J. Food Sci. Nutr.
Vol. 2, No. 2. p. 180~190(1997)

Garlic and Cancer Prevention

-Review-

Eun-Sil Kim†, Hui-Chung Chun*, Byong-Ki Kim and Khee-Choon Rhee*****

Dept. of Traditional Cuisine, Hallym Junior College, Chuncheon 200-805, Korea
**Dept. of Food and Nutrition, Sook Myung Women's University, Seoul 140-742, Korea*
***Dept. of Food Engineering, Dankook University, Cheonan 330-714, Korea*
****Food Protein Research & Development Center, The Texas A&M University System, College Station. TX 77843-2476, USA*

Abstract

Garlic(*Allium sativum* L.), originated in the Kirghiz region of Central Asia, is one of the oldest cultivated plants. It has reached Europe via Egypt in the days of Pharaohs. Since then, the legendary medicinal properties attributed to garlic have attracted human interests for thousands of years. However, the research on the medicinal effect of garlic, mostly on its anticarcinogenic actions has been systematically performed only for the last two or three decades. Many researches have proven that garlic inhibits neoplasia elicited by chemical carcinogens using *in vitro* or *in vivo* experimental systems. Attention has recently been focused on assessing the therapeutic or chemopreventive measures of garlic compounds against carcinogenesis in animals. The active principles of the garlic extract, mainly the sulfur compounds and their derivatives have been deeply scrutinized into their chemical, functional and medicinal properties.

Key words: garlic, allicin, anticarcinogen, sulfur compounds, medical property

INTRODUCTION

A great majority of human cancers, perhaps as much as 80~90%, are attributable to environmental factors (1). Improved surgical practice has significantly reduced cancer mortality. The use of additional treatment modalities, such as radiotherapy and chemotherapy has resulted in no more than a 5% reduction in the number of deaths(2). It has been estimated that a high percentage of cancer in humans is related to dietary factors(3). Thus dietary modification has been considered a powerful and cost-effective method for reducing cancer incidences. Dietary factors which may lower cancer rises have also been identified. Examples include dietary fiber, cruciferous vegetables, antioxidant vitamins and minerals(4).

The legendary medicinal properties attributed to garlic have attracted human interest for centuries(5). It has been experimentally demonstrated that several minor dietary constituents inhibit neoplasia induced by chemical carcinogens(6). Attention has been given recently to assess any possible chemopreventive properties of garlic oil in chemical carcinogenesis of animals. Strong smell compounds are distinguishable by an allyl (CH_2=$CHCH_2$) or methyl grouping bonded to sulfur(7). Although the mechanism of action for the medicinal effects remains obscure, there is little doubt that sulfur-rich chemicals have pharmacological activities(4). The medicinal value of garlic is now believed to be due to the properties of its active principle, allylthiosulfinic ester, allicin(8).

Allicin is produced by the enzymatic degradation of alliin, S-allyl-L-cysteine-S-oxide. Inhibition of sulfhydryl enzymes is associated with the presence of the -SO-S-group(9). This report deals with some antitumor effects observed with a series of compounds in relation to the active principle of garlic. A study of these compounds has started because of the observation that an active principle of garlic, allicin, can inactivate many sulfhydryl(-SH) enzymes to affect rapidly with related malignancies. The availability of reduced -SH compounds has often been shown in the processes of cell growth and division. Observations supporting the importance of -SH compounds in these processes include the following: 1) a high -SH content in multiplying tissues, 2) the increase in soluble thiols within the cell prior to cell division and 3) the inhibition of cell division by thiol poisons, such as alkylating agents and heavy metals. Substances which oxidize -SH compounds(-SH →

†Corresponding author

-S-S-) may also act as inhibitors. Reduced -SH compounds may stimulate cell growth and division. In some instances, the inhibition of cell division by -SH poisons can be reversed by -SH compounds such as cysteine, glutathione or thioglycolate present in a wide variety of biological subjects. Additional dietary inhibitors of cancer are expected to be discovered(10).

GARLIC IN HISTORY

Garlic is one of the most popular cooking ingredients throughout the world. It is a bulbous plant of the lily family, *Liliaceae* which includes onion, garlic, leek, and so on. Its botanical name, genus '*Allium*' means any strong-smelling bulb plant of this family(11). The Latin name *Allium sativum* was given by Lannaeus in 1753 (12). It is one of the oldest of all cultivated plants(13) and is believed to be native to Kirghiz region(on the Soviet-China border) of Central Asia(14). The ancient 5,000-year-old Sanskrit, 4,500-year-old Babylonian and 3,000-year-old Chinese writings have referred this herb. In Old Testament, the wandering Hebrews in the wilderness regretted not having the garlic they had left behind in Egypt(15). Garlic probably reached Europe via Egypt in the days of the Pharaohs. For thousands of years they have been a part of folk medicine. The Greek historian Herodotus, who visited Egypt around 450 B.C., saw an inscription on the Great Pyramid of Cheops(built around 2800 B.C.) that recorded "-the quantity of radishes, onions and garlic consumed by the laborers who constructed it". Six actual bulbs of garlic were found stored in the tomb of King Tutankhamen(1350 B.C.)(16). Garlic was forbidden to Egyptian priests, and Roman senate prohibited the use of garlic for people who visit the temple of Cybele. Garlic is still a taboo for many Buddhist priests and Hindu Brahmans who believe this 'hot' food distracts minds and souls from a spiritual path. Aristotle, Hippocrates and Aristophanes praised garlic for its medicinal properties (14). The Roman naturalist Pliny the Elder recorded numerous therapeutic uses of garlic. During the first Olympic games in Greece, garlic had been eaten by athletes as a stimulant. Roman legionnaires attributed their strength, courage and stamina to garlic and took it with them as they conquered the world, thus spreading its use and cultivation wherever they went(17). Since then, garlic has been very important in the cooking and cultures of Mediterranean countries such as Italy, Spain and Turkey and countries on the North African coast, in particular, Morocco and Tunisia. In England and later in America, there had been quite a bit of resistance to garlic(18). In 1858, Louis Pasteur reported that garlic had an antibacterial property. In both World Wars, garlic had been used as an antiseptic in the prevention of gangrene. In France, horses suffering from blood clots in the legs were fed garlic. In America, native Americans used garlic as a charm to rid young maidens of unwanted suitors. In South America, revolutionary San Martin who led the fight for independence of Argentina, Chile and Peru in the 19th century had his men, horses and mules sniff and chew garlic to combat altitude sickness as they crossed the towering Andes mountain range. In Cuba, 13 cloves(each sections) of garlic at the end of a string worn around the neck for a period of exactly 13 days was regarded as a way to prevent jaundice.

Global production of garlic in 1995 was 7,811,000M/T. Asia predominantly accounts for 80% of the world production of garlic, whereas less amounts are grown in Europe(5%), the Americas(3%) and Africa(5%)(19).

TUMOR INHIBITION BY A SULFHYDRYL-BLOCKING AGENT RELATED TO GARLIC

Food contains a large number of inhibitors of carcinogenesis including phenols, indoles, aromatic isothiocyanates, methylated flavones, coumarins, plant sterols, selenium salts, protease inhibitors, ascorbic acid, tocopherols, retinol, allicin and carotenes(20-31). Inhibitors of carcinogenesis can be divided into three categories; 1) compounds that prevent the formation of carcinogens from precursor substances(eg. ascorbic acid and α-tocopherol), 2) compounds that act subsequently after exposure to carcinogenic agents. These are termed as 'suppressive agents' since they suppress the expression of neoplasia in cells previously exposed to doses of a carcinogenic agent(eg. retinoids)(32) and 3) compounds that prevent carcinogenic agents from reaching or reacting with critical target sites in the tissues. These are called 'blocking agents' descriptive of their mechanism of action(33). Most studies have been focused on blocking the initiation of carcinogenesis. Recently, it has been demonstrated that the neoplastic effects of promoters can also be prevented by blocking agents, in particular, antioxidants and garlic(34). Extracts of garlic contain a powerful bactericidal agent, allylthiosulfinic allyl ester (allicin)(23,35,36). This compound is formed by the in-

teraction of an enzyme and substrate present in garlic bulbs(37). The enzyme, alliinase, is liberated when the garlic bulb is crushed. It acts on the substrate, S-allyl L-cysteine sulfoxide (alliin) as follows(38):

$$2R\text{-}SO\text{-}CH_2\text{-}CH(NH_2)\text{-}COOH \xrightarrow{+H_2O} R\text{-}SO\text{-}S\text{-}R + 2CH_3\text{-}CO\text{-}COOH + 2NH_3$$

(alliin) (alliinase) (allicin)

where, R is $-CH_2-CH=CH_2$

Wills(39) reported that this reaction product inhibits many sulfhydryl(-SH) enzymes but no other enzymes. The structures required for bactericidal action and inactivation of -SH enzymes are closely related. Thus, compounds containing the -SO-S- groups are effective for both, whereas compounds containing the -SO-, -S-S- and -S- linkages are ineffective. The -SH inactivation obtained by alkylthiosulfinic alkyl ester may be the result of a strong combination of this compound with cysteine or may be due to oxidation of -SH to -S-S- by the labile oxygen(40). Although most of the allicin studies have been centered on its bactericidal action, its reactivity with -SH groups suggests the possible inhibitory effect on malignant cells. An increase in -SH compounds prior to cell division has been demonstrated in various tissues, plants and organisms(41). Reduced -SH compounds stimulate cell growth and division, whereas substances which oxidize -SH to -S-S- inhibit cell division. Thiol poisons may provide similar inhibition of cell division to alkylating agents and heavy metals. Abnormalities of -SH metabolism may be implicated in malignant cell growth since a high -SH content has been demonstrated in some tumor cells(42) or during the growth of tumors in plants inoculated with a tumor-producing microorganism(43). Low plasma -SH levels have been found during the growth phase of malignant tumors, and this has been attributed to an increased demand for -SH by the rapidly proliferating neoplasm(44). Observations supporting the importance of -SH compounds in these processes can be summarized as; 1) a high -SH content in proliferating tissues, 2) the increase in soluble thiols within the cell prior to cell division and 3) the inhibition of cell division by thiol (In some instances this can be reversed by -SH compounds such as cysteine, glutathione or thioglycolate) and 4) the decreased availability of these compounds may result in decreased tumor growth. Accordingly, diets deficient in the -SH amino acid or L-cysteine can suppress malignant tumor growth in some animals, whereas the addition of either cystine or glutathions to the diet can give an increase in tumor growth(45). The limited availability of sulfhydryl compounds has also seen in both normal and abnormal leukopoiesis. Substances which inactivate -SH groups such as x-ray, nitrogen mustard, arsenic, gold and benzol may produce leukopenia. Low -SH levels have been found in leukocytes in leukopenic states. The application of a high -SH content has been reported in several therapies of leukemic cell(46,47).

RESEARCH ON GARLICS ANTICARCINOGENIC EFFECT

Dietary intakes of garlic

Criss et al.(48) reported that dietary preparations from fresh garlic bulbs inhibited the growth of Morris hepatoma 3924. A low dietary protein could diminish the tumor growth as much as 60~70%. Furthermore, all diets containing 5% garlic yielded 10~25% decreased tumor growth. In another study(49), dietary garlic supplement significantly reduced the tumor size in a dose-related manner among groups of rats received a diet containing 5, 2.5 and 0%, respectively. Using an *in vitro* assay, garlic extract was shown to inhibit the guanylate cyclase activity of hepatoma cells. In studying the spontaneously-occurring tumors in mice, Kroning(50) found that the fresh garlic feedings could completely inhibit the mammary tumors in the C_3H mice. According to Choy et al. (51), the survival time of the intraperitoneal(i.p.) tumor-innoculated mice was significantly increased through dietary administration of garlic. 42~59% inhibitory effect on the growth of Ehrlich ascites in the peritoneal cavity was achieved by a daily dose of 0.6~1.2g of a dietary garlic suspension. Kim et al.(52) found that nodule formation was suppressed in hamsters fed garlic juice in contrast to control animals. The average nodule volume was 81.10mm for hamsters fed 3% garlic juice and 181.26mm for hamsters without garlic in their diet after 90 days of treatment. Liu et al.(53) studied the influence of dietary supplements of garlic powder(0, 1, 2 or 4%) on 7,12-dimethylbenz[a]anthracene(DMBA)-induced mammary tumors and on the *in vivo* occurrence of mammary DMBA-DNA adducts in rats. Dietary garlic powder supplementation significantly delayed the onset of first tumors($p<0.01$) and reduced the final

mammary tumor incidence($p<0.01$). Consumption of garlic powder also depressed the *in vivo* binding of DMBA to mammary cellular DNA significantly. The higher activity of glutathione S-transferase(GST) in mammary and liver tissues from rats fed 2% dietary garlic powder was observed than in tissues from rats fed the basal diet. Most recently, in 1997, Riggs et al.(54) studied the therapeutic effects of AS(*Allium sativum*) in the MBT2 murine bladder carcinoma model. Five weekly-immunizations of AS showed significantly reduced tumor incidence/growth and increased survival in animals than those received the saline control.

In the practical field study with human subjects, Mei et al.(55) reported that residents who consume an average of 20g of fresh garlic per person per diet at Shenshan people's commune in Changshan county(China) had a stomach cancer mortality rate of 3 per 100,000 populations. In another county, Qixia, where the residents lately began to consume garlic, the stomach cancer mortality rate was 40 per 100,000 populations. The nitrite concentration in gastric juice of the residents in Changshan county was significantly lower than that in Qixia county. Garlic may have inhibited nitrate reduction caused by bacteria in the stomach. Subsequently, the lower gastric nitrite(a nitrosamine precursor) concentration might have reduced the development of stomach cancer. Steinmetz et al.(56) monitored cancer incidence for 5 years via the State Health Registry of Iowa for 41,837 women aged 55~69 years who had completed a 127-item food frequency questionnaire in 1986. The result of prospective cohort study indicated that the consumption of garlic has been inversely related with risk, with an age- and energy-adjusted relative risk of 0.68(0.46~1.02, $p<0.05$) for the uppermost versus the lower most consumption levels.

Garlic oil and protein fraction

Belman(57) reported that tumor yield and incidence of phorbol-myristate-acetate promotion were inhibited in a dose-dependent manner over the range of 10~10,000mg onion oil, applied three times a week. Garlic oil was also inhibitory but was less effective. He also found that onion and garlic oil inhibited soybean lipoxygenase, an enzyme known to enhance the tumor promotion stage of carcinogenesis(58). Belman et al.(59) also found that onion and garlic oils(1mg, thrice a week) applied to the epidermis of mice inhibited the promotion caused by lipoxygenase and ornithine decarboxylase. The pure components ajoene from garlic and propenyl sulfide from onion were partly responsible for the inhibitory action. The allyl methyltrisulfide(AMT) of garlic oil given orally could increase GST activity which is related with inhibition of benzo[a]pyrene(BP)-induced tumor of mouse forestomach(60). In this study, greater than 70% reduction in the number of tumors was shown at the end of the experiment, although AMT was not effective in the lung.

To study the effects of garlic oil on tumor promoter activity, an experiment employing the two-step model of carcinogenesis in isolated epidermal cells was designed by Perchellet et al.(61). Here, garlic oil, onion oil and dipropenyl sulfide all increased glutathione peroxidase(GSH-PX) activity and inhibited ODC induction by various tumor promoters. In addition to the enhanced antioxidant protection noted by increased GSH-PX activity, garlic oil prevented the drop in the reduced/oxidized glutathione ratio(GSH/GSSG) that is usually accompanied by the treatment with promoters. According to Perchellet et al.(62), onion and garlic oils inhibited the TPA (12-*o*-tetradecanoylophorbol-13-acetate)-stimulated DNA synthesis when given as a single dose of 5mg, one hour before TPA administration. Garlic oil was the most effective when given one hour before TPA administration, but was also evident when given between two hours before and after TPA administration. Garlic oil is reported to rapidly(in 2~6 hours after single/multiple administration) lessen the cell number in S phase on cell cycle of S180 tumor cells. This suggests that garlic oil may blockade cells to progress from G1 phase to S phase, thus arresting cells in G1 phase and inhibit the synthesis of DNA and the cell cycle in the end(63).

The topical application of garlic oil was also effective in reducing skin tumors in Swiss Albino mice(64). Hirao et al.(65) have isolated a protein fraction from garlic. This fraction enhanced carbon clearance by *in vitro* macrophage cytotoxicity against P815 target cells and also stimulated proliferation of lymphocytes isolated from the spleen.

Garlic as a therapeutic or chemopreventive agent

The growth-inhibitory actions of garlic on various human and animal malignant tumors, including Jensen sarcoma and benzo[a]pyrene-induced sarcoma were reported as early as in 1950's(66). Garlic extract showed

antimitotic effects on MTK-sarcoma in Albino rats, resulting in damage of tumor cells(67). I.P. injection of fresh garlic extract rendered Ehrlich asites tumor cells non-tumorigenic during *in vitro* incubation as tumors failed to develop following i.p. injection of these attenuated cells, indicating the development of antitumor immunity(68). In comparison, all the control mice injected with tumor cells preincubated with saline died within two to four weeks. Lau et al.(69) studied the immunotherapeutic effects of garlic extract and other agents on hindlimb transplanted transitional cell carcinoma in mice. The intralesional administration was the most effective route. Tumor growth as well as the production of macrophages and lymphocytes which lead to cytotoxic destruction of tumor cells was inhibited by introducing five intralesional treatments of 25mg garlic extract to the bladders of mice which had been previously transplanted with murine transitional cell carcinoma. Marsh et al.(70) observed the cellular infiltration by macrophages and lymphocytes at tumor sites with a liquid garlic extract treatment into a murine bladder tumor model. More intense cellular infiltration was shown through the intralesional treatment, being heightened with repeated treatments. The necrosis and hemorrhage at tumor sites were the prominent features of garlic treatment.

Tumor cells(Ehrlich ascites) attenuated with either an aqueous or alcoholic extract rendered animals immune to subsequent challenge with viable tumor cells (71). It was also suggested that garlic could be developed as a potential chemopreventive agent for oral and gastric cancers. Meng and Shyu(72) found the inhibitory effect of topically applied garlic extract on DMBA-induced oral carcinogenesis in Syrian hamsters which was designed to define the local anticarcinogenicity of garlic. The apparent local inhibitory effect of garlic on DMBA-induced carcinogenesis was stronger than that of the two other cancer-inducing chemicals, BP(benzo[a]pyrene) and 5-nitroso-2,4,6-triaminopyrimidine(NTP) as testing materials. Kao et al.(73) also reported the similar result. Garlic could reduce the incidences of skin tumors to 31.8%($p<0.01$) in DMBA-induced carcinogenesis system from mice. Garlic gave another epidemiological evidence as a chemopreventive agent on gastric cancer(74). Kim and Chun(75) reported the anticarcinogenic effects of garlic juice against DMBA-induced hamster buccal pouch carcinoma in 135 hamsters. The BrdU immunoreactivity on normal pouch mucosa epithelium which represents the mitotic status was less in the garlic juice-feeding group than the control one. In contrast, all in the control group showed an invasive tumor growth histopathologically. Meanwhile, the neoplastic epithelium of all the experimental groups showed much increased BrdU immunostaining irregularity. In cancer prevention, Se-garlic, given continuously to the animals, could also inhibit the post-initiation phase of mammary carcinogenesis(76). In this case, a short-term exposure to the Se-garlic for 1 month immediately after carcinogen administration was just as effective as the continuous-exposure regimen(5 months), possibly due to the irreversible change in the process of clonal expansion and/or selection of transformed cells during their early stage of development. However, on the later intervention period (week 13 to 22) of mammary carcinogenesis, the number of new tumor-bearing rats in supplemented groups were statistically not different from control group.

Active principles of garlic

The inhibitory actions of sulfur compounds in garlic extract on various tumors have been widely discussed. Among them of which names of the compounds frequently are referred diallyl sulfide(DAS or DS, a natural extract of garlic), diallyl disulfide(DADS, an oil-soluble organosulfur compound in processed garlic), diallyl trisulfide(DAT), ajoene, S-allyl-cysteine, S-ethyl-cysteine and S-propyl-cysteine, and so on.

In 1949, VonEuler and Lindeman(77) found that pure alliin had a growth-inhibitory action on various tumors in rats, including Jensen Sarcoma and benzo[a]pyrene-induced sarcoma. Nakata(78) could reverse the development of Ehrlich ascites tumor and Yoshida sarcoma tumor cells in mice by injecting fresh garlic extract containing at least 2.77×10^{-3}M allicin. The inhibition of sarcoma 180 tumor growth was also observed by direct injection of isolated allicin or allithiamine(0.75mg) from garlic into the tumor site(79).

The role of -SO-S- linkage in the structure of allicin was experimentally defined by Weisberger and Pensky (80). Sarcoma 180 ascribes tumor incubated with the enzyme alliinase and the substrate S-ethyl-L-cysteine sulfoxide(0.07mg thiosulfinic per inoculum of 5,000,000 cells) was i.p. innoculated to CFW Swiss mice. Tumor growth was completely inhibited and survival of the animal was extended beyond the six-month observation period. The oxidation of -SH to -S-S- inhibited cell division, while a high -SH content has been noted in

some tumor cells. In addition, the extracts of garlic contained a bactericidal agent which had been formed by the action of an enzyme on a substrate present in garlic bulbs(81). The active principle formed in this enzymatic process is an alkylthiosulfinic alkylester(R-SO-S-R) which is an -SH inactivator and reacts rapidly with cysteine. Since normal and malignant growth of cell needs reduced -SH groups, several alkylthiosulfinic esters were assumed to have tumor inhibiting effects. Preincubating certain concentrations of enzymatically prepared allicin with tumor cells resulted in a complete inhibition of tumor growth.

A conflict of ideas exists concerning the inhibitory act of organosulfur compounds against carcinogenesis. Welch et al.(82) reported that S-allyl cysteine(SAC), a derivative of aged garlic extract, was unable to affect the *in vitro* proliferation and differentiation of LA-N-5 human neuroblastoma cells. SAC could not block retinoic acid and 8-bromo-cyclic AMP, agents known to enhance *in vitro* neuroblastoma cell growth, either. Similarly, in testing the modifying effects of four organosulfur compounds from garlic and onions, 1ALE, DPT and AM promoted hepatocarcinogenesis of diethylnitrosamine(DEN)-induced neoplasia of the male F344 rat liver, possibly due to increased cell proliferation with increased polyamine biosynthesis(83). In contrast, Sumiyoshi and Wargovich(84) reported that organosulfur compounds(OSC), present in garlic and onion oil could inhibit the chemical carcinogenesis. Oral administration of DAS and SAC, at a dose of 200mg/kg, 3 hours prior to i.p. 1,2-dimethylhydrazine(DMH) injection(20mg/kg) significantly inhibited the carcinogenesis. The allyl group containing a single sulfur atom might play an essential role in the inhibition of DMH-induced colonic nuclear toxicity and carcinogenesis. The OSC containing allyl groups stimulated glutathione S-transferase activity in both liver and colon.

Wargovich and Goldberg(85) found sulfide and disulfide components of garlic inhibit nuclear damage which leads to chemical carcinogenesis. The efficacy of the agents DAS and DADS as inhibitors was correlated with neoplastic growth in a mouse gastrointestinal epithelium as measured by a nuclear aberration bioassay. Wargovich et al.(86) reported that DAS inhibited the DNA-damaging and tumorigenic effects of N-nitrosomethybenzylamine(NMBA) administration. DAS inhibited the carcinogen-induced nuclear toxicity by 56 to 64% respectively at the two doses(3 and 5mg/kg) of NMBA tested. A nuclear damage in murine colon mucosal cells which occurred as a result of radiation treatment was partially inhibited by DAS pretreatment(87). The protection afforded by DAS was evident through the suppression of ornithine carboxylase activity, an enzyme important in the regulation of DNA synthesis. DAS also showed the potential to inhibit MNNG-induced nuclear aberration(NA) and ornithine decarboxylase (ODC) activity in Wistar rat glandular stomach mucosa(74). The parenteral pretreatment with DAS brought a significant and dose-dependent inhibition of NA and ODC activities, supporting the epidemiological evidence of garlic as a chemopreventive on gastric cancer. A suicide-inhibitory action of diallyl sulfide(DAS) by the competitive inhibition on P-450 II E1 which mediates *p*-nitrophenol hydroxylase activity was confirmed by Brady et al.(88). Ajoene and DAS, the organosulfur compounds of garlic, inhibited the metabolism and DNA binding of aflatoxin B_1(AFB_1) in rat liver 9,000×g supernatant, the metabolic activation system(89). DAS and capsaicin inhibited VC- and NDMA-induced mutagenesis/tumorigenesis, in part, through inhibition of the cytochrome P-450 II E1 isoform which activates these carcinogens. DAS, a thioether found in garlic, which inhibits P-450 II E1 selectively, also reduced the mutagenicity of the aforementioned carcinogens in a concentration-dependent manner. The mutagenesis correlated with their inhibition of P-450 II E1-mediated *p*-nitrophenol hydroxylation and NDMA N-demethylation by capsaicin and DAS. Pretreatment of female ICR mice with a topical dose of capsaicin lowered the average number of VC-induced skin tumors by 62% at 22 weeks after promotion. DAS also showed a similar result(90). Significant anticarcinogenic activities of diallyl selenide (DASe, volatile synthetic compound and DASe flavor component of garlic) in the DMBA-induced mammary tumor models were also found with the two doses of DASe and the highest dose of DAS(91).

The mechanisms by which DAS inhibits 1,2-dimethylhydrazine(DMH)-induced hepatocarcinogenicity of male Fischer 344 rats were examined by Hayes et al.(92). Rats were subjected to partial hepatectomy to stimulate hepatocellular proliferation initiated by DMH(50~200mg/kg, I.P.) given 12 hours later. Inhibition of hepatocarcinogenicity was rather due to the reduced post-necrotic regeneration of cells as low dosages of DAS preferentially binds with DMH, thus limiting the chance of reacting with tumor cells. Another inhibitory action

of DAS against DMH-induced colon and liver cancer in rodents(Sprague-Dawley rat) was reported by Brady et al.(93). The effect of oral administration of DAS on P-450ⅡE1, an isozyme of cytochrome P-450 which is active in the oxidative metabolism of DMH, was expressed by N-dimethylnitrosamine demethylase(NDMAd) activity at 1mM N-dimethyl nitrosamine in liver microsomal incubations. Here, DAS acted as a competitive inhibitor of NDMAd. Inhibition of the demethylation by DAS in several substrates occurred selectively. Microsomes prepared after intragastric administration of DAS(200mg/ng corn oil) showed a moderate (<30%) inhibition of several demethylase activities at 3 hours, followed by a marked decrease(about 80%) in NDMAd activity at 18 hours post-treatment. A minor effects on other demethylase activities and a 6-fold increase in pentoxyresorufin dealkylation were accompanied. These trends at 18 hours agreed with immunoblot analyses which showed a P-450ⅡE1 suppression and elevated P-450ⅡB1 levels.

Among six organosulfur compounds found in garlic, oil-soluble organosulfur compounds(diallyl sulfide, diallyl disulfide and diallyl trisulfide) markedly inhibited the growth of canine mammary neoplastic cell(CMT-131) in a dose-dependent manner. However, water-soluble organosulfur compounds(S-allyl-cysteine, S-ethyl-cysteine and S-propyl-cysteine) did not significantly alter the growth of CMT-13 cells when added to cultures at 1.0mM or less(94).

The diallyl disulfide(DADS), another major volatile compounds in garlic, along with DAS, has been also cited for its anticarcinogenic activities by many researchers. George and Eapen(95) found that garlic oil and its main component, DADS equally inhibited oxidative phosphorylation in hepatic mitochondria of mice. Takahashi et al.(96) reported that DS(or DAS) and DDS(or DADS) exert anticarcinogenic activity at several organs in rodents. DS showed a clear enhancing effect on the development of glutathione S-transferase placental form positive foci in both experiments. An inhibitory potential in colon and renal carcinogenesis was observed in rats treated with DDS. Therefore, it may be said that DS promotes hepatocarcinogenesis, while DDS acts as a chemopreventive.

Milner et al.(97) examined the antiproliferative effects of diallyl disulfide(DADS/DDS) on the growth of human colon tumor cell line xenografts(HCT-15) in 6-wk-old female NCr nu/nu mice(body weight, 20~22g). Intraperitoneal injection of 1mg DADS thrice weekly reduced tumor volume by 69%($p<0.05$) without apparent ill consequences, such as altered growth of the host. This quantity of DADS provided intragastrically also inhibited the growth of HCT-15 tumor. At equivalent dosages of DADS's, intraperitoneal treatment was proportionately more effective($p<0.05$) than gastric incubation in reducing tumor growth. The effectiveness of tumor inhibition of DADS treatment(0.5mg thrice weekly) was comparable with that of 5-fluorouracil(0.5mg thrice weekly). The similar study was performed by Sundaram et al.(98) who compared the treatment effect of 5-FU and DADS with the same testing subject as above. Intraperitoneal injection of DADS(1mg, thrice weekly) caused the similar occurrence as with 5-FU (10.5mg, thrice weekly). Combining DADS and 5-FU gave no more extra effects in inhibiting tumor growth than using either compound alone. However, concurrent treatment of DADS and 5-FU inhibited the depression significantly($p<0.05$) and prevented the elevation of plasma urea that is usually accompanied by a 5-FU treatment alone. It could be said that DADS reduces the toxicity of 5-FU and is an effective antitumorigenic agent against xenografts in established human colon tumor cell line. Sundaram et al.(99) found that DADS(oil-soluble) was more effective in inhibiting the *in vitro* growth of human tumor cell lines; HCT-15(colon), A549(lung) and SK MEL-2(skin) than SAC(water-soluble) in isomolar quantities. However, the saturated analogue, dipropyl disulfide(DPDS) lacked the comparable depression in the growth of HCT-15 cells, confirming the role of allyl- and disulfide groups. The activity of calcium-dependent APTase enzyme in HCT-15 cells decreased as quantities of DADS increased. Alteration in calcium homeostasis caused by DADS is likely being involved in the growth inhibition/cytotoxicity.

Deng et al.(100) studied the effect of diallyl trisulfide (DAT) on the induction of UDS by mutagenic drugs in primary rat hepatocytes. Results showed that 1.0~4.0nmol/ml of DAT did not induce UDS, while MMC, CP and DDP resulted in a significant induction of UDS dose-dependently. Instead, DAT enhanced induction of UDS by these drugs. A dose-effect relationship was observed between dose of DAT and enhanced induction of UDS.

CONCLUSION

The famous medicinal properties of the garlic have been proven through the extensive studies of the late 1940's to 1970's. The dietary administration, intraperitoneal injection or topical application of the garlic extract or its active compounds were experimentally proven to lessen or inhibit the malignant tumor development. Allicin(alkylthiosulfinic allyl ester), the enzymatically degraded product of alliin(S-allyl-L-cysteine-S-oxide) is now reported to provide the medicinal value of garlic as its active principle. The fact that cells depend upon the availability of reduced -SH groups for their normal and malignant growth indicates the possible role of several closely related alkylthiosulfinic esters in tumor inhibitory effects. Alliin can readily react with cysteine group of protein and inactivate by changing -SH's into -S-S's. In the latest research, several oil-soluble, sulfur-based compounds have been proven to inhibit the growth of tumor cells effectively. S-allyl cysteine(SAC), a water soluble sulfur compound found in processed garlic, is expected to make their effective use in preventing chemically induced cancer, rather than suppressing the tumor cell growth as had been reported in 1980's. On the occasion of 1990's, many studies have shown that diallyl sulfide(DAS) inhibited oral cancer, tumor cell in culture and the growth of human colon tumor cell. The epidemiological, clinical and laboratory data have proven that garlic has many medically important compounds which are profitable to keep human health from various cancers. It appears that garlic will play an important dietary role in the process of cancer as is evidenced by the fewer occurrences of stomach cancers, correlated with intakes of 20g of garlic per day in some areas of the world. Studies on the development of more effective and odorless garlic preparations, and the isolation of active compounds that may be therapeutically useful and defining functional mechanisms are the research subjects expected to be continued.

REFERENCES

1. Doll, R. : Strategy for detection of cancer hazards to man. *Nature*, **265**, 589(1977)
2. Cairns, J. : The treatment of disease and the war against cancer. *Sci. Am.*, **253**, 31(1985)
3. Willett, W. C. and MacMahon, B. : Diet and cancer-An overview. *New Eng. N. J. Med.*, **310**, 633(1974)
4. Ames, B. N. : Dietary carcinogens and anticarcinogens. *Science*, **221**, 1256(1983)
5. Bolton, S., Null, G. and Torete, W. M. : The medical uses of garlic-Fact and fiction. *Am. Pharm.*, **22**, 448(1982)
6. Wattenberg, L. W. : Inhibition of neoplasia by minor dietary constituents. *Cancer Res.*, **43**, 2448(1983)
7. Brodnitz, M. H., Pascale, J. V. and Derslice, L. V. : Flavor components of garlic extract. *Food Ch. J. Agric. M.*, **19**, 273(1971)
8. Stoll, A. and Seebeck, E. : Chemical investigations on alliin, the principle of garlic. *Adv. Enzymol.*, **11**, 377(1951)
9. Wills, E. D. : Enzyme inhibition by allicin, the principle of garlic. *J. Biochem.*, **63**, 514(1956)
10. Boyland, E. : Experiments on the chemotherapy of cancer. 1. The effect of certain antibacterial substances and related compounds. *Biochem. J.*, **32**, 1207(1933)
11. Fujiwara, M. and Natata, T. : Induction of tumor immunity with tumor cells treated with extract of garlic. *Nature*, **216**, 83(1967)
12. Tredici, P. D. : Never enough garlic *Horticulture*, October, p.15(1987)
13. Block, E. : The chemistry of garlic and onions. *Sci. Am.*, **252**, 114(1985)
14. Criss, W. E., Fakunle, J., Knight. E., Morris, H. P. and Dhillon, G. : Inhibition of tumor growth with low dietary protein and with dietary garlic extracts. Proc. 66th Ann. *Meeting Federation of Am. Soc. Exp. Biology*, **41**, 281 (1982)
15. Edmond, J. : The miracle of garlic and vinegar. Globe Communications corp. New York, p.13(1996)
16. Roger, F. G. and Hanley, A. B. : The genus *Allium*. Vol. 22, CRC, p.199(1996)
17. Warren, C. P. W. : Some aspects of medicine in the Greek bronze age. *Medical History*, **14**, 364(1970)
18. Airola, P. : The miracle of garlic. Health Plus Publishers, Phoenix, AZ, p 4(1978)
19. Gruffydd, R. F. and Anthony, B. H. : The genus *Allium*. Vol. 20, CRC, p.205(1996)
20. Jones, H. A. and Mann, L. K. : Onions and their Allies. Leonard Hill, Ltd., London, p.18(1963)
21. Cohen, B. I. and Raicht, R. F. : Plant sterols-Protective role in chemical carcinogenesis. In "*Inhibition of tumor induction and development*" Zedeck, M. S. and Lipkin, M. (eds.), New York Plenum Publishing Corp., New York, p.189(1981)
22. Cook, M. G. and McNamara, P. : Effect of dietary vitamin E on dimethylhydrazine-induced colonic tumors in mice. *Cancer Res.*, **40**, 1329(1980)
23. Griffin, A. C. : The chemopreventive role of selenium in carcinogenesis. In "*Molecular interrelations of nutrition and cancer*" Arnott, M. S., Eys, J. V. and Wang, Y. M. (eds.). New York Raven Press, p.401(1982)
24. Mathews, R. M. : Anti-tumor activity of beta-carotene, canthaxanthin and phytoene. *Oncology*, **39**, 33(1982)
25. Mergens, W. J., Kamm, J. J., Newmark, H. L., Fiddler, W. and Pensabene, J. : Alpha-tocopherol uses in preventing nitrosamine formation. In "*Environmental aspects of N-nitroso compounds*, No. 19" Walker, E. A., Castegnaro, M., Griciute, L. and Lyle, R. E.(eds.), International Agency for Research on Cancer(IARC) Publication, Lyon, France,

p.199(1978)
26. Mirvish, S. S. : Inhibition of the formation of carcinogenic N-nitroso compounds by ascorbic acid and other compounds. In "*Achievements, challenges and prospects for the 1980's cancer*" Burchenal, J. H. and Oettgen, H. F. (eds.), New York Grune and Stratton, p.557(1981)
27. Saffiotti, U., Montesano, R., Sellakumar, A. R. and Borg, S. A. : Experimental cancer of the lung-inhibition by vitamin A of the induction of tracheobronchial squamous metaplasia and squanous cell tumors. *Cancer*, **20**, 857(1967)
28. Saifter, E., Rettund, G. and Lebenson, S. M. : Dietary beta-carotene is an effective tumor preventive agent. Paper presented at 13th Annual Meeting of International Cancer Congress, Seattle, WA(1982)
29. Sparnins, V. L. and Wattenberg, L. W. : Enhancement of glutathione S-transferase activity of the mouse forestomach by inhibitors of benzo(a)pyrene-induced neoplasia of this anatomic site. *J. Natl. Cancer Inst.*, **66**, 769(1981)
30. Wattenberg, L. W. : Inhibitors of chemical carcinogens. In "*Cancer-Achievements, challenges and prospects for the 1980's*" Burchenal, J. H.(ed.), New York Grune and Stratton, New York, NY, p.517(1981)
31. Wattenberg, L. W. : Inhibitors of chemical carcinogens by minor dietary components. In "*Molecular interrelations of nutrition and cancer*" Arnott, M. S., Eys, J. V. and Wang, Y. M.(eds.), Raven Press, New York, NY, p.43(1982)
32. Sporn, M. B. and Newton, D. L. : Recent advances in the use of retinoides for cancer prevention. In "*Cancer-Achievements, challenges and prospects for the 1980's.*" Burchenal, J. H.(ed.), New York Grune and Stratton, New York, NY, p.541(1982)
33. Sparnins, V. L., Vemegas, P. L. and Wattenberg, L. W. : Glutathione S-transferase activity-Enhancement by compounds inhibiting chemical carcinogenesis and by dietary constituents. *J. Natl. Cancer Inst.*, **68**, 493(1982)
34. Slaga, I., Klein-Szanto, A. J. P., Triplett, L. L. and Yotti, L. P. : Skin tumor-promoting activity of benzoyl peroxide, a widely-used free radical-generating compound. *Science*, **213**, 1023(1981)
35. Benson, A. M., Batzinger, R. P., Ou, S. L., Bueding, E., Cha, Y. N. and Talalay, P. : Elevation of hepatic glutathione S-transferase activities and protection against mutagenic metabolites by dietary antioxidants. *Cancer Res.*, **12**, 4486 (1978)
36. Benson, A. M., Cha, Y. N., Bueding, E., Heine, H. S. and Talalay, P. : Elevation of extrathepatic glutathione S-transferase and epoxide hydratase activities by 2(3)-tert-butyl-4-hydroxyanisole. *Cancer Res.*, **39**, 2971(1979)
37. Cha, Y. N. and Bueding, E. · Effects of 2(3)-tert-butyl-4-hydroxyanisole administration on the activities of several hepatic microsomal and cytoplasmic enzymes in mice. *Biochem. Pharmacol.*, **28**, 1917(1979)
38. Cha, Y. N., Martz, F. and Bueding, E. : Enhancement of liver microsome epoxide hydratase activity in rodents by treatment with 2(3)-tert-butyl-4-hydroxyanisole. *Cancer Res.*, **38**, 4496(1978)
39. Wills, E. D. : Enzyme inhibition by a principle of garlic. *Biochem. J.*, **63**. 514(1956)
40. Cavallito, C. J., Buck, J. and Suter, C. : Allicin, the antibacterial principle of *Allium sativum*. II. Determination of the chemical structure. *J. Am. Chem. Soc.*, **66**, 1952(1944)
41. Goerner, A. and Goerner, M. M. : The metabolism of sulfhydryl compounds in tumor tissue. *Am. J. Cancer*, **16**, 360(1932)
42. Voegtlin, C. J. and Thompson, J. W. : Glutathione and malignant growth. *Public Health Rep.*, **31**, 1650(1980)
43. Hammett, F. S. : An interpretation of malignant growth based on the chemistry of cell division. *Arch. Path.*, **8**, 575(1929)
44. Schacter, B., Entenman, C. and Shimkin, M. B. : Blood plasma sulfhydryl levels during growth and regression of the murphy lymphosarcoma of the rat. *J. Nat. Cancer Inst.*, **13**, 647(1932)
45. White, J. and Edwards, J. E. : Effect on the development of hepatic T dimethylaminoazobenzene. *J. Nat. Cancer Inst.*, **2**, 535(1942)
46. Contopolous, A. N. and Anderson, H. H. : Sulfhydryl content of blood cells in dyscrasias. *J. Lab. & Clin. Med.*, **36**, 929(1950)
47. Kuzell, W. C., Koets, P., Schaffarzick, R. W. and Naugler, W. E. : Variation of blood glutathione during Neutropenia. *Case Report Stanford M. Bull.*, **13**, 284(1955)
48. Criss, W. E., Dhillon, G., Deu, B. and Sahai, A. : Inhibitor of the *in vivo* and *in vitro* guanylate cyclase activity from garlic. *Paper presented at 72nd Annual Meeting of AACR*, **69**, 17(1981)
49. Criss, W. E., Fakunle, J., Night, E., Adkins, J., Morris, H. P. and Dhillon, G. : Inhibition of tumor growth with low dietary protein and with dietary garlic extracts. *Paper presented at 66th Annual Meeting of FASEB*, **74**, 281 (1982)
50. Kroning, F. : Garlic as an inhibitor for spontaneous tumors in mice. *Acta Unio Contra Canctum*, **20**, 855(1964)
51. Choy, Y. M., Kwok, T. T., Fung, K. P. and Lee, C. Y. : Effects of garlic, Chinese medicinal drugs and amino acids on growth of Erlich ascites tumor cells in mice. *Am. J. Chin. Med.*, **11**, 69(1983)
52. Kim, E. S., Baik, J. E. and Chun, H. J. : Anticarcinogenic effect of garlic juice on hamster buccal pouch. *J. Korean Soc. Food Nutr.*, **23**, 44(1994)
53. Liu, J., Lin, R. I. and Milner, J. A. : Inhibition of 7,12-dimethybenz[a]anthracene-induced mammary tumors and DNA abducts by garlic powder. *Carcinogenesis*. **13**, 1847(1992)
54. Riggs, D. R., Dehaven, J. I. and Lamm, D. L. : *Allium sativum*(garlic) treatment for murine transitional cell carcinoma. *Cancer*, **79**, 1987(1997)
55. Mei, X., Wang, M. C., Xu, H. X., Pan, X. P., Gao, C. Y., Han, N. and Fu, M. Y. : Garlic and gastric cancer-The effect of garlic on nitrite and nitrate in gastric juice. *Acta Nutr. Sinica*, **4**, 53(1982)
56. Steinmetz, K. A., Kushi, L. H., Bostick, R. M., Folsom, A. R. and Potter, J. D. : Vegetables, fruit and colon cancer in the Iowa Women's Health Study. *Am. J. Epidemiol.*, **139**, 1(1994)
57. Belman, S. : Onion and garlic oils inhibit tumor promotion. *Carcinogenesis*, **4**, 1063(1983)
58. Belman, S. : Inhibition of soybean lipoxygenase by onion and garlic oil constituents. *Proc. AACR*, **26**, 131(1987)

59. Belman, S., Block, E., Perchellet, J. P., Perchellet, E. M. and Fischer, S. M. : Onion and garlic oils inhibit promotion whereas the oils enhance the conversion of papillomas to carcinomas. *Proc. Am. Asso. Cancer Res.*, **28**, 166(1987)
60. Sparmins, V. L., Mott, A. W., Barany, G. and Wattenberg, L. W. : Effects of allyl methyl trisulfide on glutathione S-transferase activity and BP-induced neoplasia in the mouse. *Nutr. Cancer*, **8**, 211(1986)
61. Perchellet, J. P., Perchellet, E. M., Abney, N. L., Zirnstein, O. A. and Belman, S . Effects of garlic and onion oils on glutathione peroxidase activity, the ratio of reduced/oxidized glutathione and ornithine decarboxylase induction in isolated mouse epidermal cells treated with armor promotors. *Cancer Biochem. Biophys.*, **8**, 299(1986)
62. Perchellet, J. P., Perchellet, E. M. and Belman, S. : Inhibition of DMBA-induced mouse skin tumorigenesis by a garlic oil and inhibition of two tumor-promotion stages by garlic and onion oils. *Nutr. Cancer*, **14**, 183(1990)
63. Xie, J. Y., Gao, Y. M. and Shen, L. C. : Flow cytometric analysis of the garlic oil effect on DNA content of cancer cell cycle. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih*, **12**, 69(1992)
64. Sadhana, A. S., Rao, A. R., Kucheria, K. and Bijani, V. : Inhibitory action of garlic oil on the initiation of benzo [a]pyrene-induced skin carcinogenesis in mice. *Cancer Lett.*, **40**, 193(1988)
65. Hirao, Y., Sumioka, I., Nakagami, S., Yamamoto, M., Hatono, S., Toshida, S., Fuwa, T. and Nakagawa, S. : Activation of immunoresponder cells by the protein fraction from aged garlic extract. *Phytotherapy Res.*, **1**, 161(1987)
66. Romanyuk, N. M. : The influence of the antibiotics of garlic on the activity of proteolytic enzymes of malignant tumors of humans and experimental animals. *Werain Biokhim Zhur*, **24**, 53(1952)
67. Kimura, Y. and Yamamoto, K. : Cytological effect of chemicals on tumors. XXIII. Influence of crude extracts from garlic and some related species on MTK-sarcoma III. *Gann.*, **55**, 325(1964)
68. Fujiwara, M. and Natata, T. . Induction of tumor immunity with tumor cells treated with extract of garlic. *Nature*, **216**, 83(1967)
69. Lau, B. H. S., Woolley, J. L., Marsh, C. L., Barker, G. R., Koobs, D. H. and Trrey, R. R. : Superiority of intralesional immunotherapy with *Corynebacterium parvum* and *Allium sativum* in control of murine transitional cell carcinoma. *J. Urol.*, **136**, 701(1986)
70. Marsh, C. L., Baker, G. R., Lau, B. H. S., Wooley, J. L., Koobs, D. H. and Torrey, R. R. : Superiority of intralesional immunotherapy with *Corynebacterium parvum* and *Allium sativum* in control of murine transitional cell carcinoma. *J. Urol.*, **136**, 701(1986)
71. Aboul-Enein, A. M. : Inhibition of tumor growth with possible immunity by Egyptian garlic extracts. *Die Nahrung*, **30**, 161(1986)
72. Meng, C. L. and Shyu, K. W. : Inhibition of experimental carcinogenesis by painting with garlic extract. *Nutr. Cancer*, **14**, 207(1990)
73. Kao, A. R., Sadhana, A. S. and Goel, H. C. : Inhibition of skin tumors in DMBA-induced complete carcinogenesis system in mice by garlic(*Allium sativum*). *Indian J. Exp. Biol.*, **28**, 405(1990)
74. Hu, P. J. : Protective effect of diallyl sulfide, a natural extract of garlic, on MNNG-induced damage of rat glandular stomach mucosa. *Chung Hua Chung Liu Tsa Chih*, **12**, 429(1990)
75. Kim, E. S. and Chun, H. J. : The anticarcinogenic effect of garlic juice against DMBA induced carcinoma on the hamster buccal pouch. *J. Korean Soc. Food Nutr.*, **22**, 398(1993)
76. Ip, C., Lisa, D. J. and Thompson, H. J. : Selenium-enriched garlic inhibits the early stage but not the late stage of mammary carcinogenesis. *Carcinogenesis*, **17**, 1979(1996)
77. VonEuler, H. and Lindeman, G. : Zur biochemie der tumorentwicklung und der tumorhemmung. *Ark. Kemi.*, **1**, 87 (1949)
78. Nakata, T. : Effect of fresh garlic extract on tumor growth. *Jpn. J. Hyg.*, **27**, 538(1973)
79. Cheng, H. and Tung, I. : Effect of allithiamine on Sarcoma-180 tumor growth in mice. *J. Formosan Med. Assoc.*, **80**, 385(1981)
80. Weisberger, A. S. and Pensky, J. : Tumor inhibiting effects derived from an active principle of garlic(*Allium sativum*). *Science*, **126**, 1112(1957)
81. Weisberger, A. S. and Pensky, J. : Tumor inhibition by a sulfhydryl-blocking agent related to an active principle of garlic(*Allium sativum*). *Cancer Res.*, **18**, 1308(1958)
82. Welch, C. and Wuarin, L. N. : Antiproliferative effect of the garlic compound S-allyl cysteine on human neuroblastoma cells *in vitro*. *Cancer Lett.*, **63**, 211(1992)
83. Takada, N., Kitano, M., Chen, T., Yano, Y., Otani, S. and Fukushina, S. . Enhancing effects of organosulfur compounds from garlic and onions on hepatocarcinogenesis in rats - Association with increased cell proliferation and elevated ornithine decarboxylase activity. *Jpn. J. Cancer Res.*, **85**, 1067(1992)
84. Sumiyoshi, H. and Wargovich, M. J. : Chemoprevention of 1,2-dimethylhydrazine induced colon cancer in mice by naturally occurring organosulfur compounds. *Cancer Res.*, **50**, 5084(1990)
85. Wargovich, M. J. and Goldberg, M. T. : Diallyl sulfide-A naturally occurring thioether that inhibits carcinogen-induced nuclear damage to colon epithelial cells *in vivo*. *Mutat. Res.*, **143**, 127(1985)
86. Wargovich, M. J., Woods, C., Eng, V. W. S., Stephens, L. C. and Gray, K. : Chemoprevention of N-nitrosomethylbenzylamine-induced esophageal cancer in rats by the naturally occurring thioether, diallyl sulfide. *Cancer Res.*, **48**, 6872(1988)
87. Bayer, A. R. and Wargovich, M. J. : Role of ornithine decarboxylase in diallyl sulfide inhibition of colonic radiation injury in the mouse. *Cancer Res.*, **49**, 5073(1989)
88. Brady, J. F., Ishizaki, H., Fukuto, J. M., Lin, M. C., Fadel, A., Gapac, J. M. and Yang, C. S. : Inhibition of cytochrome P-450 IIE1 by diallyl sulfide and its metabolites. *Chem. Res. Toxico.*, **4**, 642(1991)
89 Tadi, P. P., Lau, B. H., Teel, R. W and Herrmann, C. E. : Binding of Aflatoxin B_1 to DNA inhibited by ajoene and diallyl sulfide. *Anticancer Res.*, **11**, 37(1991)
90. Surh, Y. U., Lee, R. C., Park, K. K., Mayne, S. T., Lien, A. and Miller, J. A. : Chemoprotective effects of capsaicin

and diallyl sulfide against mutagenesis or tumorigenesis by vinyl carbamate and N-nitrosodimethylamine. *Carcinogenesis*, **16**, 2467(1995)

91. Chae, Y. H., Upadhyaya, P., Ip, C. and EL-Bayoumy, K. : Chemoprevention of mammary cancer by diallyl selenide, a novel organoselenium compound. *Anticancer Res.*, **16**, 2911(1996)
92. Hayes, M. A., Rushmore, T. H. and Goldberg, M. T. : Inhibition of hepatocarcinogenic responses to 1,2-dimethylhydrazine by diallyl sulfide, a component of garlic oil. *Carcinogenesis*, **8**, 1155(1987)
93. Brady, J. F., Dechun, L., Ishizaki, H and Yang, C. S. : Effect of diallyl sulfide on rat liver microsomal nitrosamine metabolism and other monooxygenase activities. *Cancer Res.*, **48**, 5937(1988)
94. Sundaram, S. G. and Milner, J. A. : Impact of organosulfur compounds in garlic on canine mammary tumor cells in culture. *Cancer Lett.*, **74**, 85(1993)
95. George, E. and Eapen, J. : Mode of garlic oil-Effect on oxidative phosphorylation in hepatic mitochondria of mice. *Biochem. Pharmacol.*, **23**, 931(1974)
96. Takahashi, S., Hakoi, K., Yada, H., Hirose, M., Ito, N. and Fukushima, S. : Enhancing effects of diallyl sulfide on hepatocarcinogenesis and inhibitory action of the related diallyl disulfide on colon and renal carcinogenesis in rat. *Carcinogenesis*, **13**, 1513(1992)
97. Milner, J. A., Sujatha, G. and Sundaram, S. G. : Diallyl disulfide suppresses the growth of human colon tumor cell xenografts in athymic nude mice. *J. Nutr.*, **126**, 1355 (1996)
98. Sundaram, S. G. and Milner, J. A. : Diallyl disulfide suppresses the growth of human colon tumor cell xenografts in athymic nude mice. *J. Nutr.*, **126**, 1355(1996)
99. Sundaram, S. G. and Milner, J. A. : Diallyl disulfide inhibits the proliferation of human tumor cell in culture. *Biochem. Biophys. Acta*, **1315**, 15(1996)
100. Deng, D. J., Mueller, K., Kasper, P. and Mueller, L. : Effect of diallyl trisulfide on induction of UDS by mutagenic drugs in primary rat hepatocytes. *Biomed. Environ. Sci.*, **7**, 85(1994)

(Received April 17, 1997)