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## Oxidative Stress in Alzheimer's Disease: Pathogenesis, Biomarkers and Therapy

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### 1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly with profound medical and social consequences. The pathogenesis of AD is a complex and heterogeneous process which classical neuropathological hallmarks found in the brain are extracellular deposits of beta-amyloid ( $A\beta$ )-containing plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. Mutation of *presenilin-1* (PS-1), *presenilin-2* (PS-2), and altered *amyloid precursor protein* (APP) genes has been reported to cause inherited AD. In addition, other genes such as apolipoprotein E-4 (APOE), endothelial nitric oxide synthase-3, and alpha-2-macroglobulin have also been associated with AD. A further number of hypothesis have been proposed for AD mechanism, which include: the amyloid cascade, vascular damage, excitotoxicity, deficiency of neurotrophic factors, mitochondrial dysfunction, trace element neurotoxicity, inflammation and oxidative stress hypothesis.

The oxidative stress (OS) hypothesis of aging postulated by Dr. Denham Harman in 1956 proposed that brain aging is associated to a progressive imbalance between the anti-oxidant defenses and the pro-oxidant species that can occur as a result of either an increase in free radical production or a decrease in antioxidant defence. The fact that age is the main risk factor for AD development provides considerable support to the OS hypothesis since the effects produced by reactive oxygen species (ROS) can accumulate over the years (Nunomura et al., 2001). The link between AD and OS is additionally supported by the finding of decreased levels of antioxidant enzymes, increased protein, lipid and DNA oxidation and advanced glycation end products (AGEs) and ROS formation in neurons of AD patients (Perry et al., 2000; Barnham et al., 2004). It has been reported that the accumulation of the oligomeric form of  $A\beta$ , the most toxic form of the peptide, induces OS in neurons (Butterfield, 2002), supporting the hypothesis and suggesting that OS plays a causative role in the development of AD. Then, a large amount of literature has demonstrated that OS is an important feature in AD pathogenesis that deserves to be deeply studied (Perry et al, 2002; Markesbery et al, 1999). In this Chapter, we address the main factors involved in the generation of oxidative stress and provide an overview of the oxidative stress biomarkers status in Alzheimer's disease. The Chapter concludes with a revision of the controversial efficacy of antioxidants as potential treatment in AD therapy as well as an update of the main antioxidant compounds found to have a beneficial effect in AD.

## 2. Mitochondria as a source of reactive oxygen species

Several years after the postulation of the OS hypothesis, Dr. Harman proposed that life span is determined by the rate of ROS damage to the mitochondria (Harman, 1972) giving for the first time an important role to this organelle in the ageing process and establishing the basis for "mitochondrial theory of ageing". It is important to note that the central nervous system (CNS) is especially vulnerable to oxidative damage as a result of the high oxygen consumption rate (20% of the total oxygen consumption), the abundant content of easily peroxidizable fatty acids, and the relative paucity of antioxidant enzymes compared to other tissues. In aerobic organisms, mitochondria produce semireduced oxygen species during respiration. The initial step of the respiratory chain reaction yields the superoxide radical ( $^{\circ}\text{O}_2^-$ ), which produces hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) by addition of an electron. The reduction of  $\text{H}_2\text{O}_2$  through the Fenton reaction produces the highly reactive hydroxyl radical ( $^{\circ}\text{OH}$ ), which is the chief instigator of oxidative stress damage and reacts indiscriminately with all biomacromolecules (Figure 1). Under normal conditions, damage by ROS is prevented by an efficient antioxidant cascade, including both enzymatic and non-enzymatic entities. The enzymes responsible of the detoxification machinery are the cytosolic copper-zinc superoxide dismutase (CuZnSOD) and the mitochondrial manganese superoxide dismutase (MnSOD), which convert superoxide to  $\text{O}_2$  and  $\text{H}_2\text{O}_2$ . Moreover, monoamine oxidases (MAOs) and L-amino acid oxidase can also produce  $\text{H}_2\text{O}_2$  during its metabolism which is effectively removed by catalase (CAT) and peroxidases (e.g. glutathione peroxidase, GPx). Since CAT is compartmentalized into peroxisomes the detoxification of cytosolic and mitochondrial peroxides depends predominantly on GPx.

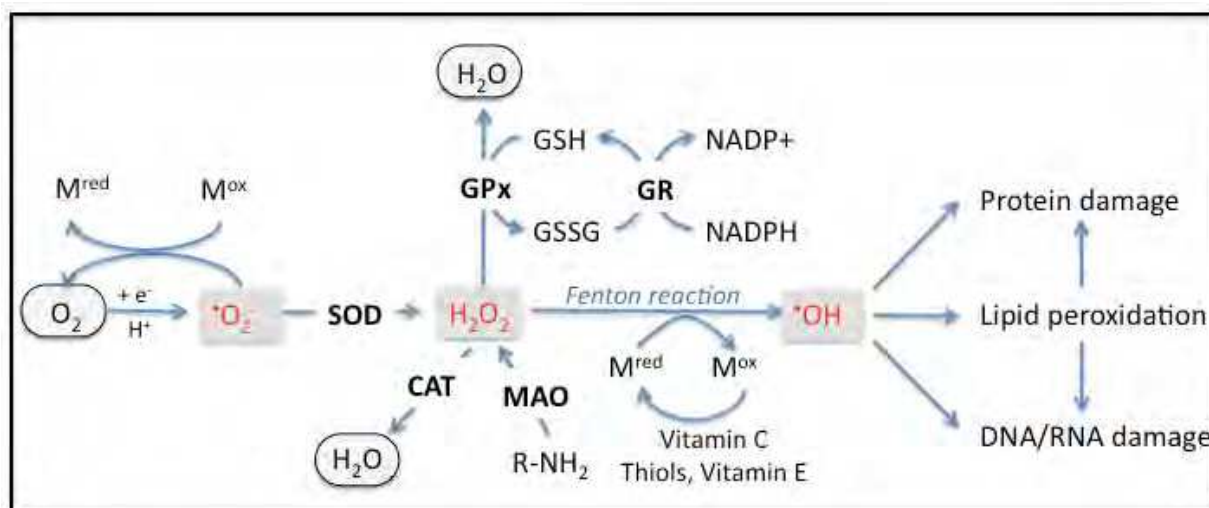


Fig. 1. Schematic illustration of the mechanism involved in reactive oxygen species (ROS) formation and elimination. Glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT), monoamine oxidase (MAO), glutathione (GSH), glutathione disulfide (GSSG).

The non-enzymatic antioxidant defenses include the reduction of the resulting oxidized transition metal ions (usually  $\text{Fe}^{3+}$  and  $\text{Cu}^{2+}$ ) by cellular reductants such as vitamin C, thiols and perhaps even vitamin E. In this context, SOD can also serve as the reductant of oxidized metal ions for the production of hydroxyl radical from  $\text{H}_2\text{O}_2$ , which coupled with the Fenton reaction, is known as the Haber-Weiss reaction. In AD, this situation is further exacerbated by the fact that redox active transition metals are aberrantly accumulated in cytoplasm of

neurons. Moreover, A $\beta$  peptide is considered a strong redox active agent capable of reducing transition metals and allowing for conversion of O<sub>2</sub> to H<sub>2</sub>O<sub>2</sub> (Bondy et al, 1998).

### 3. Biomarkers of oxidative stress in Alzheimer's disease

Biomarkers, as indicators of signalling events in biological systems or samples, can be used as intermediate endpoints or early-outcome predictors of disease development for preventive purposes. Most effort is nowadays focused on the search of reliable and robust biomarkers which would be useful for an earlier AD diagnosis. The emphasis is being placed on the incorporation of oxidative stress biomarkers to study the increased oxidative damage (Lovell & Markesbery, 2007a). It has recently been a significant improvement in assay methods and measurement accuracy for oxidative biomarkers. Nevertheless, it appears imperative that biomarkers of oxidative damage must be validated (Dalle-Donne et al., 2006a) in order to incorporate them into epidemiological studies and provide a better understanding regarding the role of ROS in the pathogenesis and progression of AD, as well as to assess the possible effectiveness of an antioxidant therapy (Griffiths et al., 2002). Strong evidence show that oxidative markers are more prevalent in initial rather than in later stages of the disease, and thus suggesting that targeting the earlier events of the disease may be more successful than targeting the later events (e.g. beta-amyloid (A $\beta$ ) plaque deposition and/or intracellular neurofibrillary tangles formation). On the other hand, many studies provided evidence for the deleterious consequences of oxidative stress products on certain cellular targets in AD. Therefore, most highly reactive oxidants react with virtually all biomolecules, including, lipids, DNA/RNA, carbohydrates and proteins. Table 1 summarizes the main OS biomarker candidates for MCI and AD diagnosis.

Biomarker	Specimen	Diagnosis	Reference
<b>Lipid Peroxidation</b>			
4-HNE	Plasma	AD	Mc Grath et al., 2001
	Ventricular fluid	AD	Lovell et al., 1997
F2-Isoprostanes	Urine	AD	Kim et al., 2004
	CSF	AD	Montine et al., 2011
	CSF, plasma and urine	MCI	Pratico et al., 2002
<b>DNA oxidation</b>			
8-OHdG	Peripheral lymphocytes	MCI	Migliore et al., 2005
		AD	Mecocci et al., 2002
<b>AGEs</b>			
CML	CSF	AD	Ahmed et al., 2005
<b>Oxidized Protein</b>			
$\alpha$ -1-antitrypsin	CSF	AD	Puchades et al., 2003
Ig $\lambda$ light chain	CSF	MCI	Korolainen et al., 2007
$\alpha$ -1-antitrypsin	Plasma	AD	Yu et al., 2003; Choi et al., 2002

Table 1. Potential OS biomarkers under validation for Alzheimer's disease. MCI, mild cognitive impairment; AD, Alzheimer's disease; CSF, cerebrospinal fluid; Ig, immunoglobulin; 4-HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-oxo-7,8-dihydro-2'-deoxyguanosine; AGEs, Advanced Glycation end products; CML, N-carboxymethyl-lysine.

### 3.1 Biomarkers of lipid peroxidation

Lipid oxidation (also called lipid peroxidation) has dramatic consequences in ageing and age-related disorders. Phospholipids present in brain membranes are mainly polyunsaturated fatty acids (PUFAs: arachidonic acid, linoleic acid, linolenic acid, docosahexaenoic acid, etc...), which are especially vulnerable to a free radical attack since their double bonds allow an easy removal of hydrogen ions. Oxidation of PUFAs produces a variety of reactive  $\alpha,\beta$ -unsaturated aldehydes such as, acrolein, 4-hydroxy-2-nonenal (4-HNE), 4-oxo-2-nonenal (4-ONE), 4-hydroxy-2-hexenal (4-HHE), 2-hexenal, crotonaldehyde as well as the dialdehydes glyoxal and malondialdehyde (MDA). These species are highly reactive cytotoxic substances that can form stable covalent adducts with free amino groups of proteins (Lys, His and Cys residues) through Michael addition (Calingasan et al., 1999; Carini et al., 2004; Esterbauer et al., 1991; Montine et al., 1997) which are known as advanced lipoxidation end products (ALEs). 4-HNE is a major and toxic aldehyde generated by free radical attack on PUFAs and is considered a second toxic messenger of oxygen free radicals. Therefore, it has a high biological activity and exhibits numerous cytotoxic, mutagenic, genotoxic, and signalling effects in neurons (Eckl et al., 1993; Williams et al., 2006). In addition, 4-HNE may be an important mediator of OS-induced apoptosis, cellular proliferation and signalling pathways (Uchida, 2003). HNE is permanently formed at basal concentrations under physiologic conditions, but its production is greatly enhanced in the AD brain where increased lipid peroxidation occurs (Butterfield et al., 2010; McGrath et al., 2001). Increased concentrations of 4-HNE, 4-HHE and acrolein have been found in cerebrospinal fluid (CSF) and in multiple brain regions from individuals with mild cognitive impairment and early AD compared with age-matched controls (Bradley et al., 2010a and 2010b; Lovell et al., 1997; Williams et al., 2006). In addition, a positive feedback in the pathogenesis of AD is provoked by HNE that increases  $A\beta$  production (Tamagno et al., 2008) which, in turn, induces lipid peroxidation (Butterfield et al., 2002). Furthermore, HNE-adducts have been identified in amyloid plaques and neurofibrillary tangles, the two hallmarks of AD pathogenesis (Sayre et al., 1997; Ando et al., 1998; Wataya et al., 2002).

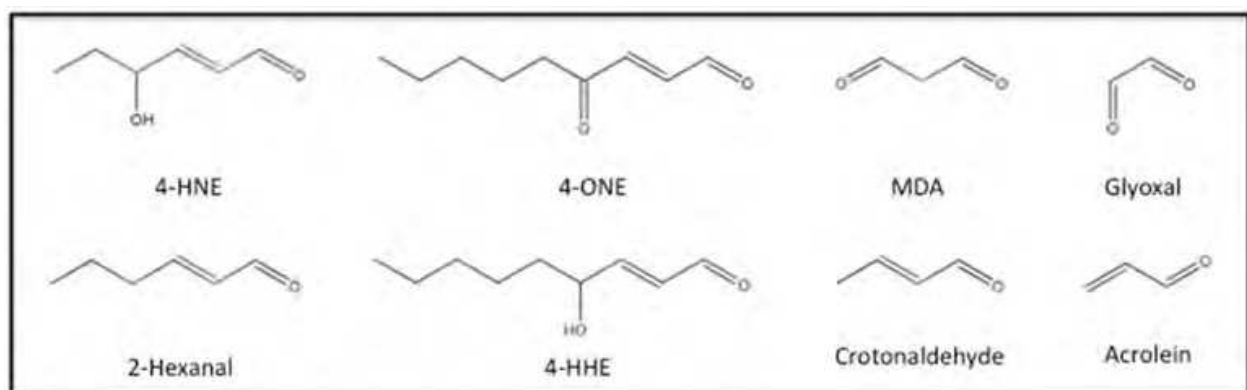


Fig. 2. Lipid peroxidation products. ROS stimulate peroxidation of polyunsaturated fatty acids (PUFA) to generate  $\alpha,\beta$ -unsaturated aldehydes and dialdehydes.

F2-Isoprostanes (F2-IsoPs), which contain an F-type prostane ring, are a group of bioactive prostaglandin-like compounds generated via a non-enzymatic mechanism involving the free radical-initiated peroxidation of esterified arachidonic acid (AA). Then, they are cleaved and released into the circulation by phospholipases before excretion in the urine as free

isoprostanes (Basu, 1998). The most studied class of isoprostanes, due to their urine stability, is 8-iso-Prostaglandin  $F_{2a}$  (8-iso-PGF $_{2a}$ ; Figure 3). Urinary F2-IsoPs determination has been proposed as specific, reliable, and non-invasive marker to assess lipid peroxidation *in vivo* (Cracowski et al., 2002; Montushchi et al., 2004) since an increase in 8-iso-PGF $_{2a}$  levels in CSF and urine have been found in subjects with AD (Montine et al., 1998 and 2011; Kim et al., 2004). On the other hand, oxidation of docosahexanoic acid (DHA) produces F4-neuroprostanes (F4-NeuroPs; Figure 3) (Morrow et al., 1999; Roberts et al., 1998) which levels are elevated in postmortem ventricular CSF of AD patients and are more abundant in the brain than F2-isoprostanes. Nevertheless, plasma F2-IsoPs and F4-NeuroPs do not accurately reflect central nervous system levels and are not reproducibly elevated in body fluids outside of central nervous system in Alzheimer's disease patients (Montine et al., 2002).

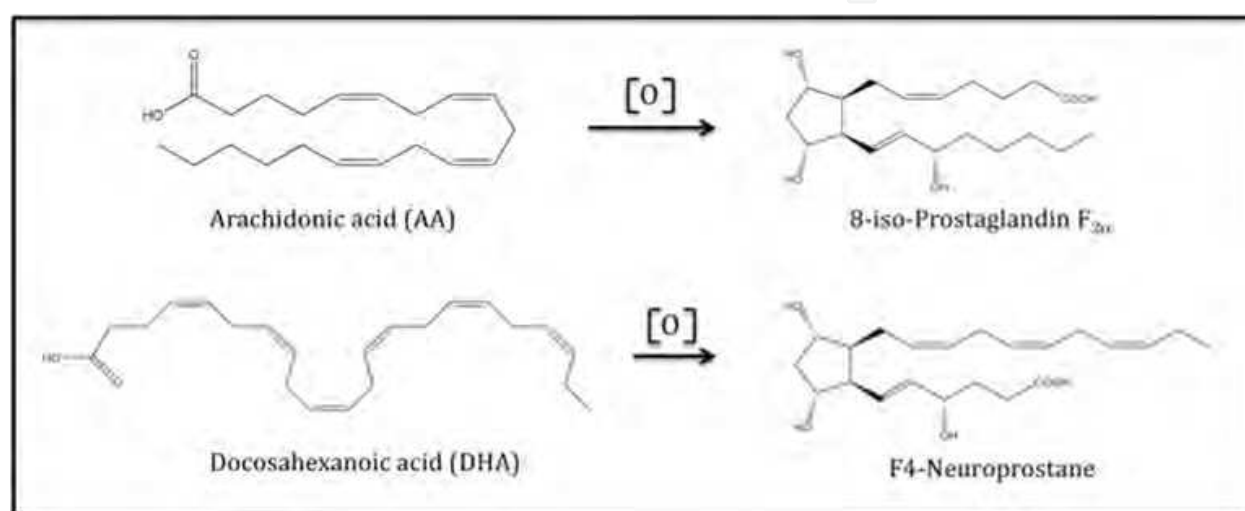


Fig. 3. Chemical structures of F4-neuropropane and 8-iso-Prostaglandin  $F_{2a}$  arising from direct oxidation of docosahexanoic and arachidonic acids, respectively.

### 3.2 Biomarkers of oxidative DNA damage

Among over 30 nucleobase modifications that have been described, the most extensively studied that reflect oxidative DNA damage is 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG; also known as 8-OHdG), a product of oxidatively modified DNA base guanine (Figure 4). The detection of this oxidation is important not only due to its abundance but also to its mutagenic potential through GC-to-TA transversion mutations upon replication of DNA (Cheng et al., 1992). Nevertheless, oxidatively damaged DNA can be repaired and released into the bloodstream and consequently appear without further metabolism in the urine (Fraga et al., 1990; Shigenaga et al., 1989). In addition, urinary levels of 8-OHdG have been found to be independent of dietary influence in humans. The modified base 8-oxo-7,8-dihydroguanine (8-oxoGua; Figure 4) and modified nucleoside (8-oxodG; Figure 4), which are found in urine, represent the major repair products of oxidatively damaged DNA *in vivo* and have been considered to reflect the whole-body oxidative DNA damage (Hamilton et al., 2001; Olinnski et al., 2007). There is considerable evidence supporting that oxidative stress occurs in AD, and increased 8-oxodG levels have been found in DNA isolated from brain tissues, leukocytes and ventricular CSF of AD patients. In contrast, free 8-OHdG was found dramatically decreased in AD samples as compared to the controls (Lovell & Markesbery, 2001; Markesbery & Carney, 1999; Mecocci et al., 2002; Migliore et al., 2005).

Taken together, these data indicate a double insult in AD patients by increasing oxidative damage and decreasing DNA repair mechanisms efficiency. More recent studies showed an elevated 8-OHdG in both nuclear and mitochondrial DNA (mtDNA) isolated from vulnerable brain regions in amnesic mild cognitive impairment (MCI), the earliest clinical manifestation of AD, and thus suggesting that oxidative DNA damage is an early event in AD and is not merely a secondary phenomenon (Lovell & Markesbery, 2007b).

Many methods such as HPLC-ECD, GC-MS, LC-MS, and immunoassay have been established to measure 8-OHdG in biological specimens. In this concern, the European Standards Committee of Urinary (DNA) Lesions Analysis (ESCUA) was formed in 2006 in order to validate the measurement methods of oxidatively damaged DNA and to establish reference urine values (Cooke et al., 2008; Evans et al., 2010). Finally, it is important to mention that DNA can also be modified by products of lipid peroxidation (ALEs). These  $\alpha$ - $\beta$ -unsaturated aldehydes can react with deoxyguanosine through an initial Michael addition of the exocyclic amino group followed by ring closure of N-1 onto the aldehydic group to generate a bulky exocyclic 1-N<sup>2</sup>-propanodeoxyguanosine adduct (Liu et al., 2006; Kozekov et al., 2003) and therefore participate in the propagation of the oxidative DNA damage.

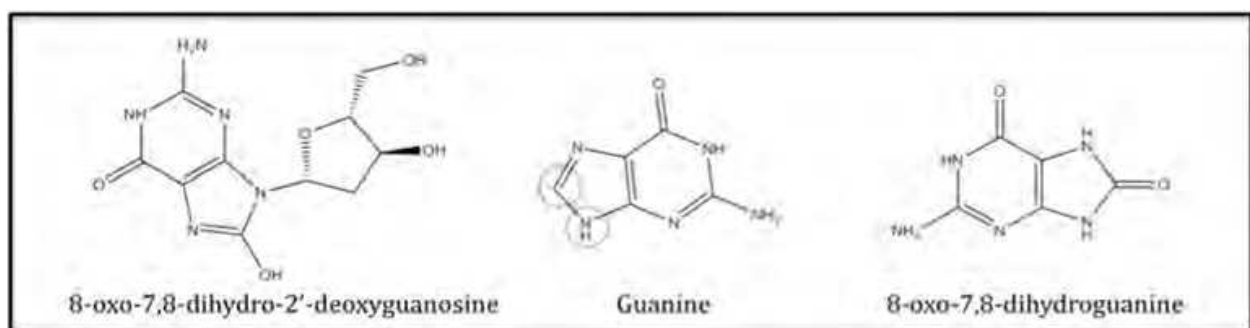


Fig. 4. Chemical structure of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG; 8-OHdG), guanine and 8-oxo-7, 8-dihydroguanine (8-oxoGua).

### 3.3 Advanced glycation end products

Advanced glycation end products (AGEs), formed by a non-enzymatic reaction of sugars with amino groups in long-lived proteins, lipids, and nucleic acids, are also potent neurotoxins and proinflammatory molecules. Glycation of proteins starts as a non-enzymatic process with the spontaneous condensation of ketone or aldehyde groups of sugars with a free amino acid group of proteins to form a labile Schiff base, consistent with the classical reaction described by Louis Camille Maillard in 1912 (Figure 5).

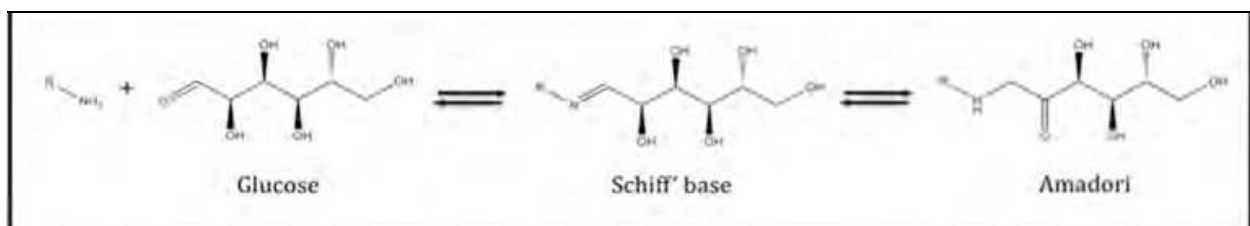


Fig. 5. Non-enzymatic reaction of the carbonyl groups of reducing sugars with primary amino groups produce corresponding Schiff bases, which undergo Amadori rearrangement to give ketoamines.

Glycation is the first step in the cascade of a complex series of very slow reactions in the body known as Amadori reactions, Schiff base reactions and Maillard reactions, all leading to the formation of irreversibly cross-linked heterogeneous aggregates. AGEs are continuously formed in the human body and progressively accumulate with age in plasma and tissues. In diabetes mellitus and AD the rate of AGEs formation is accelerated and consequently, they have been considered potentially useful biomarkers for monitoring the treatment of these disorders. Chemical structures of representative markers of AGEs are summarized in Figure 6. Supporting the argument that AGEs are involved in the pathogenesis of AD, some studies have shown the presence of AGEs in association with two major proteins of AD, A $\beta$  and MAP-tau (Smith et al., 1995; Vitek et al., 1994; Yan et al., 1994). Extracellular AGEs accumulation has been demonstrated in senile plaques in different cortical areas. Intracellular proteins deposits including NFTs, Lewy bodies of patients with Parkinson's disease and Hirano bodies are also crosslinked by AGEs, which may explain their insolubility in detergents and resistance to proteases (Loske et al., 2000). The major component of the NFTs, the microtubuli-associated protein tau (MAP-tau) has been shown to be subject to intracellular AGEs formation. MAP-tau

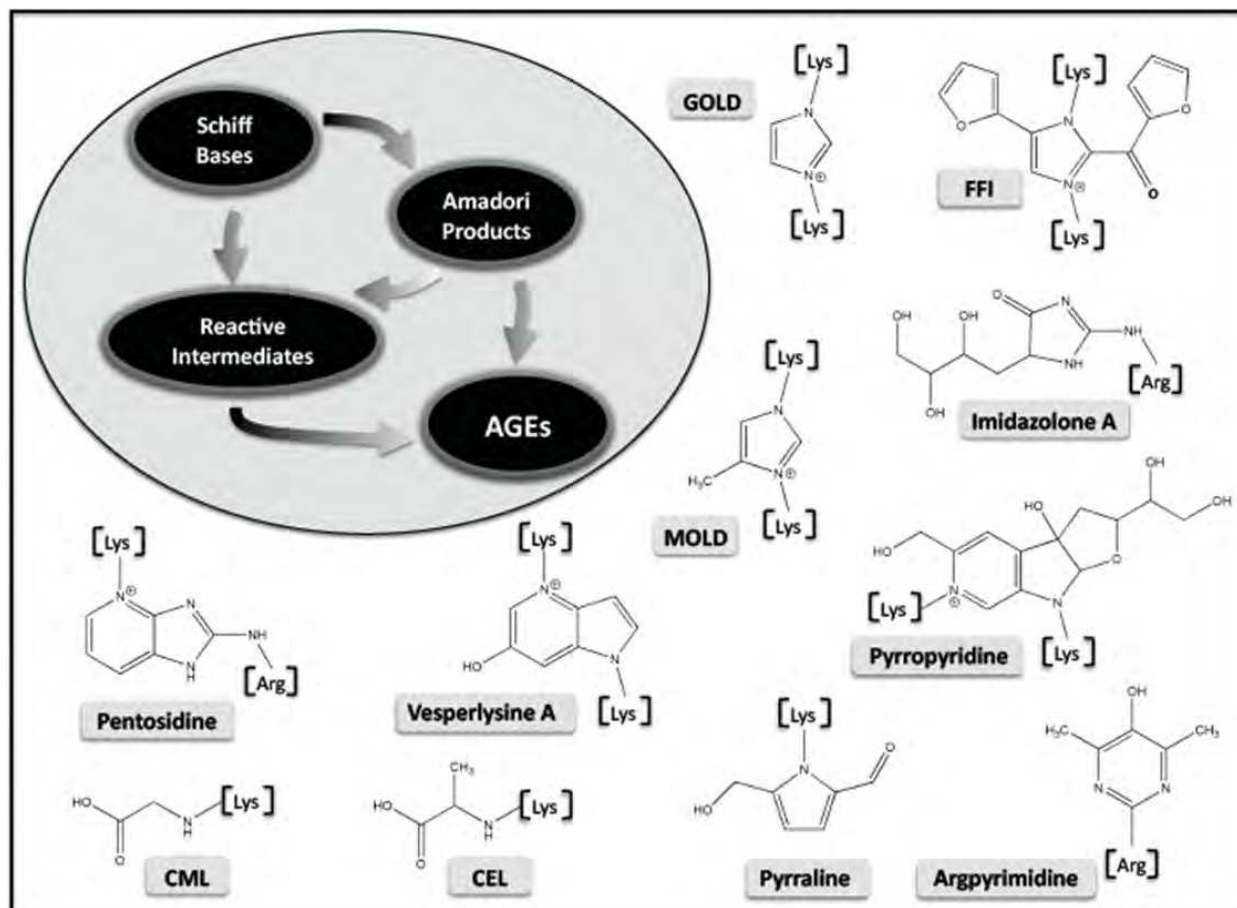


Fig. 6. A variety of highly reactive carbonyl intermediates such as 3-deoxy-glucosone, glyoxal and methyl-glyoxal can be formed by glucose or Schiff's base or Amadori product auto-oxidation which, in turn, can react with free amino groups to form AGE products. N-carboxymethyl-lysine (CML), N-carboxyethyl-lysine (CEL), glyoxal-derived lysine dimer (GOLD), methylglyoxal-derived lysine dimer (MOLD), furoyl-furanyl-imidazole (FFI), Lysine (Lys) and arginine (Arg).



can be glycosylated in vitro, inhibiting its ability to bind to microtubules. In addition, MAP-tau isolated from brains of AD patients is glycosylated in the tubulin-binding region, giving rise to the formation of  $\beta$ -sheet fibrils (Ledesma et al., 1998). AGEs accumulate in the human brain during aging (Kimura et al., 1996) and are present in neurofibrillary tangles and senile plaques in patients with AD (Castellani et al., 2001). Furthermore; AGE-modified A $\beta$  peptides accelerate aggregation of soluble nonfibrillar A $\beta$  peptides. In older adults with cerebrovascular disease, elevated N-carboxymethyl-lysine (CML) has been found in cortical neurons and cerebral vessels and has been related to the severity of cognitive impairment (Southern et al., 2007). Brain tissue AGEs can therefore be considered tissue biomarkers for AD, and increased brain AGEs concentrations are reflected in CSF (Ahmed et al., 2005) but not necessarily in plasma (Thome et al., 1996).

A positive feedback loop in the pathogenesis of AD is provoked by AGEs which increase OS and inflammation through binding with AGEs receptor (RAGE). The RAGE signalling pathway, found upregulated in AD brains, can be initiated by a diverse repertoire of pro-inflammatory ligands that include AGEs, S100/calgranulins, amphotericin, and amyloid- $\beta$  peptide. Ligand binding with RAGE triggers the induction of increased reactive oxygen species, activates NADH oxidase, increases the expression of adhesion molecules, and up-regulates inflammation through NF- $\kappa$ B and other signalling pathways.

### 3.4 Biomarkers of oxidative protein damage

Carbonylation of proteins is an irreversible oxidative process, often leading to a loss of protein function, which is considered a widespread indicator of severe oxidative damage and disease-derived protein dysfunction (Dalle-Donne et al., 2006). Protein carbonyl groups are introduced to proteins by direct oxidation of several amino acid residues into ketone or aldehyde derivatives (particularly lysine, arginine, threonine and proline; Figure 7) or by secondary reaction with the primary oxidation products of sugars (forming AGEs) and lipids (forming ALEs) (Berlett & Stadtman, 1997). Several studies have proved that proteins are major initial cell targets of ROS, leading to earlier formation of the protein carbonyls in biological systems. Detection of increased levels of protein carbonyls in AD has been proposed as a sign of disease-associated dysfunction, suggesting the potentiality as biomarkers for early AD diagnosis.

Recent studies show an increase in protein carbonyls together with NFTs in multiple brain regions of AD subjects (Sultana & Butterfield, 2011). Oxidative modifications of proteins can cause cross-linking of covalent bonds of proteins leading to fibril formation and insolubility. NFTs are characterized by the aggregation and hyperphosphorylation of tau proteins which is linked to oxidation through the microtubule-associated protein kinase pathway and through the activation of the transcription factor NF- $\kappa$ B. A wide number of studies have reported differences in specific carbonylated proteins in brain, plasma and CSF of AD patients compared with control group by using 2-dimensional gel electrophoresis in combination with mass spectroscopy techniques (Castegna et al., 2002a, 2002b; Davidsson et al., 2001; Puchades et al., 2003). Some of these studies reveal the presence of specific targets of protein oxidation in AD brain: creatine kinase BB, glutamine synthase, ubiquitin carboxy-terminal hydrolase L-1, dihydropyrimidinase-related protein 2, alpha-enolase and heat shock cognate 71. Glutamine synthase and creatine kinase, both markedly decreased in AD brains, are especially sensitive to oxidative modifications since they may cause alteration of glutamate concentrations (glutamine synthase), and therefore enhance excitotoxicity, and decrease

energy metabolism (creatine kinase). Recently, several oxidized carbonylated proteins have been characterized in frontal cortex (Korolainen et al., 2006), plasma (Yu et al., 2003; Choi et al., 2002) and CSF (Korolainen et al., 2007) of patients suffering from AD by two-dimensional oxyblotting technique.

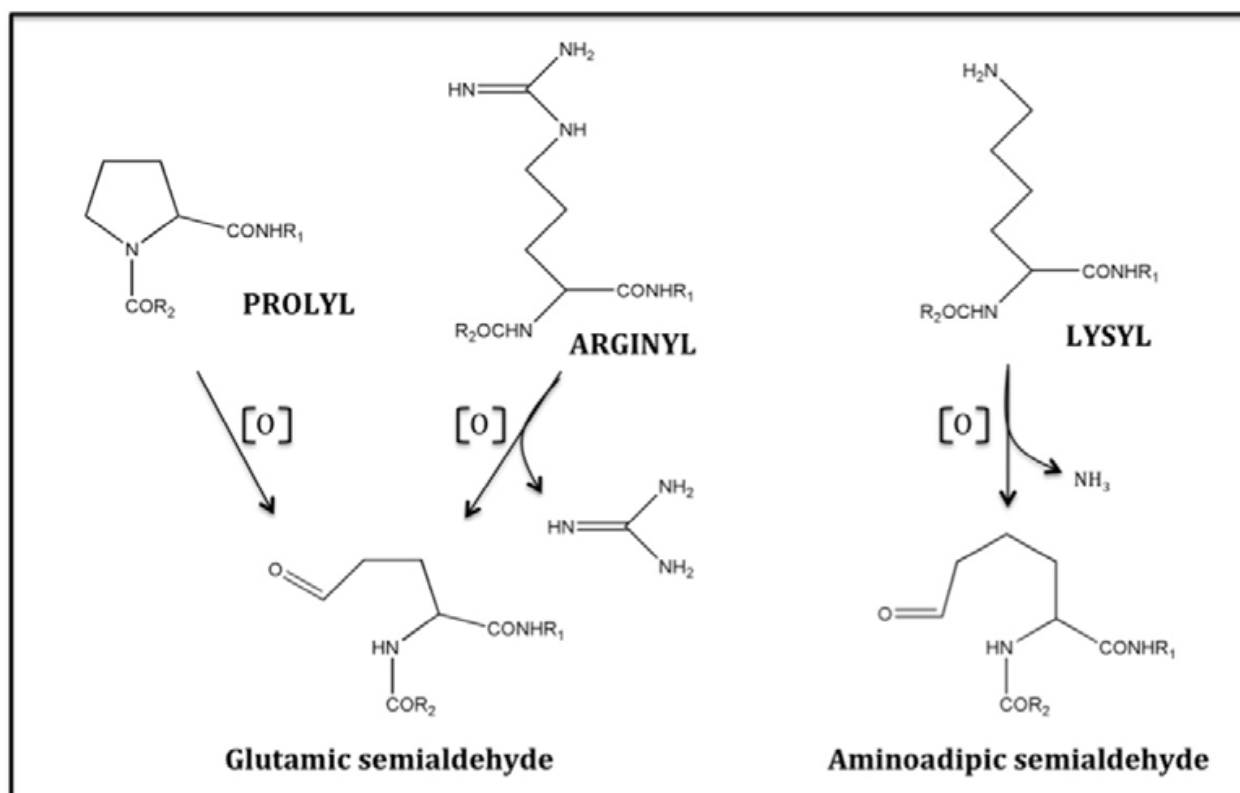


Fig. 7. Chemical structures of protein carbonyls arising from direct oxidation of aminoacid side chains. Glutamic semialdehyde (resulting from direct oxidation of arginyl and prolyl residues) and amino adipic semialdehyde (resulting from direct oxidation of lysyl residue).

#### 4. Antioxidant therapies in Alzheimer's disease

Currently, the only Food and Drug Administration (FDA) approved treatment for AD is the administration of the cholinesterase inhibitors (AChEI) donepezil, galantamine and rivastigmine and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine (Birks et al., 2000, 2006; Loy et al., 2004; Areosa et al., 2005). Nevertheless, to date, these drugs have demonstrated to produce only modest symptomatic improvements in some of the patients, but not to cure or stop the disease progression. Moreover, AChEI are expensive and may have side effects resulting from activation of peripheral cholinergic systems (Green et al., 2005). Then, effective treatments are greatly needed. The current therapeutic strategies being investigated for AD include targeting neurotransmission with multifunctional compounds, anti-amyloid and anti-tau therapies, drugs targeting mitochondrial dysfunction, neurotrophins, statins and also other approaches such as PUFAs and antioxidants (for review see Mangialasche et al., 2010). Among them, antioxidant therapies and PUFAs are particularly attractive due to their low toxicity, low cost and their ability to target earlier changes of the disease (e.g oxidative stress) which are linked to cognitive and functional decline. However, there is still much skepticism regarding the likelihood of success with an

antioxidant therapy since to date these compounds tested in randomised controlled trials (RCTs) have given controversial results.

#### 4.1 Vitamins

A large amount of literature exists in relation to the potential benefits of vitamins, which act as natural free radical scavengers, in the prevention of AD (Figure 8). Vitamin A has been traditionally considered as antioxidant and it seems essential for learning, memory and cognition. Retinoic acid, a metabolic product of vitamin A, is known to slow cell death and protect from A $\beta$  (Sahin et al., 2005). Thus, since levels of vitamin A decline with age and are found lower in AD individuals (Goodman et al., 2006) vitamin A supplementation might be useful for the treatment of some features in the ageing process. B-vitamins (B<sub>6</sub>, B<sub>12</sub> and folic acid) are lipid soluble antioxidants involved in the methylation of homocysteine (Hcy) which is highly cytotoxic. Cellular catabolism and cellular export mechanisms are the responsible for keeping low intracellular Hcy concentration. AD patients typically present high levels of Hcy (McIlroy et al., 2002) and low levels of vitamin B<sub>12</sub> and folate which appear to be associated with an increased rate of cognitive decline (Tucker et al., 2006; Morris et al., 2007). Nevertheless, in a recent study, a combination of vitamins B<sub>12</sub>, B<sub>6</sub> and folate in mild to moderate AD individuals, although lowering Hcy, did not produce any effect on cognition compared to controls. Vitamin C (ascorbic acid), found in many fruits and vegetables, is the major water-soluble antioxidant and acts as first defence against free radicals in blood and plasma. Bagi et al, 2003, have shown that chronic vitamin C treatment is able to decrease high levels of isoprostanes in animal models. In contrast, other studies have shown that it can also act as pro-oxidant inducing neuronal oxidative stress via its

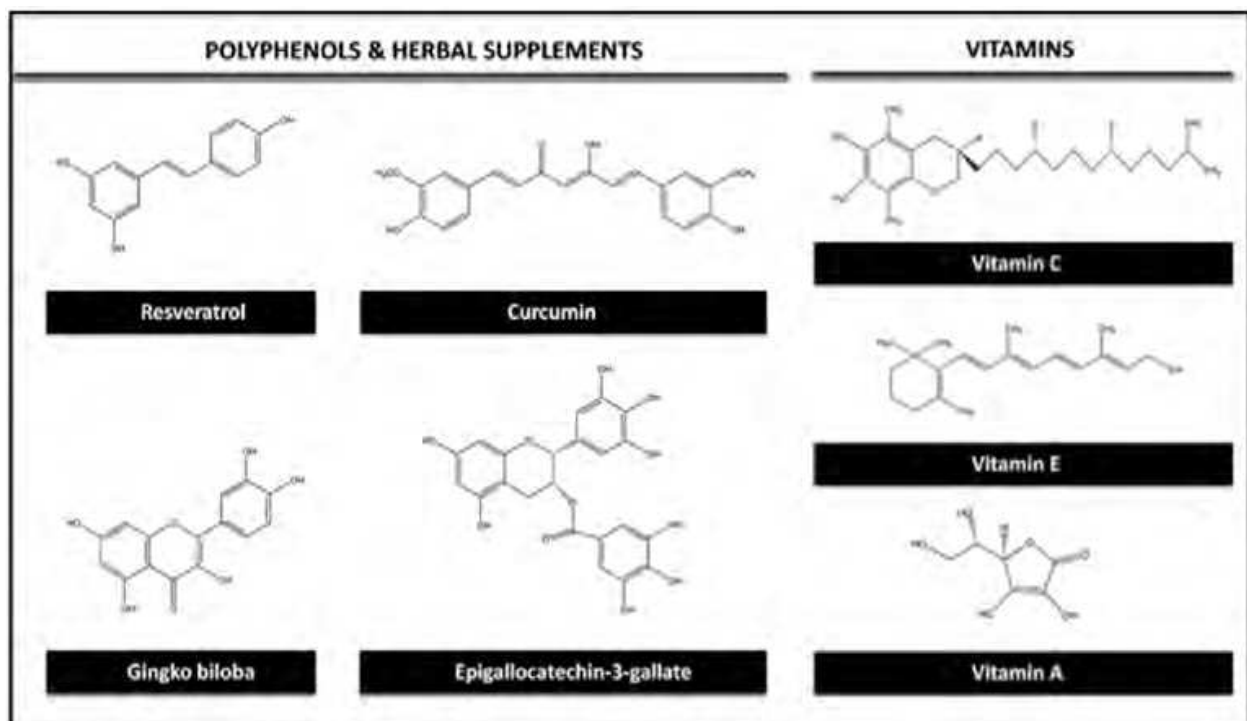


Fig. 8. Chemical structures of the principal polyphenols, herbal supplements and vitamins investigated as promising agents for the treatment of AD.

interaction with metal ions (White et al., 2004). Vitamin E ( $\alpha$ -tocopherol), present in whole grains, cereals and vegetable oils, is a lipid-soluble vitamin found in cell membranes and circulating lipoproteins. Its antioxidant capacity acts directly to a variety of ROS. It is found low in AD patients (Jiménez-Jiménez et al., 1997) and although in vitro and animal studies have been encouraging, human trials have produced conflicting results (Berman et al., 2004). A Cochrane study shows that tocopherol is not effective in a prevention trial in mild cognitive impairment (MCI) to reduce progression to AD nor clearly effective in AD patients (Tabet et al., 2000; Luchsinger et al., 2003). Besides, a harmful effect of tocopherol at high doses has also been suggested (Tucker et al., 2005). However, several studies correlate a reduced risk to AD in elderly persons treated with vitamin E and C alone or in combination (Grundman et al., 2004; Morris et al., 1998; 2002; 2005). On the other hand, brain bioavailability of vitamin E in humans is very low and, as suggested elsewhere may not be enough to quickly inhibit AD neuropathology unless administered as a prophylactic at very early ages. The large amount of contradictory data found in literature about the use of vitamins as antioxidants indicates intricate physiological and pharmacological features of AD and remain questionable its use in human.

#### 4.2 Polyphenols and herbal supplements

Polyphenols are a group of plant-derived chemical substances which protect plants from the stress induced by physical damage, disease, radiation and pests (Figure 8). It has been suggested that curcumin, the yellow pigment extracted from the plant *curcuma longa* (turmeric), may be a promising therapy for AD due to its extended neuroprotective actions (Mishra et al., 2008; Cole et al., 2007), including antioxidant, anti-inflammatory, inhibition of A $\beta$  formation and removal of existing A $\beta$ , as well as copper and iron chelation. Epigallocatechin-3-gallate (EGCg) is found in green tea and it has been described that prevents A $\beta$  aggregation by directly binding to the unfolded peptide. It also modulates signal transduction pathways, expression of genes regulating cell survival and apoptosis and its actions in mitochondrial function make it a potent antioxidant (Mandel et al., 2008). Resveratrol is present in red wine, peanuts and other plants and it has been found that it reduces OS, inflammation and A $\beta$  deposition, decreases cell death and protects DNA (Mishra et al., 2008; Karuppagounder et al., 2009). A recent study suggests that moderate consumption of red wine reduces the risk of developing AD. Nevertheless, the translation to humans is still somewhat problematic and has some caveats since although polyphenols easily penetrate blood-brain barrier, they show bioavailability problems such as low absorption, rapid metabolism and quick elimination. Efforts to increase bioavailability have been reviewed (Anand et al., 2007) and the adjuvant use widely extended (Shoba et al., 1998). Indeed, there is currently a clinical trial underway addressing curcumin bioavailability (<http://clinicaltrials.gov/NCT01001637>). Furthermore, the anti-AD effects of polyphenols may not be mediated solely through their direct antioxidant action but rather indirectly through any other functions. Then, it is still to be clarified whether polyphenols are able to slow the progression of AD. Herbal supplements such as *gingko biloba* have been suggested to possess beneficial properties against AD (Luo et al., 2002). Numerous animal and in vitro studies report that *gingko biloba* extract EGb761 possess neuroprotective benefits (Defeudis et al., 2002) including antioxidant, anti-inflammatory, and regulator of A $\beta$  processing. It has also been described that *gingko* improves cognitive function in mild to moderate AD patients (Oken et al., 1998; Le Bars et al., 2003) and reduces deterioration in

subjects with more severe dementia via inhibition of the A $\beta$  induced free radical generation (Napryeyenko et al., 2009; Yao et al., 2001). Nevertheless, a double-blind placebo controlled study found no beneficial effect of *gingko* on dementia in AD patients (Schneider et al, 2005) and DeKosky et al, 2008 showed that *gingko* was not better than placebo at preventing the onset of dementia. Additionally, there are two more studies finding no correlation between cognitive decline and the use of *gingko biloba* (Snitz et al., 2009; Dodge et al., 2008). Although data is controversial, it then appears that *gingko* may be useful delaying cognition impairment but not preventing the onset of AD. The ongoing clinical trial will help to elucidate this question (<http://clinicaltrials.gov/NCT00814346>).

### 4.3 Mitochondrial-related antioxidants

Since mitochondria are the major sources of ROS in the central nervous system, therapeutic strategies have largely focused in targeting mitochondria and mitochondrial-related pathways. There are several compounds showing an in vitro and in vivo antioxidant and neuroprotective action but only a few have been tested in human clinical trials with mixed results.

#### 4.3.1 Quinone family

Ubiquinone (Coenzyme Q, CoQ) and idebenone, a synthetic analog of CoQ, (Figure 9) are the major mitochondrial targets used as therapeutics against ROS-mediated damage. They have demonstrated antioxidant properties in vitro and in animal models (Wadsworth et al., 2008). CoQ has not been yet tested in humans but idebenone has been investigated in clinical trials for its capacity to inhibit lipid peroxidation. Several studies report a significant effect in memory and attention improvements (Gutzmann et al., 2002; Senin et al., 1992; Weyer et al., 1997) but a larger study reported no effect in slowing the disease progression (Thal et al., 2003).

#### 4.3.2 Other mitochondrial antioxidants

Alpha-lipoic acid (LA) is an organosulfur compound derived from octanoic acid and primarily a cofactor in aerobic metabolism for pyruvate dehydrogenase complex. Its reduced bioactive form produced into cells provides its antioxidant properties (Haenen et al., 1991). Acetyl L-carnitine (ALCAR) is formed within mitochondria by carnitine-O-acetyltransferase. Both LA and ALCAR (Figure 9) are good candidates for being used therapeutically as mitochondrial antioxidants since it was found that a combination of both decreased mitochondrial dysfunction and its consequent ROS-mediated damage in aged rats, improving cognitive functions (Aliev et al., 2009). Additional neuroprotective functions, including binding to targets involved in A $\beta$  production have been reported (Epis et al., 2008). However, several clinical trials with ALCAR have been conducted with contradictory results: one showed no effectiveness in early onset AD (Thal et al., 2000) whereas another showed a slower deterioration in cognition (Pettergrew et al., 1995). A recent meta-analysis of ALCAR treatment trials showed an improvement in clinical scales in patients with MCI and AD (Montgomery et al., 2003). Dimebon (Figure 9), a non selective antihistamine, possesses several mechanisms of action including the inhibition of A $\beta$  toxicity and the prevention of ROS-mediated damage (Doody et al., 2009; Okun et al., 2010). Several clinical trials have been performed in AD patients with contradictory results: in a phase 2 clinical trial, dimebon improved cognition and behaviour, overall

function in MCI and AD (Doody et al., 2008) whereas more recently, a phase 3 CONNECTION trial with AD patients showed no improvement in any parameter (<http://clinicaltrials.gov/NCT00675623>).

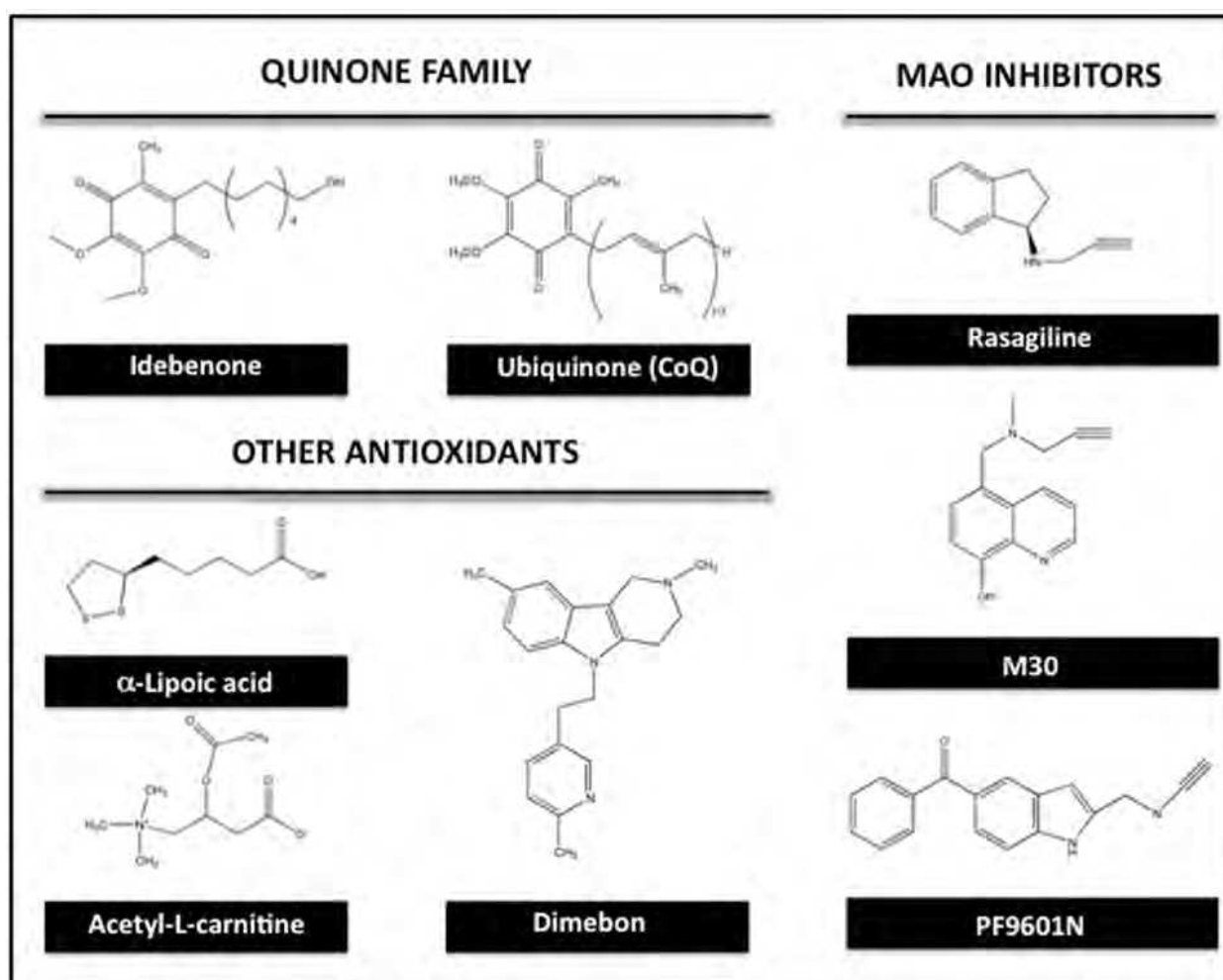


Fig. 9. Chemical structures of mitochondrial-related antioxidants investigated as promising agents for the treatment of AD.

#### 4.3.3 Monoamine oxidase inhibitors

The therapeutic potential of monoamine oxidase inhibitors (MAOIs) for the treatment of AD has been largely reported (Thomas, 2000; Riederer et al., 2004; Youdim et al., 2005) due to their capacity to reduce the formation of toxic metabolites or oxygen radicals by blocking the catalytic activity of monoamine oxidase (MAO), enzyme located in the mitochondrial membrane and responsible of amine metabolism. It has been extensively reported that MAO-B activity besides increasing with age is found in high levels in AD patients. Selegiline, the classic MAO-B inhibitor, and also other propargylamines (Figure 9) possess potent antioxidant properties (Kitani et al., 2000; Sanz et al., 2004). Moreover, it has also been described that propargylamine-derived MAOIs exert neuroprotective effects by acting in very diverse type of targets, including metal chelation (e.g M30), reduction of A $\beta$  aggregation and toxicity (Bar-Am et al., 2009; Youdim et al., 2005) as well as direct

actions on diverse mitochondrial-related components. Among this direct functions, propargylamines increase the expression of anti-apoptotic proteins (Akao et al., 2002), prevent cytochrome c release and preserve the mitochondrial membrane potential (Mayurama et al., 2000). The great amount of beneficial functions found for MAOIs make them promising molecules for the treatment of AD. Indeed, current pharmacological challenges in AD involve the design and development of multifunctional compounds able to bind to a very diverse type of targets and among them MAO inhibition is strongly recommended.

#### 4.4 PUFAs

The beneficial effects of omega-3 polyunsaturated fatty acids (PUFAs) have been widely reported which make them good candidates for AD therapy (Cole et al., 2005) since they act directly on intracellular pathways and regulate oxidative stress mechanisms. DHA is the major omega-3 fatty acid in the brain. A recent study although showing no effect of DHA on subjects with mild-to-moderate AD it found a slower rate of cognitive decline among those patients without the APO  $\epsilon$ 4 allele (Quinn et al., 2009). As reviewed by Mangialasche et al., 2010, some studies have reported a beneficial effect of DHA on cognitive function in patients with AD (Yurko-Mauro et al., 2009; Chiu et al., 2008) whereas others did not find a correlation (Quinn et al., 2009). In effect, a recent study showed that treatment of patients with PUFAs did not modify the neuropathology of this disorder in CSF or plasma, nor the biomarkers of inflammation (Freund-Levi et al., 2009) and a randomised control trial in patients with mild to moderate AD did not delay the rate of cognitive decline (Freund-Levi et al., 2006). Some authors suggest that benefits of omega-3 fatty acids are limited to those with very mild cognitive impairment. A phase 2 randomised clinical trial is currently ongoing (<http://clinicaltrials.gov/NCT01058941>).

#### 4.5 Multiple nutrients

Dietary supplementation with a plethora of nutrients such as apple juice concentrate, red wine, caffeine, fish oil or green tea as well as calorie restriction diets have been conducted. Diverse human studies have shown that multiple formulations improve all measures of cognition, although some authors reported that the increase in memory was not found significant (Chan et al., 2008). A recent study correlates frequent consumption of fruits and vegetables, fish, and omega-3 rich oils with a decreased risk of dementia in AD (Barberger-Gateau et al., 2007). In contrast, interventional trials with antioxidants, B-vitamins and DHA did not give the promising expectations from the epidemiological data. As reported by Von Arnim et al., 2010, although some trials are encouraging, larger randomised clinical trials with combined supplements are needed to draw any conclusion. Supplement composition is still a matter of debate, because high doses of a single antioxidant have been associated with no beneficial effects for AD patients and even with an increase in mortality risk (e.g. vitamin E). Many interventional studies are started very late in the disease state, when AD pathology is already at a fulminant level which severely reduces therapeutic effectiveness of tested agents. The multifactorial nature of AD and the necessity to target the earlier production of OS makes important the combination of multiple supplements. Therefore, studies combining nutrients are of particular interest and at present in progress (e.g. T-diet, NKO™, and Memory XL; <http://clinicaltrials.gov/NCT01192529>, [NCT00867828](http://clinicaltrials.gov/NCT00867828), [NCT00903695](http://clinicaltrials.gov/NCT00903695)).

Exposure	Assessment	Design	Case source	Major findings	Reference
EGB 761 (intravenous)	NA	RCT	AD VaD	ADL improvement. Clinical impression of change	Haase et al, 1996
EGB 761 (oral)	NA	RCT	AD VaD	Cognitive improvement	Le Bars et al, 2000
PUFAs	Plasma assay	Cross-sectional	Normal, CI, dementia	Low n-3 and high n-6 associated with CI and AD	Conquer et al, 2000
PUFAs	Plasma assay	Cross-sectional	Normal, CI, dementia	High n-3 associated with CI and AD. Strengthened in ApoEε4 non-carriers	Laurin et al, 2003
PUFAs	Plasma assay	Prospective	Normal	No association between PUFAs and reduced risk of dementia	Kroger et al, 2009
Fish intake	FFQ	Prospective	Normal	Reduced risk of incident dementia	Barberger-Gateau et al, 2002
DHA	Serum assay	Case-control	Normal AD	MMSE and CDR improvement	Tully et al, 2003
Fish oil	FFQ	Prospective	Elderly	Slow rate of decline but not on overall cognitive status	Morris et al, 2005
PUFA	FFQ	Prospective	Elderly	Reduced MMSE decline over 5 years	Van Gelder et al, 2007
β-carotene	NA	Prospective	Elderly	Less cognitive decline only in ApoE4 carriers	Hu et al, 2006
Vitamin E	NA	RCT	MCI	No significant differences compared to placebo or donepezil	Petersen, 2005
α-tocopherol and/or selegiline	NA	RCT	Moderate AD	Longer time to institutionalization in all cases	Sano et al, 1997

Table 2. Studies on antioxidants. EGB 761, Ginkgo biloba special extract 761; NA, not applicable; VaD, Vascular Disease; ADL, Activities of Daily Living; RCT, Randomised Controlled Trial; ApoE, apolipoprotein E; n-3, omega-3 fatty acids; n-6, omega-6 fatty acids; FFQ, food frequency questionnaire; AD, Alzheimer's Disease; CI, cognitive impairment; MCI, Mild cognitive impairment; DHA, docohexanoic acid; PUFAs, polyunsaturated fatty acids; MMSE, Folstein Mini- Mental State examination; CDR, Clinical Dementia Rating Scale.



## 5. Conclusions

Oxidative stress increases with ageing and seems to be a consequence of an imbalance between ROS production and antioxidant defences. The accumulation of endogenous oxygen radicals generated in mitochondria and the consequent oxidative modifications of biological molecules have been indicated as responsible for the ageing process. There is therefore an urgent need to identify biomarkers that would help to diagnose and monitor the early AD or "preclinical AD". Indeed, a few CSF proteins (e.g. amyloid- $\beta_{1-42}$ , total tau and phospho-tau) have already shown promise as diagnostic biomarkers for AD. Nevertheless, these biomarkers are not yet optimal diagnostic tools to identify those MCI patients at higher risk of conversion to AD. Thus, a key objective in the research of OS biomarkers is to identify prodromal stages of the disorder, prior to cognitive decline, for gauging the long-term therapeutic effects of drugs. The contradictory results obtained with diverse antioxidants in clinical trials may be explained by other related differences in health problems as well as due to the fact that most studies are very short and conducted with very few subjects. Methodological problems and poorly matched epidemiological studies have also been pointed as reasons for mixed findings. In fact, very few trials are adequately addressing the effect of antioxidants in AD. Although at this time there is no rationale for recommending antioxidant use for prevention or treatment of AD, the current epidemiologic evidence points toward an important role of nutrition in this pathology. The optimal time for prevention seems to be important and still to be determined. Nevertheless, it seems clear that therapies acting in the beginning of the pathological cascade may be more effective than treatments that act after the fact (e.g., removal of amyloid plaques). Then, therapy should begin as early as possible while reversal of cellular pathologies is still achievable. In conclusion, properly addressed studies with antioxidants are greatly needed to obtain convincing data about its beneficial effects as anti-AD. There is also an urgent need for better formulations with increased bioavailability. Due to the multifactorial nature of AD, it seems imperative that future trials may use drug combinations or even multifunctional molecules, rather than a single compound, able to bind to a very diverse type of target and that an antioxidant capacity may be contemplated.

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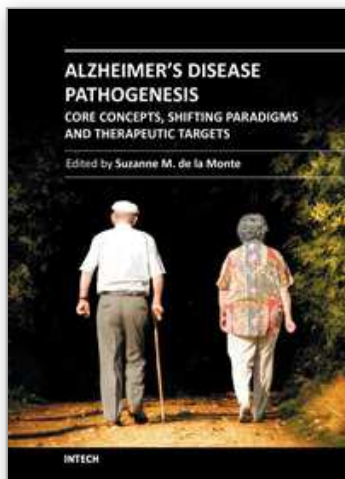
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## **Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets**

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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