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Anticarcinogenic and antitumorigenic effect of Garlic and factors affecting its activity: A Review

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ABSTRACT

Garlic (Allium satium) belongs to family Liliaceae, contains various chemical compounds which are helpful in prevention and treatment of different types of cancer. Both oil and water-soluble allyl sulfur compounds from garlic have been found to possess antitumorogenic properties. Generally, oil-soluble allyl sulfur compounds are more effective antiproliferative agents than their water-soluble counterparts. The ability of these compounds to suppress proliferation is associated with a depression in cell cycle progression and the induction of apoptosis. This depression in cell division coincides with an increase in the percentage of cells blocked in the G2/M phase of the cell cycle. A depression in p34cdc2 kinase may account for this blockage in cell division. Preclinical and clinical studies suggested that allicin- a compound responsible for the antitumour and antitumorigenic effect. Part of the protection from these compounds probably inhibit the enzyme cytochrome P450 2E1. This enzyme activates a number of xenobiotic substances, including carcinogens such as nitrosamines, hydrazines and halogenated hydrocarbons. This review will focus on evidence that garlic is anticarcinogenic and antitumorigenic and identify some dietary components that should be considered as important variables when assessing the true anticancer potential of garlic and the factor affecting its activity.

KEY WORDS: Garlic, antitumour, antitumorigenic, allyl sulfur

INTRODUCTION

Garlic (Allium satium) is the edible bulb of the lily family, Liliaceae. It contains the aromatic sulfur-based compounds, which contribute to the Characteristic odour and taste, as well as garlic beneficial healing effects (1). Among the different chemical compounds found in garlic, allicin (2-propenyl 2-propenethiosulfinate) has long been recognized as the main antimicrobial agents of crushed garlic cloves (2). More recent studies have provided strong evidence that allicin is also essential to most of the hypolipidemic effects of garlic, and much of the antithrombotic, antioxidant, and anticancer effects of garlic also appear to be due to allicin (3). It is a remarkable plant, which has multiple beneficial effects. A number of studies have been demonstrated the chemopreventive activity of garlic by using different garlic preparations including fresh garlic extract, aged garlic, garlic oil and a number of organosulfur compounds derived from garlic. Fresh and ground garlic has been shown to inhibit cancer growth (4-7). Epidemiologic studies in China and Italy indicate that frequent consumption of garlic associated with decreased gastric cancer incidence (8-9), skin (10-13), cervical (14), fore stomach (15), lung (16), colon (17) and oesophageal tumours (18). These and other biological activities of garlic have been reviewed (19-22). Collectively, these studies provide evidence that increased consumption of garlic is accompanied by a marked reduction in cancer risk and tumour behaviour.

ANTICARCINOGENIC AND ANTITUMORIGENIC ACTIVITY

The use of garlic in the treatment of tumours dates all the way back to 1550 BC when ancient Egyptians administered it orally and topically; the modern era, however, begins in the 1950s when Weisberg and Pensky (23) demonstrated in vitro and in vivo that thiosulfinate extracts of garlic inhibited the growth of malignant cells and prevented growth of sarcoma 180 ascites tumour. Since that time, garlic has been demonstrated in epidemiologic studies to be associated with a reduced risk of stomach cancer (9) and, in animal models, to have antitumour activity in sarcoma, mammary carcinoma, hepatoma, colon cancer, and squamous cell carcinoma of skin and oesophagus (19).

Several lines of evidence point to allyl sulfur compounds as potentially important antitumorigenic agents (24-37). Some of the allyl sulfur compounds that have been found to alter significantly the proliferation of neoplastic cells (Table 1). The ability of these compounds to depress tumour cells of different origin suggests that a critical stage in the cancer process is being modified. Active cellular proliferation appears to be a factor in enhancing the growth inhibitory affects ascribed to allyl sulfides (33). Scharfenberg et al (31) found that A549 lung and BJA-B Burkitt lymphoma cells were more than twice as sensitive to the antiproliferative effects of DATS and ajoene than were nonneoplastic MRC-5 lung and FS4/BHK fibroblasts cells. In vivo studies provide evidence that the observations made in vitro have physiologic significance (23, 38-40). Studies from Sundaram and Milner (39) and Pinto et al. (29) provide evidence that the allyl group is instrumental in bringing about the growth depression. However, not all allyl sulfides are equal in their ability to reduce tumor proliferation (29, 34). Studies by Sundaram and Milner (34) demonstrated that diallyl sulfide, DADS and diallyl...
trisulfide (DATS) were far more effective in retarding the growth of neoplasms than were water-soluble allyl sulfur compounds such as SAC. Shifts in the cell cycle have been found to correlate with the depression in growth of neoplasms treated with DADS (25). The loss of cancer progression after treatment with allyl sulfur compounds likely relates to several epigenetic changes. Two extensively examined mechanisms for epigenetic gene regulation are patterns of DNA methylation and histone acetylations/deacetylations. Several studies indicate that DNA hypermethylation is an important factor involved in the activity of key regulatory genes. DNA methylation and histone acetylation can be modified by enhanced intake of garlic and/or related allyl sulfur compounds. Ludeke et al. (41) reported that DAS inhibited the formation of O\textsuperscript{2}-methyldeoxyguanosine in esophagus (26%), nasal mucosa (51%), trachea (68%) and lung (78%) that arose after treatment with N-nitrosomethylbenzylamine. Similarly, studies by Lin et al. (42) and Schaffer et al. (43) provide evidence that DADS, SAC and deodorized garlic are effective in retarding the DNA methylation caused by NMU. Lea et al. (44) reported that at least part of the ability of DADS to induce differentiation in DS19 mouse erythroleukemic cells might relate to its ability to increase histone acetylation. Diallyl disulfide caused a marked increase in the acetylation of H4 and H3 histones in DS19 and K562 human leukemic cells, consistent with other studies showing that the disulfide was more effective that the monosulfide. Similarly results were also obtained with rat hepatoma and human breast cancer cells. Allyl mercaptan was a more potent inhibitor of histone deacetylase than diallyl disulfide. Interestingly, DADS has also been reported to inhibit the growth of H-ras oncogene-transformed tumours in nude mice (40). This inhibition correlated with the inhibition of p21\textsuperscript{WAF1} membrane association in the tumor tissue. As the molecular targets for allyl sulfur compounds become more evident, it will become easier to determine who might benefit most from their exaggerated intake.

**POSSIBLE MECHANISM**

The exact pharmacologic mechanism for anticarcinogenic and antitumorigenic activity of garlic has not yet been determined. Both water-soluble and lipid-soluble allyl sulfides can influence a number of molecular events involved with cancer (Fig. 1). These include inhibiting mutagenesis, blocking carcinogen DNA adduct formation, scavenging free radicals, as well as blocking cell proliferation, differentiation, and angiogenesis. Although there is a large body of evidence supporting each of these and other mechanisms, there is a need for additional research to demonstrate whether these changes are causally related to a cancer-preventive activity or not. Below is a brief account of some of the evidence linking garlic and related sulfur compounds with some of the processes linked to cancer.

**ALLYL SULFIDES AFFECT CELL DIVISION**

Lipid-soluble allyl sulfur compounds are formed from the parent sulfur compound allin by the action of allinase, an enzyme released by crushing or chopping of garlic. Some of the more commonly used lipidsoluble allyl sulfur compounds in tumorigenesis research are ajoene, diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS). Water-soluble compounds can also occur in garlic, especially after alcoholic fermentation. Basically, γ-glutamyl-S-allylcysteine, a parent compound to allin, is converted to S-allylcysteine (SAC), S-allylmercaptocysteine (SAMC) and others. (45) Lipid soluble DAS, DADS and DATS (100 µmol/L) were more effective in suppressing canine tumor cell proliferation than isomolar water-soluble SAC, S-ethylycysteine and S-propylcysteine (34). SAMC, one of the more effective water-soluble allyl sulfur compounds, did not reduce the viability of human erythroleukemia cells until concentrations reached ~100 µmol/L (33). The breakdown of allicin, a product of alliin, appears to be necessary for achieving maximum growth inhibition. Studies by Scharfenberg et al. (31) found that the 50% effective dose for lymphoma cells was 2 times lower for ajoene than for alllicin. This true difference in efficacy may be even larger because the instability of allicin (46) may have resulted in downstream products that accounted for some of its effects. The antiproliferative effect of garlic’s organosulfur compounds is dependent on the allyl and sulfur groups (34, 39). Similar to chemical carcinogenesis, the antitumorigenic effects of organosulfur compounds are not limited to a specific tissue or a particular cell type (Table 2).

**CELL CYCLE**

Uncontrolled cellular division caused by the transformation of genetic material is a primary cancer characteristic. Nonneoplastic cell division is governed by a tightly controlled process that is regulated at several checkpoints by internal and external signals (47). A number of antitumorigenic compounds modify division by blocking cells within the G\textsubscript{1}, S or G\textsubscript{2}/M phases of the cell cycle (48-50). Increased DADS exposure led to a proportional increase in the percentage of cells arrested in the G\textsubscript{2}/M phase of the cell cycle (25). Although the G\textsubscript{2}/M accumulation was evident within 4 h after DADS exposure, cell numbers were not influenced until 8 h. These changes in cell division induced by DADS were found not to be permanent because refeeding was accompanied by a return toward a normal cell cycle (25). Cells exposed to DADS (25 and 50 µmol/L) also recovered on their own from treatment. Exposure to 25 µmol/L DADS resulted in a return to normal cell cycle distribution by 12 h, whereas it took longer for cells to recover from the higher concentration. This return to normalcy after low exposure to DADS suggests that cells can adapt by either changing their rates of absorption or metabolism of allyl sulfur compounds. SAMC and DAS have also been reported to increase the percentage of cells blocked within the G\textsubscript{2}/M phase (51-52). Within 6 h, 250 mol/L SAMC resulted in a G\textsubscript{2}/M phase arrest (51). The transitory increase in G\textsubscript{2}/M cells was also evident after exposure to DAS (52). Thus, the induction of a G\textsubscript{2}/M phase arrest may explain the observed antiproliferative properties of a number of allyl sulfur compounds. The ability of garlic to block the G\textsubscript{2}/M phase is not limited to in vitro studies. Kimura and Yamamoto (53) observed an increased number of metaphase-arrested tumor cells in MTK sarcoma III xenographs in rats fed an aqueous extract of garlic (1-10 mg/100 g body) for 4 d.
Table 1. Allyl sulfides with antineoplastic properties

<table>
<thead>
<tr>
<th>Sulfur compound</th>
<th>Cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajoene</td>
<td>Lymphocytes, colonic, leukemic</td>
</tr>
<tr>
<td>Allicin</td>
<td>Lymphoid</td>
</tr>
<tr>
<td>Diallyl sulfide</td>
<td>Prostate, leukocytes</td>
</tr>
<tr>
<td>Diallyl disulfide</td>
<td>Lung, colonic, skin, prostate, mammary</td>
</tr>
<tr>
<td>Diallyl trisulfide</td>
<td>Lung</td>
</tr>
<tr>
<td>S-Allyl cysteine</td>
<td>Neuroblastoma, melanoma</td>
</tr>
<tr>
<td>S-Allylmercaptocysteine</td>
<td>Prostate, mammary</td>
</tr>
</tbody>
</table>

Table 2. Studies documenting the inhibitory effects of organosulfur compounds isolated from garlic on cultured human tumor cell proliferation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tissues</th>
<th>Cell line</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allicin</td>
<td>Lymphoid</td>
<td>BJA-B</td>
<td>31</td>
</tr>
<tr>
<td>Ajoene</td>
<td>Lymphoid</td>
<td>BJA-B</td>
<td>31,32</td>
</tr>
<tr>
<td>Diallyl sulfide</td>
<td>Prostate</td>
<td>LNCaP</td>
<td>29</td>
</tr>
<tr>
<td>Diallyl disulfide</td>
<td>Lung</td>
<td>A549</td>
<td>30, 39</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>HCT-15</td>
<td>25,39,43</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>SK MEL-2</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>LNCaP</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BeWo</td>
<td>77</td>
</tr>
<tr>
<td>Diallyl trisulfide</td>
<td>Lung</td>
<td>A549</td>
<td>30</td>
</tr>
<tr>
<td>S-Allylcysteine</td>
<td>Skin</td>
<td>UCLASO-M7, M10, M12, M14, M16, M25, M210, M223</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>LNCaP</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Neural crest</td>
<td>LA-N-5</td>
<td>37</td>
</tr>
<tr>
<td>S-Allylmercaptocysteine</td>
<td>Blood</td>
<td>HEL, OCIM-1</td>
<td>33,51</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>MCF-7</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>CRL-1740, LNCaP</td>
<td>29,33</td>
</tr>
</tbody>
</table>

Table 3. Tests showing heating reduces the effects of garlic

<table>
<thead>
<tr>
<th>Garlic Preparation</th>
<th>Temperature</th>
<th>Testing</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic bulb</td>
<td>60-100°C</td>
<td>Fungal growth</td>
<td>79</td>
</tr>
<tr>
<td>Green garlic</td>
<td>60-80°C</td>
<td>Fungal growth</td>
<td>79</td>
</tr>
<tr>
<td>Garlic</td>
<td>Boiling</td>
<td>Bacterial growth</td>
<td>83</td>
</tr>
<tr>
<td>Garlic</td>
<td>Boiling</td>
<td>TXB₂ level</td>
<td>80</td>
</tr>
<tr>
<td>Garlic</td>
<td>100°C/20, 40 and 60 min</td>
<td>Oxygen free radical-scavenging activity</td>
<td>82</td>
</tr>
<tr>
<td>Garlic</td>
<td>Boiling</td>
<td>Cyclooxygenase activity</td>
<td>81</td>
</tr>
<tr>
<td>Garlic</td>
<td>Heating</td>
<td>Antioxidant</td>
<td>84</td>
</tr>
<tr>
<td>Garlic</td>
<td>Boiling</td>
<td>Prostagland synthesis</td>
<td>85</td>
</tr>
<tr>
<td>Garlic</td>
<td>Boiling</td>
<td>Bacteria growth</td>
<td>78</td>
</tr>
</tbody>
</table>

Figure 1. Dietary garlic may influence genetic and epigenetic events associated with several disease states, including cancer. Alterations in each of these processes are highly dependent on the form and quantity of allyl sulfur and the duration of exposure.
Figure 2. Illustration of the p34cyclin B

The p34cyclin B kinase complex

The p34cyclin B kinase complex governs the progression of cells from the G1 into the M phase of the cell cycle. Activation of this complex promotes chromosomal condensation and cytoskeletal reorganization through the phosphorylation of multiple substrates, including histone H1 (41, 54). Factors that inhibit p34cyclin B kinase activity lead to a block in the G1/M phase. Recent studies provide evidence that the G2/M phase arrest induced by DADS coincides with suppression in p34cyclin B kinase activity (25). Exposure of synchronized HCT-15 cells to 50 µmol/L DADS resulted in 60% suppression in p34cyclin B kinase activity. The formation of the p34cyclin B kinase complex is controlled by the association of the p34cyclin B catalytic unit with the cyclin B1 regulatory unit (55). Activation of this complex is governed by both cyclin B1 protein synthesis and degradation, and by the phosphorylation and dephosphorylation of threonine and tyrosine residues on the p34cyclin B subunit (54-55). The formation of the p34cyclin B complex and its conversion to the active kinase (Fig. 2). Recent studies provide evidence that a 12-h exposure to 50 µmol/L DADS causes a twofold increase in cyclin B1 protein expression in cultured HCT-15 cells (25). Thus, other factors involved with the p34cyclin B kinase must account for the ability of DADS to inhibit its activity.

MULTIPLE TARGETS

Carcinogen bioactivation

Studies using a variety of chemical carcinogens indicate that the anticancer properties associated with garlic are not limited to a specific animal species or to a particular tissue and that both lipid- and water-soluble allyl sulfur compounds are effective. Because different types of allyl sulfur compounds offer protection against chemical carcinogenesis, multiple mechanisms are possible (56-59). Certainly, it does not appear that a single mechanism could account for the observed protection based on the variety of carcinogens that have been examined. Nevertheless, a carcinogenic class that appears to be particularly sensitive to blockage by water- and lipid-soluble allyl sulfur is the nitrosamines by forming nitrosothiols (60). Their decrease in carcinogenicity may stem from an impediment in the formation and/or bioactivation of nitrosamines (59, 60). A competitive block or autocatalysis of cytochrome 2E1 (CYP2E1), a member of the cytochrome P-450 superfamily, may account for part of this inhibition, at least for lipid-soluble organosulfur agents (59). DAS is sequentially converted to diallylsulfide and diallylsulfone by CYP2E1. Whereas polymorphisms in CYP2E1 might logically be assumed to influence the response to garlic, no such relation has been observed at least with the risk of esophageal and stomach cancer (61). Nevertheless, several studies have shown that a number of garlic compounds can reduce CYP2E1 activity presumably by serving as a competitive inhibitor. Because allyl sulfurs inhibit the actions of several carcinogens not requiring CYP2E1 activity, it is logical to assume that alterations in other phase I, or phase II, enzymatic targets may also account for protection (58, 59, 62, 63).

Hormonal regulation

The association between estrogen exposure, either with or without progestin, and breast cancer risk continues to be a topic of immense interest and debate (64). Whereas no significant effects of garlic or its constituents on estradiol metabolism have been reported, a change in the biological response to diethylstilbestrol (DES), a synthetic estrogen known to increase mammary cancer in animal models, has been observed (65). Part of the effects of DES may stem from its ability to increase lipid hydroperoxides in mammary tissue. Recent studies demonstrate that this increase in ROS can be attenuated by providing DES in the diet. This reduction was also related to a depression in DNA adducts (65). The androgen dependence of the prostate gland, as well as some other tissues, is well established. Tissue culture studies provide evidence that several allyl sulfur compounds, in particular S-allylmercaptocysteine (SAMC), can enhance the rate of testosterone disappearance from the medium and presumably account for part of the antitumorigenic properties of this agent (66). Collectively, SAMC treatment behaves similarly to androgen deprivation and thus provides clues that this effect may be mediated, at least in part, by the diminished effects of testosterone. Whereas it remains to be determined which mechanism accounts for these changes, it
is conceivable that it involves the conversion of testosterone to metabolites that are less reactive with receptors (66).

**Inflammation and immunocompetence**

Part of the anticancer properties linked with garlic may arise from its ability to alter inflammation and subsequent immunocompetence. Leukocyte helper cells and inflammatory cytokine production have been reported to be reduced significantly in the presence of garlic extract (67). Studies by Lang et al. (68) suggest that allicin exerts an inhibitory immunomodulatory effect on intestinal epithelial cells and may thereby attenuate intestinal inflammation. Their studies revealed that allicin markedly inhibited the spontaneous and TNF-α-induced secretion of IL-1β, IL-8, IP-10, and monokine induced by INF-γ (MIG) from the two different cell lines in a dose-dependent manner and suppressed the expression of IL-8 and IL-18 mRNA levels. In addition, allicin was found to suppress the degradation of IκB. However, the effect is complex because garlic derivatives appear to have both stimulatory (69) and inhibitory (70) properties in lymphocyte proliferation and LPS-induced TNF-α generation. Whether these variations in response relate to the type of sulfur compound tested, the duration of exposure, or some other modifier remains to be determined. The nonsteroidal anti-inflammatory drug (NSAID)-activated gene (NAG-1) has been reported to possess both proapoptotic and antitumorigenic activities and is up-regulated by anticancer agents such as NSAIDs and, more recently, by DADS (71). Studies in vitro revealed that DADS treatment led to an induction of NAG-1 in a dose-dependent manner and that the induction of p53 preceded that of NAG-1. DADS did not induce NAG-1 or p53 in a p53 mutant cell line (71).

**Antiproliferation and apoptosis**

A variety of allyl sulphur compounds have been reported to reduce the growth rate of neoplastic cells in culture and in vivo (66,72,73,74). At least part of this reduced growth rate relates to a blockage in the cell cycle and most frequently in the G2/M phase. Most evidence points to the transitory nature of this inhibition, suggesting that the rate of clearance of allyl sulfur from cells is a determinant of the overall response. It is also clear that not all cells are equally susceptible to the deleterious effects of these sulfur compounds and, in particular, non-neoplastic cells tend to be less susceptible. As the concentration of the allyl sulfur compound increases, there is also a shift from depression in cell proliferation to greater involvement of apoptosis. This response may again relate to several changes with the cell as a consequence of an increase in oxidative stress caused by the various test compounds (75). Overall, the antiproliferative and apoptotic responses are dependent on the presence of the allyl molecule and the number of sulfur atoms. DATS is often observed to be .10 times more effective than DADS in retarding tumors. As reviewed previously, alterations in several molecular targets may explain the antiproliferative and apoptotic effects of allyl sulfur compounds (56,66,72,73,75). As additional information about the specific targets for the various allyl sulfur compounds surfaces, it will be possible to develop better models for predicting those individuals who will benefit most from dietary change. This nutritional pre-emption approach should allow for the use of specific foods, such as garlic, at critical points that allow for a block in the initiation and progression of a pathway that leads to an unhealthy or lethal phenotype.

**FACTORS AFFECTING GARLIC ACTIVITY**

**Influencing of heating**

Chen et al. (78) found that boiling garlic at 100°C for 20 min completely suppressed its antibacterial activities. Research also showed that increasing the temperature from 60 to 100°C produced a significant decrease in the inhibitory effect of garlic bulbs against the fungi tested (79). Although garlic has been suggested for many years by epidemiology and laboratory experiments to have cardiovascular benefits, these health effects are lost in heat-treated garlic. In a recent study (80), a dose-dependent inhibition of serum thromboxane B2 (TXB2) concentration was observed in rats treated with aqueous extracts of raw garlic. However, boiled garlic extracts had little effect on TXB2 synthesis, even at a high concentration. Ali (81) also found that boiled garlic had little effect on inhibition of cyclooxygenase activity in rabbit tissue compared with raw garlic. Similarly, heating garlic to 100°C for 20, 40 or 60 min can reduce its antioxidant activity (82). A more complete list of the effects of heating on garlic's functioning can be found in Table 3. Microwave treatment of garlic for 30 s did not influence the degree of protection; however, garlic crushed or not crushed before microwave heating for 30 s resulted in a 62 and 61% reduction, respectively, in adduct formation. Microwaving uncrushed garlic for 60 s completely blocked the ability of garlic to suppress the adduct formation.

**Interaction with food components**

Various food components may modify the ability of garlic to influence the cancer process. Notable among these are the depression in response caused by variation in dietary sulfur amino acids, unsaturated fats, and selenium (76). In DNA carcinogen adduct studies; combining dietary garlic, selenite, and retinyl acetate was far superior to providing each ingredient individually. More recently, the effects of combining tomato and garlic were examined using a hamster buccal pouch carcinogenesis model (63). Combining tomato and garlic suppressed the incidence and mean tumor burden of hamster buccal pouch carcinomas that appeared to relate to a decrease in phase I enzyme and an increase in phase II
enzyme activities. The effect of combining bioactive food components on the antitumorigenic properties of allyl sulfur compounds has not been adequately examined (72). However, similar to that observed with chemical carcinogenesis, there is evidence of a greater effect of allyl sulfur when combined with selenium than when provided alone. As the era of molecular nutrition unfolds, a greater understanding about which of the many processes modified by garlic is critical to bringing about a phenotypic change. This information will be fundamental to the development of tailored strategies for reducing cancer burden. The identification of biomarkers that can be used to predict who will respond will be essential for effective intervention to occur.

CONCLUSION

Garlic and its related compounds (DAS, DADS, DATS, SAC and SANC) have inhibitory effects on chemical carcinogenesis and mutagenesis. The ability of these compounds to competitively inhibit a major carcinogen activating enzyme, CYP2E1, is a viable mechanism in systems in which CYP2E1 substrates are governed by a number of factors that modulate proliferation mutagenesis. The ability of these compounds to competitively

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