



## Garlic, Aged Extracts (*Allium sativum*)

### Common Indications:

- Hypertension
- Hyperlipidemia
- Diabetes mellitus
- Infection
- Inflammation
- Antiplatelet

### General Comments:

Garlic (*Allium sativum*) is a plant in the Alliaceae family along with onions and leeks and chive. These foods are well studied for their effects on health in general and detoxification in particular. Fermented garlic represents a very different element than standard garlic as the fermentation process alters the color, odor, taste, smell, and nutritional value of garlic. Garlic bulbs contain organosulfur compounds, proteins, amino acids, fiber, lipids, phytic acid, saponins, beta-sitosterol, and small amounts of vitamins and minerals such as vitamin C, vitamin E, beta-carotene, chromium, iron, and selenium.<sup>1</sup>

### Benefits & Mechanism of Action:

The pharmacological actions of the herb are due to its organosulfur components: alliin, allyl cysteine, allyl disulfide and allicin.<sup>2</sup> Aged garlic extract (AGE) is aged for 20 months at room temperature producing the water-soluble, antioxidant organosulfur compounds, including S-allyl mercaptocysteine (SAMC, unique to aged garlic extract) and S-allyl cysteine (SAC). SAC has a high absorption rate in the body (98%) and is used for standardizing AGE. AGE and its constituents, SAC and SAMC, may act as cellular donors of thiol-containing reducing equivalents comparable to *N*-acetylcysteine or glutathione. When garlic is cut, crushed, chewed, or dehydrated, the enzyme alliinase is released which allows the biotransformation of alliin to active organo-sulfur compounds.

### Hypertension

The current clinical evidence indicates that garlic treatment has a slow-onset mild-moderate blood pressure-reducing effect when taken for approximately 12 weeks with various garlic preparations.<sup>3-8</sup> An early meta-analysis reported in 1994 analyzing results from seven trials using Kwai 600-900mg daily showed a mean reduction of 7.7mmHg for SBP and 5mmHg for diastolic blood

pressure. <sup>6</sup> The exact mechanism of action is unknown however in vivo research suggests that both the renin-angiotensin-aldosterone system and the nitric oxide system are responsible. <sup>9,10</sup>

## **Hyperlipidemia**

Evidence from in vivo, animal and human research has shown that garlic supplementation significantly reduces the atherosclerotic process. <sup>11-17</sup> A critical review conducted on in vitro studies established that garlic inhibits enzymes involved in lipid synthesis, platelet aggregation, and oxidization of LDL, all while increasing antioxidant status. <sup>17</sup> Administration of high dose (500mg/kg) of raw garlic extract on rats showed a 38% reduction in triglycerides and cholesterol. <sup>18</sup> A reduction in cholesterol and triglycerides and an increase in HDL were achieved in patients taking 5g of raw garlic twice daily for 42 days. <sup>10</sup>

## **Diabetes mellitus**

Garlic may be of benefit to people with diabetes, according to the available clinical research; however mixed results hamper the interpretation of results. Animal studies have shown that garlic and its constituents exhibit a hypoglycemic action<sup>19,20</sup> and produces changes in glucose tolerance and insulin secretion. <sup>21,22</sup> A single-blind placebo-controlled, escalating dose study was conducted with 210 people with T2DM comparing the effects of garlic, metformin, and placebo for 24 weeks. Results showed significant effects on both fasting blood sugar and A1C with higher doses of garlic (1200mg and 1500mg) compared to placebo and comparable to metformin. <sup>23</sup>

## **Infection**

Helps improve immune activation; may help prevent viral, bacterial and yeast activity. Garlic oil is effective against numerous bacteria, viruses, fungi and parasites, including *S. aureus*, methicillin resistant *S. aureus*, *E. coli*, *Shigella* spp., *Salmonella* spp., *P. mirabilis*, *Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans* in vitro. <sup>24-27</sup> It can be used both externally and internally for various infections to prevent wound infections.

## **Inflammation**

Fresh garlic extracts and garlic oil exert anti-inflammatory action in various models. Mechanisms of action identified include a direct action upon toll-like receptor-mediated signaling pathway, inhibiting NF-kappa activation, <sup>28</sup> modification of the expression of cyclooxygenase (COX) activity <sup>18</sup> and suppression of inducible nitric oxide synthase and nitric oxide production. <sup>29</sup> May enhance vigor, reduce fatigue and stress. <sup>30</sup>

## **Antiplatelet**

In vitro studies indicate that garlic inhibits platelet aggregation through multiple mechanisms, including inhibition of COX activity and thromboxane A<sub>2</sub> formation, via the suppression of intraplatelet Ca<sup>2+</sup> mobilization and by increasing the cAMP and cGMP levels. The antioxidant action of garlic also increased platelet-derived NO, and interactions with glycoprotein IIb/IIIa receptors reduces platelets' ability to bind to fibrinogen. <sup>31-33</sup>

## Antioxidant

Garlic and many of its constituents have strong anti-oxidant activity and is capable of directly scavenging free radicals, and indirectly enhancing endogenous antioxidant systems such as glutathione, superoxide dismutase, catalase and glutathione peroxidase.<sup>34,35</sup> Alliin scavenges superoxide via the oxanthine oxidase system; alliin, allyl cysteine, and allyl disulfide act as hydroxyl scavengers; and allyl disulfide prevents lipid peroxidation.<sup>36</sup> Reported in human and laboratory studies to reduce homocysteine induced endothelial dysfunction by inhibiting homocysteine-induced scavenger receptor CD36 expression and oxidized low-density lipoprotein cholesterol uptake in macrophages.<sup>37</sup> Antioxidant activity helps protect against toxic effects of pollution, UV light and drug toxicity by increasing hepatic glutathione levels.<sup>30</sup>

## Dosing Guide

- **General:**
  - Fresh Garlic: 2-5g/day \*Bruised, Crushed, or Chewed\*
  - Dried Powder: 0.4-1.2g/day
  - Oil: 2-5mg/day
  
- **Dosing Indications:**
  - **Diabetes mellitus:** Allicor 300mg twice daily
  - **Hypertension:** Aged Garlic Extract 480-960mg/day standardized to S-allylcysteine (SAC) 4.8mg/day
  - **Hyperlipidemia:** 600-900mg/day
  - **Hyperglycemia:** 1200-1500mg/day
  - **Fungal infection:** Topical 0.4%-0.6% ajoene cream applied twice daily

## Cautions & Side Effects:

- Garlic has been reported to be safe in recommended doses.
- Garlic should not be used if there is an allergy to any component of this dietary supplement.
- Mild gastrointestinal symptoms: Bloating, Reflux, Flatulence, Nausea, Diarrhea
- Headache, Myalgia, and Fever

## Drug Interactions

- Saquinavir, Darunavir, and Ritonavir
  - Garlic can increase concentrations of the aforementioned drugs
- Anticoagulants
  - Aged garlic extract has not been reported to interact with anticoagulant medications.<sup>38</sup>
  - Use caution when taking doses >7g/day

- Antiplatelet
  - Theoretical pharmacodynamic interaction is possible when using garlic in high doses however a study had shown that there is no effect on platelet efficacy/function. <sup>39</sup>
- Antihypertensives
  - Observe blood pressure for additive effects when using garlic in high doses
- Antihyperlipidemics
  - Observe lipid panels for additive effects when using garlic in high doses
- Hydrochlorothiazide
  - Co-administration may require a reduction in the dose of HCTZ due to raised serum concentrations. <sup>40</sup>

## References:

### General Comments

1. Duke Dr. Dr Duke's phytochemical and ethnobotanical database. Available online at: <http://www.ars-grin.gov/duke/> (accessed 2003).

### Benefits & Mechanism of Action

2. Chung LY. The antioxidant properties of garlic compounds: allyl cysteine, alliin, allicin, allyl disulfide. *J Med Food* 9.2 (2006): 205-213

### Hypertension

3. Andrianova IV, Fomchenkov IV, Orekhov AN. [Hypotensive effect of long-acting garlic tablets allicor (a double-blind placebo controlled trial)]. *Ter Arkh* 74.3 (2002): 76-78
4. Dhawan V, Jain S. Garlic supplementation prevents oxidative DNA damage in essential hypertension. *Mol Cell Biochem* 275.1-2 (2005): 85-94
5. Ried K et al. Effect of garlic on blood pressure: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 8 (2008): 13.
6. Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens* 12.4 (1994): 463-468.
7. Stabler, S. N., et al. Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients., *Cochrane database of Systematic Reviews*, no. 8, Article ID CD007653, 2012
8. Tsai, C-W., et al. Garlic: health benefits and actiond. *Biomedicine* (2012) 17-29.
9. Al-Qattan KK et al. Nitric Oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. *J Nutr* 136 (3 Suppl) (2006): 774S-776S.
10. Mohamadi A et al. Effects of wild versus cultivated garlic on blood pressure and other parameters in hypertensive rats. *Heart Dis* 2.1 (2000): 3-9.

### Hyperlipidemia

11. Campbell JH et al. Molecular basis by which garlic suppresses atherosclerosis. *J Nutr* 131.3s (2001): 1006S-1009S.
12. Durak I et al. Effects of garlic extract on oxidant/antioxidant status and atherosclerotic plaque formation in rabbit aorta. *Nutr Metab Cardiovasc Dis* 12.3 (2002): 141-147
13. Ferri N et al. Ajoene, a garlic compound, inhibits protein prenylation and arterial smooth muscle cell proliferation. *Br J Pharmacol* 138.5 (2003): 811-8118.
14. Koscielny J et al. The antiatherosclerotic effect of *Allium sativum*. *Atherosclerosis* 144.1 (1999): 237-249
15. Kwon MJ et al. Cholesteryl ester transfer protein activity and atherogenic parameters in rabbits supplemented with cholesterol and garlic powder. *Life Sci* 72.26 (2003): 2953-2964.
16. Orekhov AN et al. Direct anti-atherosclerosis-related effects of garlic. *Ann Med* 27.1 (1995): 63-65
17. Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. *J Nutr* 136 (3 Suppl) (2006): 736S-740S
18. Thomson M, Mustafa T, Ali M. Thromboxane-B(2) levels in serum of rabbits receiving a single intravenous dose aqueous extract of garlic and onion. *Prostaglandins Leukot Essent Fatty Acids* 63.4 (2000): 217-221

### Diabetes mellitus

19. Hattori A et al. Antidiabetic effects of ajoene in genetically diabetic KK-A(y) mice. Tokyo: *J Nutr Sci Vitaminol*, 51.5 (2005): 382-40.
20. Jelodar GA et al. Effect of fenugreek, onion and garlic on blood glucose and histopathology of pancreas of alloxan-induced diabetic rats. *Indian J Med Sci* 59.2 (2005): 64-69
21. Liu CT et al. Effects of garlic oil and diallyl trisulfide on glycemic control in diabetic rats. *Eur J Pharmacol* 516.2 (2005): 165-173.
22. Padiya, R., et al. Garlic improves insulin sensitivity and associated metabolic syndromes in fructose fed rats. *Nutrition and metabolism* (2011); 8: 53.
23. Phil, R. A. M., et al. Effects of garlic on blood glucose levels and HbA1c in patients with type 2 diabetes mellitus. *J. of Med. Plants Research* 5.13 (2011): 2922-28.

### Infection

24. Davis LE, Shen J, Royer RE. In vitro synergism of concentrated *Allium sativum* extract and amphotericin B against *Cryptococcus neoformans*. *Planta Med* 60.6 (1994): 546-549
25. Tsao SM, Yin MC. In-vitro antimicrobial activity of four diallyl sulphides occurring naturally in garlic and Chinese leek oils. *J Med Microbiol* 50.7 (2001): 646-649.
26. Yoshida S et al. Antifungal activity of ajoene derived from garlic. *Appl Environ Microbiol* 53.3 (1987): 615-6117
27. Eja ME et al. A comparative assessment of the antimicrobial effects of garlic (*Allium sativum*) and antibiotics on diarrheagenic organisms. *Southeast Asian J Trop Med Public Health* 38.2 (2007): 343-348

### Inflammation

28. Youn HS et al. Garlic (*Allium sativum*) extracts inhibits lipopolysaccharide-induced Toll-like receptor 4 dimerization. *Biosci Biotechnol Biochem* 72.2 (2008): 368-375.
29. Liu KL et al. DATS reduces LPS-induced iNOS expression, NO production, oxidative stress, and NF-kappaB activation in RAW macrophages 264.7. *J Agric Food Chem* 54.9 (2006): 3472-3478.
30. Morihara, N., Nagatoshi, I., Weiss, N. Aged garlic extract inhibits homocysteine-induced scavenger receptor CD36 expression and oxidized low-density lipoprotein cholesterol uptake in human macrophages in vitro. *J of ethnopharm.* 134 (2011): 711-716.

### **Antiplatelet**

31. Allison GL, Lowe GM, Rahman K. Aged garlic extract may inhibit aggregation in human platelets by suppressing calcium mobilization. *J Nutr* 136 (3 Suppl) (2006): 789S-792S.
32. Chan KC, Yin MC, Chao WJ. Effects of diallyl trisulfide-rich garlic oil on blood coagulation and plasma activity of anticoagulation factors in rats. *Food Chem Toxicol* 45.3 (2007): 502-507.
33. Rahman K. Effects of garlic on platelet biochemistry and physiology. *Mol Nutr Food Res* 51.11 (2007): 1335-1344.

### **Antioxidant**

34. Arhan M et al. Hepatic oxidant/antioxidant status in cholesterol-fed rabbits: effects of garlic extract. *Hepatol Res* 39.1 (2009): 70-77
35. Hassan A., et al. Garlic Oil as a modulating agent for oxidative stress and neurotoxicity induced by sodium nitrite in male albino rats. *Food and Chemical Toxicology* 48 (2010): 1980-1985.
36. Chung LY. The antioxidant properties of garlic compounds: allyl cysteine, alliin, allicin, and allyl disulfide. *J Med Food* 9.2 (2006): 205-213
37. Weiss N et al. Aged garlic extract improves homocysteine-induced endothelial dysfunction in macro- and microcirculation. *J Nutr* 136 (3 Suppl) (2006): 750S-754S.

### **Drug Interactions**

38. Macan H et al. Aged garlic extract may be safe for patients on warfarin therapy. *J Nutr* 136 (3 Suppl) (2006): 793S-795S
39. Beckert BW et al. The effect of herbal medicines on platelet function: an in vivo experiment and review of the literature. *Plast Reconstr Surg* 120.7 (2007): 2044-2050.
40. Asdaq, S. M. B., and M. N. Inamdar. The potential for interaction of hydrochlorothiazide with Garlic in Rats. *Chemico-biological Interactions* 181 (2009): 472-479