Significance of Garlic and Its Constituents in Cancer and Cardiovascular Disease

Diallylsulfide and Allylmethylsulfide Are Uniquely Effective among Organosulfur Compounds in Inhibiting CYP2E1 Protein in Animal Models

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ABSTRACT Garlic is a popular culinary herb that is also used throughout the world as a traditional medicine for the prevention and treatment of disease. Epidemiologic studies have suggested that long-term consumption of garlic reduces risk for certain cancers, most notably stomach and colon cancer. This article summarizes the key findings behind one important mechanism explaining the anticarcinogenic effects of garlic-derived agents in animal models: the inhibition of cytochrome p4502E1 (CYP2E1), with some commentary on other aspects of carcinogen metabolism modified by these unique phytochemicals. J. Nutr. 136: 832S–834S, 2006.

KEY WORDS: • garlic • colon cancer • CYP2E12e1 • carcinogenesis • chemoprevention

It has long been known that populations that have relied more on plants in their diets have lower risks for common cancers, such as those of the breast, colon, lung, and prostate (1). On the basis of these observations and a wealth of experimental evidence, national health agencies have taken a strong position on the benefits of adding fruits and vegetables to the diet in the hope of preventing chronic diseases (2). Although official dietary advice has not extended to particular herbs and spices, there has, again, been a wealth of studies indicating that these minor dietary components may harbor phytochemicals with significant biologic activity that can prevent cancer (3–5).

The aroma and taste of herbs and spices have always suggested health-promoting properties. Notable among the culinary herbs are members of the family Alliaceae, and probably the most popular of the edible alliums is garlic (Allium sativum). The characteristic odor and taste of garlic have fascinated chemists for years (6,7). As with any natural product, the responsible phytochemicals fall into water-soluble and lipid-soluble classes. Garlic derives its taste and smell through the generation of organosulfur compounds when cell walls of the bulb are breached (8). An enzyme, allinase, acts on a precursor molecule called allin, forming allicin. Allicin is an unstable compound that breaks down under a variety of conditions, especially heat, to generate the myriad organosulfur compounds responsible for garlic’s culinary and medicinal properties (9–11). Through the work of food chemists seeking flavorings for processed foods, many organosulfur compounds have made been available for research purposes. However, it must be remembered that the garlic bulb generates these molecules when the cell wall is compromised to elicit a response to injury. Garlic and its constituents have antibacterial, antifungal, and antiviral properties (12). Some of these compounds that enhance the survival of the plant may help to prevent cancer in humans. Animal models for cancer have been widely used as an intermediate step toward an understanding of how phytochemicals might have preventive effects in humans. "Garlic constituents: effects in animal cancer models."

Because of the general availability of purified organosulfur compounds from garlic, many of them have been tested in animal models for cancer (13–18). A partial list of the garlic constituents that have been investigated in animal models is...
Organosulfur compounds from garlic tested in animal cancer models

<table>
<thead>
<tr>
<th>Structure Name</th>
<th>Model</th>
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<tbody>
<tr>
<td>CH₃ = CH -CH₂-S-CH₂-CH = CH₂ diallyl sulfide (DAS)</td>
<td>Colon</td>
</tr>
<tr>
<td>CH₃ -CH₂ -CH₂ -S -CH₂-CH₂ -CH₂-CH₃ dipropyl sulfide (DPS)</td>
<td>Mammary</td>
</tr>
<tr>
<td>CH₃ -CH₂ -CH₂ -S -CH₂-CH₂ -CH₂ -CH₃ diallyl disulfide (DADS)</td>
<td>Mammary</td>
</tr>
<tr>
<td>CH₃ -CH₂ -CH₂ -S -CH₂-CH₂ -CH₂ -CH₂ -CH₃ di-n-propyl disulfide (DPDS)</td>
<td>Mammary</td>
</tr>
<tr>
<td>CH₂-S-CH₂-CH = CH₂ allyl methyl sulfide (AMS)</td>
<td>DMBA</td>
</tr>
<tr>
<td>CH₂ -CH₂ -CH₂ -S -CH₂-CH₂ -CH₂ -CH₂ -CH₃ allyl allyl methyl sulfide (APAS)</td>
<td>MNJU</td>
</tr>
<tr>
<td>CH₂ = CH -CH₂ -S -CH₂-CH₂-CH₂ -CH₂ -CH₂ -COOH S-allylcysteine (SAC)</td>
<td>DMBA/BaP</td>
</tr>
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that CYP2E1 is inhibited by this particular carcinogen, and this effect serves as a model for several nitrosamines, including dimethylnitrosamine, diethylnitrosamine, liver carcinogens, colon carcinogens, and small-bowel carcinogens.

F344 rats have been used for the majority of studies on the chemopreventive effects of garlic. In these experiments, these animals are administered clearly defined semipurified diets, with the only variable being an oral dose of diallylsulfide or other garlic compounds. We have found that oral doses in excess of 50 mg/kg effectively shut down the CYP2E1 protein, indicating that 50 mg/kg is the inflection point in animal studies in which this CYP can be suppressed. Suppression of CYP2E1 in our studies effectively occurs by ~24 h after administration, which may possibly reflect what would happen if garlic were consumed on a daily basis.

Diallylsulfide is one of the more effective garlic compounds in terms of shutting down the CYP2E1 protein, as is diallylsulfide. The propyl allyl compounds, however, are not effective as inhibitors for CYP2E1. With regard to transcription and posttranscriptional activity, the lipophilic garlic compounds do not appear to have any effect on mRNA levels; however, there is an effect on synthesis of proteins, suggestive of a possible mechanism.

In terms of the water-soluble garlic compounds, studies of structure-activity relations indicate that, again, an allyl compound attached to sulfur with a methyl group is one of the strongest inhibitors of the CYP2E1 protein. Interestingly, s-allylcysteine is not a very good inhibitor of CYP2E1. In a comparison of the water-soluble compounds with the lipophilic compounds with regard to potency, the lipophilic compounds have been found to be much more potent. As is the case with the lipophilic compounds, the water-soluble compounds of garlic do not appear to have an effect on CYP2E1 mRNA.

Our research has also addressed the effects of sustained exposure to oil-soluble garlic compounds. Short-term exposure to diallylsulfide results in a rapid functional loss of CYP2E1, and we have used F344 rats as a proxy to mimic human chronic exposure to these compounds over an extended period. A strong suppression of CYP2E1 protein is observed after 4 wk of animal exposure by oral intubation, and by 8 wk of sustained suppression, the influence of CYP2E1 is eliminated. This raises questions regarding potential interactions with drugs or low-molecular-weight compounds that are metabolized through CYP2E1 and regarding the effects of garlic in a long-term situation in which CYP2E1 is not present. Longer-term studies have suggested that liver damage could ensue under these conditions. A comparison of allylmethylsulfide and diallylsulfide indicates that over time, diallylsulfide increases liver weight. Histologic studies indicate that some cholangitis is evident in diallylsulfide-treated animals in their livers after at least 8 wk. This is unlikely to be of concern in humans, because the doses of sulfur compounds used in these trials are much higher than those that would be consumed by humans.
higher than those in typical exposure to humans, as are the doses of carcinogen. Additional research has shown that diallylsulfide is a very effective substrate for CYP2E1 and goes through several passes in the liver, producing diallylsulfoxide and diallylsulfone, which are eventually ubiquitinated and destined for proteosomal degradation (23).

DISCUSSION

Taken together, research results from our laboratory indicate that of the many organosulfur compounds tested, only diallylsulfide and allylmethylsulfide are effective in significantly reducing levels of hepatic CYP2E1 protein, indicating that the presence of an allylic side chain coupled to a single sulfur is necessary—perhaps ideal—for inhibition of the CYP2E1 protein. This finding correlates highly with the chemopreventive effects in models of carcinogenesis wherein CYP2E1 activates the carcinogen. Phase II enzymes involve a general response of an organism to xenobiotic plant exposure. When the lipid-soluble compounds are examined, no significant structure-activity effect or conclusion can be drawn. However, although it is difficult to generalize, research indicates that garlic compounds do induce Phase II enzymes, particularly glutathione-S-transferase, uridine diphosphate-glucuronyl transferase, and quinone reductase. Generally, the greater the number of sulfur atoms in a given compound, the better inducer it is of these Phase II enzymes. Trisulfurs are more effective inducers of glutathione-S-transferase than are disulfurs and monosulfurs (24–26).

This observation also explains the results in many classic animal models. Induction of glutathione-S-transferases and other detoxification enzymes may not be specific to garlic and its constituents but is generally related to xenobiotics in plants. However, sulfur chemistry appears to dictate induction of this class of enzymes. Inhibition of CYP2E1 may not be relevant in human cancers, except where exposure to low-molecular-weight aliphatic carcinogens is known or suspected. There is some concern about side effects (e.g., acetaminophen metabolism). The future development of genetic models of cancer may reveal more about garlic’s true chemopreventive potential.

LITERATURE CITED