Garlic-Townsend Letter

Garlic (Allium sativum) is a well-known culinary and therapeutic herb which has been used since ancient times in many parts of the world. A feature of the Alliaceae family is the presence of allylic sulfides. These are sulfur-containing compounds responsible for the characteristic smell of plants in this family. In recent decades considerable research interest has been focussed on the active constituents of garlic, and on the variety of products available commercially. The many types of modern garlic products have a number of therapeutic applications, but this monograph will mainly review the effects of garlic powder preparations on the cardiovascular system, although some information from dietary intake of garlic has been included.

Products & Constituents

The chemistry of garlic is complex and the multitude of garlic products available in the marketplace reflect this complexity. (1)

The major components of garlic cloves are the sulfur compounds, which make up about 2.0% or more of its dry weight. Of these, the amino acid S-allyl-cysteine sulfoxide known as alliin is the most important. This sulfoxide is compartmentalized in the cytoplasm of the cell and thus separated from the hydrolytic enzyme alliinase, which is present in the vacuole. Disruption of the cell compartment results in the release of alliinase and the breakdown of alliin to volatile sulfides. The strong smelling diallyl disulfide-D-oxide, known as allicin, makes up the majority of such products. Allicin is rather unstable and decomposes further, producing a range of compounds including diallyl sulfides (diallyl disulfide as the major product), ajoenes and vinyldithiins (see Figure 1).

The types of garlic preparations available to consumers can be divided into four main groups:

1. Carefully dried garlic powder which preserves the odorless compound alliin and the enzyme alliinase. On disintegration in the digestive tract of tablets or capsules containing this powder, alliin comes into contact with alliinase and is converted to allicin which has a strong odor. (This mimics the chemical process that occurs when a fresh clove of garlic is crushed). Allicin is unstable and breaks down further into the compounds described above. (It is important to note however that the metabolic pathways for allicin in the human body are not fully understood).

2. Aged garlic extracts or 'odorless' garlic products which are produced by a fermentation process. These preparations contain modified sulfur compounds such as S-allylcysteine.

3. Steam-distilled preparations of garlic (garlic oil) which are rich in diallyl sulfides.

4. Oil macerates or extracts where the crushed garlic is soaked in a vegetable oil over several weeks. Such preparations have been found to be rich in ajoene.

Of course, there is also the use of fresh or raw garlic, which is sometimes favoured by herbalists. Another way to make garlic powder products is to use a blend of garlic extract and garlic powder. The garlic extract (if made by an appropriate extraction technique) provides the source of alliin and the dried garlic powder provides the source of alliinase.

The primary objective of garlic powder preparations is to mimic the chemical reaction which takes place when fresh garlic is consumed. However the drying of garlic can affect the integrity of alliinase (2) and alliinase is inactivated by stomach acid. (3) Therefore high quality garlic powder preparations should be enteric-coated (acid resistant, dissolving in the small intestine) and the activity of the alliinase should be tested before the product is cleared for sale. This can be achieved by using US Pharmacopoeia Method 724A which measures the allicin produced when the product is subjected to simulated gastrointestinal dissolution conditions. (4)

Scientific Studies

Lipid Lowering Effects of Garlic Powder Products

Many studies have demonstrated the lipid-lowering effects of garlic and the results of two meta-analyses supported the premise that garlic acted as a lipid-lowering agent. The first of these examined five selected clinical trials on various garlic preparations with a total of 410 patients. (5) The authors Warshafsky and coworkers concluded that the best available evidence suggests that garlic, in an amount approximating one half to one clove per day, decreased total serum cholesterol levels by about 9%. About a year later a second meta-analysis was published by Silagy and Neil. (6) These scientists included 16 clinical trials for a total of 952 patients. Again a variety of garlic preparations were included in the meta-analysis. They found that garlic lowered cholesterol levels by 12%. The dosage required varied from 600-900 mg per day of garlic powder preparations to fresh garlic in the range of 10-20 g per day, over a 1-3 month period. Dried garlic powder preparations also lowered serum levels of triglycerid es.

Not long after this, Silagy Neil and coworkers published the results of a randomised, double-blind, placebo-controlled trial conducted on 115 individuals over six months. (7) They found no significant difference between garlic powder and placebo. When they added the results of their own trial to their previous meta-analysis, the outcome was still that garlic lowers cholesterol, albeit by a reduced amount. However, they did caution that publication bias (where positive outcomes are more likely to be published) might explain a false positive result from meta-analysis. This caution was picked up strongly by Beaglehole who, in a damning commentary in the Lancet, suggested that garlic was only useful as a culinary agent. (8) However, Beaglehole was also accused of publication bias in a follow-up letter, in that he may have been selective in his interpretation of what was still a positive meta-analysis. (9) Another letter questioned the value of the meta-analyses since they included what were, in effect, different pharmaceutical preparations of garlic. (10)

A later meta-analysis of clinical trials using garlic products for treating hypercholesterolemia arrived at a similar conclusion to Silagy and Neil (11) and several trials published since their meta-analysis have shown no effect on cholesterol levels (12 13) although others have found benefit. (14)

Recent publications have examined the problems surrounding the production of allicin from allicin-releasing tablet preparations of garlic. (4,15,16) The failure of five recent clinical trials to show significant reduction in serum cholesterol by nonenteric-coated garlic powder tablets, four of which used an allicin-standardised product (brand 1), contrasts to many prior positive trials with the same brand. Some evidence indicates that allicin, formed enzymatically from alliin, is favourable for the hypolipidaemic effects of garlic, although this issue is hotly debated between companies. Efficient allicin formation from tablets requires high tablet alliinase activity (the plant enzyme that converts alliin to allicin), protection of alliinase from gastric acid, and alliinase activation by rapid tablet disintegration at neutral pH. The study was undertaken to determine if impaired release of allicin from these tablets under US Pharmacopeia-defined gastrointestinal dissolution conditions could account for the inconsistency between the trials and if enteric-coated tablets release the expected amounts of allicin.

USP Method 724A in vitro drug release test was applied to 10 lots of brand 1, five each of which were manufactured during the years when the trials were positive or negative, as well as to brand 2 and 23 other brands of enteric-coated tablets.

The more recent lots of brand 1, manufactured when the negative trials were conducted, were found to be significantly less resistant to acid-disintegration (1.3 vs. 2.6 h, $p < 0.001$) than the older lots and to release three times less allicin (15 vs. 44% of their potential, $p < 0.001$). Brand 2 released no allicin at all. Most brands of enteric-coated tablets released <10% of their allicin claim, due to low tablet alliinase activity and slow buffer disintegration. Breath content of the allicin metabolite, allyl methyl sulfide, was found to correlate well with allicin release determined by USP 724A.

Ineffective allicin release is therefore a serious problem for most brands of garlic powder tablets and is centered on alliinase activity rather than alliin content. This may well account for much of the discrepancy found in the clinical trial outcomes. Clinical trials employing garlic powder supplements should make sure the allicin release has been determined under USP-standardised drug release conditions.

But perhaps the real value of garlic in the prevention and treatment of cardiovascular disease lies elsewhere. For example, a recent double-blind, placebo-controlled study on 23 patients found that garlic powder tablets reduced the atherogenicity of low density lipoprotein (p value not specified). This reduction may be due to increased sialic acid content rather than to decreased susceptibility to oxidation. (17) In a controlled retrospective study on healthy adults (aged 50 to 80 years), 101 individuals who had been taking a garlic powder preparation for two years or more were compared with 101 controls. (18) Pulse wave velocity (PWV) and elastic vascular resistance (EVR) were used to measure the elastic properties of the aorta. While blood pressures, heart rate and plasma lipid levels were similar in the two groups, PWV ($p<0.000l$) and EVR ($p<0.000l$) were significantly lower in the garlic group. The authors concluded that chronic garlic powder intake reduced age-related increases in aortic stiffness.

The results of a randomized, double-blind, placebo-controlled clinical trial suggest that intake of high-dose garlic powder may provide a curative as well as a preventive role in atherosclerosis. After two years of treatment the garlic tablets significantly reduced the increased plaque volume in the carotid and femoral arteries by 5-18%.(19) The integrity of this study was hotly debated in scientific journals.

Blood Pressure Lowering Effect

A meta-analysis of eight clinical trials (415 patients), all using the same garlic powder preparation, found that garlic caused a modest but significant reduction in both systolic and diastolic blood pressures. (20) Only three of the trials were specifically conducted in hypertensive patients, and many had other methodological shortcomings.

Effects of Garlic Powder Products on Blood Parameters

A platelet-inhibiting effect has been described for garlic. (21) In a double-blind, placebo-controlled study on 60 volunteers with elevated cerebrovascular risk factors and increased spontaneous platelet aggregation, it was demonstrated that 800 mg of garlic powder per day over 4 weeks led to a significant reduction in platelet aggregation and

circulating platelet aggregates ($p<0.01$). There were no significant changes in the placebo group and garlic treatment was significantly different to placebo ($p<0.05$). This inhibition of platelet aggregation for garlic powder was confirmed by another research group. (22) However, the confounding issue of the various dosage forms of garlic was highlighted by a study of an oil extract of garlic, which found no significant effect on platelet aggregation, (23) and yet a more recent trial on an oil extract observed inhibition of induced platelet aggregation. (24) In contrast, consumption of a fresh clove of garlic daily for a period of 16 weeks reduced serum thromboxane by ab out 80%. (25) One of the compounds responsible for the antiplatelet effect of garlic powder could be ajoene. (28) This compound inhibits aggregation induced by all known platelet agonists in all species studied and prevents the amplification of platelet responses. Unlike aspirin it acts by modifying the platelet membrane structure. Other compounds may also be responsible, since diallyl disulfide and diallyl trisulfide were shown to inhibit platelet thromboxane formation and platelet aggregation. (24)

A review of studies found that garlic consistently increased fibrinolytic activity after single or multiple doses. (27) Garlic oil and garlic powder were both active, sometimes after only a single dose. The average increase in the reviewed studies was 58%. A 1991 controlled study using raw garlic demonstrated a significant increase in clotting time and fibrinolytic activity after two months in normal volunteers. (28)

A number of case reports have reflected these effects of garlic on bleeding parameters. A spontaneous spinal epidural hematoma associated with platelet dysfunction from excessive garlic ingestion was reported. (29) A patient taking garlic prior to cosmetic surgery experienced bleeding complications and had a clotting time of 12.5 minutes. (30) After cessation of garlic her clotting time dropped to 6 minutes and there were no complications during a second procedure. A 72-year-old man underwent transurethral resection for benign hyperplasia of the prostate. (31) The resection was 'bloody,' hemostasis was only moderate and he required blood transfusions. He was not on any medication apart from garlic tablets which he had taken for many years.

In a randomized, placebo-controlled, double-blind, crossover study on ten healthy volunteers, a single dose of 600 mg of garlic powder significantly reduced haematocrit ($p<0.001$), plasma viscosity ($p<0.05$) and plasma fibrinogen ($p<0.05$). (32) Fibrinolytic activity was also significantly increased ($p<0.01$). (33) A similar study design also found that a single 900 mg dose of garlic powder significantly increased capillary skin perfusion by 55% ($p<0.01$). The difference between garlic and placebo was also significant ($p<0.01$). This observed increase in erythrocyte velocity resulted from vasodilation of precapillary arterioles, which increased the diameter of the erythocyte column by 8.6%. Simultaneous inflow of interstitial fluid accompanied by a decrease in haematocrit and plasma viscosity occurred. A related trial yielded similar results for conjunctival blood vessels. (24)

Conclusion

The value of garlic powder products as a prevention and treatment for cardiovascular disease will be best determined by controlled clinical trials using cardiovascular morbidity or mortality as end-points. In the meantime, garlic can be used on the basis that it does favorably influence hemorrheological parameters (blood flow characteristics) and some cardiovascular risk factors. However, only enteric-coated products with allicin-releasing potential verified by USP methodology can be expected to significantly lower serum cholesterol.

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