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TABLE OF

CONTENTS

What We Know, Think We Know, or Are Starting to Know 03

Geek Box: Geeking on Garlic 04

The Study 04

Results 05

The Critical Breakdown 06

Key Characteristic 06

Interesting Finding 06

Relevance 07

Application to Practice 07

References 08

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What We Know, Think We Know, or Are Starting to Know

Of the food-based interventions you may not have heard of, garlic might surprise you as having an enormous body of literature from animal and human studies [1,2]. The interest in garlic may reflect the dizzying variety of bioactive compounds which garlic contains, including sulfur-containing compounds, (poly)phenolic compounds, saponins, and polysaccharides*. These compounds exhibit a number of effects relevant to cardiovascular disease, and garlic supplementation has consistently been shown to lower blood pressure and cholesterol levels [1,3].

From the perspective of cardiovascular disease, it may be the effects on blood cholesterol level that are most interesting. The dominant effect of garlic stems from water-soluble sulfur compounds, which inhibit the synthesis of cholesterol in the liver [2]. There are a number of mechanisms of action by which garlic may exert its effect. The major active compound in garlic, allicin [a sulfuric compound], has been shown to inhibit the activity of enzymes in the pathway of cholesterol synthesis [4].

This is similar to statins, although acting 'upstream' from the target of statins. Statins target the HMG-CoA-reductase enzyme, whereas garlic inhibits two enzymes known as squalene-monooxegenase and acetyl-CoA synthetase, both of which are earlier in the stages of cholesterol synthesis [5]. Meta-analyses of garlic supplementation have shown reductions in total cholesterol of between 0.19 - 0.77mmol/L [7.4 - 29.8mg/dL], and ~0.23mmol/L [9mg/dL] lower LDL-C levels [2,3,6].

While reductions in risk factors are always positive, what about the underlying disease pathology? The present study investigated the effects of aged garlic extract on plaque progression in coronary arteries in participants with Type-2 Diabetes [T2D].

*Geek Box: Geeking on Garlic

The botanical name for garlic is Allium sativum L., and as noted above contains a multiplicity of bioactive food compounds which are likely all relevant for its wide variety of effects. Let's start with the sulfuric compounds, i.e., compounds that contain sulfur. You know these compounds; they're what give onions and garlic their pungent aromas and flavour! There are a number of important sulfuric compounds in garlic, in particular allicin and alliin, and these compounds appear to have a greater bioavailability in raw garlic rather than cooked. Saponins are bioactive compounds that derive their name due to their ability to form 'soapy' substances, particularly in the digestive tract. Because they are poorly absorbed, the main action of saponins is in the digestive tract, where they may exert anti-inflammatory and anti-microbial effects. Garlic also contains over 20 (poly)phenolic compounds, with their associated cardiovascular effects, particularly for blood pressure. And there is also the 'prebiotic' effect of garlic polysaccharides, i.e., providing selective fibre types to the colon which are preferentially fermented by beneficial bacterial species, in particular the Bifidobacteria species. At this point, you may also be thinking, "what is aged garlic extract?" AGE is produced from organically-produced garlic bulbs that have aged for around 20-months at room temperature, soaked in ethanol. The ageing process allows for the sulfuric compounds, which are usually quite volatile [chemically speaking!], to become more stable and be standardised into doses. This makes it more amenable to use as a supplement, with measurable potency.

The Study

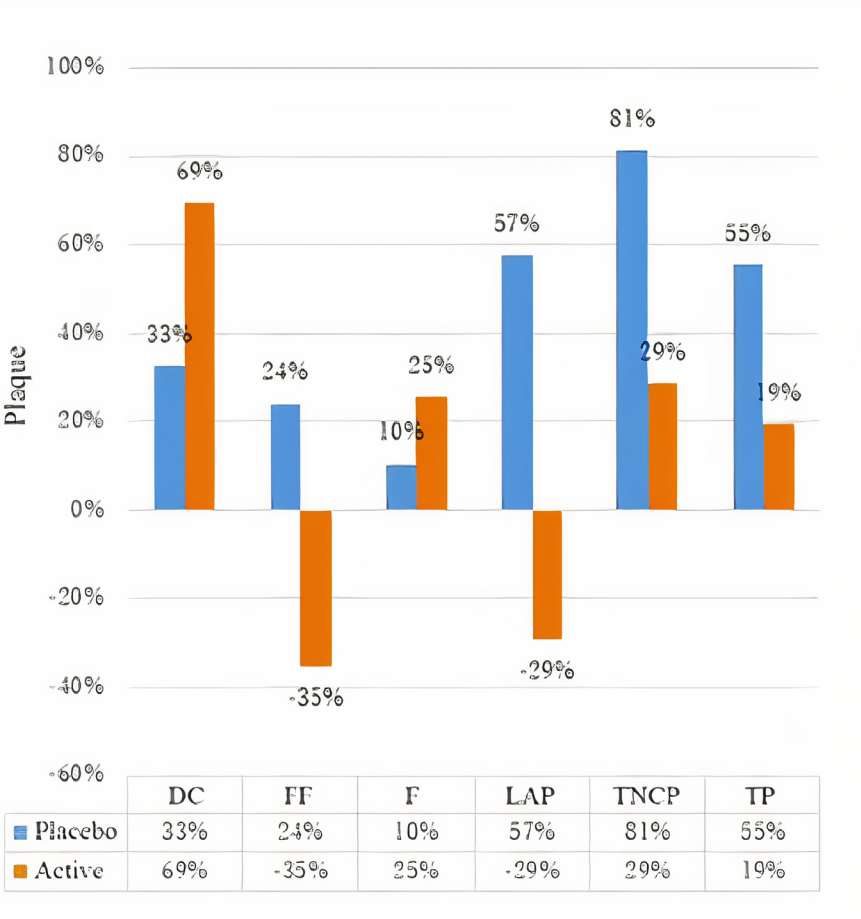
80 participants with diagnosed T2D were randomised to receive either 2,400mg/d aged garlic extract [AGE] or a placebo [cellulose]. Participants were instructed to take 2 capsules, twice per day, for the 12-month duration of the study. While participants had T2D, they did not have history of cardiovascular disease [CVD].

The primary outcome measure was rate of change in coronary plaque volume and vulnerable components of plaque. Plaque was measured using coronary computed tomography angiography [CCTA], a reliable and sensitive method of imaging for the arteries.

Results: 66 participants completed the study with both baseline and follow-up CCTA scans [*n* = 29 in the placebo group, of which 21 were male; *n* = 36 in the garlic group, of which 18 were male]. Average age of the participants were 58.7 and 59.4 years in the placebo and garlic groups, respectively.

- ***Plaque Measures:*** In the garlic group, low attenuation plaque [LAP] fibrous fatty plaque [FF] both exhibited reductions of 29% and 35%, respectively, compared to a respective 24% and 57% increase in these measures in the placebo group. Only the difference in LAP was statistically significant.

There were no other statistically significant differences between groups in other measures of plaque, including dense calcified plaque [DC], fibrous plaque [F], total non-calcified plaque [TNCP], and total plaque [TP].



	DC	FF	F	LAP	TNCP	TP
Placebo	33%	24%	10%	57%	81%	55%
Active	69%	-35%	25%	-29%	29%	19%

Figure *from the paper illustrating the differences in the various plaque markers in the intervention garlic group [**orange**] and placebo group [**blue**]. As is clearly evident in this figure, AGE resulted in a regression in two plaque parameters, while the rest still increased, albeit to a much attenuated degree than the placebo group. The exception to this is the change in dense calcified plaque, and there is more on this under* ***Interesting Finding****, below.*

The Critical Breakdown

Pros: The trial was pre-registered [and there are no apparent alterations to the protocol from the registration]. Both placebo and treatment were pill were a similar size and colour. The garlic supplement was commercially prepared. Both participants and investigators were blind to the treatment allocation, and the CCTA scans were also assessed by physicians blinded to the treatment allocation and the date of the scan. The trial retention was good [66/80] overall.

Cons: The method of randomisation was not described, which given the groups were imbalanced in terms of sex, menopausal status, and smoking status, could have been addressed with a block or stratified randomisation process to equally distribute these potentially relevant factors between groups. Participants were also taking a range of different medications for T2D or CVD management. The dropouts from the study resulted in imbalanced groups with 29 in the placebo and 36 in the garlic groups. No intention-to-treat analysis was carried out, and given the groups were imbalanced with more participants in the treatment group, this could bias the outcomes toward the garlic group. The study had a small sample size and lacked statistical power to detect significant differences in the outcomes. Finally, always something to bear in mind, the trial was funded by the producer of the AGE supplement.

Key Characteristic

The use of CCTA provides an accurate and sensitive method of looking "under the hood", so to speak. Although we have looked at the results in terms of percentage changes, in absolute terms we are talking about microscopic changes in these outcomes. These changes, however, may be highly clinically relevant, and thus having the sensitivity to detect them is crucial. CCTA also has the advantage of being non-invasive - it uses x-ray imaging techniques - and thus doesn' t require operative procedures to see into the artery. This makes it useful for research purposes, where ethically subjecting participants to an operation where it would not otherwise be indicated wouldn' t be too kosher. Thus, despite the small sample size and the lack of statistical power to detect significant differences between groups, the sensitivity of CCTA was still able to detect absolute differences in the various plaque measures.

Interesting Finding

This is an example of where there may be a difference apparent, as a point of fact, but a lack of statistical significance, which often relates to the size of the trial. In this case, the increase in dense calcified plaque is interesting. With the word 'plaque', the obvious inference is that dense calcified plaque is a negative parameter. However, where plaque is present there appears to be a "paradox" of sorts; the more the densely calcified the plaque, the more stable the plaque, i.e., less likely to rupture [(7)]. For example, athletes may have higher coronary artery calcification scores, but lower risk of CVD events, which may relate to grater plaque stability [(8)]. Thus, it could be that the increase in dense calcified plaque in the present study represents an effect of the AGE supplementation on plaque stabilisation, which would be a positive. However, despite much hyperbole from the low-carb community about coronary artery calcification, the reality is that it is an area with a lot of unknowns [(9)].

Relevance

This is one of those studies that falls under the "really interesting but that' s it for now" category. It has a number of methodological limitations, as highlighted under ***Cons*** above, and ultimately it was clearly underpowered and the findings are largely not significant.

However, let' s take it in context. First, garlic supplementation does have a longer track record of improving blood cholesterol levels, in addition to other cardiovascular risk factors [2,3,6]. Secondly, regression of plaque is a critical outcome to reducing CVD risk [10]. Finally, there was a clearly defined intervention and placebo, in addition to blinding, and we could assume that the differences observed reflect an effect of the intervention.

The question becomes whether these would be stronger and more evident effects in a larger, higher-powered trial; or indeed, whether they would be evident at all! This is the caveat with any small, underpowered intervention with suggestive findings; someone has to cough up the funds to do this again, with more methodological rigour, and a lot more humans.

The only prior study to show a similar effect, i.e., a reduction in low attenuation plaque, was a 2016 study in participants with metabolic syndrome also conducted by this research group [11]. Thus, it is only the two small human trials to date. Caveats galore.

Application to Practice

Given everything written above, this is always the conundrum for applying nutrition research in real life; wait for more evidence, or go with the evidence that is there? Garlic has a high safety profile [although some rare adverse reactions may be noted], and is not contraindicated with common lipid-lowering or anti-diabetic drugs. So the question that always begs is, "where is the harm"? And, unlike the pharmaceutical grade omega-3 supplements used in fish oil trials, the AGE in the present study [Kyolic] is commercially available. Although suggestive, I would be inclined to keep eating garlic, but wait for some more confirmatory evidence before committing to the use of supplemental AGE for cardiovascular disease risk management.

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