JN THE JOURNAL OF NUTRITION

Significance of Garlic and Its Constituents in Cancer and Cardiovascular Disease

Garlic Reduces Dementia and Heart-Disease Risk[1,2]

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ABSTRACT Risk factors for cardiovascular disease, including high cholesterol, high homocysteine, hypertension and inflammation, increase the risk of dementia, including its most common form, Alzheimer's disease (AD). High cholesterol is also associated with elevated β-amyloid (Abeta), the hallmark of AD. Oxidative damage is a major factor in cardiovascular disease and dementia, diseases whose risk increases with age. Garlic, extracted and aged to form antioxidant-rich aged garlic extract (AGE or Kyolic), may help reduce the risk of these diseases. AGE scavenges oxidants, increases superoxide dismutase, catalase, glutathione peroxidase, and glutathione levels, and inhibits lipid peroxidation and inflammatory prostaglandins. AGE reduces cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase and is additive with statins in its action. Inhibition of cholesterol, LDL oxidation, and platelet aggregation by AGE, inhibits arterial plaque formation; AGE decreases homocysteine, lowers blood pressure, and increases microcirculation, which is important in diabetes, where microvascular changes increase heart disease and dementia risks. AGE also may help prevent cognitive decline by protecting neurons from Abeta neurotoxicity and apoptosis, thereby preventing ischemia- or reperfusion-related neuronal death and improving learning and memory retention. Although additional observations are warranted in humans, compelling evidence supports the beneficial health effects attributed to AGE in helping prevent cardiovascular and cerebrovascular diseases and lowering the risk of dementia and AD. J. Nutr. 136: 810S–812S, 2006.

KEY WORDS: • *garlic* • *aging* • *antioxidants* • *cholesterol* • *neuroprotection*

Recent evidence suggests that midlife risk factors for cardiovascular disease, such as high cholesterol, hypertension, high homocysteine, and inflammation, are important risk factors for dementia in later years (1–5), with high cholesterol and hypertension showing a consistent association with increased risk of Alzheimer's disease (AD)[4] and vascular dementia, pathological conditions whose frequency increases with age.

High cholesterol levels promote the formation of atherosclerotic plaques that are risk factors for both heart attacks and stroke, in the latter case the resulting ischemia may result in neuronal death and lead to dementia. High cholesterol is also associated with increased levels of free-radical–producing β-amyloid peptides (Abeta), the hallmark of AD. Hypertension may contribute to cognitive decline seen in AD by causing cerebral small-vessel pathology and increasing the number of neurofibrilar tangles and amyloid plaques. Small-vessel disease resulting from hypertension may be associated with the observed atrophy of the hippocampus and amygdala in AD (6).

Elevated plasma homocysteine (hyperhomocysteinemia) is an independent risk factor for cardiovascular disease, stroke, and dementia, including AD (7,8). Studies on people 65 y and older and on young people ages 4–18 show that plasma levels of homocysteine increase progressively with age, posing a serious threat for these diseases in aging individuals. Hyperhomocysteinemia is caused largely by deficiencies in vitamins B-6, B-12, and folate. The adverse vascular and neurotoxic effects of homocysteine are associated with oxidant stress;

[1] Published in a supplement to *The Journal of Nutrition*. Presented at the symposium "Significance of Garlic and Its Constituents in Cancer and Cardiovascular Disease" held April 9–11, 2005 at Georgetown University, Washington, DC. The symposium was sponsored by Strang Cancer Prevention Center, affiliated with Weill Medical College of Cornell University, and Harbor-UCLA Medical Center, and co-sponsored by American Botanical Council, American Institute for Cancer Research, American Society for Nutrition, Life Extension Foundation, General Nutrition Centers, National Nutritional Foods Association, Society of Atherosclerosis Imaging, Susan Samueli Center for Integrative Medicine at the University of California, Irvine. The symposium was supported by Alan James Group, LLC, Agencias Motta, S.A., Antistress AG, Armal, Birger Ledin AB, Ecolandia Internacional, Essential Sterolin Products (PTY) Ltd., Grand Quality LLC, IC Vietnam, Intervec Ltd., Jenn Health, Kernpharm BV, Laboratori Mizar SAS, Magna Trade, Manavita B.V.B.A., MaxiPharm A/S, Nature's Farm, Naturkost S. Rui a.s., Nichea Company Limited, Nutra-Life Health & Fitness Ltd., Oy Valioravinto Ab, Panax, PT. Nutriprima Jayasakti, Purity Life Health Products Limited, Quest Vitamins, Ltd., Sabinco S.A., The AIM Companies, Valosun Ltd., Wakunaga of America Co. Ltd., and Wakunaga Pharmaceutical Co., Ltd. Guest editors for the supplement publication were Richard Rivlin, Matthew Budoff, and Harunobu Amagase. *Guest Editor Disclosure:* R. Rivlin has been awarded research grants from Wakunaga of America, Ltd. and received an honorarium for serving as co-chair of the conference; M. Budoff has been awarded research grants from Wakunaga of America, Ltd. and received an honorarium for serving as co-chair of the conference; and Harunobu Amagase is employed by Wakunaga of America, Ltd.

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[4] Abbreviations used: AD, Alzheimer's disease; AGE, aged garlic extract; Abeta, β-amyloid ; SAC, S-allylcysteine.

homocysteine impairs DNA repair in the hippocampus, sensitizing neurons to amyloid toxicity (9).

Reactive oxygen species. Reactive oxygen species and oxidant stress are implicated in cardiovascular disease, cancer, and various forms of dementia including AD (10). Oxidative damage to DNA, proteins, lipids, and other molecules rank high as a major cause in the onset and development of these diseases. Reactive oxygen species, including free radicals, are by-products of normal metabolism and increase during infection and inflammation, hyperhomocysteinemia, and exposure to exogenous sources, including nitrous oxide metabolite pollutants, smoking, certain drugs (e.g., acetaminophen), and radiation.

Oxidative modification of LDL cholesterol increases the risk of atherosclerosis, cardiovascular, and cerebrovascular disease. Free radical–producing Abeta triggers neuronal apoptosis, increasing the risk of brain atrophy and dementia, including AD, its most common form (11).

Garlic antioxidants. Garlic ranks highly among foods that help prevent disease, largely due to its high content of organosulfur compounds and antioxidant activity. Fresh garlic, however, may cause indigestion, and its pungent odor that lingers on the breath and skin can be a social deterrent. These disagreeable effects of fresh garlic are due to allicin, an oxidant released upon cutting or chewing the clove.

Aged garlic extract. An alternative source of garlic that is odorless and rich in antioxidants is aged garlic extract (AGE) (12,13). The well-standardized and highly bioavailable supplement is produced by prolonged extraction and aging of organic fresh garlic at room temperature. The process converts unstable compounds, such as allicin, to stable substances and produces high levels of water-soluble organosulfur compounds that are powerful antioxidants. These include S-allylcysteine (SAC), AGE's major component, and S-allylmercaptocysteine, unique to AGE. Among other compounds present are low amounts of oil-soluble organosulfur compounds, flavonoids, a phenol, allixin, selenium, and saponins.

AGE and cardiovascular disease. AGE has been shown to modulate cardiovascular risk factors in both clinical and preclinical settings (14–23). AGE has been shown to reduce blood pressure, inhibit platelet aggregation and adhesion, lower LDL and elevate HDL cholesterol, reduce smoking-related oxidative damage, inhibit the production of prostaglandins involved in inflammation, and lower homocysteine. SAC has been found to lower cholesterol by deactivating 3-hydroxy-3-methylglutaryl-CoA by as much as 41% (15). AGE efficacy in reducing cholesterol synthesis is additive with statins, which inhibit 3-hydroxy-3-methylglutaryl-CoA reductase at a transcriptional level. Other possible contributors to protection against cardiovascular disease and dementia are the effects of AGE in increasing microcirculation (21) and protecting endothelial cells from oxidative damage, a factor most important in diabetes where the microvasculature is damaged, and the risk of dementia is high. AGE can also temporarily increase, by 30–40% (23), the synthesis of constitutive nitric oxide, a protective factor against myocardial ischemic or reperfusion injury, risk factors in cardiovascular disease and dementia following stroke (24). AGE has been found to inhibit the progression of coronary-artery calcification (25), thus reducing the risk of a myocardial infarct.

AGE and the heart-dementia risk link: neuroprotective effects. The broad range of cardiovascular protection afforded by AGE may be extended to a protective effect on the brain, helping reduce the risk of dementia, including vascular dementia and AD. AGE has potential to protect the brain against neurodegenerative conditions. Mechanisms include lowering cholesterol, inhibiting inflammation, reducing homocysteine, preventing oxidative brain injury following ischemia, protecting neuronal cells against apoptosis (a programmed cell suicide triggered by oxidative stress) by inhibiting caspase 3, and preventing Abeta-induced neurotoxicity.

Homocysteine. People with cardiovascular risk factors and a history of strokes have an increased risk of both vascular dementia (arteriosclerotic dementia), which can occur after a stroke, and AD, the most common form of progressive dementia, accounting for over 70% of all cases.

Elevated homocysteine damages endothelial cells that line blood vessels and induces thrombosis that can lead to heart attacks and stroke. Homocysteine produces breaks in DNA and induces apoptosis, a major cause of neuronal death in dementia (7–9). The link between high levels of homocysteine and dementia, including AD, has been observed in epidemiological studies and confirmed in case-control studies, where people with vascular dementia and AD had higher levels of homocysteine than healthy people. A recent study (7) provided compelling evidence of a direct link between increased plasma homocysteine and loss of cognition, showing that in adults with intact cognition, an elevation in plasma homocysteine, over time, is associated with an increased incidence of dementia, including AD.

Consumption of AGE has been shown to reduce homocysteine levels. In a preclinical study, levels of homocysteine in a 4-wk folate-deficient diet containing AGE were compared with a folate-fortified diet containing AGE. Plasma homocysteine was 30% lower in the folate-deficient animals that received AGE, but not in those with adequate folate. The results suggest that AGE may serve as an added treatment in hyperhomocyteinemia (26). A clinical study, showing that AGE inhibits the progression of coronary artery calcification, also showed a trend in lowering homocysteine levels (25).

Protection against ischemic or reperfusion adverse effects. Single ischemic or thromboembolic infarcts that occur in strategic areas of the brain hemispheres may cause a dementia-like syndrome; multiple temporally staggered small cerebral infarcts can give rise to progressive cognitive deficits and dementia. Areas of the brain supplied by small penetrating arterioles are especially prone to degenerative changes in patients with hypertension and diabetes. Ischemia followed by reperfusion results in an increased production of free radicals and oxidant stress that may lead to neuronal death by apoptosis and contribute to the development of dementia following stroke.

AGE has been shown to lower blood pressure and protect brain cells from the deleterious effects of ischemia, increasing their survival. The high antioxidant level in AGE helps prevent the oxidant damage that occurs during ischemia or reperfusion. The protective effects of AGE were observed in a preclinical study of ischemia, and the findings showed that treatment with SAC attenuated damaging reactive oxygen species and prevented brain injury, reducing infarct volume. None of the lipid-soluble compounds tested had a protective effect (27). SAC prevented neuronal death following ischemia and increased cell survival in the hippocampus, the memory region of the brain, by 30%, compared with controls (28).

Preventing neuronal apoptosis. The brain of an individual with AD exhibits extracellular plaques of aggregated Abeta, intracellular neurofibrillary tangles that contain hyperphosphorylated tau protein and a loss of forebrain cholinergic neurons that enervate the hippocampus and the neocortex. The accumulation of Abeta may trigger or contribute to neurodegeneration. Neuronal apoptosis, one of the characteristics of Alzheimer's disease, is associated with Abeta. Reactive oxygen species produced by Abeta are thought to play a role in the apoptotic mechanism of Abeta-mediated neurotoxicity.

Several routes lead to apoptotic cell death; a major route is through a mitochondrial- dependent pathway that results in the release of cytochrome C, followed by the activation of caspases, with caspase-3 leading cells to their death (29). AGE and SAC have been shown in a number of in vitro studies to protect neuronal cells against Abeta toxicity and apoptosis (30–34). In one of the studies, PC12 cells exposed to Abeta showed a significant increase in reactive oxygen species. Treatment with AGE and SAC suppressed the generation of reactive oxygen species and also attenuated caspase-3 activation and DNA fragmentation, associated with apoptosis, and protected the cells against Abeta-induced apoptosis. In another study AGE was found to inhibit caspase-3 in a dose-dependent manner (33).

Caspase-3 catalyzes the formation of Abeta peptide (34) and is activated by Abeta (35). Their neurotoxic effects, however, appear to be independent; that is, in the presence of specific caspase inhibitors, Abeta-induced neuronal death still occurred with different morphological features (35). The findings that AGE can inhibit Abeta toxicity, attenuate caspase-3 activation, and inhibit apoptosis enhances the potential of AGE as a neuroprotector against AD.

Other anti-aging neuroprotective effects. Preclinical studies in models that are genetically prone to early aging show that AGE has additional anti-aging effects (36,37). Treatment with AGE or SAC prevented the degeneration of the brain's frontal lobe, improved learning and memory retention, and extended life span. Isolated neurons from the hippocampus area, grown in the presence of AGE or SAC, showed an unusual ability to grow and branch, which may be linked to the findings that AGE increases learning and cognition (37).

DISCUSSION

An accumulating body of evidence points to a heart-dementia risk link. Risk factors for cardiovascular disease and dementia include high cholesterol, hypertension, high homocysteine, inflammation, and oxidative stress, that, when occurring in the brain following ischemic or increased levels of Abeta peptides, result in neuronal apoptosis that can lead to dementia including Alzheimer's disease.

In clinical and preclinical studies, AGE, an odorless form of garlic that is rich in bioavailable water-soluble organosulfur compound, and has a higher antioxidant activity than fresh garlic with none of its adverse effects, has been found to protect against a wide range of risk factors that are common to cardiovascular disease and dementia. Although more clinical studies are warranted, available evidence supports the potential benefits of garlic in the form of Kyolic AGE in helping to reduce risk factors for cardiovascular and cerebrovascular diseases and dementia, including AD.

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