Health and Anti-Aging Benefits of Aged Garlic Extract
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Introduction
Garlic has been used as a medicinal remedy since antiquity to treat maladies as well as prevent disease and enhance vigor. Modern science and medicine have validated many of the traditional uses of garlic and identified its health-promoting compounds. Most of the benefits of garlic are attributed to its high content of organosulfur compounds and antioxidant activity, which protect against oxidative damage by reactive oxygen species (ROS) and offer other beneficial effects.\(^1\)\(^2\)\(^3\)\(^4\)

Reactive Oxygen Species
Reactive oxygen species (ROS) that include free radicals are produced internally in cells during energy production and increase during inflammation. Exposure to external sources of ROS comes from exposure to pollutants, cigarette smoke, radiation, some medicinal drugs, and charcoal-broiled food.\(^5\) Oxidative damage to DNA, proteins, and lipids affect a wide range of metabolic events that can trigger and/or exacerbate cardiovascular diseases, neurodegenerative diseases, including Alzheimer's disease, cancer, and other age-related conditions.\(^6\) Oxidative damage increases with age,\(^7\) as do oxidative stress and fatigue.\(^8\)

Garlic and Aged Garlic Extract
The best way to combat ROS-mediated aging and age-related diseases is to have a diet rich in antioxidants, including phytochemicals with antioxidant activity.\(^1\)\(^5\)\(^9\) Garlic is one of the most potent naturally occurring sources of antioxidant/phytochemicals. Yet many people avoid fresh garlic because of its lingering pungent odor, due to volatile allicin that is produced upon cutting or macerating the bulb. Another deterrent is the ability of allicin and the lipid soluble compounds produced from allicin, by a cascade of reactions, to cause gastrointestinal disorders.\(^\)\(^3\)

Enter odorless aged garlic extract (Kyolic), with high antioxidant activity and health benefits that are as effective or even more so than those of fresh garlic.\(^1\)\(^4\) Aged garlic extract (AGE) is manufactured by Wakunaga, by extraction and aging of organic fresh garlic for over 20 months. The aging produces a rich content of water-soluble stable organosulfur compounds such as S-allyl cysteine (SAC) and S-allyl mercaptocysteine (SAM) (unique to AGE), allixin, and
S-allyl cysteine, the most abundant organosulfur compound in AGE, has a 98% bioavailability (i.e., it is readily absorbed from the intestine to the circulation) and provides most of AGE's health benefits; SAC is used for standardization of AGE. Aged garlic extract is the chosen form of garlic in studies to determine the medicinal benefits of garlic; AGE is manufactured under high quality control and contains "a standardized amount of SAC that can be measured in the blood to monitor compliance." In well over 400 scientific publications, AGE has been shown to counteract oxidative stress more effectively than fresh garlic and help prevent cardiovascular disease, cancer, and neuronal death that leads to neurodegenerative diseases such as Alzheimer's disease. AGE also boosts immunity, protects against events linked to diabetes, prevents radiation and drug toxicity, and acts as an anti-aging supplement helping prevent fatigue and increase endurance. Preclinical studies show the potential of AGE to increase memory, learning, and longevity in senescence-prone models. This article reviews the effects of AGE in preventing age-related diseases and aging, updating information on the benefits of AGE that were discussed in an earlier Townsend Letter article.

Antioxidant Activity of AGE

Besides the major watersoluble organosulfur compounds S-allyl cysteine and S-allyl mercaptocysteine that have powerful antioxidant activity, AGE contains other antioxidants including allisin and small amounts of selenium. In addition, AGE increases cellular levels of glutathione (GSH), one of the body's most important intracellular antioxidants. In addition to playing a central role in quenching free radicals, glutathione protects against cataract formation, enhances immune function, acts as a detoxifying agent preventing drug toxicity, prevents DNA damage that can lead to cancer, and aids in the elimination of heavy metals. Glutathione levels can quickly be depleted when the body is exposed to high levels of oxidative stress during times of illness, infection, trauma, or surgery. Thus, intake of AGE and the potential increase in glutathione provide additional antioxidant protection in disease prevention.

AGE and Cardiovascular Disease

Aged Garlic Extract has been shown to modulate cardiovascular risk factors in both clinical and preclinical settings. AGE has been shown to lower blood pressure, inhibit platelet aggregation and adhesion (thus helping prevent blood clots), reduce LDL cholesterol (the bad cholesterol), and elevate HDL (the protective cholesterol); AGE prevents LDL oxidation that is an exacerbating factor in athrogenesis. S-allyl cysteine inhibits the cholesterol synthesizing enzyme HMA-CoA reductase by 30-40%, with an additive effect with lipid-lowering statins. AGE intake is safe for patients on medical treatment with the anticoagulant warfarin (coumadin), as shown in a randomized, double-blind, placebo-controlled clinical trial. AGE has been found to reduce smoking-related oxidative damage and inhibit the production of prostaglandins that are involved in inflammation, shown to be a major culprit in cardiovascular disease (CVD), neurodegenerative diseases, and other age-related conditions. AGE reduces levels of homocysteine, a risk factor for CVD as well as for dementia. In addition, AGE reduces the levels of nuclear factor kappa B, which are involved in oxidation and inflammation linked to atherosclerosis.

AGE, Microcirculation, and Endothelial Function

AGE has been shown to increase blood flow, including microcirculation, and protect endothelial cells (cells that line blood vessels) from oxidative damage; improved microcirculation is most important in cases of diabetes where the microvasculature is damaged, increasing the risk of CVD as well as neurodegeneration. AGE also increases the production of an endothelial-relaxing factor cellular nitric oxide that improves endothelial function and helps reduce hypertension. In a randomized, double-blind, placebo-controlled trial, 15 men with coronary artery disease were treated with 2.4 grams of AGE a day for two weeks, or placebo. AGE treatment resulted in a 44% increase in endothelium function (dilation and increased blood flow), compared to placebo, indicating that a short-term treatment with AGE can improve impaired endothelial function in men with coronary artery disease treated with aspirin and a statin.

AGE has been found to inhibit the progression of coronary artery calcification, thus reducing the risk of heart attacks. Coronary calcification, is nearly 100% specific for atherosclerotic plaques. Twenty-three patients, who were at high risk for heart disease, received either 1200 mg/day AGE, for one year, or a placebo. As all patients were on statin and aspirin therapy, any improvement seen under the influence of AGE would be an additional benefit to the statin treatment. Using a non-invasive, electron-beam-computed tomography to measure calcification, the investigators found that in patients on placebo, coronary artery plaques progressed at a rate of 22% a year.
while the addition of AGE to the diet reduced progression to 7.5%. AGE elevated HDL and decreased LDL and triglycerides, as well as homocysteine, as compared to placebo.\textsuperscript{14}

\textbf{AGE and the Heart-Dementia Risk Link}

Recent evidence suggests that mid-life risk factors for cardiovascular disease, such as high levels of cholesterol, hypertension, high homocysteine, and inflammation, are important also risk factors for forms of dementia, including Alzheimer disease (AD) and vascular dementia, which increase with age.\textsuperscript{1,5,9}

\textbf{High Cholesterol and Hypertension}

High cholesterol and atherosclerosis that are high risk for CVD increase the risk of embolism and stroke (ischemic stroke), when neurons die as they are deprived of oxygen and nutrients; exposure to ROS formed when oxygen is replenished (reperfusion) puts neurons at further risk of death, increasing the risk of dementia.\textsuperscript{9} High cholesterol is also linked to increased ROS-producing [beta] amyloid peptides (Abeta) in the brain, the hallmark of Alzheimer's disease. Hypertension is another risk factor for AD, linked to the degeneration (atrophy) of the hippocampus, the center of learning and memory, and the amygdala.\textsuperscript{9}

AGE has been shown to protect against the consequences of ischemia and reperfusion\textsuperscript{1,9} and reduce hypertension.\textsuperscript{12} Recent preclinical studies show that AGE lowered blood pressure and increased flexibility of the arteries, increasing the levels of blood vessel-relaxing factor nitric oxide more than raw garlic.\textsuperscript{17} The reduction of hypertension by inhibiting atherosclerosis and increasing blood vessel relaxation and circulation may serve well in protecting the heart and the brain, preventing brain atrophy that leads to AD.\textsuperscript{9}

\textbf{AGE and Homocysteine}

Elevated plasma homocysteine (hyperhomocysteinemia) increases the risk of CVD\textsuperscript{11,25} and is an independent risk factor for stroke and dementia, including AD.\textsuperscript{9} Plasma levels of homocysteine increase progressively with age, posing a serious threat to aging individuals. The adverse vascular and neurotoxic effects of homocysteine are associated with oxidant stress; homocysteine impairs DNA repair in the hippocampus, sensitizing neurons to toxicity by the amyloid beta peptides that are linked to AD.\textsuperscript{9}

Hyperhomocysteinemia is caused largely by deficiencies in folate and vitamins B6 and B12. AGE can prevent hyperhomocysteinemia in folate deficiency, protecting against the damaging effects of homocysteine. While the antioxidant effects of AGE can protect against ROS damage produced by homocysteine,\textsuperscript{1,2} AGE is now reported to elevate plasma and liver folate levels in folate deficiency and play an important role in the enzymatic reactions that reduce homocysteine by converting it to methionine.\textsuperscript{26}

\textbf{AGE and Brain Function}

Alzheimer's disease is associated with extracellular plaques of aggregated [beta]-amyloid protein (Abeta), intracellular neurofibrillary tangles containing tau protein, and a loss of neurons in the hippocampus and other areas of the brain. ROS produced by Abeta are thought to play a role in neuronal death by programmed cell suicide (apoptosis) leading to neurodegenerative conditions.\textsuperscript{9}

AGE and SAC have been shown in a number of studies to protect against Abeta toxicity and cell death.\textsuperscript{28-36} Neurons exposed to Abeta showed a significant increase in ROS. Treatment with AGE and SAC suppressed the generation of the ROS and inhibited the enzymes caspases 3 and 12 that are critical in inducing cell death by apoptosis.\textsuperscript{30-32}

The potential of AGE as a potential protector against AD was further shown in a recent preclinical study, using an AD model. Researchers found that AGE and SAC protected the brain against AD-associated events, with AGE being the more effective in preventing beta amyloid peptides, neurofibrillar tangles composed of abnormal tau protein, and inhibiting inflammation.\textsuperscript{33}

\textbf{Other Anti-Aging Neuroprotective Effects}

Preclinical studies in models that are genetically prone to early aging show AGE or SAC prevented frontal lobe degeneration associated with aging; improved learning; and memory retention; extended life span; and enhanced the growth and branching of neurons from the hippocampus area, the brain area associated with memory and cognition.\textsuperscript{9,34,35}

\textbf{AGE and Cancer Cancer Prevention}

High intake of garlic has been linked to a dramatic reduction in gastrointestinal cancer in humans, sometimes by 50\textsuperscript{\%}.\textsuperscript{1,5,36} Preclinical studies have shown that AGE and its organosulfur components inhibit the growth of many types of cancer.\textsuperscript{1,2,10,36-41} The cancer-preventive mechanisms of the antioxidant-rich AGE include inhibition of ROS-induced DNA damage, prevention of chemical modification of DNA by carcinogenic chemicals, increased detoxification of carcinogens, increased immunity by boosting cancer-killing natural killer cells (NK cells),\textsuperscript{42} inhibition of tumor growth-promoting
vascularization (angiogenesis), modulation of immunity and cell signals, modification of hormonal support, and increased cancer cell death by apoptosis.

AGE has been found to suppress colorectal adenomas in humans. In a year-long, double-blind, randomized clinical trial, patients with pre-cancerous lesions of the colon (colorectal adenomas) received either a high AGE dose (2.4 mL/day) or a very low dose (0.16 mL/day), as control. The results showed that in controls, the number of adenomas increased continuously over the year, but in the AGE group, AGE significantly suppressed both the size and number of the colon adenomas, showing that AGE suppresses the progression of pre-cancerous colon lesions and thus would prevent them from developing into full blown colon cancer.

**AGE**

**and Cancer Therapy**

AGE, SAC, and SAM have been reported to inhibit the growth of a variety of human cancer cells including prostate, breast, erythroleukemia, and colon cancers, suggesting that AGE, besides its cancer-preventive effects, has potential as an adjuvant in cancer therapy.

Preclinical studies have shown that SAC and SAM reduce human prostate cancer cell growth, decrease PSA, a characteristic marker for prostate cancer, and cut the production of testosterone by the prostate cells, thus depriving them of a critical growth factor. SAM dramatically inhibits the growth of human colon cells, disrupting and arresting mitosis and inducing death by apoptosis.

**AGE Prevents Drug Toxicity**

As reviewed earlier, AGE protects against cardiotoxicity and liver toxicity induced by carcinogens and by some drugs used in cancer therapy. AGE also prevents liver toxicity by acetaminophen (e.g., Tylenol), a popular pain-killing medication.

Gastrointestinal toxicity during cancer treatment with methotrexate (MTX) presents a problem in therapy. Preclinical studies show that AGE protects against MTX-induced toxicity in the small intestine by preventing MTX-induced apoptosis, suggesting a protective role for AGE during MTX cancer treatment by preventing the toxic side effects to normal cells.

Kidney toxicity is an adverse side effect in gentamicin (GM) treatment, limiting the use of this antibiotic. AGE and SAC and SAM were found to protect the cells against GM nephrotoxicity, without...
interfering with the antibiotic action of GM; moreover, SAC enhanced the antibiotic action of GM, suggesting that AGE, rich SAC and SAM may be co-administered with GM-treatment to ameliorate GM-induced nephrotoxicity and possibly enhance its antibiotic activity.\(^1\)\(^2\)\(^4\)\(^5\)

**AGE, Cancer, Immunity**

Aged garlic extract has a wide range of immuno-potentiating effects.\(^1\)\(^2\)\(^4\)\(^6\) A recent randomized, double-blind, placebo-controlled clinical trial underscored the efficacy of AGE in increasing immunity. Patients with inoperable cancers of the digestive system (colorectal, pancreas, or liver cancer) received AGE or placebo. Advanced stages of cancer are associated with a decrease in immune functions including a decline in Natural Killer (NK) cells. The results of the trial showed that patients who received AGE (500 mg/day) for three months showed a significantly increase in NK cell counts, compared to controls whose levels of NK cells decreased.\(^4\)\(^2\)

**AGE, Endurance, and Fatigue**

Aging is associated with reduced levels of energy, reduction in physical endurance, and increased fatigue. As seen in a number of preclinical studies and studies with athletes, AGE provides help on all fronts.\(^1\)\(^2\) A new preclinical study on endurance and fatigue found that AGE ameliorates the various impairments linked to physical fatigue following exercise by improving aerobic glucose metabolism, reducing oxidative stress, and promoting oxygen supply.\(^8\)

**AGE and Diabetes**

Diabetes is a disease characterized by high glucose levels (hyperglycemia); some of the pathological complications in diabetes arise from glucose interacting with proteins (glycation). The glycation products, called Maillard reaction products, are accompanied by increased ROS and play a role in damaging various organs including eyes, blood vessels, nerves, and kidneys. AGE and SAC, with their high antioxidant activity, have anti-glycation activity, which would help prevent pathological complications in diabetes. The potential therapeutic role of AGE in diabetes is now being tested in a clinical trial involving patients with type 2 diabetes.

**AGE and Sickle Cell Anemia**

Sickle-cell anemia is a hereditary disorder with high risk of mortality. In the course of this genetic disease, small clusters, called Heinz bodies, are formed in the red blood cells (RBC) by oxidative damage to the hemoglobin molecules and damage to the RBC membrane. AGE, with its antioxidant activity, is effective in reducing Heinz bodies.\(^3\)\(^2\) Patients with sickle-cell anemia received a daily dose of 5 mL AGE. After four weeks of treatment, the number of Heinz bodies decreased significantly (58.9 +/- 20.0% at baseline to 29.8 +/- 15.3%), suggesting that AGE may be considered a potential therapeutic agent to ameliorate complications of sickle-cell anemia.

**Summary**

The medicinal effects of garlic have a long history. Fresh garlic, though an excellent condiment, when taken in high doses that provide medicinal benefits may have unpleasant side effects, including lingering odor on the breath and skin, and gastrointestinal disturbances. Aged garlic extract, or Kyolic, an odorless form of organic fresh garlic, has health benefits that are as effective as fresh garlic and often even more so, being richer in antioxidants than are other garlic preparations, including the fresh bulb, and high in stable bioavailable, water-soluble organosulfur compounds, such as S allyl cysteine, which is used for standardization, and S allyl mercaptocysteine, which is unique to AGE. To the wide range of health benefits of AGE discussed previously,\(^1\)\(^3\) we can add recent findings that underscore the health effects and add others found in preclinical and clinical trials. These include cardioprotective and neuroprotective effects, anti-aging effects, potential prevention of complications in diabetes, amelioration of fatigue, potential therapeutic effects in sickle cell anemia, protection against toxic side effects from chemotherapy and antibiotic treatment, and new studies on the cancer-preventive and therapeutic effects of AGE. Taken daily in doses suggested by the manufacturer (Wakunaga), AGE, as shown in over 400 scientific studies, can help maintain good health, protect the heart and brain, and help prevent aging symptoms, thus increasing quality of life.
Aged Garlic Extract


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