present in wine frequently are caffeoyltartaric, coumaroyltartaric and feruloyltartaric (**Table 1C**). Their concentration in wine range from 65 to 165 mg/L (Guerrero *et al.* 2009b). Bioavalability data are still too limited for an informed assessment of hydroxycinnamics (Manach *et al*. 2005).

Table 1 Flavonoids of red wine.

A Anthocyanins (malvidin) 	e.g. cyanidin, pelargonidin, peonidin, delphinidin, malvidin Source: red, blue and purple berries, red and purple grapes, red wine, cherry, rhubarb
B Flavonols (quercetin) 	e.g. quercetin, kaempferol, myricetin Sources: red cabbage, yellow onion, curty pale, cherry, tomato, broccoli, blueberry, apricot, apple, grape, wine, green and black tea
C Hidroxycinnamic acids (caffeic acid) 	e.g. caffeic acid, chlorogenic acid, coumaric acid, ferulic acid, sinapic acid Sources: blueberry, kiwi, cherry, plum, apple, pear, peach, chicory, artichoke, potato, coffee
D Monomeric and polymeric flavonols  (epicatechin)  (theaflavin)	Monomeric: (catechins) e.g. catechin, epicatechin, epigallocatechin, epigallocatechin gallate Dimers and polymers: theaflavins, thearubigins Monomeric source: green and black tea, chocolates, grapes, berries, apples Dimers and polymers source: black teas

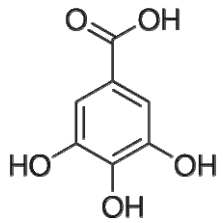
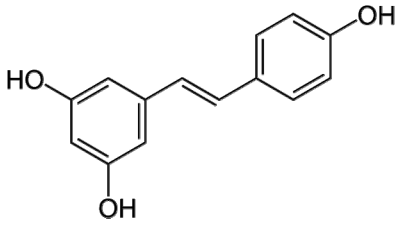
Hydroxycinnamates have shown antioxidant and anti-inflammatory properties *in vivo* and *in vitro*; they contribute to DNA protection and help prevent AD (Tomera 1999; Luceri *et al*. 2007).

PHENOLIC ACIDS

Phenolics acids are present in wine as gallic, hydroxybenzoic, vainillic and syringic acids (**Table 2A**). Their total concentration in wines is around 10-60 mg/L (Guerrero *et al.* 2009b). They are the most well-absorbed polyphenols (Manach *et al.* 2005). Moreover, phenolics compounds that are not absorbed in the small intestine, but which pass into the large intestine where they are degraded by the colonic microflora to phenolic acids, which can be absorbed into the circulatory system (Crozier *et al.* 2009).

Few researches have been developed on the relationship AD and phenolic acids. Studies in model transgenic mice (Tg2576) showed that, a difference of other phenolis, ferulic acid did not prevent the development of AD pathology

Table 2 Non-flavonoids of red wine.

A  Hydrobenzoic acids (gallic acid)	Protocatechuic acid, gallic acid, *p*-hydroxybenzoic acid Source: blackberry, raspberry, strawberry, black current
B  Stilbenes (*trans*-resveratrol)	e.g. resveratrol Source: grapes, wine, groundnut

by affecting different Aβ aggregation pathways *in vivo* (Hamaguchi *et al.* 2009).

Gallic acid, seems to a very effective phytochemical in on oxidative neuronal cell death and antioxidants differ in ROS-mediated neuronal cell death (Kang *et al.* 2009).

In the present manuscript we focus on two phenolics goups: flavan-3-ols and stilbenes. Flavan 3-ols are the most abundant phenolics in wine. Stilbenes, mainly resveratrol, have shown a high neuroprotective activity both *in vitro* and *in vivo*.

FLAVAN-3-OLS

Flavan-3-ols, also known as catechins, are present in a wide range of botanical sources as both monomers and oligomeric procyanidins (**Table 1D**). The richest sources of flavanols include cocoa, red wine, green tea, red grapes, berries and apples (Commenges *et al.* 2000). Flavanol monomers are (-)-epicatechin and (+)-catechin, and procyanidins are oligomers of epicatechin and catechin. Unlike other classes of flavonoids, which exist in plants primarily in glucoside forms, flavanols are usually present in the aglycone form as monomers, oligomers or esterified with gallic acid to form epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) (Hackman *et al*. 2008). Its concentration in wine is around 100 mg/L for monomers and 1000 mg/L for procyanidins (Guerrero *et al.* 2009b).

The bioavailability of flavan-3-ols monomers is generally good although it differs markedly among different compounds. procyanidins are less permeable through cell walls and so are absorbed less readily. In fact, their polymerization impairs intestinal absorption. However the health effects of proanthocyanidins may not require efficient absorption through the gut. These compounds may have direct effects on the intestinal mucosa and protect it against oxidative stress. Biological effects may be attributable not to direct actions of proanthocyanidins themselves but to actions of some of their metabolites formed by the action of colonic flora that can be more readily absorbed (Aron and Kennedy 2008).

Catechins intake has been associated with a wide variety of beneficial health effects *in vitro* and *in vivo* (Sutherland *et al.* 2006). Foods rich in flavonoids have been reported to augment oxidative defense, promote vascular health, protect the central nervous system and reduce the risk of certain cancers (Hackman *et al.* 2008). The antioxidant flavanols epicatechin and catechin from diet have shown great promise in their influence on neurodegenerative disorders (AD, PD) (Patel *et al.* 2008).

Reznichenko *et al*. (2006) have found that (-)-epigallocatechin-3-gallate (EGCG) helps to regulate the iron metabolism proteins APP and transferrin receptor (tfR) due to its metal-chelating and radical-scavenging properties. The amount of APP in the cells was significantly reduced but the amount of mRNA encoding APP remained the same, suggesting a post-transcriptional effect. EGCG also reduced the formation of toxic β-amyloid that overexpressed the 'Swedish' mutation. Further, EGCG has been found to hinder lipopolysaccharide (LPS)-activated microglial secretion of nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α) by down-regulating inducible NO synthase and TNF-α expression. It was also found that EGCG protects against microglial activation-induced neuronal injury in the human SH-SY5Y cell line and in primary rat mesencephalic cultures, suggesting that it may have powerful therapeutic effects in treating and/or preventing AD and PD by promoting neuronal health (Li *et al.* 2004).

Both catechin and epicatechin have been found to have anti-fibrillogenic properties as well in that they have been shown to reduce already existing alphaS fibrils in addition to causing a reduction in the formation of alphaS fibrils in brain cells (Ono and Yamada 2006).

EGCG, a main phenollic constituent of seed grape, may promote the nonamyloidogenic α-secretase pathway and epicatechin may reduce the formation of Aβ amyloid fibrils (Ono *et al.* 2003). However, the presence of another catechin epigallocatechin (EGC) in conjunction with EC together inhibits the ability of EGCG to reduce Aβ amyloid peptide generation (Razai-Zadah 2005).

Studies with radioactively labelled EGCG in mouse or chemiluminescence-based detection of EGCG in rats, demonstrated its incorporation into brain, as well as in various organs including kidney, heart, liver, spleen, and pancreas (Nakagawa and Miyazawa 1997; Suganuma *et al.* 1998). Furthermore, a recent study has shown that the methylated and glucuronidated derivatives of epicatechin are both detected in rat brain following oral administration. EGCG prevented neuronal cell death in culture caused by Aβ (Choi *et al.* 2001; Levites *et al.* 2003).

As discussed earlier, the neuroprotective effect of polyphenols *in vivo* may also involve the regulation of antioxidant protective enzymes. EGCG was found to elevate the activity of two major oxygen-radical species metabolizing enzymes, superoxide dismutase and catalase in mice striatum (Levites *et al.* 2001). This is supported by a previous finding where 1-month administration of a catechin containing antioxidant preparation increased superoxide dismutase (SOD) activity in the mitochondria fraction of striatum and midbrain and decreased thiobarbiturate reactive substance formation in the cortex and cerebellum of aged

rats (Komatsu and Hiramatsu 2000). Catechins can also decrease oxidative stress by inhibiting the activity of xanthine oxidase (Bickford *et al.* 2000), and pretreatment with epicatechin also attenuated ox-LDL induced neurotoxicity in mouse-derived striatal neurons (Schroeter *et al.* 2001).

Differents flavanols display antioxidant properties in the order EGCG > ECG > EGC > EC (Guo *et al.* 1996). The galloylated catechins are more active antioxidants due their higher phospholipid/water partition coefficients (Caturla *et al*. 2003). Moreover, the free radical scavenger property increases with the number of hydroxyl groups.

Catechins can exert antioxidant activity through different mechanisms, such as by chelating metal ions like copper (II) and iron (II) to form inactive complexes and prevent the generation of potentially damaging free radicals. This property may have an implication in AD (Singh *et al.* 2008). Indeed, changes in the levels of iron, ferritin, and transferring receptor have been reported in hippocampus and in cortex from AD (Honda *et al.* 2005). Iron could also promote deposition of Aβ or contribute to the regulation of APP translation (Rogers *et al.* 2002), thus, reduction of the free iron poll by EGCG chelation may lead to suppression of the translation of APP mRNA.

In conclusion, it may be suggested that EGCG could not only influence the basic pathogenic mechanism underlying AD but may have a significant benefits for slowing the disease progression.

RESVERATROL

Resveratrol (3,5,4'-*trans*-trihydroxystilbene, RES) is a member of the stilbene family of phenolic compounds (**Table 2B**). RES, and stilbenes in general, are commonly found in many plants of several different families including *Pinaceae*, *Moraceae*, *Liliaceae*, *Myrtaceae*, *Fagaceae*, *Vitaceae*, *Gnetaceae*, *Cyperaceae*, *Dipterocarpaceae* and *Leguminoseae*. However, their dietary sources are rather limited: peanut and its derivatives, pistachio, berries, dark chocolate, and grapes and their derivatives. Of all of these, grape present the highest content but red wine is the most notable dietary source of RES (Guerrero *et al.* 2009a).

RES is found in the seed and skin of grapes (not in flesh) and hence in grape juice and wine. Concentrations ranging from undetectable to 14.3 mg/L have been described (Stervbo *et al.* 2007). RES is present in *cis* and *trans* isoforms and the major *trans* isomer is the biologically active one (Orallo 2006).

Numerous studies in animals and humans have shown that the bioavailability of RES is low. Once it is absorbed, at least 70% of RES ingested is readily metabolized to form mainly glucuronide and sulphate derivatives.

Bertelli *et al.* (1996) demonstrated that a fraction of RES present in red wine (6.5 mg/L as *cis* and *trans* forms) was absorbed in rats. After chronic consumption of moderate amounts of red wine containing a known concentration of RES, range from 100 nM to 1 mM. These authors suggested that an average drinker of wine could, particularly in the long term, absorb a sufficient quantity of RES to explain the beneficial effect of red wine on human health. More importantly, this could help to explain how a relatively low dose of RES obtained from red wine or other dietary sources could be therapeutic in some cases (Bertelli *et al.* 1998). However there are still three issues that need to be addressed. The first is how much RES can be taken and recovered from the organism; the second is how active the metabolites derived from RES are. The third issue is the possible influence on RES bioavailability in humans produced by the type of meal consumed in association with the ingestion of red wine. Researchers are starting to explore RES treatment in combination with other agents in some preclinical studies.

RES has been described as a compound that can prevent and/or reduce a wide range of diseases such as cancer, cardiovascular diseases, and ischemic damage; it can also increase the resistance to stress and prolong the lifespan of various organisms, from yeast to vertebrates. Most of the protective biological actions associated with RES have been associated with its intrinsic radical scavenger properties (Guerrero *et al.* 2009a).

One of the most remarkable activities of RES is its neuroprotective activity. RES is capable of penetrating the blood–brain barrier and exerts strong neuroprotective effects, even at low doses. It has been published that only 500 nM per day, an amount which is provided in one glass of red wine, is needed to protect neurones (Parker *et al.* 2005). The prevention of neurodegenerative disease is based on the scavenging mechanism performed by RES (Karlsson *et al.* 2000). The efficacy of RES against various different mechanisms has recently been confirmed, and RES has been shown to be potentially useful in protecting against brain damage following cerebral ischaemia (Dong *et al.* 2008).

REShas been shown to protect against various neurological disorders in experimental models, including brain ischemia, seizures, and neurodegenerative disease models. RES has anti-inflammatory activity in the brain from both *in vivo* and *in vitro* studies, mainly due to the inhibition of activated microglia. Taken together, microglia is an important target for anti-inflammatory activities of RES in the brain (Zhang *et al.* 2009).

Marambaud *et al.* (2005) reported that RES has a potent anti-amyloidogenic activity by reducing the levels of amydoid-β peptides produced from different cell lines expressing wild type or Swedish mutant APP695. They showed that RES does not inhibit Aβ production, because it has no effect on the Aβ-producing enzymes β- and γ-secretases, but promotes instead intracellular degradation of Aβ via a mechanism that involves the proteasome. Indeed, the RES-induced decrease of Aβ could be prevented by several selective proteasome inhibitors and by siRNA-directed silencing of the proteasome subunit β5. These findings demonstrate a proteasome-dependent anti-amyloidogenic activity of RES and suggest that this natural compound has a therapeutic potential in AD.

Additional good news is that RES may also be effective in fighting other human amyloid-related diseases such as Huntington's, Parkinson's and prion diseases. Studies have shown that RES may protect neurons against amyloid-like polyglutamines, a hallmark of Huntington's disease (Marambaud *et al.* 2005; Singh *et al.* 2008).

This fact was supported by Karuppagounder *et al.* (2009). They fed mice with clinically feasible dosages of RES for 45 days. Neither RES nor its conjugated metabolites were detectable in brain. Nevertheless, RES diminished plaque formation in a region specific manner. The largest reductions in the percent area occupied by plaques were observed in medial cortex (-48%), striatum (-89%) and hypothalamus (-90%). The changes occurred without detectable activation of SIRT-1 or alterations in APP processing. However, brain GSH declined 21% and brain cysteine increased 54%. The increased cysteine and decreased GSH may be linked to the diminished plaque formation. This study supports the concept that onset of neurodegenerative disease may be delayed or mitigated with use of dietary chemo-preventive agents that protect against β-amyloid plaque formation and oxidative (Karuppagounder *et al.* 2009).

In the same line, Feng *et al.* (2009) studied the effects of RES, on the polymerization of Aβ42 monomer, the destabilization of Aβ42 fibril and the cell toxicity of Aβ42 *in vitro* in order to understand the mechanism of this neuroprotection. Their results showed that RES could dose-dependently inhibit Aβ42 fibril formation and cytotoxicity but could not prevent Aβ42 oligomerization. The studies confirmed that the addition of RES resulted in numerous Aβ42 oligomer formation. Thus, with the concept that Aβ oligomers are linked to Aβ toxicity, RES may directly bind to Aβ42, interfere in Aβ42 aggregation, change the Aβ42 oligomer conformation and attenuate Aβ42 oligomeric cytotoxicity.

Although some recent studies on red wine bioactive

compounds suggest that RES modulates multiple mechanisms of AD pathology. Emerging literature indicates that mechanisms of aging and AD are intricately linked and that these mechanisms can be modulated by both calorie restriction regimens and calorie restriction mimetics, the prime mediator of which is the SIRT1 pathway (Parker *et al*. 2005; Hung *et al*. 2010). RES-induced SIRT1 was found to protect neurons against ployQ toxicity and in Wallerian degeneration slow mice. Moreover RES was found to protect the degeneration of neurons from axotomy (Anekonda 2006).

RES directly increases sirtuin 1 (SIRT1) activity, a NAD+ (oxidized form of nicotinamide adenine dinucleotide)-dependent histone deacetylase related to increased lifespan in various species similar to calorie restriction. It has been recently demonstrated that brief RES pretreatment conferred neuroprotection against cerebral ischemia via SIRT1 activation. This neuroprotective effect produced by RES was similar to ischemic preconditioning-induced neuroprotection, which protects against lethal ischemic insults in the brain and other organ systems. Inhibition of SIRT1 abolished ischemic preconditioning-induced neuroprotection in CA1 region of the hippocampus. Since RES and ischemic preconditioning-induced neuroprotection require activation of SIRT1, this common signaling pathway may provide targeted therapeutic treatment modalities as it relates to stroke and other brain pathologies (Raval *et al.* 2008).

One hypothesis is that by activating Sirtuin 1, RES modulates the activity of numerous proteins, including peroxisome proliferator-activated receptor coactivator-1α (PGC-1 alpha), the FOXO family, Akt (protein kinase B) and nuclear factor-κβ (NFκβ) (Pallas *et al.* 2009).

The goal is to provide a better understanding of the mode of action of RES and its possible use as a potential therapeutic agent to ameliorate age-related neurodegenerative disorders (Sun *et al.* 2010).

Finally, it is worth to mention that synergistic effects may occur among phenolic compounds. Synergy has been reported among the three phenols, RES, caffeic acid and catechin (Norata *et al*. 2007). Despite their relatively low plasma concentrations following moderate wine consumption, this synergy gives them useful biological activity, such as inhibition of oxidative stress. Interaction between polyphenols may influence their kinetics and metabolism. The lack of systematic information on the effects of other components on the bioavailability of polyphenols needs to be addressed, and more human studies should be conducted in this field to establish general principles affecting absorption *in vivo*.

CONCLUSIONS

Since AD has no cure or preventive treatment, an urgent need exists to find a means of preventing, delaying the onset, or reversing the course of the disease. Clinical and epidemiological evidence suggests that lifestyle factors, especially nutrition, may be crucial in controlling AD. Unhealthy lifestyle choices lead to an increasing incidence of many diseases, including AD.

Based on multiple evidences, it is reasonable that dietary consumption rich in polyphenols can offer benefits to limit neurodegeneration and to preserve cognitive functions in aging and age-related neurodegenerative disease such as AD.

Wine intake is associated with a lower incidence of AD since wine is enriched in antioxidant compounds with potential neuroprotective activities. Although excessive consumption of ethanol in alcoholic beverages causes multiorgan damage, moderate consumption, particularly of red wine, is protective against all-cause mortality. These protective effects could be due to one or many components of the complex mixture of bioactive compounds present in red wine including flavonols, monomeric and polymeric flavan-3-ols, highly colored anthocyanins as well as phenolic acids and the stilbene polyphenol, RES.

If the non-alcoholic constituents of red wine are to become therapeutic agents, their ability to get to the sites of action needs to be understood.

The neuroprotective activity of polyphenols in various models of neurodegenerative diseases *in vitro* and *in vivo* have been documented, but it would be unwise to extrapolate these results to the human situation without proper clinical trials in patients suffering from irreversible and extensive neuronal loss. In addition, most cell culture or animal studies have been conducted on a short-term basis. Therefore, more long-term studies should be undertaken to determine their beneficial effects in slowly developing neurodegenerative disorders such as AD.

Thus, specific recommendation for the prevention of AD can not be made at this time. However, some diets that may be beneficial for AD are beneficial for other disorders such as cardiovascular disease. In this sense moderate alcohol intake may be related to a decreased risk of cardiovascular disease and AD, and in the absence of trial data, it seems reasonable to recommended moderation of intake to those already consuming alcoholic drinks.

ACKNOWLEDGEMENTS

The authors express their gratitude for financial support from FEDER and INIA of the Spanish government (RTA2008-00014).

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