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## Aged Garlic Extract

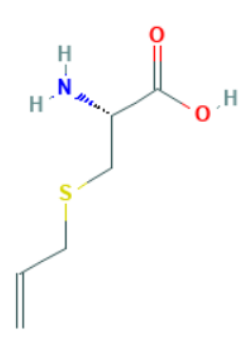
### Evidence Summary

Evidence suggests that aged garlic extract may reduce blood pressure in hypertensive individuals, though data for other cardiovascular effects is mixed.

**Neuroprotective Benefit:** Many preclinical studies suggest that aged garlic extract may be beneficial for Alzheimer's disease, but no human studies have been conducted.

**Aging and related health concerns:** Aged garlic extract may reduce blood pressure in hypertensive adults, though mixed evidence exists for other measures of cardiovascular health (e.g., lipid levels).

**Safety:** For most individuals, aged garlic extract is safe (with the potential for mild gastrointestinal side effects for some individuals), but it may interact with blood thinners and there are no long-term studies on its use.

<p><b>Availability:</b> Available OTC (e.g., Kyolic aged garlic extract which comes in several formulation such as Kyolic-100, Kyolic-109) (<a href="#">Kyolic website</a>)</p>	<p><b>Dose:</b> Doses of Kyolic aged garlic extract are generally 1.2-2.4g/day (although the recommended dose on bottle is lower). Supplement is taken with a meal.</p>	<p><b>Molecular Formula:</b> C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub>S  <b>Molecular weight:</b> 161.22g/mol  Aged garlic extract contains many active chemical components such as S-Allyl-L-cysteine</p>  <p>Source: <a href="#">PubChem</a></p>
<p><b>Half-life:</b> N/A – different constituents may have different half-lives</p>	<p><b>BBB:</b> Some of the constituents are possibly penetrant</p>	
<p><b>Clinical trials:</b> One ongoing for cholesterol levels, several studies have been conducted for cardiovascular disease (overall &gt; 1000 patients have been treated)</p>	<p><b>Observational studies:</b> More than 1000 patients treated in clinical trials</p>	

### What is it?

Garlic has long been used as a medicinal food for its beneficial cardiovascular and anti-cancer effects (due to the antioxidant and anti-inflammatory properties of its constituent ingredients). However, raw garlic is pungent and may have negative gastrointestinal effects. Therefore, aged garlic extract is commonly used as a supplement (Kyolic is the most common supplier). It is produced by soaking slices of garlic in ethanol for up to 20 months. The extract is then filtered and concentrated. It contains many compounds such as S-allylcystein, di-allyl-disulfide, ajoene, allixin, and other flavanoids, polyphenols, and thiosulfonates found in garlic. However, the levels of these components differ between aged garlic extract and raw garlic ([Sripanidkulchai, 2019](#); [Ryu and Kang, 2017](#)). In addition to its antioxidant properties, aged garlic extract is also thought to increase intracellular nitric oxide levels and the increase the production of hydrogen sulfide.



**Neuroprotective benefit:** Many preclinical studies suggest that aged garlic extract may be beneficial for Alzheimer's disease, but no human studies have been conducted.

Types of evidence:

- Eight preclinical studies in Alzheimer's models

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None

Human research to suggest benefits to patients with dementia:

None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

A study suggested that treatment of older Alzheimer's mice with aged garlic extract (40mg/kg/day) reduced levels of A $\beta$ 40 and 42 ([Chauhan, 2003](#)). In two Alzheimer's animal models, treatment with aged garlic extract (Kyolic, 2% in food) reduced levels of A $\beta$ 40 and 42 and improved memory when treatment was started before amyloid accumulation ([Chauhan and Sandoval, 2007](#)). In addition, in a model of scopolamine-induced cognitive impairment (which causes loss of cholinergic neurons), treatment with aged black garlic extract (50mg/kg/day) improved cognition, reduced levels of malondialdehyde (MDA – a marker of lipid peroxidation), increased levels of antioxidant enzymes (e.g., glutathione), reduced the activity of acetylcholinesterase, and increased the activity of choline acetyltransferase (ChAT) (suggesting an improvement of cholinergic activity – one of the targets of symptomatic AD drugs) ([Li and Kim, 2019](#)).

Another study compared the effects of aged garlic extract, S-allyl-cysteine (SAC) and di-allyl-disulfide (DADS) (two components of garlic) in Alzheimer's mice. They found that the reduction of beta-amyloid and p-tau was most effective with aged garlic extract. In addition, aged garlic extract, but not the individual components, reduced the inflammatory cytokine IL-1 $\beta$  in the brain ([Chauhan, 2006](#)).

In another study, rats were pretreated with aged garlic extract for 50 days before intracerebroventricular (i.c.v.) injection of A $\beta$ 42. Treated rats had improved cognition, reduced cholinergic neuronal loss (at 250mg/kg/day, but not the 125 or 500mg/kg/day dose), and increased levels of synaptic markers (VGLUT1, GAD) ([Thorajak et al, 2017](#)). A follow-up study suggested that aged



garlic extract could also reduce microgliosis and levels of inflammatory cytokines (IL-1 $\beta$  and TNF- $\alpha$ ) in the hippocampus ([Nillert et al, 2016](#)).

*In vitro* studies suggested that exposure of an ethyl acetate fraction from aged garlic extract reduced ROS production and improved survival of neuronal cells exposed to A $\beta$ . When the extract was administered to animals injected i.c.v. along with A $\beta$ , it improved memory and learning ([Jeong et al, 2013](#)). *In vitro* experiments also suggested that treatment with aged garlic extract improved cell survival when cells were exposed to reactive oxygen species (via treatment with H<sub>2</sub>O<sub>2</sub>) ([Ray et al, 2011](#)).

#### APOE4 Interactions:

None reported

**Aging and related health concerns:** Aged garlic extract may reduce blood pressure in hypertensive adults, though mixed evidence exists for other measures of cardiovascular health (e.g., lipid levels).

#### Types of evidence:

- One systematic review and one meta-analysis for uncontrolled hypertension
- 13 clinical trials for effects on cardiovascular health
- Three clinical trials for effects on metabolic health
- Multiple preclinical studies for longevity and cardiovascular disease

#### Longevity

In a mouse model of accelerated aging (SAMP8 mice), a diet containing 2% aged garlic extract started from two months of age increased lifespan and improved cognition. It had no effect on survival in mice resistant to senescence (a control for SAMP8 mice – R1 mice) ([Moriguchi et al, 1994](#); [Moriguchi and Nishiyama, 1996](#)).

#### Cardiovascular disease

##### Cholesterol levels

Forty-one moderately hypercholesterolemic men were treated with aged garlic extract (800mg/day) or placebo for six months. Treatment with aged garlic extract reduced LDL-c levels by ~4.6% and systolic blood pressure by ~5.5% compared to placebo ([Steiner et al, 1996](#)). Another study compared three different garlic supplements (raw garlic, Garlicin – from Nature's Way, and Kyolic-100) to placebo over six months in 192 patients with moderate hypercholesterolemia. There were no differences in lipid



levels (LDL-c, HDL-c, triglycerides, total cholesterol) over the treatment period. The authors note that these results may differ from the previous study with the Kyolic-100 supplement because the dose of Kyolic-100 was lower (the dose in this study was chosen to match the dose of raw garlic used) ([Gardner et al, 2007](#)). Note, however, that doses commonly used in clinical trials are ~1.5-3 times the dose recommended on the bottle. Similarly, another study of aged garlic extract (from Doulu Agricultural Farming Corporation – 6 grams/day) suggested that treatment over 12 weeks in 60 patients with mild hypercholesterolemia had no effect on blood lipid levels (LDL-c, triglycerides, HDL-c). However, it did decrease levels of apoB ([Jung et al, 2014](#)).

### Hypertension

A systematic review of nine RCTs (n = 482 individuals) reported that treatment with different preparations of garlic extracts over 8-26 weeks reduced blood pressure (systolic blood pressure – SBP – reduction ~9.1 mmHg). However, the authors noted that when only high-quality trials with concealed treatment allocations were included, the effect size for SBP reduction was lower (though still significant). They conclude that although garlic extracts may reduce blood pressure in hypertensive individuals, the quality of the data was low ([Rohner et al, 2015](#)). A more recent meta-analysis of 12 trials with 553 hypertensive individuals investigated the use of garlic supplements (garlic supplements from either Kwai, Allicor, or Kyolic) over 8-24 weeks. They reported that supplementation reduced SBP by an average of 8.3 mmHg and diastolic blood pressure (DBP) by an average of 5.5 mmHg ([Ried, 2020](#)).

### *Kyolic High Potency Formula (studies were included in the meta-analysis above)*

Fifty individuals with treated, but uncontrolled, hypertension based on medical records were given aged garlic extract (960mg/day, Kyolic) or placebo over 12 weeks. There were no differences in the change in SBP between groups. However, in those with SBP >140mm Hg, there was a significant reduction in blood pressure (-15.2mm Hg compared to baseline vs. -7.4mm Hg for placebo) ([Ried et al, 2010](#)). Seventy-nine patients with uncontrolled hypertension were treated with aged garlic extract (240, 480, or 960mg/day - Kyolic) over 12 weeks. Treatment reduced SBP in the 480 and 960mg groups. The most common adverse events were gastrointestinal side effects ([Ried et al, 2013](#)).

### *Kyolic Reserve Formula (studies were included in the meta-analysis above)*

Eighty-eight patients with uncontrolled hypertension were treated with aged garlic extract (1.2g/day) or placebo over 12 weeks. Treatment reduced blood pressure (SBP reduction 5.0 mmHg) and improved other measures of cardiovascular health (pulse-wave velocity, arterial stiffness). Changes in other cardiovascular and inflammatory markers (CRP, IL-1 $\beta$ , lipid levels) did not significantly change ([Ried et al, 2016](#)). Similar results were reported in a study by the same group (same study design) with aged garlic



extract improving both SBP and DBP. However, they noted that non-responders to aged garlic extract all had low levels of Vitamin B12 ([Ried et al, 2018](#)).

### Atherosclerosis

Fifty-five patients with metabolic syndrome were treated with aged garlic extract (2400mg/day, Kyolic) or placebo over 40 days and underwent a cardiac computed tomography angiography. There was no change in total coronary plaque volume, plaque calcification, or non-calcified plaques over the treatment period between the two groups. However, the aged garlic extract group saw a reduction in low-attenuation plaque burden (LAP – lipid-rich plaques which may be a better predictor of future myocardial infarction) ([Matsumoto et al, 2014](#)). Similar results were reported in another study of 80 patients with diabetes treated with aged garlic extract (2400mg, Kyolic) over one year. No significant results were reported for total plaque volume, dense calcium, or fibrous plaque volume. However, there was a reduction in LAP ([Shaikh et al, 2019](#)).

A hundred and four patients with a high Framingham Heart Score were randomized to either aged garlic extract (2400mg, Kyolic) or placebo over one year. Treatment with aged garlic extract reduced progression of coronary artery calcification (20% vs. 28% for drug vs. placebo). Aged garlic extract also reduced levels of inflammation (IL-6), blood pressure, as well as glucose levels (but had no effect on LDL-c) ([Wloniska et al, 2020](#)).

In an animal model of atherosclerosis (ApoE-KO animals) treatment with aged garlic extract (3% concentration in food) reduced the progression of atherosclerosis, the plasma levels of cholesterol and triglycerides, and the number of inflammatory cells in the lesion area ([Moriyama et al, 2016](#)). In another study in ApoE-KO mice, treatment with aged garlic extract (3% concentration in food) reduced atherosclerotic lesion progression (by 27%), reduced serum levels of C-reactive protein (by 39%), and levels of TNF- $\alpha$  (by 35%) ([Moriyama et al, 2017](#)). Animal models also suggest that aged garlic extract can increase the levels of nitric oxide ([Moriyama et al, 2006](#)).

### Vasculature (General)

A hundred and twenty-two patients with a high risk of cardiovascular disease (measured with a high Framingham Risk Score) were treated with aged garlic extract (2400mg/day, Kyolic) or placebo over 12 months. Laser Doppler velocimetry (LDV) was used to measure endothelium-dependent microvascular reactivity over the forearm. Treated patients had increased levels of microvascular blood flow over the treatment period ([Wlosinska et al, 2019](#)). In another study with 57 individuals who had elevated blood pressure, 12-week treatment with aged garlic extract improved arterial elasticity by 21.6% (measured



with the Endo PAT device) and reduced blood pressure and triglycerides ([Gruenwald et al, 2020](#)). In a randomized cross-over trial in 15 men with coronary artery disease, two-week treatment with aged garlic extract (2400mg/day, Kyolic) improved endothelial flow-mediated dilation (44%, results were especially prominent in those with low baseline FMD). There were no effects on plasma markers of oxidative stress, lipid levels, or inflammation over the treatment period ([Williams et al, 2005](#)).

### Metabolic syndrome

Forty-six individuals with metabolic syndrome were randomized to aged garlic extract (1200mg/day, Kyolic) or placebo in a 24-week cross-over trial. Aged garlic extract had no effect on most measures of cardiovascular or metabolic health (e.g., SPB, DBP, body mass index, lipid levels, IL-6, HOMA-IR index). However, treatment increased levels of serum adiponectin ([Gomez-Arbelaez et al, 2013](#)). In 65 patients with type 2 diabetes, three-month treatment with aged garlic extract (2400mg/day, Kyolic) also improved endothelial function (measured by the cardio-ankle vascular index – CAVI) ([Hamal et al, 2019](#)). In 51 obese, but otherwise healthy, individuals, six-week treatment with aged garlic extract (3600mg/day, Kyolic) reduced levels of IL-6 and TNF- $\alpha$ . There were no changes in CRP or adiponectin ([Xu et al, 2017](#)).

### Cancer

Aged garlic extract has been reported to be beneficial in several *in vitro* studies of cancer cell lines and in several animal models of cancer (e.g., colon, prostate, gastric cancer) ([Yi et al, 2019](#)). Studies suggest that it has pro-apoptotic properties and anti-metastatic properties in cancer cell lines *in vitro*. However, no human studies have been conducted examining the effect of aged garlic extract for cancer ([Ryu and Kang, 2017](#)).

**Safety:** For most individuals, aged garlic extract is safe (with the potential for mild gastrointestinal side effects for some individuals), but it may interact with blood thinners and there are no long-term studies on its use.

### Types of evidence:

- One review of aged garlic extract RCTs
- One review of garlic supplements
- Four clinical trials of aged garlic extract RCTs
- One clinical trial in patients taking warfarin



A review of RCTs reported that aged garlic extract is generally safe and tolerable. The most common adverse event is mild gastrointestinal side effects. It is also safe when taken with other blood pressure medications ([Cicero and Colletti, 2015](#)). Individual clinical trials that report safety results also suggest that aged garlic extract could cause mild gastrointestinal side effects in some patients, but no serious adverse effects have been reported (e.g., [Ried et al, 2018](#), [Ried et al, 2016](#), [Ried et al, 2010](#), [Ried et al, 2013](#)). However, no long-term safety studies have been conducted on the use of aged garlic extract, and no large-scale trials have examined its effects in combination with other drugs.

There is some concern that garlic supplements may interact with blood thinning medications (e.g., aspirin, warfarin) and should not be taken before surgery ([Wong et al, 2012](#), [Elmer et al, 2007](#)) However, one small study (n=48) of patients on warfarin suggested no increased risk with the use of aged garlic extract over 12 weeks ([Macan et al, 2006](#)). There are no large, long-term safety studies, and individuals should be careful before combining aged garlic extract with blood thinners.

#### **Drug interactions:**

Aged garlic extract could possibly interact with blood thinners such as aspirin and warfarin. However, there is insufficient evidence from clinical trials ([drugs.com](#)).

#### **Sources and dosing:**

Aged garlic extract is produced by soaking slices of garlic in ethanol for up to 20 months. The extract is then filtered and concentrated, and it contains many compounds such as S-allylcystein, di-allyl-disulfide, ajoene, allixin, and other flavanoids, polyphenols, and thiosulfinates found in garlic. Kyolic is the most common brand for aged garlic extract and doses are generally 1.2-2.4g/day (although the recommended dose on bottle is lower). Supplement is taken with a meal.

#### **Research underway:**

One study is testing the effects of a new aged black garlic extract (250mg) in 60 patients with high LDL-c levels (>115mg/dL) with to see if it improves LDL-c ([NCT04010565](#)). Black garlic differs from white garlic in that it is fermented and contains more S-allyl-cystein and allin and less sugar and furfural (an organic compound) derivatives.

#### **Search terms:**

aged garlic extract + alzheimer, longevity, [clinical trials], [meta-analysis],  
neuropathy, cardiovascular, aging, apoe, cancer, stroke, diabetes





**Websites visited:**

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Pubmed](https://pubmed.ncbi.nlm.nih.gov/)
- [Drugs.com](https://www.drugs.com/)

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