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A Review of Antioxidants and Alzheimer's Disease

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Background. *In this article, we review a diverse body of research and draw conclusions about the usefulness, or lack there-of, of specific antioxidants in the prevention of Alzheimer's disease (AD).*

Methods. *The National Library of Medicine's database was searched for the years 1996–2004 using the search terms "Alzheimer's, anti-oxidants, antioxidants."*

Results. *Over 300 articles were identified and 187 articles were selected for inclusion based on relevance to the topic. Agents that show promise in helping prevent AD include: 1) aged garlic extract, 2) curcumin, 3) melatonin, 4) resveratrol, 5) Ginkgo biloba extract, 6) green tea, 7) vitamin C and 8) vitamin E.*

Conclusions. *While the clinical value of antioxidants for the prevention of AD is often ambiguous, some can be recommended based upon: 1) epidemiological evidence, 2) known benefits for prevention of other maladies, and 3) benign nature of the substance. Long-term, prospective studies are recommended.*

Keywords Alzheimer's, Anti-oxidants, Antioxidants, Dementia, Neurodegenerative

INTRODUCTION

The incidence of Alzheimer's disease (AD) increases strongly with age. It has been estimated that within the next 50 years approximately 30% of the population will be aged 65 years or older. Of those between 75 and 84 years of age, 6 million will exhibit some form of AD symptoms, and of those older than 85 years, over 12 million will have some form of dementia associated with AD (1). A recent statistical modeling analysis of the data from a study of 3308 elderly residents of Cache County, Utah estimated the 100-year lifetime incidence of AD at 72%, implying that only 28% of individuals would not develop AD over any reasonable life expectancy (2). The analysis also revealed that, while the APOE epsilon4 allele acts as a potent risk factor for AD by accelerating onset, the overall risk of developing AD appears independent of APOE. In addition, the relative risk of death from dementia is two to three times greater than from other life-shortening illnesses (3).

Pathophysiology of Alzheimer's Disease (AD)

The pathophysiology of AD is complex and involves numerous pathways. These include defective beta-amyloid (Abeta) protein metabolism, abnormalities of glutamatergic, adrenergic, serotonergic and dopaminergic neurotransmission, and the involvement of inflammatory, oxidative and hormonal pathways (4).

Even though the precise cause of AD is not known, it is clear that genetic factors play a major role. So far, four genes have been linked to AD: amyloid precursor protein (APP), presenilin 1, presenilin 2 and apolipoprotein E. In AD, two types of fibrillar protein aggregates are present: extracellular deposits (plaques) consisting mainly of Abeta (beta-amyloid peptide—and its fragments (Abeta(40) and Abeta(42)), and intracellular deposits (tangles) composed predominantly of microtubule-associated protein tau. Abeta fragments are produced in a process of abnormal proteolytic cleavage of their precursor, APP. Mutations in the APP, presenilin 1 and presenilin 2 genes cause the enhanced production of Abeta and its fragments that are found in plaques. While apolipoprotein E allele e4 does not cause enhanced production of Abeta, it does enhance its deposition. The genes identified so far are linked to only 10% of total AD cases, and there are a number of familial cases that are not linked to any of the four genes.

Beta-Amyloid peptides (A beta s) accumulate in the AD brain in areas subserving information acquisition and processing, and memory formation. It now appears that A beta s have direct neurotoxic effects, and, N-methyl-D-aspartate (NMDA) receptors are felt to play a critical role in the neurotoxic processes.

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In addition, A beta s might become internalized and induce free radical generation and subsequent oxidative injury. Calcium-mediated neurotoxic events and generation of oxygen free radicals may even potentiate each other, or converge to the same neurotoxic events, leading to cell death.

Neuroprotection against A beta insult can be achieved by both pre- and post-treatment with NMDA receptor channel antagonists. Moreover, direct radical-scavengers, such as alpha-tocopherol (the most common isoform of vitamin E) or ascorbic acid (vitamin C), can attenuate A beta toxicity with great efficacy. A beta neurotoxicity may be modulated by trace metals, such as zinc (Zn) and iron (Fe). Combined trace element supplementation with selenium (Se), manganese (Mn), or magnesium (Mg), which impacts the expression of detoxifying enzymes or counteracts intracellular elevations of calcium, may reduce the neurotoxic impact of A beta s.

McLellan and others have recently shown that a subset of amyloid plaques produces free radicals in living, Alzheimer's models and in human Alzheimer tissue (5). Antioxidant therapy neutralizes these highly reactive molecules and may therefore be of therapeutic value in AD.

Non-genetic factors also play extremely important roles in the pathophysiology of AD. In fact, some researchers feel that, in idiopathic AD, epigenetic components of neurons such as mitochondria, proteasomes and post-translation protein modifications (processing of amyloid precursor protein to beta-amyloid and hyperphosphorylation of tau), rather than nuclear genes, are the primary targets for the actions of diverse groups of neurotoxins (6). Increased levels of inflammatory proteins have been found in the brains and plasma samples of patients with dementia. Engelhart and others reported a population-based prospective cohort study of 915 individuals, 188 of whom developed dementia at follow-up, which lasted up to six years (7). The researchers found that high levels of alpha1-antichymotrypsin, interleukin 6, and, to a lesser extent, C-reactive protein were associated with an increased risk of dementia. Most notably, they concluded that plasma levels of inflammatory proteins are increased before clinical onset of dementia, AD, and vascular dementia.

Three metals that have been implicated in free-radical-induced oxidative stress in AD include iron, zinc and mercury (8). Other researchers have also implicated iron and copper in the pathophysiology of AD (9). The increased levels of iron and zinc in AD brains have the potential of augmenting neuron degeneration through free radical processes.

Iron is a metal capable of generating hydroxyl radicals, the most potent reactive oxygen species (ROS). Accumulating evidence supports the hypothesis that brain iron misregulation and oxidative stress, resulting in reactive oxygen species (ROS) generation from H_2O_2 and inflammatory processes, trigger a cascade of events leading to apoptotic (programed) cell death in neurodegenerative disorders, including AD (10). Because of these facts, iron has been postulated to have a role in the pathogenesis of AD. Indeed, research has shown that senile plaques and neurofibrillary tangles as well as neurons in the earliest stages of the disease, show elevated iron deposition.

Hypercholesterolemia is considered a risk factor for AD. However, the link with neuronal damage is not clear. An intriguing possibility is that hypercholesterolemia can increase brain iron load and both the aggregation of beta-amyloid and the ability of iron on plaques to catalyze oxidative damage (11). This could explain why hypercholesterolemia is a risk factor for AD. In an animal experiment involving rabbits treated with a high cholesterol diet for 8 weeks, researchers found an increase in the number of iron positive cells in brain parenchyma (12). The researchers postulated that cholesterol could have subtly damaged brain endothelial cells, resulting in increased iron transport across brain endothelial cells. Hypercholesterolemia is known to be associated with increased plasma lipid peroxidation which might contribute to such damage.

An elevated blood level of homocysteine (a neurotoxic amino acid homolog of cysteine), is an independent risk factor for cardiovascular disease. Epidemiological observations of elevated homocysteine blood levels in AD have also been found. It has been proposed that homocysteine is involved in an iron dysregulation/oxidative stress cycle that has a central role in the pathogenesis of AD (13).

The cause of neuronal degeneration in AD has also been attributed to increases in cytosolic calcium and increased generation of reactive oxygen species (ROS). Abeta induces calcium influx, ROS and apoptosis. There is increasing evidence that oxidative stress and apoptosis are closely linked physiological phenomena and are implicated in the pathophysiology of some chronic diseases including AD (14). Homocysteine also induces calcium influx and oxidative stress, which has been shown to enhance neuronal excitotoxicity, leading to apoptosis. Researchers studying human neuroblastoma cells found that homocysteine potentiated the Abeta-induced increase in cytosolic calcium and apoptosis (15). It was also shown that the antioxidant vitamin E blocked apoptosis following treatment with homocysteine and Abeta, indicating that apoptosis is associated with oxidative stress.

Brains of AD patients undergo many changes, such as disruption of protein synthesis and degradation, classically associated with the heat shock response, which is one form of stress response. Heat shock proteins help protect cells from various forms of stress. Given the broad cytoprotective properties of the heat shock response, there is growing interest in discovering and developing pharmacological agents capable of inducing the heat shock response. In particular, curcumin, a powerful antioxidant derived from the spice turmeric and the major component in yellow curry, has emerged as a strong inducer of the heat shock response. In light of this finding, curcumin supplementation has been recently considered as an alternative, nutritional approach to reduce oxidative damage and amyloid pathology associated with AD (16).

Oxidative stress and mitochondrial dysfunction have been linked to neurodegenerative disorders such as Parkinson's disease

(PD) and AD. Some reactions of the mitochondrial electron transport chain with molecular oxygen generate a number of potent ROS, which cause damage to mitochondrial components and initiate degradative processes. Such toxic reactions contribute significantly to the aging process and form the central dogma of "The Free Radical Theory of Aging" (17).

Recently, Hinerfeld and others reported results of an animal experiment wherein they observed a striking pattern of neuronal cell death as a result of mitochondrial oxidative stress, and were able to significantly reduce the loss of neurons via antioxidant treatment (18). It has also been shown that Alzheimer's fibroblast mitochondria have impaired calcium transport processes and show increased sensitivity to oxygenic free radicals (19). Some researchers, however, have found that oxidative damage occurs primarily within the cytoplasm rather than in mitochondria (20,21).

The accumulation of lipid peroxidation (LPO) products in the brains of patients with AD has been described (22). Oxidative damage to lipid, protein, and DNA is an important early event in the pathogenesis of AD (23).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed under physiological conditions and are removed by cellular antioxidant defense system. During oxidative stress their increased formation leads to tissue damage and cell death. This process may be especially important in the central nervous system (CNS) which is vulnerable to ROS and RNS damage as the result of high brain O_2 consumption, high lipid content, and relatively low antioxidant defenses, compared with other tissues. Recently, it has become more apparent that the RNS pathway is highly relevant to normal brain metabolism as well as neurodegenerative disorders (24,25). The interactions of RNS and ROS, their inter-conversions and the ratio of RNS/ROS could be important neural tissue injury mechanisms involved in the etiology and pathogenesis of AD, PD and schizophrenia (26).

Reactive oxygen species (ROS) are generated through the process of oxidation (i.e., the loss of hydrogen or one or more electrons to another atom or ion) by a variety of sources from the environment (e.g., photo-oxidations such as ozone and emissions) and normal cellular functions (e.g., mitochondrial metabolism and neutrophil activation). ROS include free radicals (e.g., superoxide and hydroxyl radicals), non-radical oxygen species (e.g., hydrogen peroxide and peroxynitrite) and reactive lipids and carbohydrates (e.g., ketoaldehydes, hydroxynonenal). Oxidative damage to DNA can occur by many routes including the oxidative modification of the nucleotide bases, sugars, or by forming crosslinks. Such modifications can lead to mutations, pathologies, cellular aging and death. Oxidation of proteins appears to play a causative role in many chronic diseases of aging including neurodegenerative diseases such as AD. Researchers have shown that: (a) cells from old individuals are more susceptible to oxidative damage than cells from young donors; (b) oxidative protein modification is not random; (c) some of the damage can be prevented by antioxidants, but there is an age-dependent difference; and (d) an age-related impairment of recognition and destruction of modified proteins exists (27).

It is now recognized that virtually every disease state involves some degree of oxidative stress (28). Accumulating data from experimental and human studies indicate that oxidative stress plays a major role in the pathogenesis of AD (29–32). It has even been shown that the enhancement of acetylcholinesterase (AChE) activity induced by Abeta (25–35) is mediated by oxidative stress, and that vitamin E can have an important role in the maintenance of acetylcholine synaptic levels, thus preventing or improving cognitive and memory functions of AD patients (33). The production of ROS can occur very early in the disease process, even before the appearance of beta-amyloid plaques and neurofibrillary tangles, leading to tissue damage via several different cellular pathways. Therefore, treatment with antioxidants might act to prevent propagation of tissue damage and improve both survival and neurological outcome.

Although not a uniformly consistent observation, researchers conducting a number of epidemiological studies have found a link between antioxidant intake and a reduced incidence of dementia, AD and cognitive decline in elderly populations (34). Researchers in one recent study lasting six years, for example, found that the use of antioxidative supplements or high intake of vitamin C along with vitamin E was associated with lower risk of AD (rate ratios were 0.82 and 0.82, respectively) (35). The authors concluded that a high dietary intake of vitamin C (i.e., more than 133 mg per day) and vitamin E (i.e., more than 15.5 mg per day) may lower the risk of AD.

However, other researchers, who also conducted a study of the relationship between the intake of antioxidant vitamins and the risk of AD, found no association between the risk of AD and either supplemental or dietary intake of carotenes and vitamins C and E (36). In a separate study of 2,459 middle-aged, Japanese-American men, Laurin and others concluded that midlife dietary intake of antioxidants does not modify the risk of late-life dementia (37).

A number of studies of peripheral markers of oxidative stress in Alzheimer patients have been done, often using the radical-trapping antioxidant potential (TRAP) test or the total antioxidant capacity (TAC) test; results have been mixed. Some researchers have found elevated levels of oxidative stress in AD patients, and lower levels of at least some antioxidants (38,39,40). However, other researchers have not found significant associations (41,42).

Although numerous studies show the importance of oxidative stress in the pathogenesis of AD, there are few studies of the role of reactive oxygen species (ROS) in Mild Cognitive Impairment (MCI). Researchers reported results from one such study, finding a marked decrease of the main components of the endogenous antioxidant defense system in patients with MCI (43). The authors noted that, since MCI represents a condition of increased risk for AD, use of antioxidants in MCI could be of importance for prevention. Rinaldi and others, reporting results from a similar study,

found that peripheral levels and activities of antioxidants were similarly lower in MCI and AD patients as compared to controls (44). These authors also noted that, as MCI may represent a prodromal stage of AD and oxidative damage appears to occur as one of the earliest pathophysiological events in AD, an increased intake of antioxidants in patients with MCI could be helpful in lowering the risk of conversion to dementia.

Researchers studying the association of oxidative stress with DNA damage have found an association with age and gender. Mendoza-Nunez and others found that there was a non-statistically significant trend with increasing age and DNA damage (45). With respect to gender, 64% of males and 38% of females had DNA damage with an odds ratio (OR) of 2.86. The authors concluded that the interaction of male sex factors and low levels of antioxidants would justify the use of antioxidant supplements. Results from another study revealed that mitochondrial oxidative stress was four times greater in males (46).

RESULTS

Acetyl-L-Carnitine (ALCAR)

Acetyl-L-carnitine (ALCAR), normally produced in mitochondria, is synthesized in the human brain, liver, and kidney. It facilitates the uptake of acetyl CoA into the mitochondria during fatty acid oxidation, enhances acetylcholine production, stimulates protein and membrane phospholipid synthesis, and may have other neurobiological effects as well. ALCAR, similar in structure to acetylcholine, also exerts a cholinomimetic effect. Some researchers have shown that ALCAR may be of benefit in treating numerous central and peripheral neuropathic conditions, including AD (47,48).

Dhitavat and others found that the oxidative stress, ATP depletion, and/or cell death that occurred after exposure of human neuroblastoma cells to beta-amyloid (Abeta) was attenuated by ALCAR (49). Other researchers have found similar results (50,51).

Brooks and others conducted a longitudinal, double-blind, parallel-group, placebo-controlled study of the effects of ALCAR on patients diagnosed with AD and found that ALCAR slowed the progression in younger subjects (less than 61 years of age), but not in older subjects (52). This study and other human studies are listed in Table 1.

The efficacy of ALCAR in mild cognitive impairment (MCI) and early AD was investigated by two different research groups performing separate meta-analyses, with one group finding an advantage for ALCAR over placebo (53), while the other group found no benefit (54). Some researchers have suggested that a combination of ALCAR and a cholinesterase inhibitor may be a useful therapeutic option in AD patients (55,56).

Aged Garlic Extract (AGE)

Extracts of fresh garlic that are aged over a prolonged period (6–18 months) to produce aged garlic extract (AGE) contain antioxidant phytochemicals (i.e., plant-derived chemicals) that prevent oxidant damage. Four compounds have been identified in AGE that are not present in raw garlic, including flavonoids (57). Flavonoids are a family of antioxidants found in fruits and vegetables as well as in beverages such as red wine and tea. In a mouse hippocampal cell model of oxidative stress, many, but not all, flavonoids were shown to protect primary neurons from glutamate toxicity as well as from five other oxidative injuries (58).

AGE exerts antioxidant action by scavenging ROS and enhancing cellular antioxidant enzymes. AGE inhibits lipid peroxidation, reducing ischemic/reperfusion damage and inhibiting oxidative modification of LDL, thus protecting endothelial cells from injury by oxidized molecules, which contribute to atherosclerosis. AGE protects DNA against free radical-mediated damage and mutations, inhibits multistep carcinogenesis and defends against ionizing radiation and UV-induced damage. Compelling evidence supports the beneficial health effects attributed to AGE, i.e., reducing the risk of cardiovascular disease, stroke, cancer and aging, including the oxidant-mediated brain cell damage that is implicated in AD (59).

A key mechanism in apoptosis is the activation of caspase-3. Caspase-3 catalyzes the formation of beta-amyloid peptide, and AGE has been shown to inhibit caspase-3 in a dose dependent manner (60). As a caspase-3 inhibitor, AGE may be effective in reducing apoptotic death of neurons since caspase inhibitors have been shown to inhibit neuronal cell death. Other researchers have found a variety of neuroprotective effects of AGE (61,62,63).

Alpha Lipoic Acid (LA)

Substantial evidence has been presented that the accumulation of beta-amyloid (Abeta)-derived peptides contributes to the etiology of AD by stimulating formation of free radicals. Because of this, the antioxidant alpha lipoic acid (AL), which is able to cross the blood-brain barrier, would seem an ideal substance in the prevention and/or treatment of AD. Numerous researchers have demonstrated neuroprotective effects of LA (64–67).

The effects on cognitive function, brain mitochondrial structure, and biomarkers of oxidative damage were studied after feeding old rats two mitochondrial metabolites, ALCAR and/or LA (68). Supplementation with ALCAR and/or LA improved memory, the combination being the most effective. Electron microscopic studies of the hippocampus showed that ALCAR and/or LA reversed age-associated mitochondrial structural decay. The authors concluded that feeding ALCAR and LA to old rats improves performance on memory tasks by

Table 1 Human Studies of Antioxidants and Alzheimer's Disease

Study Author(s); Reference; Date	Description	Number Subjects	Dose	Duration	Study Outcome	Overall Results
Acetyl-L-Carnitine (ALCAR)						
Brooks JO et al. (52); 1998	Probable AD outpts; DB, PC, R; 24 sites	334	1 gm tid	1 year	Slowed progression in pts. <age 61, but not in older pts.	Postitive
Montgomery SA et al. (53); 2003	2003 **meta-analysis** of DB, PC, R, Prospective pts. with MCI or early AD; 21 studies	1204	1.5–3.0 gm/day	3–12 months	Clear advantage over placebo on clinical scales & psychometric tests as well as the integrated summary effect. ALCAR was well tolerated.	**Postitive**
Hudson S et al. (54); 2003	2003 **meta-analysis** of DB, PC, R, Prospective pts. with AD; 7 studies (5 multicenter)	1078	1.5–3.0 gm/day	3–12 months	Benefits shown on CGI at 12 & 24 mos. but no evidence of benefit overall on CGI nor on other measures. Authors found "no evidence" to recommend ALCAR; no side effects noted.	**Negative**
Thal LJ et al. (55); 2000	DB, PC, R pts. with probable AD, 45–65	229	1 gm tid	1 year	No difference between groups	Negative
Bianchetti A et al. (56); 2003	open; mild AD pts. who hadn't responded to AChE-I; ALCAR added to AChE-I (donepezil or rivastigmine)	23	2 gm/day	3 months	Response rate was 38% after AChE-I Rx, and 50% after addition of ALCAR.	Postitive
Alpha lipoic acid (LA)						
Hager et al. (69); 2001	Open study of pts. with AD being treated with AChE-I, given LA	9	600 mg/day	1 year	MMSE and ADAScog stabilized, but study was small & not randomized.	Positive
Sauer et al. (71); 2004	Literature search for meta-analysis of LA in dementia	0	N/A	N/A	No DB, PC randomized trials exist (meta-analysis could not be performed).	Negative
Bacopa monniera (BM)						
Nathan PJ et al. (76); 2004	DB, PC, R study of healty subjects treated with BM & Ginkgo biloba	85	BM = 300 mg/day; GB = 120 mg/day	2 weeks & 4 weeks	No cognitive benefits in this short duration study in normal volunteers.	Negative
Curcumin (CC)						
Chainani-We N (84); 2003	Literature review of safety and anti-inflammatory potency of CC	137	1125 mg/day to 8000 mg/day	up to 22 months	CC found to be safe, even at high doses, in 6 human trials. CC found to have potent anti-inflammatory effects.	Positive
Ginkgo biloba extract (GBE; Egb 761)						
Kanowski et al. (94); 2002	DB, PC, R multicenter outpt. With mild to moderate AD or MID	205	240 mg/day	24 weeks	GBE improved cognitive function in a clinically relevant manner.	Positive
Mix JA et al. (95); 2002	DB, PC, R outpt. Cognitively intact adults	262	180 mg/day	6 weeks	Both objective, standardized neuropsychological tests & subjective results positive.	Positive
Birks J et al. (96); 2002	**Meta-analysis** included all unconfounded, DB, PC, R trials of people with acquired cognitive impairment, including dementia, of any severity; 33 studies	3278	80 to 600 mg/day; usually less than 200 mg/day	3 to 52 weeks; majority were 12 weeks	The published literature strongly supports the safety & potential benefits of GBE in treating memory loss and cognitive disorders associated with age-related dementias, but larger trial recommended.	**Positive**
van Dongen MC et al. (97); 2000	DB, PC, R, multicenter pts. with AD or MID, mild to moderate.	214	160 or 240 mg/day	24 weeks	No benefits found; no adverse reactions.	Negative
Huperzine A (HA)						
Bai DL et al. (127); 2000	Multicenter (15), DB, PC, R effects of HA in pts. with possible or probable AD.	202	400 mcgs/day	12 weeks	HA shown to remarkably improve cognition, behavior, ADLs, and mood; shown to be safe.	Positive
Xu SS et al. (128); 1999	Multicenter, DB, PC, R effects of HA in AD pts.	60	200 mcgs/day	60 days	HA safe and effective. Shown to reduce the pathological changes of oxygen free radicals in plasma & erythrocytes.	Postitive

(Continued)

Table 1 (Continued)

Melatonin (ML)						
Maurizi CP (143); 2001	Therapeutic trials (3) of ML in AD pts.	26+	1–9 mg/day	up to 3 yrs	ML resulted in improved functioning, decreased "sundowning," improved sleep, significant slowing of progression of AD.	Positive
Singer C et al. (144); 2003	Sleep study of AD pts. given ML	157	2.5 mg/day or 10 mg/day	1 year	No benefit found in improving sleep of pts. with AD.	Negative
Vitamins C & E (alone & combinations)						
Kontush A et al. (165); 2001	Studied levels of vit. E & C in CSF & plasma in AD pts. before & after supplementation	20	400 IU vit. E alone/day, or 400 IU vit. E & 1000 mg vit C/day	4 weeks	Supplementation increased levels of vits. E & C in plasma & CSF; vit. C alone & combination (but not vit. E alone) decreased lipoprotein oxidation. Combination was superior.	Positive
Morris MC et al. (166); 1998	Prospective study of people 65 or older comparing the use of vit. C & E	633	apx.200 – 800 IU vit. E/day; apx. 60 – 500 mg vit. C/day	4.3 years	91 pts. developed AD; but none of the 27 vit. E supplement users, and none of the 23 vit. C supplement users developed dementia.	Positive
Zandi PP et al. (167); 2004	Studied risk of developing AD in people 65 & older & use of vit. E & vit. C, multivits, or vit. b complex supplements	4740	400+ IU vit. E alone/day; 500+ mg vit. C alone/day, or both	3 years	Only combination of vits. C & E decreased risk.	Prevalence OR (adjusted): 0.22 (.05-.60); Incidence HR (adjusted): 0.36 (.09-.99)
Vitamin E						
Helmer C et al. (173); 2003	Prospective study of elderly people; risk of developing AD	626	N/A (only studied serum levels)	3 years	46 pts. developed dementia; those with low plasma vit. E at higher risk.	Postitive
Talbot N et al. (174); 2000	**Meta-analysis** of all DB, R trials where vit. E at any dose was compared to PB in pts. with AD	341	2000 IU vit. E/day	2 years	Only 1 study met criteria for inclusion. Authors concluded there was sufficient evidence of possible benefit to warrant further studies.	Postitive

Note: AD = Alzheimer's disease; DB = Double blind; R = random; PC = Placebo controlled; MID = Multi-infarct dementia; MMSE = Mini Mental Status Exam; OR = Odds ratio; CSF = Cerebral spinal fluid; IU = International units.

lowering oxidative damage and improving mitochondrial function.

Hager and others reported an open study of nine patients with AD and related dementias, who were receiving a standard treatment with acetylcholinesterase inhibitors, over an observation period of, on average, 337+/–80 days (69). Subjects were given 600 mg of LA daily. The treatment led to a stabilization of cognitive functions in the study group. Despite the fact that this study was small and not randomized, it is the first indication that treatment with LA might be a successful "neuroprotective" therapy option for AD and related dementias.

However, two reports have urged caution in using LA in dementia. In a study by Lovell and others the effects of LA and its reduced form, dihydrolipoic acid (DHLA), in neuron cultures treated with amyloid beta-peptide (Abeta 25–35) and iron/hydrogen peroxide (Fe/H_2O_2) were examined (70). Pretreatment with LA significantly protected against Abeta and Fe/H_2O_2 toxicity. In contrast, concomitant treatment with LA and Fe/H_2O_2 significantly potentiated the toxicity. Overall, the researchers concluded that the oxidation state of LA is critical to its function and that in the absence of studies of LA/DHLA equilibria in human brain, the use of LA as an antioxidant in disorders where there is increased Fe such as AD is of questionable efficacy.

Sauer and others attempted to conduct a meta-analysis of the use of AL in dementia, but could find no suitable trials to examine (71). The authors concluded that until data from trials become available for analysis, AL cannot be recommended for people with dementia.

Bacopa Monniera (BM)

As stress is linked to many diseases, research on effective anti-stress agents (referred to as "adaptogens") from plants has gained importance. Bacopa monniera (BM), an Ayurvedic medicinal plant clinically used for memory enhancement, epilepsy, insomnia and as a mild sedative in India, has been shown to be a potent adaptogen in a rat model of acute and chronic stress (72). Das and others reviewed the efficacy of both BM and Ginkgo biloba, which are well-known cognitive enhancers in Indian and Chinese traditional medicine systems, in mice (73). The researchers concluded that both extracts possess significant anticholinesterase and anti-dementia properties. Researchers conducting other animal experiments have also found beneficial effects (74,75).

In a randomized, double-blind, placebo-controlled, study of 85 healthy subjects, the sub-chronic (2 weeks) and chronic (4 weeks) effects of an extract containing Ginkgo biloba (120 mg) and Bacopa monniera (300 mg) on cognitive function were examined (76). As in many studies of putative cognitive-enhancing agents in healthy subjects, researchers conducting this study failed to demonstrate any benefit.

Co-enzyme Q10 (Ubiquinone; CoQ10)

CoQ10, which serves as the electron acceptor for complexes I and II of the mitochondrial electron transport chain and acts as an antioxidant, has the potential to be a beneficial agent in neurodegenerative diseases in which there is impaired mitochondrial function and/or excessive oxidative damage. Substantial data have accumulated to implicate these processes in the pathogenesis of certain neurodegenerative disorders, including PD, Huntington's disease and Friedreich's ataxia. Although no study to date has unequivocally demonstrated that CoQ10 can slow the progression of a neurodegenerative disease, recent clinical trials in these three disorders suggest that large doses (in the range of 1 gm or more per day) of supplemental CoQ10 can slow the functional decline in these disorders, particularly PD (77,78). CoQ10 could have similar effects in AD.

The oxidative modification of low density lipoprotein (LDL) is thought to play an important role in atherogenesis. Drugs of the beta-hydroxy-beta-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor family (commonly referred to as "statins") are used as lipid-lowering preparations, but they simultaneously block biosynthesis of both cholesterol and CoQ10. Antioxidants may be very effective in the prevention of atherogenic oxidative modification of LDL during HMG-CoA reductase inhibitor therapy (79). And, because statins block the endogenous production of CoQ10, at least to some degree, it can be argued that it makes sense to add exogenous CoQ10 when taking statin drugs.

Curcumin

The rhizomes (i.e., underground rootlike stems bearing both roots and shoots) of tropical ginger and turmerics (e.g., Zingiber and Curcuma spp.) contain curcumin, the yellow curry spice which has an extensive history as a food additive and herbal medicine throughout Asia, but especially India. It is a potent complexing agent for metal ions such as iron(III), and potent polyphenolic antioxidant. In addition, curcumin is a powerful anti-inflammatory agent, potentiates the anti-atherogenic effect of alpha-tocopherol (the most common isoform of vitamin E), and decreases total blood lipid peroxides as well as HDL- and LDL-lipid peroxidation (80). As noted previously, curcumin is also a strong inducer of the heat shock response.

Curcumin has specific anti-amyloidogenic effects, wherein it dose-dependently inhibits fAbeta formation from Abeta (1–40) and Abeta(1–42). In addition, it destabilized preformed fAbetas. Although the mechanism by which curcumin inhibits fAbeta formation from Abeta and destabilizes preformed fAbeta in vitro remains unclear, it could be a key molecule for the development of therapeutics for AD (81).

Epidemiological studies suggest reduced AD risk associated with long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Chronic treatment with ibuprofen has been shown to suppress inflammation and plaque-related pathology in an

Alzheimer transgenic mouse model, but can cause gastrointestinal, liver, and renal toxicity. One alternative NSAID is curcumin. Researchers compared the ability of curcumin and ibuprofen to protect against amyloid beta-protein (Abeta)-induced damage in rats and found superior results with curcumin (82). Other researchers have also demonstrated the protective effects of curcumin in an animal model of AD (83). These researchers concluded that, because of its low side-effect profile and long history of safe use, curcumin may find clinical application for AD prevention.

Chainani-Wu recently conducted a literature review in order to review the safety and anti-inflammatory activity of curcumin (84). Studies on the toxicity and anti-inflammatory properties of curcumin have included in vitro, animal, and six human studies, and no toxicity has been found. The human studies revealed some evidence of anti-inflammatory activity, and researchers conducting laboratory studies have identified fifteen different molecules involved in inflammation that are inhibited by curcumin, including cyclooxygenase 2 (COX-2).

Ferulic Acid

Ferulic acid is a little known compound with powerful antioxidant properties. In a recent in vitro study, Trombino and others evaluated the ability of ferulic acid to inhibit lipid peroxidation in rat liver microsomal membranes and ROS production in fibroblasts (85). They also compared its antioxidant efficiency with that of other antioxidants, such as alpha-tocopherol, beta-carotene, and ascorbic acid, either alone or in combination. The researchers found that ferulic acid acted as a potent antioxidant, and was, in fact, the most effective among the antioxidants tested. Synergistic interactions were observed when the compound was used in combination with the other antioxidants, suggesting that they can cooperate in preserving physiological integrity of cells exposed to free radicals.

Ginkgo Biloba Extract (EGb 761)

Ginkgo biloba comes from a single type of tree, a living fossil, the only remaining representative of its phylum; it contains chemical substances unknown in other living things. Although the seeds are most commonly employed in traditional Chinese medicine, in recent years standardized extracts of the leaves have been widely sold in Europe and as a dietary supplement in the United States. An extract of Ginkgo biloba (EGb 761), has been available in Europe as an herbal extract since the early 1990s. Ginkgo biloba and EGb 761 are currently used as symptomatic treatment for cerebral insufficiency that occurs during normal aging or which may be due to degenerative dementia, vascular dementia or mixed forms of both, and for neurosensory disturbances.

EGb 761 is purported to have many biochemical effects including:

1. direct effects against necrosis and apoptosis of neurons and improves neural plasticity,
2. acts as a free radical scavenger and an inhibitor of lipid peroxidation with nearly all reactive oxygen species,
3. maintains ATP content by protection of mitochondrial respiration and preservation of oxidative phosphorylation,
4. exerts arterial and venous vasoregulatory effects involving the release of endothelial factors and the catecholaminergic system,
5. regulates ionic balance in damaged cells,
6. exerts a specific and potent platelet-activating factor antagonist activity,
7. facilitates behavioral adaptation to stress and may decrease the excess of cortisol release to stress, and
8. shows a specific neuroprotective effects to hippocampal cells (86).

EGb 761 also reverses age-related losses in brain alpha 1-adrenergic, 5-HT1A (serotoinergic) and muscarinic receptors, protects against ischemic neuronal death, preserves the function of the hippocampal mossy fiber system, increases hippocampal high-affinity choline uptake, inhibits the down-regulation of hippocampal glucocorticoid receptors, enhances neuronal plasticity, and counteracts the cognitive deficits that follow stress or traumatic brain injury (87). Other researchers have noted its potent antioxidant properties and its beneficial effects on neuron degenerative diseases, including AD, by preventing chronic oxidative damage (88,89). It is thought to be a potent adaptogen, helping the organism cope with any number of stresses (90,91).

Numerous authors have concluded that ginkgo biloba appears to be a useful and sensible supplementary medication to treat AD (92–96). Some clinical studies of the use of EGb 761, however, have not shown a positive effect (97,98). In a variety of animal experiments, other researchers have determined that EGb 761 may benefit individuals with AD by affecting the release of amyloid precursor protein (APP) (99), by affecting the cholinergic system (100), by interaction with the glutamatergic system (101), and by directly protecting cells against Abeta toxicity (102). Taken together, these results and those obtained by other groups highlight the neuroprotective abilities of EGb 761 against dysfunction and death of neurons caused by Abeta deposits.

Although human experiments have not revealed significant side effects of EGb 761, because of its potent antiplatelet effect, it should not be used in patients on antiplatelet therapy, and used cautiously in people taking high doses (1000 mg or greater) of vitamin E or those using NSAIDs because of potential synergistic effects, which could result in bleeding.

Ginseng (Panax Ginseng C.A. Meyer)

Ginseng is a perennial herb native to Korea and China that has been used as an herbal remedy in eastern Asia for thousands

of years. There are at least five varieties of "ginseng"—Russian, Korean, Chinese, American, and Indian; the latter is actually an extract from the roots of *Withania somnifera*. Therapeutic claims refer to vitality, immune function, cancer, cardiovascular diseases, improvement of cognitive and physical performance and sexual function. In spite of its extensive use worldwide, it is often scoffed at by educated people and the medical profession, although this is changing. For example, there are now at least three reports in the literature supporting ginseng's ability to enhance libido and copulatory performance on par with sildenafil (103,104,105). Ginseng exerts antioxidative, antiinflammatory, and anti-tumor-promoting effects (106).

Researchers studied ginseng in senescence-accelerated mice and determined that it was able to attenuate the oxidative damage, suppression of the antioxidative defense system, and accumulation of lipid peroxidation that accompanies the aging process (107). Other researchers have demonstrated that ginseng is effective in protecting hippocampal cells against artificially-induced neurotoxicity (108). In another study, researchers found that ginseng was able to prevent the artificially induced disruption of hippocampal information processing in an animal model of diabetes (109).

The safety of ginseng was extensively reviewed by Coon and others who concluded that ginseng monopreparations are rarely associated with adverse events or drug interactions (110).

Green Tea

On a worldwide basis, only water surpasses the consumption of tea. Tea leaves are obtained from the plant *camellia sinensis* and, depending upon the fermentation process, are transformed into black, green, red, white, or oolong tea. Black tea represents approximately 78% of total consumed tea in the world, whereas green tea accounts for approximately 20% of tea consumed. Diseases for which tea drinkers appear to have lower risk are bacterial and viral infections, and chronic debilitating diseases, including cancer, coronary heart disease, stroke, and osteoporosis. For cancer prevention, evidence is so strong that the U.S. Chemoprevention Branch of the National Cancer Institute has initiated a plan for developing tea compounds as cancer-chemopreventive agents in human trials (111).

Various growth factors such as platelet derived growth factor (PDGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) transduce their mitogenic signals through the activation of tyrosine kinase receptors (RTKs). Researchers conducting cell culture and animal studies have shown that catechins, the main compounds of green tea leaves, are potent natural inhibitors of several RTKs (112).

In the course of searching for BACE1 (beta-secretase) inhibitors from natural products, the soluble fraction of green tea, which was suspected to be rich in catechin content, showed potent inhibitory activity (113).

The green tea polyphenol, epigallocatechin-3-gallate (EGCG), has been shown to be a potent anti-inflammatory, apoptotic and cancer chemopreventive agent (114). Researchers comparing the protective effects of EGCG and other well-known antioxidants (trolox—a vitamin E analog, lipoic acid, and melatonin) against experimentally induced oxidative stress in gerbil brain homogenates found that EGCG was the most potent (115). Other researchers studying the potential protective effect of ECGC on hippocampal neuronal cells exposed to Abeta found that EGCG has protective effects through scavenging ROS, which may be beneficial for the prevention of AD (116).

Both experimental and epidemiological evidence demonstrate that flavonoid polyphenols, particularly from green tea and blueberries, improve age-related cognitive decline and are neuroprotective in models of PD, AD and cerebral ischemia/reperfusion injuries. However, recent studies indicate that the radical scavenger property of green tea polyphenols is unlikely to be the sole explanation for their neuroprotective capacity and in fact, a wide spectrum of cellular signaling events may well account for their biological actions (117). Because tea extracts have been previously reported to possess radical scavenger, iron chelating and anti-inflammatory properties in a variety of tissues, researchers examined the potential neuroprotective effects of green tea and black tea extracts on brain mitochondrial membrane fraction, against iron-induced lipid peroxidation (118). The researchers found that both types of tea exhibited highly potent antioxidant-radical scavenging activities and were shown to attenuate the neurotoxic action. Neuroprotection was attributed to the potent antioxidant and iron chelating actions of the polyphenolic constituents of the tea extracts. The authors noted that the brain-penetrating property of polyphenols may make such compounds an important class of drugs for treatment of neurodegenerative diseases.

Oxidative stress has been implicated in vascular injury and atherogenesis, and antioxidant treatment has shown favorable results in preclinical studies. Despite this, antioxidant therapy has generally failed to show benefit in clinical trials. This may be partly because such therapy is started after atherosclerosis is already well established, whereas the benefits in animal models may result from early initiation of antioxidants while atherosclerosis is still evolving. Researchers addressed this issue in an animal model of dementia and found that EGCG differentially reduces evolving atherosclerotic lesions without influencing established atherosclerosis (119). By extension, this observation may also help explain the often negative or marginal results obtained in trials of antioxidants and AD. That is, these agents may not be effective once clinical symptoms are apparent, but may be effective in preventing AD if initiated early enough in the disease process.

Huperzine A (Hup A)

Hup A, a novel alkaloid originally discovered in the Chinese herb Qian Ceng Ta (club moss; *Huperzia serrata*), is a reversible,

potent, and selective acetylcholinesterase (AChE) inhibitor and has been extensively used for the treatment of AD in China. Huperzine readily crosses the blood-brain barrier and has a prolonged biological half-life. Apart from its potent AChE inhibitor activity, Hup A is now know to possess other beneficial mechanisms of action. For example, researchers investigated the effects of Hup A on amyloid beta-peptide fragment 25–35 (Abeta25–35)-induced neuronal apoptosis and potential mechanisms in primary cultured rat cortical neurons (120). Pretreatment of the cells with Hup A prior to Abeta25–35 exposure significantly increased cell survival and reduced Abeta25–35-induced nuclear fragmentation. Tests demonstrated that Hup A reduced ROS formation and attenuated caspase-3 activity in a dose-dependent manner. Other researchers have also shown that Hup A was able to protect neuronal and glial cells against the cytotoxicity of beta-amyloid (Abeta), and the researchers concluded that the neuroprotective properties of Hup A enantiomers have no relation to anti-cholinesterase activity (121). Still other researchers have also shown that Hup A had protective effects against free radical–induced cell toxicity (122,123). Tests confirm that Hup A can alleviate the cognitive dysfunction induced by intracerebroventricular infusion of beta-amyloid protein-(1–40) in rats (124). The researchers noted that the beneficial effects are not confined to the cholinergic system, but also include favorable changes in the expression of apoptosis-related proteins and in the extent of apoptosis in widespread regions of the brain.

Hup A has been shown to reduce glutamate-induced cell death and to be protective against organophosphate intoxication. Hup A is a non-competitive antagonist of NMDA receptors (125). Hup A has been shown to exert beneficial effects on memory deficits in various rodent and monkey models of amnesia (126).

Hup A has memory-enhancing activities. Compared to tacrine and donepezil, in clinical trials Hup A was shown to possess a longer duration of action and higher therapeutic index, and minimal peripheral cholinergic side effects at therapeutic doses (127). Several other research groups have also found positive results in AD patients (128,129).

Melatonin

Melatonin, which is a potent antioxidant, is a highly conserved molecule that not only exists in animals, but is also present in bacteria, unicellular organisms and in many plants. In a study of more than 100 Chinese medicinal herbs for the presence of melatonin, 64 contained melatonin in significant amounts (130).

This pineal hormone, which can readily pass through the blood-brain barrier, has two major functions: as a regulator of the circadian day-night cycle, and as a vasoactive substance regulating cerebral circulation. The vasoconstrictive effects of melatonin are thought to be mediated by melatonin 1a-receptors, and the density of these receptors has been shown to be increased in AD patients, possibly indicating a regulatory response to impaired melatonin levels in those patients (131).

A disturbed sleep-wake cycle is common in AD patients and correlated with decreased melatonin levels. The precursor of melatonin, serotonin has been shown to have a stepwise depletion during the course of AD, and melatonin has been found to be decreased in preclinical AD patients (132).

Melatonin has been shown to be a neuroprotective antioxidant. In experimental models of AD, melatonin was reported to have free radical scavenging and antioxidative properties, as well as anti-amyloidogenic effects (133,134). Melatonin is also capable of scavenging nitrogen-based reactants, stimulates endogenous antioxidative enzymes and also the enzymes that are involved in the synthesis of glutathione—an important antioxidant which is at high concentrations within cells, increases the efficiency of the electron transport chain thereby limiting electron leakage and free radical generation, and promotes ATP synthesis (135). Other actions include limiting cytokine production and inflammatory processes, and synergistic effects with other classical antioxidants (e.g., vitamins C, E and glutathione) (136). Via these mechanisms, melatonin preserves the integrity of the mitochondria and helps to maintain cell functions and survival. In AD, inadequate melatonin, which is normally concentrated in mitochondria, allows ROS to damage mitochondria and initiate a cascade of oxygen radicals that causes the neuropathological changes in AD.

Researchers have shown that melatonin is much more efficient than vitamin C in reducing the extent of oxidative stress and lipid peroxidation, and by the protective effect of melatonin on endogenous antioxidant enzyme activity (137). The protective effects of melatonin against cellular damage caused by aluminum-induced oxidative stress have been demonstrated (138). Researchers conducting experiments with other animal models of AD have shown melatonin to be neuroprotective (139–142).

Results from initial therapeutic trials of melatonin in AD patients have been mixed. One such trial demonstrated improved function, decreased “sundowning,” improved sleep, and significant slowing of the progression of the disease (143). However, researchers conducted another study, using 2.5 mg slow release or 10 mg of melatonin, and concluded that melatonin was not an effective soporific agent in people with AD (144). A group of patients with AD, who were exposed to music therapy 5 days a week over 4 weeks, were found to have sustained increases in their melatonin levels, even at the 6-week follow-up (145). The authors concluded that increased levels of melatonin following music therapy may have contributed to patients’ relaxed and calm mood. It is evident from in vitro experiments and clinical studies that melatonin has a neuroprotective role (146).

Polyphenolic Compounds

Polyphenolic compounds are present in high concentration in the skin from red grapes, from red grape seeds, and from red

wine. A consistent protective effect of wine consumption against AD has been documented by epidemiological studies. In addition, epidemiologic studies have revealed a reduced incidence of cardiovascular risk in consumers of red wine; this has been popularized as the "French paradox," given that the French eat a relatively high fat diet but have a low incidence of heart disease. The beneficial effects of wine are associated with the physiological protection conferred by phenolic compounds such as anthocyanins and resveratrol. A study of 19 Sicilian wines determined that the highest concentration of resveratrol was found in Merlot wine, and that the highest concentration of anthocyanins was found in Cabernet Sauvignon wine (147). Antioxidant capacity was also studied, and the results showed that the antioxidant capacity of wines is strictly related to the amount of phenolic compounds.

Resveratrol has been shown to attenuate beta-amyloid-induced cytotoxicity, apoptotic features, and intracellular ROS accumulation (148). Specifically, it has been shown to inhibit fAbeta formation from Abeta(1–40) and Abeta(1–42) and destabilize preformed fAbeta(1–40) and fAbeta(1–42) dose-dependently in vitro. Other researchers have documented the fact that Abeta and oxidized brain lipoproteins can synergistically enhance oxidative damage in neurons and antioxidants such as resveratrol can ameliorate these damages (149). Polyphenols could be a key molecule for the development of preventives and therapeutics for AD (150).

Researchers found significant protective effects of the polyphenols resveratrol, quercetin, and (+)-catechin against nitric oxide free radical donors in cultured rat hippocampal cells (151). Resveratrol also maintains cell viability and exerts an anti-oxidative action by enhancing the intracellular free-radical scavenger glutathione (152). In a cognitive model of AD in rats, researchers demonstrated the effectiveness of resveratrol in preventing the cognitive deficits as well as the oxidative stress in the treatment of neurodegenerative diseases such as AD (153).

Vitamin C

A large body of evidence shows that both vitamins E and C are important for the CNS and that a decrease in their concentrations causes structural and functional damage to the cells (154). A longitudinal analysis of cerebral spinal fluid (CSF) biomarkers of lipid peroxidation from patients with mild AD, showed that these markers: 1) were significantly increased in patients followed over one year, 2) correlated with some clinical indices of dementia, and 3) were significantly lower in patients who used both alpha-tocopherol and ascorbic acid (155). Free radical lipid peroxidation could initiate the chain polymerization of amyloid peptides found in AD. The onset of AD could be delayed if the initiation of free radical chain polymerization were inhibited or limited by nutrients that act as "chain terminators." Alpha-tocopherol, ascorbic acid and Co Q10 are chain terminators (156). Besides the presence of elevated levels of oxygen radicals, prostaglandins produced by neurones and microglial cells seem to play an important role in prolonged tissue damage. Vitamin C has also been shown to inhibit synthesis of prostaglandin E2 (PGE2) in a dose-dependent manner, and to augment the inhibitory effect of acetylsalicylic acid on prostaglandin synthesis as well (157). In addition, it has been shown that vitamin C can completely abolish Abeta-induced calcium increase and cell death in PC12 cells, indicating that calcium elevation and cell death are associated phenomena induced by Abeta that can be rescued by antioxidants (158). Vitamin C has shown promise as a powerful memory-improving agent particularly effective in aged animals (159).

Blood and cerebrospinal fluid (CSF) levels of vitamin C (and/or vitamin E) in AD patients, and the correlation with daily intake of these vitamins and the severity of dementia, have been studied extensively. Many researchers have found an association between plasma vitamin C and/or vitamin E levels and AD (160–163), but not all (164). Researchers conducting several studies have found that supplementation with both vitamin C and vitamin E is superior to supplementation with either vitamin alone in AD patients, and that antioxidant supplements merit further study as agents for the primary prevention of AD (165,166,167).

How much is enough? To answer this question, Polidori and others found that vitamin C supplementation in humans dose-dependently increases plasma vitamin C concentrations and, thus, the resistance of plasma to lipid peroxidation ex vivo, and that plasma and body saturation with vitamin C in humans appears desirable to maximize antioxidant protection and lower risk of oxidative damage (168). Their results indicated that approximately 1000 mg per day would accomplish this goal.

Vitamin E

When people think of vitamin E, they are usually thinking of alpha-tocopherol, the only isoform of vitamin E that is widely available in vitamin E supplements. However, there are eight isoforms and numerous biologically active metabolites of vitamin E. Recent discoveries have generated renewed interest in desmethyl tocopherols, such as gamma-tocopherol, and for specific tocopherol metabolites. The beneficial activities of these other tocopherols do not map directly to their antioxidant behavior but rather reflect anti-inflammatory, antineoplastic, and natriuretic functions possibly mediated through specific binding interactions. In addition, a nascent body of epidemiological data suggests that gamma-tocopherol is a better negative risk factor for certain types of cancer and myocardial infarction than is alpha-tocopherol. The potential public health implications are immense, given the extreme popularity of alpha tocopherol supplementation which can unintentionally deplete the body of gamma-tocopherol (169). Notably, trials of vitamin E in AD patients have used only the alpha isoform.

Researchers studying the effects of artificially induced oxidative stress, in a mouse hippocampal neuronal cell line, found that pretreatment with vitamin E prevented the oxidative damage (170). Studies using primary rat embryonic hippocampal neuronal cultures, coupled with electron microscopy, have revealed that vitamin E appears to exert its neuroprotective effects through the scavenging of Abeta-associated free radicals (171).

Increased brain oxidative stress is a key feature of AD and manifests predominantly as lipid peroxidation. However, clinical evidence that antioxidants can affect the clinical course of the disease is limited. In order to shed light on this seeming paradox, Sung and colleagues investigated the effect of vitamin E on a transgenic mouse model of AD, before or after amyloid plaques were deposited (172). Markers of lipid peroxidation were significantly reduced in both the group treated with vitamin E as well as the control group. However, the mice who received vitamin E at a younger age showed a significant reduction in Abeta levels and amyloid deposition. In contrast, mice receiving the diet supplemented with vitamin E at a later age did not show any significant difference in either Abeta levels or amyloid deposition when compared with placebo. The authors concluded that their findings support the hypothesis that oxidative stress is an important early event in AD pathogenesis, and antioxidant therapy may be beneficial only if given early in the course of the disease process.

A study by Helmer and others of 626 subjects, 46 of whom developed a dementia during follow-up, found that subjects with low plasma vitamin E concentrations are at a higher risk of developing dementia in subsequent years (173). Tabet and colleagues performed a meta-analysis of all double blind, randomized trials in which treatment with vitamin E at any dose was compared with placebo for patients with AD (174). Only one study was identified which met the inclusion criteria, and the authors found the published results difficult to interpret. However, they concluded that there is sufficient evidence of possible benefit to justify further studies.

As noted in the vitamin C section above, researchers concluded that the use of vitamin E and vitamin C supplements in combination is associated with reduced prevalence and incidence of AD, and that antioxidant supplements merit further study as agents for the primary prevention of AD (175).

Other Antioxidants from Asia

A number of Indian medicinal plants have been used for thousands of years in the Indian traditional system of medicine (Ayurveda). The part of the Ayurvedic system that provides an approach to prevention and treatment of degenerative diseases is known as *Rasayana*, and plants used for this purpose are classed as rejuvenators. This group of plants generally possesses strong antioxidant activity, but only a few have been investigated in detail (176).

There are perhaps thousands of plants with active phytochemicals used in Traditional Chinese Medicine (TCM), but only a few have been scientifically examined. Thirty-three TCM extracts were examined for their antioxidant activity, and five extracts were found to have high activity (177).

The Japanese also have a long history of the use of medicinal herbs, mushrooms, and phytochemicals. A Japanese herbal medicine termed "Kami-Umtan-To" (KUT) was first described in Japanese literature in 1626; KUT consists of 13 different herbs, and it has been used for a long time in the treatment of a variety of neuropsychiatric problems including neurosis and insomnia. Arai and colleagues examined the ability of KUT to slow the progression of AD, in a 12-month open trial of KUT and the combination of estrogen, vitamin E and NSAID (178). The rate of cognitive decline was significantly slower in the KUT group and the combination group as compared to the control group.

DISCUSSION

Knowledge about the pathophysiology of Alzheimer's disease (AD) is rapidly evolving, as is our knowledge of the benefits of antioxidants in the prevention of diseases such as heart disease, cancer, arthritis, and neurodegenerative disorders such as PD and AD. On balance, well designed clinical studies of antioxidants and AD are limited. What studies do exist often have diametrically opposed results. In addition, a significant problem with many of the intervention studies of antioxidants, vitamin E, for example, is that they have been conducted on patient populations who already have AD or some other form of dementia. This makes it difficult to assess the full potential of the substance in question to help prevent AD. In addition, antioxidants have been most frequently tested as single agents, while it is becoming clearer that, in many instances, combinations of antioxidants are more effective.

Numerous authors have found a scientific basis for the use of multiple antioxidants in the prevention of neurodegenerative disorders (179,180,181). However, *proving* that combinations of potential treatments are clinically effective is extremely expensive and time consuming. Saver, for example, noted that in order to test just seven combinations of potential treatments for AD would yield 127 trials (182). According to Saver, hierarchical, serial clinical trials would permit identification of the optimum combination of these agents through 127 trials, enrolling 63,500 patients, requiring 286 years for AD. The author concluded that marked limitations in the ability of clinical trials to elucidate varied treatment combinations to determine the most effective ensemble exist, and their scope is widely underappreciated. This practical problem needs to be kept in mind as we review possible prevention strategies for AD, and the associated demands for "proof" from evidence-based medicine, especially in light of the fact that, for the most part, patent protection is unattainable and therefore, few

resources are available for the scientific study of "alternative" treatments.

In general, a healthy lifestyle involving regular exercise and avoidance of tobacco or alcohol abuse is the key to the prevention of several age-related diseases including cardiovascular diseases, cancer and dementia. Staying mentally active has also been found to help maintain mental acuity (183,184,185). A balanced diet with at least five portions of fruits and vegetables per day is a critical constituent of such a healthy lifestyle (186). Unfortunately, in spite of years of encouragement to consume five portions (or more) of fruits and vegetables each day, Centers for Disease Control and Prevention (CDC) surveys clearly demonstrate that more than 75% of people in all age groups never meet this goal (percent meeting goal: in 1996, 23.6%; 1998, 23.8%; 2000, 23.1%; and in 2002, 22.6%) (187).

On the other hand, many—but not all—epidemiological studies have shown that individuals who do consume larger amounts of fruits and vegetables, as well as those who use vitamin supplements, have lower rates of AD. Combinations of vitamins with antioxidant properties, like vitamin C and vitamin E, have shown the greatest benefit.

Well designed prospective clinical studies of antioxidants and AD are very limited. What studies do exist often have diametrically opposed results. For example, in the case of acetyl-L-carnitine (ALCAR), one recent meta-analysis by Montgomery and others (53) found a clear advantage over placebo, while another recent meta-analysis by Hudson and others (54) found "no evidence" to recommend ALCAR.

A significant problem with many of the intervention studies of antioxidants, vitamin E, for example, is that they have been conducted on patient populations that already have AD or some other form of dementia. It would seem more useful, albeit more difficult and costly, to conduct prospective trials on adults without any signs of dementia, or those with mild cognitive impairment (MCI), over long periods of time. It is known, for example, that green tea may help prevent prostate cancer, but is of limited use in treating prostate cancer.

CONCLUSION

While the clinical value of these agents for prevention of AD is often ambiguous, and will remain so until properly designed human trials have been performed, some of these agents can be recommended based upon: 1) epidemiological evidence, 2) known benefits for prevention of other maladies, and 3) the benign nature of the substance. Agents that fall into this category include: 1) aged garlic extract (AGE), 2) curcumin, 3) melatonin, 4) resveratrol, 5) Ginkgo biloba extract, 6) green tea, and 7) vitamins C & E.

The remainder of the substances reviewed in this analysis must be placed in the category of intriguing, but have data that is too conflicting or too limited to recommend them. These include: 1) acetyl-L-carnitine, 2) alpha lipoic acid, 3) Bacopa monniera, 4) ferulic acid, and 5) Ginseng. Huperzine A falls into a special category because of its potent acetylcholinesterase (AChE) inhibiting property. There is good clinical evidence of its efficacy, but it should probably be used for the treatment of AD rather than its prevention.

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