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Cancer Chemoprevention by Garlic - A Review

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Abstract

Natural products remain an important source of new drugs, new drug leads and new chemical entities. They offer a great opportunity to evaluate totally new chemical classes of anticancer agents, as novel lead compounds with potentially relevant mechanisms of action. Numerous agents identified from fruits and vegetables can used in anticancer therapy, of which Allium vegetables, especially garlic, is one among them. The anticarcinogenic effect of garlic is attributed to organosulfur compounds (OSC) such as alliin, alliinase, allicin, S-allyl cysteine (SAC), diallyldisulphide (DADS), diallyltrisulphide (DATS) and methylallyltrisuphide, which are highly effective in affording protection against cancer. Other beneficial effects include anti-atherosclerosis, blood lipids and sugar modulation, antifungal, antimicrobial, antithrombotic, cardiovascular disease treatment and stimulating immune system. Chewing or cutting the bulbs of garlic activates the enzyme allinase which transforms the amino acid alliin to allicin which is a precursor to several sulphur containing compounds that are responsible for the flavour, odour and pharmacological properties of *Allium sativum*. An attempt has been made to review current knowledge on molecular targets of cancer chemoprevention by OSC present in garlic.

Keywords: Natural products; Allium vegetables; Garlic; OSC; Cancer chemoprevention

Introduction

For thousands of years, man has been using natural products of animals, plants and microbial sources either in the pure forms or crude extracts to treat many diseases [1]. Garlic (*Allium sativum L.*) is one of those plants that were seriously investigated over several years and used for centuries to fight infectious diseases [2]. Garlic is known in different names such as stinking rose, rustic treacle, poor man's treacle, *Allium sativum*, and camphor of the poor, maindenhair tree and nectar of the Gods.

For almost three thousand years Garlic (Allium sativum) has been used in medicines and foodstuff as evidenced by ancient writings from China, Egypt, Greece, and India [3,4]. Epidemiological studies have shown that the enhanced dietary intake of garlic could reduce the incidence of various types of tumors [5-11]. Other beneficial effects include anti-atherosclerosis [12], blood lipids and sugar modulation [13], antifungal [14], antimicrobial [15], antithrombotic [16], cardiovascular disease treatment [17] and stimulating immune system [18]. The most recent classification of garlic based on nuclear ribosomal DNA [19] is shown in Table 1 and pharmacological actions and health-promoting benefits of garlic are summarized in Table 2.

Class	Liliopsida
Subclass	Liliidae
Superorder	Liliianae
order	Amary-llidales
Family	Alliaceae
Subfamily	Allioideae
Tribe	Allieae
Genus	Allium

Table 1: Classification of garlic based on nuclear ribosomal DNA.

Mechanisms of action	Health effect(s)
Anticarcinogenic/Antimutagentic	Inhibit cell division, induce apoptosis, block carcinogen activation, enhance DNA repair, induce detoxifying enzymes
Antimicrobial (antifungal, antiviral, antibacterial)	Inhibit microbiological growth as antibiotics
Antioxidant	Scavenge oxidizing agents, induce SOD, GPX, GST, catalase
Immunomodulatory	Increase proinflammatory cytokine release, stimulate natural killer cells
Anti-hypolipidemic	Inhibit enzymes in cholesterol and fatty acid synthesis
Anti-hypocholesterolemic	Inhibit cholesterol synthesis, enhance cholesterol turnover

Anti-hypertensive	Inhibit angiotensin II, induce NO and H_2S, cause vasodilation
Anti-diabetic	Stimulate insulin production, interfere glucose absorption
Anti-thrombic	Reduce trombosane formation, change platelet membrane
Hepatoprotective	Increase GSH levels by induction of GST

Table 2: Summary of garlic pharmacological actions and health-promoting benefits [20].

Potentially active chemical constituents of garlic

Allium sativum contains more than 100 biologically useful secondary metabolites, which include alliin, alliinase, allicin, S-allyl cysteine (SAC), diallyldisulphide (DADS), diallyltrisulphide (DATS) and methylallyltrisuphide. The γ-glutamyl-S-alk(en)yl-L-cysteines are the primary sulfur compounds in the intact garlic, which can be hydrolyzed and oxidized to yield S-alkyl(en) yl-L-cysteine sulfoxide (alliin). Chewing or cutting the bulbs of garlic activates the enzyme allinase which transforms the amino acid alliin to allicin which is a precursor to several sulphur containing compounds that are responsible for the flavour, odour and pharmacological properties of Allium. Allicin is highly unstable and instantly decompose to form various oil-soluble compounds involving diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), vinyl dithiin and ajoene if conditions are appropriate [21]. At the same time, γ-glutamyl -S-alk(en)yl-L-cysteines are also converted to water-soluble organosulfur compounds including S-allyl cysteine (SAC) and S-allyl mercaptocysteine (SAMC). Water-soluble organosulfur compounds are odorless and possess more delicate and less characteristic flavor compared to the oil-soluble organosulfur compounds [22]. Recent studies revealed that the antioxidant properties of garlic are due to presence of bioflavonoids quercetin and cyanidin [23]. The transformed pathways and chemical structures of the widely studied organosulfur compounds are depicted in Figure 1.

Apart from above said sulphur compounds, garlic also contains several enzymes; minerals germanium, calcium, copper, iron, potassium, magnesium, selenium, zinc; vitamins A, B1, C, amino acids, fiber and water [24].

Mechanism of anticarcinogenic activity of garlic

Possible anticarcinogenic mechanisms of garlic and its constituents may include the inhibition of carcinogen activation [25], the enhancement of detoxification [26], excretion [27], and the protection of DNA from activated carcinogens [28]. Furthermore, DATS reduced mitosis in tumors, decreased histone deacetylase activity, increased acetylation of H3 and H4, inhibited cell cycle progression, and decreased pro-tumor markers (survivin, Bcl-2, c-Myc, mTOR, EGFR, VEGF) [29]. Garlic components have been found to block covalent binding of carcinogens to DNA, enhance degradation of carcinogens, have anti-oxidative and free radical scavenging properties, and regulate cell proliferation, apoptosis, and immune responses. Ajoene, garlic-derived natural compound, have been shown to induce apoptosis in human leukemic cells via stimulation of peroxide production, activation of caspase-3-like and caspase-8 activity. Garlic synergizes the effect of a breast cancer suppressor, eicosapentaenoic acid, and antagonizes the effect of a breast cancer enhancer, linoleic acid [30].

Modulation of activity of phase I and phase II metabolizing enzymes by garlic organosulfur compounds

To protect all living organisms from environmental toxic effects biotransformation of xenobiotics is important. In mammalian systems these xenobiotic metabolizing enzymes are usually classified as phase I and phase II enzymes. Drug metabolism starts with phase I reactions, generally modifying the functional groups, while phase II reactions involve conjugation with endogenous compounds, thus facilitating the excretion from the body.

Modulation of activity of phase I metabolizing enzymes

Increased or decreased activities of specific CYP450 enzymes which play a key role in catalyzing the microsomal biotransformation of many xenobiotic compounds [31,32] can be directly beneficial by decreasing metabolism and/or increasing excretion of some carcinogens as well as by circumventing the DNA damage. Various garlic active components have been found to exert their chemopreventive effect by selectively enhancing or suppressing the levels of cytochrome P450 genes or proteins [32,33].

CYP2E1 is responsible for the activation of numerous carcinogenic chemicals [34]. The CYP2E1 enzyme kinetics studies performed using diallyl sulfide as a substrate have revealed that the sulfur atom on diallyl sulfide is oxidized by CYP2E1 to diallyl sulfone (DASO), then subsequently to diallyl sulfoxide (DASO2) and the final metabolite was an epoxide, generated by oxidation of the terminal double bond of $DASO_2$, which bonded irreversibly to the CYP2E1 enzyme and lead to the autocatalytic destruction of the enzyme [35,36]. Diallyl sulfide (DAS), diallyl disulfide (DADS), and allyl mercaptan (AM) suppressed hepatic CYP2E1 protein expression and N-nitrosodimethylamine demethylase (NDMA) activity in a time- and NADPH-dependent manner [37] while the alkyl sulfides such as dipropyl sulfide (DPS), dipropyl disulfide (DPDS), and propyl methyl sulfide (PMS) did not inhibit the hepatic CYP2E1 protein expression, indicating that the alkenyl group on the organosulfur compounds may be critical for inhibiting the CYP2E1 enzyme [38].

Modulation of activity of phase II metabolizing enzymes

Garlic constituents may function as a double-edge sword in the prevention of chemically induced cancers by inhibiting carcinogen activation and enhancing detoxification of activated carcinogenic intermediates through the induction of Phase 2 enzymes [39-42] such as glutathione S-transferase (GST), epoxide hydrolase (EH), quinone reductase (QR), and UDPglucuronosyl transferase (UGT), [43]. Recently, special emphasis has been placed on the study of the effects of the garlic organosulfur compounds on the GST enzymes. GSTs are detoxification enzymes, that catalyze the conjugation of a wide variety of electrophiles and carcinogens with glutathione (GSH) [42]. Diallyl sulfide (DAS), allyl methyl disulfide (AMDS), allyl methyl trisulfide

(AMTS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and S-allyl cysteine (SAC) compared to their corresponding saturated compounds in which propyl groups were substituted for the allyl groups were found to be an inducer of GST, catalyzing the conjugation of a wide variety of electrophiles and carcinogens with glutathione (GSH) in the forestomach, small-bowel mucosa, liver, colon and lung of mice [42,44-47]. DATS possessing triple sulfur bonds (–S–S–S) in its structure was found to be the most active than mono and di-sulfur compounds in the induction of detoxifying enzymes while the saturated analogs were almost without inhibitory activity, indicating the importance of the allyl group on the sulfides. Organosulfur compounds exert antitumor properties by up-regulation of the GST-α, GST-μ, and GST-π [41,48-53]. Lipid-soluble organosulfur compounds increased the activity of GST as well as other detoxifying enzymes such as epoxide hydrolase (EH), quinone reductase (QR), and UDP-glucuronosyl transferase (UGT). Thus, it is reasonable to conclude that the induction of Phase 2 enzymes, especially GST, represents another potential mechanism to explain OSC-mediated prevention of chemically induced cancers.

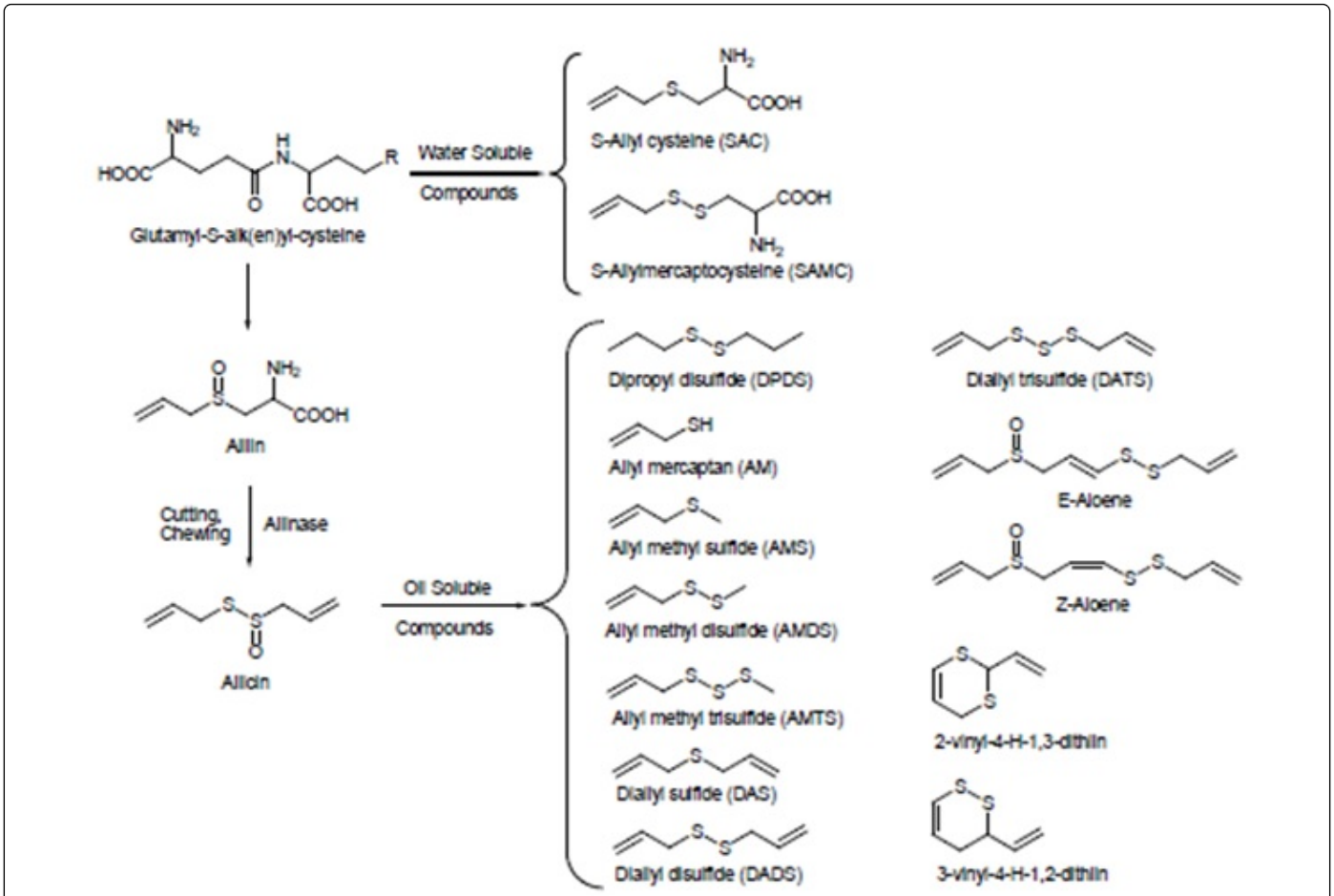

Figure 1: Chemical structures of commonly studied organosulfur compounds from garlic [20].

Inhibition of post-translational modification of oncogenic ras

Studies from Prof Shivendra V Singh laboratory have revealed that oral administration of DADS (8.25, 16.5 and 33 μmol, 3 times per week beginning the day of tumor cell injection), but not its saturated analogue dipropyl disulfide, suppressed growth of H-ras oncogene transformed tumor xenografts in nude mice without causing weight loss or any other side effects [54,55].

Inhibition of cell cycle progression

Cellular stresses may activate signal transduction pathways, referred to as checkpoints, which ensure completion of phase specific events and protect against genomic instability or, in cases where the damage is too severe, switch the cell fate to programmed cell death [56,57]. Studies have shown that garlic-derived OSC can suppress growth of cancer cells of different anatomical locations in association with cell cycle arrest, mainly in the G2/M phase of the cell cycle. The DADS-mediated G2/M phase cell cycle arrest in human colon cancer cells was accompanied by a decrease in the kinase activity of the Cdk1/cyclin B1 complex, reduction in complex formation between Cdk1 and cyclin B1, and a decrease in Cdc25C protein level [58]. Thorough investigation of the mechanism of DATS-induced G2/M phase cell cycle arrest using PC-3 and DU145 human prostate cancer cells as a model [59-62] have revealed that DATS was much more effective than either DADS or DAS in causing G2/M phase cell cycle arrest [59] and further show that even a subtle change in OSC structure (the oligosulfide chain length) could have a significant impact on its

biological activity. Further studies on the DATS-treated PC-3 cells revealed that Chk1, which is an intermediary of DNA damage checkpoints [63], may regulate APC/C activity [61,63]. The mechanism of DATS-induced G2/M phase cell cycle arrest in human prostate cancer cells is shown in Figure 2.

Recent studies have revealed that DATS-mediated cell cycle arrest in human prostate cancer cells is linked to c-Jun N-terminal kinase (JNK)-dependent generation of reactive oxygen species (ROS) which appears to be caused by degradation of the iron-storage protein ferritin that leads to liberation of labile (chelatable) iron [62]. OSC affect the microtubule network in cancer cells that might initiate mitotic block or apoptosis. DATS has been shown to induce mitotic arrest in HCT-15 and DLD-1 human colon cancer cells in association with disruption of the microtubule network in interphase cells and inhibition of spindle formation in mitotic cells and further revealed DATS-mediated oxidative modification of tubulin β at residues Cys12 and Cys354 [64]. Z-ajoene, an oil-soluble garlic compound caused G2/M phase cell cycle arrest and disruption of the microtubule network in normal marsupial kidney cells and inhibited tubulin polymerization in vitro [65]. A few reports have also shown that garlic-derived OSC arrest cancer cells in phases other than G2/M [66,67].

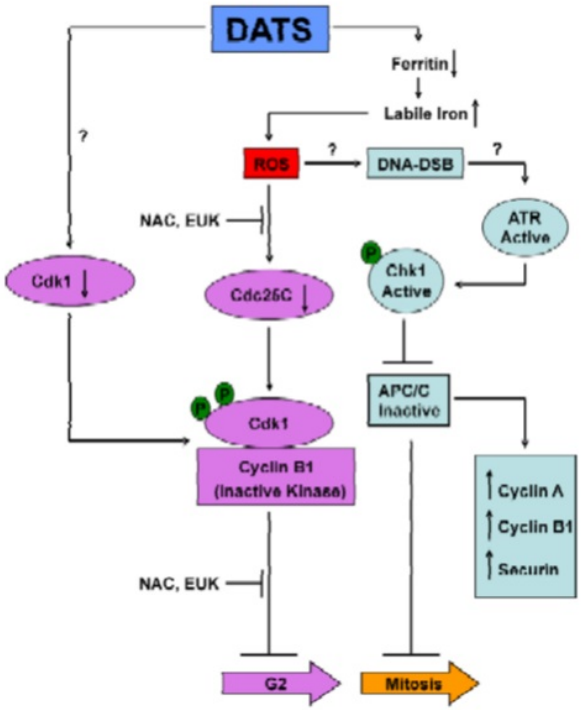

Figure 2: Proposed mechanisms to explain DATS-induced G2 and M phase cell cycle arrest in human prostate cancer cells [62].

Histone modification

OSC may affect cancer cell proliferation through modification of histone acetylation and, thus, regulation of gene expression [68].

Induction of programmed cell death (apoptosis)

Apoptosis (also known as programmed cell death) is a tightly controlled process whose dysregulation leads to numerous pathological conditions including cancer, therefore, apoptosis is a valid target in cancer therapy and prevention [69,70]. Garlic-derived OSC have been shown to modulate a number of key elements in cellular signal transduction pathways linked to the apoptotic process.

Intrinsic or mitochondria-mediated pathway in the execution of apoptosis, involves loss of mitochondrial membrane potential and release of apoptogenic molecules from the mitochondria to the cytosol [71,72] whose activation is regulated by the Bcl-2 family of anti-apoptotic (Bcl-2 and Bcl-xL) and proapoptotic (eg Bax and Bak) proteins [73]. Garlic-derived OSC are believed to trigger apoptosis by modulating the levels of Bcl-2 proteins. The mechanism of DATS-induced apoptosis in human prostate cancer cells is summarized in Figure 3. ROS was found to play critical role as an intermediary of OSC-induced apoptosis [74,75]. OSC might also induce apoptosis from an increase in free intracellular calcium [76-80].

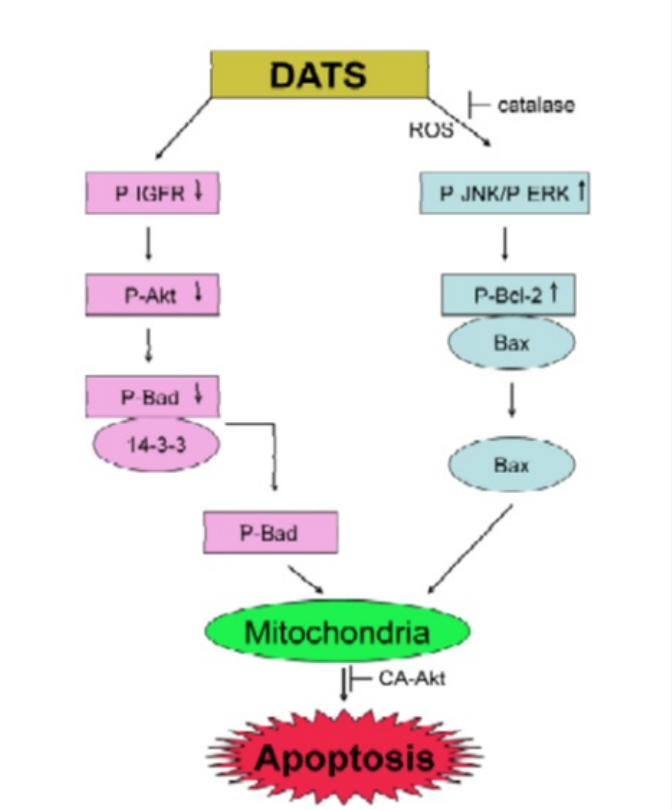

Figure 3: Proposed mechanisms for DATS-induced apoptosis in human prostate cancer cells [81].

Inhibition of angiogenesis and metastasis by garlic constituents

Studies by Matrigel chemoinvasion assay performed by Matsuura et al. [80] showed that aged garlic extract (AGE) suppressed proliferation of transformed human and rat endothelial cell lines and reduced the invasiveness of the endothelial cells by about 20%–30%. Additional

tests that were conducted indicated that AGE increased the adhesion of the endothelial cells to collagen and fibronectin in a dose-dependent manner, thereby, reducing their motility and finally, AGE reduced capillary-like tube formation by the endothelial cells in a three-dimensional collagen matrix assay [82]. Examination of the effects of DAS, DADS and DATS on human umbilical vein endothelial cell (HUVEC) viability have shown that DATS is the most potent of the three analogs in reducing the viability of HUVEC and was correlated with caspase 3 and PARP cleavage and apoptotic cell death [83]. The DATS treatment was able to significantly disrupt the capillary-like tube formation and migration by HUVEC which was accompanied by suppression of vascular endothelial growth factor (VEGF) secretion, downregulation of VEGF-Receptor 2 expression, inactivation of Akt and activation of ERK 1/2 [83]. Alliin was shown to reduce VEGF and fibroblast growth factor 2- (FGF-2) induced tube formation and angiogenesis in HUVEC and ex vivo in CAM assay [81]. Studies by Taylor et al. [84] have shown that ip injection of ajoene (5–25 μg/g body weight) significantly inhibited pulmonary metastasis in C57BL/6 mice injected with B16/BL6 melanoma cells. Thus, based on the above reviewed studies it can be concluded that components of garlic extract (in combination or alone) present a great potential as antiangiogenic and antimetastatic agents [82-90].

Modulation of multidrug resistance proteins and P-glycoproteins

One of the major challenges of effective anticancer chemotherapy is multidrug resistance (MDR). There are two main transporter proteins involved in establishing the multidrug resistance in cancer cells: P-glycoprotein (P-gp) and multidrug resistance protein 2 (Mrp2) [91-93].

Development of MDR in human cancers such as leukemias, lymphomas, multiple myeloma, neuroblastoma, and soft tissue sarcoma has been related to the over-expression of the ATP-binding cassette transporter P-gp [93]. Mrp2 is an ATP-dependent transporter for organic anions that contributes to the drug resistance by transporting a wide range of glutathione, glucuronate and sulfate conjugates out of cells [94]. Organosulfur compounds present in garlic products have different effects on the P-glycoprotein (P-gp) and multidrug-resistant proteins (Mrp1 and Mrp2) in the chemotherapeutic treatments of various tumors and therefore further studies are required to clarify the mechanisms of organosulfur compounds in affecting the cancer multidrug resistance.

Conclusion

Research over the past 25 years has revealed that garlic derived OSC appear to target multiple pathways, including the cell cycle machinery, the intrinsic pathway for apoptotic cell death and angiogenic pathway, which may all contribute to their anticancer activities. Some garlic organo sulphur compounds have been shown to protect against toxicants and carcinogens by inhibition of enzymatic activation of pro-toxicants and by increasing tissue activities of enzymes that protect against electrophiles. The enhanced detoxification and liver protection of garlic organosulfur compounds could be attributed to the modulation of cytochrome P450 phase-I and II enzymes such as CYP2E1 and GST. Future research should focus on clinical assessment of these compounds for prevention/treatment of cancers in humans.

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