MINI-REVIEW

Allium Vegetables in Cancer Prevention: An Overview

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Abstract

The *Allium* genus includes approximately 500 species. Commonly used allium vegetables include garlic, onion, leeks, chives, scallions which are used all over the world in different delicacies. Some allium vegetables have been employed for millenia in the traditional medical practice to treat cardiovascular diseases. They have been shown to have applications as antimicrobial, antithrombotic, antitumor, hypolipidaemic, antiarthritic and hypoglycemic agents. In recent years, extensive research has focused on the anticarcinogenic potential of allium vegetables and their constituents, viz., allylsulfides and flavonoids (particularly quercetin which is present abundantly in onion). Epidemiological studies have shown that higher intake of allium products is associated with reduced risk of several types of cancers. These epidemiological findings are well correlated with laboratory investigations. Organosulfur compounds present in Allium vegetables, are considered to be responsible for the beneficial effects of these herbs. Several mechanisms have been proposed to explain the cancer-preventive effects of *Allium* vegetables and related organosulfur compounds. These include inhibition of mutagenesis, modulation of enzyme activities, inhibition of DNA adduct formation, free-radical scavenging, and effects on cell proliferation and tumor growth. Although there is a large body of evidence supporting these mechanisms, they are still speculative, and further research is needed to support causality between such properties and cancer-preventive activity in experimental animals. This article reviews current knowledge concerning allium vegetables and cancer prevention.

Key Words: Allium vegetables - organosulfur compounds - quercetin - anticarcinogenic properties

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Introduction

Allium vegetables have been used as folk medicine since ancient times. Population studies and clinical research have shown that regular consumption of a variety of examples has several beneficial health effects. Allium vegetables are rich in flavonols and organosulfur compounds, which have exhibitied tumor inhibitory properties in laboratory studies (Fleischauer et al., 2000; Milner, 2001; Fenwick et al., 1985; Fukushima et al., 1997; Welch et al., 1992; Ali et al., 2000). Some components of allium vegetables are reported to block several stages of carcinogenesis, although the underlying mechanisms of action are generally unclear.

Allium is a genus belonging to the family Liliaceae. The *Allium* genus includes approximately 500 species, the most widely used of which are onions (*Allium cepa*), garlic (*Allium sativum*), leeks (*Allium porrum*), chives (*Allium schoenoprasum*), and shallots (*Allium ascalonicum*). Such plants have been employed for centuries for the pungency and flavoring value, and for their medicinal properties. The scientific community is increasingly becoming interested in the pharmacologic properties of *Allium* vegetables and their chemical constituents, particularly with regard to their ability to prevent cancer.

Some Commonly Consumed Allium Vegetables:

Garlic

Garlic has been applied since time immemorial as a culinary spice and medicinal herb and is an important constituent of traditional Chinese medicine. The chief constituent of garlic is the sulfur compound allicin, produced by crushing or chewing fresh garlic, which in turn produces other sulfur compounds: ajoene, mono-, di-, and tri-allyl sulfides, and vinyldithiins (Koch and Lawson, 1996).

Onion

The plant is native to Eurasia but now grows all over the world, due mostly to people bringing it with them as a staple food wherever they migrated. The bulb of the plant is used medicinally and onion has been consumed as food for many centuries (Onstad, 1996). Two sets of compounds make up

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the majority of onion's known active constituents, sulfur compounds, such as the alk(en)yl cysteine sulphoxides (ACSOs), and flavonoids, such as quercetin. Onions mainly contain S-propenylcysteine sulfoxide (Block, 1985), but also other sulfoxides such as S-methylcysteine sulfoxide (Virtanen and Matikkala, 1976). They have also been reported to be a major source of flavonoids (Arabbi et al., 2004).

Chives

Chives are a fragrant herb with a mild onion flavor. The subtle and pleasant taste has made them an extremely popular food addition in Central and Western Europe. Chives' constituents equal those of the close relatives, onion and garlic. The following volatile components have been identified: dipropyl disulfide, methyl pentyl disulfide, penthanethiol, penthyl-hydrodisulfid and cis/trans-3,5-diethyl-1,2,4-trithiolane. Chives also contain significant amounts of the vitamis A and C.

Leeks

The leek has a subtle, earthy flavor and milder fragrance than its cousins, garlic and onion. A phytochemical investigation of the extracts obtained from bulbs of leek *Allium porrum* L. has led to the isolation of five flavonoid glycosides based on the kaempferol aglycone.

Shallots

Shallots stem from a closely related plant, *Allium ascalonicum*. Their taste is somewhat finer and less pungent and they have also been reported to contain several phytochemicals.

From the above description, it can be seen that the main constituents of allium vegetables are organosulfur compounds (present in all allium vegetables) and flavonoids (present abundantly in onion). Thus, it can be speculated that the medicinal properties of the allium vegetables may be due to the presence of these chemical groups which would be of great importance in relation to cancer.

Epidemiological Studies

Associations between consumption of Allium vegetables and risk for cancer has been assessed in several epidemiologic, mainly case-control, studies. These have pointed to lower risks for cancers of the stomach, colon, esophagus, and perhaps breast (Fleischauer et al., 2000; Milner, 2001; Fleischauer and Arab,2001; Pinto et al., 2000; Dorant et al., 1996; You et al, 1998; Gao et al., 1999; Challier et al., 1998; You et al., 1989) .

One study, carried out in an area of China where gastric cancer rates are high, revealed a significant reduction in gastric cancer risk with increasing consumption of allium vegetables. Protective effects were seen for garlic, onions, and other allium foods (You et al., 1989). There is a low risk area for gastric cancer in Jiangsu Province, China, where people frequently consume raw allium vegetables. To clarify the factors involved in the low incidence of gastric cancer, a comparative study of the ecological factors in a high risk area (HRA), Yangzhong, and a low risk area (LRA), Pizhou, was conducted. The results of the survey suggested that frequent consumption of allium vegetables, in addition to other anticancer foods, may be a factor in low mortality for gastric cancer (Takezaki et al., 1999).

The Netherlands Cohort Study, focusing on onion and leek consumption, garlic supplement use, and the incidence of stomach and female breast carcinoma, provided evidence for a strong inverse association between onion consumption and stomach carcinoma incidence (Dorant et al., 1996). However, in the same study, after 3.3 years of follow-up, no association between the consumption of onions or leeks, or garlic supplement use, and the incidence of female breast carcinoma was found (Dorant et al., 1995). In contrast, in a French epidemiological study, higher onion intake was correlated with lower risk of breast cancer (Challier et al., 1998).

In a population-based, case-control study conducted in Shanghai, China, the association between intake of allium vegetables, including garlic, scallions, onions, chives, and leeks, and the risk of prostate cancer was investigated and it was found that the highest of three intake categories of total allium vegetables (>10.0 g/day) had a statistically significantly lower risk (P (trend) <.001) of prostate cancer (Hsing et al., 2002). A further study reported that intake of two or more servings of garlic per week were associated with a statistically nonsignificant 36% reduction in risk of prostate cancer (Key et al., 1997).

Scientists at the Nanjing Cancer Institute compared the incidence of several cancers among thousands of people who ate lots of allium vegetables versus thousands who ate little or none. ('Lots' in this case means at least once per week while 'little' means less than once per month.) It was found that allium vegetables were quite impressive in preventing cancer of stomach and esophagus.

Studies indicate that eating garlic seems to protect against colorectal cancer as well. Dr. Lenore Arab and colleagues from the University of North Carolina at Chapel Hill analyzed 18 studies looking at garlic eaters. Based on 6 studies, "the findings suggest high consumption of raw or cooked garlic decreases the risk of colorectal cancer from 10% to nearly 50%," (Fleischauer et al., 2000).

Allium Vegetables and their Constituents in Experimental Carcinogenesis

The effects of *Allium* vegetables have also been studied experimentally by testing individual organosulfur compounds or extracts and oils from garlic and onions. Several lines of evidence point to allyl sulfur compounds as potentially important antitumorigenic agents. A growing body of data indicates that allylsulfides possess anticarcinogenic and antitumor activities both in vivo and in vitro. Antineoplastic properties have been observed in experimental studies using allylsulfides, such as ajoene,

allicin, diallylsulfide (DAS), dialyldisulfide (DADS), diallyltrisulfide (DATS), S-allyl cysteine (SAC), S-allylmercaptocysteine (SAMC) (Dirsch et al., 1998; Dion et al, 1997; Knowles and Milner,1998; Lea and Ayyala, 1997; Lea et al., 1999; Li et al., 1995; Pinto et al., 1997; Sakamoto et al., 1997; Scharfenberg et al., 1990; Scharfenberg et al., 1994; Sigounas et al., 1997; Sundaram and Milner, 1993; Sundaram and Milner, 1996; Takeyama et al., 1993; Welch et al., 1993).

In Vivo Studies

A. Experiments with Extracts and Oils of Allium Vegetables

A Penn State study found that garlic and onions block the formation of a potent carcinogen better than their milder cousin, the leek, (Dion et al, 1997). It has been observed in our own laboratory that oral feeding of garlic suspensions significantly reduce the occurrence of ACF induced by AOM during colon carcinogenesis in male Sprague-Dawley rats (Sengupta et al., 2003). Thus, the results are consistent with epidemiological evidence from China which shows that those who have a higher consumption of vegetables from the onion family have a reduced cancer risk.

One in vivo study assessed the impact of various sources of garlic and their constituents (water- and ethanol-extracts and S-allylcysteine) on the in vivo binding of the carcinogen 7, 12-dimethylbenz[a]anthracene (DMBA) to rat mammary gland DNA. The provision of dietary raw garlic powder (2%) or its water-extract (1.5%) reduced DMBA-DNA binding by 33% and 46%, respectively (Amagase and Milner, 2003). Several other studies conducted in vivo have also demonstrated that garlic and associated allylsulfur components, like SAC and DADS, may also be effective inhibitors of MNU-induced mammary carcinogenesis in the rat (Schaffer et al., 1996).

Antioxidant effects of oils isolated from onion and garlic on nicotine-induced lipid peroxidation in rat tissues have been reported by a group of researchers. The lipid peroxidation products and scavenging enzymes were assessed in liver, lungs, heart and kidney. With garlic oil or onion oil supplementation; nicotine-treated rats had increased activities of antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase) and increased concentrations of glutathione. These results indicate that oils of garlic and onion are effective antioxidants against the oxidative damage caused by nicotine (Helen et al, 1999).

Sulfur compounds in onion oil have also been shown to be anti-inflammatory, both by inhibiting formation of thromboxanes and by inhibiting the action of platelet-activating factor (PAF) (Dorsch et al, 1987; Dorsch et al., 1988).

Dr Shon et al assessed the beneficial effects of red, yellow and white onion extracts, particularly their antioxidant activity and antimutagenic activities, and demonstrated that these properties against mutagens were related to their phenols and flavonoids (Shon et al., 2004).

B. Experiments with Allium Constituents

Anti-tumor properties of allium constituents have been demonstrated in several in vivo studies.

Topical application of DAS provided significant protection from neoplasia in DMBA/B(a)P-exposed animals compared to the animals exposed only to the carcinogens (Singh and Shukla, 1998). Antitumor properties of DAS on mouse skin carcinogenesis have also been apparent in several other studies (Singh and Shukla, 1998; Divedi et al., 1992).

A variety of allysulfides have been reported to inhibit gastrointestinal tract malignancies induced by the carcinogens, 1,2-dimethylhydrazine (Sumiyoshi and Wargovich, 1990), benzo(a)pyrene (Hu and Singh, 1997; Sparnins et al., 1988), and N-nitroso compounds (Wattenberg et al., 1989).

Another study demonstrated a decrease of NNK (a potent tobacco carcinogen) activation in mouse lung and rat nasal mucosa microsomes by DAS in a dose dependent manner (Hong et al., 1991; Hong et al., 1992).

DAS has also been shown to inhibit diethylnitro-samine-induced hepatocellular adenomas (Pereira, 1995), aflatoxin B1 (AFB1)-and NDEA-induced liver preneoplastic foci (Haber-Mignard et al., 1996), 2-amino-3-methyl-imidazo[4,5-f]quinoline (IQ)-induced hepatocarcinogenesis initiation (Tsuda et al., 1994). Results from another study showed that administration of SAC could prevent NDEA-induced hepatocarcinogenesis in rats (Sundaresan and Subramanian, 2003).

Water-soluble SAC (57 mmol/kg diet) and lipid-soluble DADS cause a comparable reduction in MNU-induced O^6-methylguanione adducts bound to mammary cell DNA (Schaffer et al, 1996).

Quercetin, when given intraperitoneally to animals with ascitic tumors, revealed antitumor activity. Rutin, a glycoside of quercetin also demonstrated similar effect (Molnar et al., 1991). Another animal study looked at the effect of quercetin on mice bearing abdominal tumors derived from a human pharyngeal squamous cell carcinoma line. The mice were given a daily intraperitoneal injection of different doses of quercetin. All doses tested demonstrated significant inhibition of tumor growth. The authors concluded that quercetin appears to be a selective inhibitor of tumor cell growth (Castillo et al., 1989).

Apart from their anti tumor properties, allylsulfides and quercetin also act as anti-oxidants. Several studies have demonstrated that allylsulfides can modulate drug-metabolizing and antioxidant enzyme activities (Sheen et al., 1999; Reicks and Crankshaw, 1996; Fukao et al., 2004; Guyonnet et al., 1999; Yin et al., 2002). Free radical scavenging properties and antioxidant health effects of SAC have been reported (Borek, 2001; Ide and Lau, 2001). SAC had been demonstrated to protect vascular endothelial cells from hydrogen peroxide-induced injury (Yamasaki et al., 1994) and hepatocytes from carbon tetrachloride toxicity (Nakagawa et al., 1989). SAC was found to decrease the doxorubicin-induced toxicity in the heart and liver of mice (Mostafa et al., 2000).

Highly purified forms of allylsulfides, e.g., DAS, DADS, DATS, when administered i.p. as a bolus to rats at a concentration of 10 or 100 micromol/kg body weight for 14 consecutive days, caused a significant increase in the activities of several phase II enzymes, viz., glutathione S-transferase, quinone reductase, and antioxidative enzyme glutathione peroxidase (Fukao et al., 2004).

Another experiment was designed to study the effects of 4 organosulfur compouinds such as DAS, DADS, DPS, DPDS on hepatic, intestinal, renal, and pulmonary phase II drug metabolizing enzymes, i.e., glutathione S-transferase (GST), microsomal epoxide hydrolase (mEH), quinone reductase (QR), and UDP-glucuronosyltransferase (UGT) in male SPF Wister rats. DADS significantly increased all Phase II enzyme activities, except the pulmonary mEH. DAS, DPS, and DPDS induced mEH, GST, and UGT activities in the liver (Guyonnet et al., 1999). Yet another study has proved that DADS can inhibit liver microsomal lipid peroxidation induced by NADPH, ascorbate and doxorubicin (Dwivedi et al., 1998).

Flavonoids are also considered as potential antioxidants. An experiment was designed to determine uptake as well as in vivo antioxidant effects of flavonoids from foods. Flavonoid glucosides (quercetin-3-glucoside and isorhamnetin-4-glucoside) were significantly elevated in plasma following ingestion of the onion meal and the increases were associated with an increased resistance of lymphocyte DNA to DNA strand breakage (Boyle et al., 2000).

In Vitro Studies

A number of studies have demonstrated antitumor effects of allium vegetables and their constituents on different malignant cells in vitro.

In one study it was found out that garlic oil, onion oil and one of its constituents, dipropenyl sulfide, all increase, to diverse degrees, glutathione (GSH) peroxidase activity in isolated epidermal cells incubated in the presence or absence of the potent tumor promoter 12-0-tetradecanoylphorbol-13-acetate (TPA). The same oil treatments dramatically inhibited the sharp decline in the intracellular ratio of reduced (GSH)/oxidized (GSSG) glutathione caused by TPA. Thus, it is suggested that some of the inhibitory effects of garlic and onion oils on skin tumor promotion may result from their enhancement of the natural GSH-dependent antioxidant protective system of the epidermal cells (Perchellet et al., 1986).

Extracts of wild garlic (*Allium ursinum*) and garlic (*A. sativum*) with defined chemical compositions were investigated for their in vitro inhibitory potential on 5-lipoxygenase (LO), cyclooxygenase (CO) (Sendl et al., 1992). In another study onion was also found to modulate the 5-LO pathway (Prasad et al., 2004).

Antiproliferative effects of diallyl trisulfide (DATS) and diallyl disulfide (DADS) on cultured human neoplastic (A549) and nonneoplastic (MRC-5) lung cells have been demonstarated (Sakamoto et al., 1997). In another study, Shukla et al observed a significant dose dependant cytotoxic response of DAS on Ehrlich Ascites tumor cells (Shukla et al., 2002).

Weisberger and Pensky (1958) reported that treatment of sarcoma-180 cells with allicin (0.5 μmol/L/5 x 10^6 cells) for 10 to 15 min before their transplantation into mice, completely suppressed proliferation into palpable tumors. Similarly, intravenous administration of several allyl sulfur compounds was found to retard sarcoma-180 cell proliferation (Weisberger and Pensky, 1958). It has also been reported that treatment of human colon tumor cells (HCT-15) with 100 μmol/L DADS resulted in the complete cessation of growth, 200 μmol/L SAMC was required to cause a similar depression (Knowles and Milner, 1997).

Treatment of isolated epidermal cells with a single exposure of diallylsulfide resulted in a sustained concentration dependent increase in glutathione peroxidase activity (Perchellet et al., 1986). Moreover, these cells demonstrate a marked increase in the intracellular ratio of GSH to GSSG. Quercetin (Q, 3,30,40,5,7-pentahydroxyflavone) was shown to protect CaCo-2 cells from oxidative DNA damage (Aherne and OûBrien, 2000).

Other useful model systems in which anticancer effects of garlic derivatives have been shown are the human breast cancer cell lines, MCF-7 and MCF-7ras, which retain many features of human breast cancer clinically. In cell culture, garlic extracts significantly inhibited anchorage-independent growth of these cells (Li et al., 1995). A recent study, published in the International Journal of Oncology, confirmed the potency of Quercetin against human breast cancer. Cancer cell growth was inhibited and cancer cells performed apoptosis (cancer cell suicide) when exposed to Quercetin (Choi et al., 2001).

Proposed Mechanisms of Cancer Prevention

The protective effect of allium vegetables appears to be related mainly to the presence of organosulfur compounds, which inhibit carcinogenesis in the forestomach, esophagus, colon, mammary gland, and lung of experimental animals. Moreover, the major flavonoids in onion, two quercetin glycosides, quercetin 4'-O-beta-glucoside (Q4'G) and quercetin 3,4'-O-beta-diglucosides (Q3,4'G), are recognized as bioactive substances that are good for our health (Ioku et al., 2001). Much of the recent research on quercetin (an important ingredient of onion) has shown it to be an anticarcinogen for numerous cancer types, including breast (Scambia et al., 1993; Scambia et al., 1991; Singhal et al., 1995) leukemia (Larocca et al., 1995; Larocca et al., 1991), colon (Pereira et al., 1996), ovary (Scambia et al., 1992; Scambia et al., 1990), squamous cell (Castillo et al., 1989), endometrial (Scambia et al., 1992) gastric (Yoshida et al., 1990) and non-small-cell lung (Caltagirone et al., 1997).

Several mechanisms have been proposed to explain the cancer-preventive effects of Allium vegetables and related compounds. These include inhibition of mutagenesis,

modulation of enzyme activities, inhibition of DNA adduct formation, free-radical scavenging, and effects on cell proliferation and tumor growth.

Effects on Cell Proliferation

The antitumorigenic effects of organosulfur compounds are not limited to a specific tissue or a particular cell type. Studies from various laboratories demonstrated that the lipid-soluble compounds were effective inhibitors of cultured human colon, skin and lung tumor cell proliferation (Sundaram and Milner, 1996). Therefore, these compounds possibly modify common pathway(s), controlling cell proliferation. At least some evidence support that these allyl sulfur compounds preferentially suppress growth of neoplastic over non-neoplastic cells (Sakamoto et al., 1997; Scharfenberg et al., 1990). Adding DATS (10 μmol/L) in vitro to cultures of A549 lung tumor cells inhibited their proliferation by 47%, whereas it did not influence non-neoplastic MRC-5 lung cells (Sakamoto et al., 1997). Scharfenberg et al. (1990) demonstrated a similar desensitization of fibroblast cells to ajoene exposure compared with BJA-B lymphoma. Exactly how these compounds are capable of selectively suppressing tumor cell proliferation remains to be determined.

Induction of apoptosis has been assumed to be a possible mechanism of the antiproliferative effects of DAS in solid tumors, as evident by the appearance of a sub- G1 fraction in flow cytometry as well as formation of DNA ladders on agarose gel and apoptotic bodies. Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay of skin tumors of DAS-supplemented animals showed a significant increase in the number of apoptotic cells compared with animals exposed to 7,12- dimethylbenz[a]anthracene alone. These observations suggest that induction of apoptosis may be the major contributing factor for antitumorigenic properties of DAS (Arora and Shukla, 2002).

A number of antitumorigenic compounds modify division by blocking cells within the G_1, S or G_2/M phases of the cell cycle (Darzynkiewicz, 1995; Jeitner et al., 1998; Nakajima et al., 1996). It has been observed that increased DADS exposure leads to a proportional increase in the percentage of cells arrested in the G_2/M phase of the cell cycle (Knowles and Milner, 1998). SAMC and DAS have also been reported to increase the percentage of cells blocked within the G_2/M phase (Sigounas et al., 1997; Zheng et al., 1997). Thus, the induction of a G_2/M phase arrest may explain the observed antiproliferative properties of a number of allyl sulfur compounds.

Quercetin (248 microM) was found to down regulate expression of mutant p53 protein to nearly undetectable levels in human breast cancer cell lines (Avila et al., 1994). The inhibition of expression of p53 was found to arrest the cells in the G2-M phase of the cell cycle. This down regulation was found to be much less in cells with an intact p53 gene (Avila et al., 1996). The G1 checkpoint controlled by the p53 gene is a major site for the control of cellular proliferation. Quercetin has been found to arrest human leukemic T-cells in the late G1 phase of the cell cycle (Yoshida et al., 1992).

Inhibition of Protein Tyrosine Kinase

Tyrosine kinase expression is thought to be involved in oncogenesis via an ability to override normal regulatory growth control.

In patients with advanced cancers, intravenous administration of quercetin (dosages 60-1700 mg/m2) led to inhibition of lymphocyte tyrosine kinase at one hour in nine out of eleven cases (Davis et al., 2000). It also blocks signal transduction pathways by inhibiting protein tyrosine kinase, 1-phosphatidylinositol 4- kinase and 1-phosphatidyl inositol 4-phosphate5-kinase resulting in a reduction of 1,4,5 inositoltriphosphate concentration (Csokay et al., 1997; Nishioka et al., 1989)

The $p34^{cdc2}$ kinase complex governs the progression of cells from the G_2 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 (Hartwell and Kastan, 1994; Nurse, 1990). Factors that inhibit $p34^{cdc2}$ kinase activity lead to a block in the G_2/M phase. Recent studies from our laboratory provide evidence that the G_2/M phase arrest induced by DADS coincides with suppression in $p34^{cdc2}$ kinase activity (Knowles and Milner, 1998).

Inhibition of Activation of Carcinogens

One of the possible mechanisms of action of allium derivatives may be to inhibit the enzyme cytochrome P450 2E1, which activates a number of xenobiotic substances, including carcinogens such as nitrosamines, hydrazines and halogenated hydrocarbons (Brady et al., 1991). By inhibiting the activation of carcinogens, the allium derivatives may potentially render these agents less capable of initiating the carcinogenic process. One likely event in this process may involve inhibiting the formation of DNA adducts with carcinogens. Allium constituents have been shown to inhibit the covalent binding of the carcinogen, 7,12-dimethylbenz[a]anthracene, to DNA, an intracellular event that correlates with decreased mutagenesis and carcinogenesis (Milner, 1996). The effect of allylsulfides on P450 enzymes appears to be specific rather than general in that the activities of other demethylating and hydroxylating cytochromes, namely, P450 2B1, 1A1 and 1A2, are actually elevated by allium components (Pan et al., 1993; Siess et al., 1997). Garlic organosulfur compounds exert chemopreventive effects at several organ sites in rodents after administration of chemical carcinogens, possibly by inhibiting carcinogen activation via cytochrome P-450-mediated oxidative metabolism. (Reicks and Crankshaw, 1996)

The sulphur compounds from onion have been shown to depress nitrosamine formation and bioactivation, reducing the N-nitrosomorpholine, a known liver carcinogen (Dion et al 1997). The dietary flavonoids from onion may also play a role in the protection against the harmful effects by

tobacco carcinogens (Malaveille et al, 1996).

Modulation of Phase II Enzyme Activity

In addition to modifying the metabolism of drugs, hormones and xenobiotic substances (Phase I metabolism) by regulating a number of cytochrome P450 enzymes, allium derivatives can selectively induce Phase II conjugation systems, which inactivate most carcinogens (Hu, and Singh, 1997; Sparnins et al., 1982). Allium constituents, such as diallyldisulfide or allylmethyltrisulfide, induce formation of GST (a family of Phase II enzymes). Allylsulfides also have also been reported to enhance glutathione peroxidase activity (Meister, and Anderson, 1983; Perchellet et al., 1986) and affect sulfhdryl/disulfide exchange reactions that may be critical for the control of proliferation and cell cycle regulation (Ziegler, 1985).

Another effect of allium compounds that possibly relates to inhibition of carcinogenesis is stimulation of glutathione (GSH) synthesis. GSH not only functions as a cosubstrate for the family of GST, enzymes necessary for conjugating GSH to electrophiles and thus blocking DNA-adduct formation, but also serves as a reductant for glutathione peroxidase (Perchellet et al., 1986). Similarly, Myhrstad et al. proposed that quercetin also provides defence against oxidative stress via increase of intracellular glutathione (GSH) level (Myhrstad et al. 2002) reported the elevation of GSH level in COS-1 cells by quercetin. Quercetin is also a potent in vitro inhibitor of membrane lipid peroxidation and LDL oxidation (O'Reilly et al., 2001).

Onion, due to the high-selenium content, might be used to provide this micronutrient (RDA of 70 and 55 m g/ day for male and female adults) to prevent some cancer occurrence without resulting in a excessive accumulation of tissues selenium, a concern that is associated with standard selenium compounds (Ip and Lisk, 1994a and 1994b). Quercetin may also prevent DNA damage as free radical scavengers (Wei et al., 1993).

Apart from the above mechanisms, in a recent study it was found that quecetin can downregulate estrogen receptor in an estrogen-sensitive breast cancer cell line MCF-7 (Miodini et al., 1999)

Conclusions

Studies in experimental animals indicate that the benefits of Allium vegetables are not limited to one species, tissue, or carcinogen. Organosulfur compounds can hinder activation of active carcinogen from precursors, increase its metabolic detoxification, or prevent its reaction with vulnerable target cells. The ability of allylsulfides (present in all the allium vegetables) to suppress carcinogen-activating P450 (CYP2E1), induce phase II GST and scavenge ultimate carcinogenic species may all contribute, singly or in combination, to the reduction of tumorigenesis. Additional mechanisms include a delay or a reversion of the expression of malignancy by antiproliferative activity in tumor cells and modification of signal transduction mechanisms ultimately leading to inhibition of carcinogenic insult. Overall, evidence shows that allium vegetables have strong cancer-preventive activity but there are many horizons that still need to be explored.

Additional studies on the chemopreventive nature of these allium vegetables and their constituents on human cancers are warranted. At the present time there are considerable *in vitro* data that support the concept of quercetin and allylsulfides acting as anti-cancer compounds. These promising data have not been followed up with extensive human or animal research. Extrapolation of the doses of pure chemicals that are effective in animals to their equivalents in terms of allium vegetables leads to unrealistic estimates of the amounts that would have to be consumed by humans to benefit from the anti -tumor effects of these substances. It seems logical that this a major concern that must be addressed when extrapolating animal findings to human. Accurate doses will have to be taken into consideration in the design of human epidemiologic studies and in evaluating the role of allium vegetables as effective chemopreventors.

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References

Aherne SA, O'Brien NM (2000). Mechanism of protection by the flavonoids, quercetin and rutin, against tert-butylhydroperoxide- and menadione-induced DNA single strand breaks in Caco-2 cells. *Free Rad Biol Med*, **29**, 507-14.

Amagase H, Milner JA (1993). Impact of various sources of garlic and their constituents on 7,12-dimethylbenz[a]anthracene binding to mammary cell DNA. *Carcinogenesis*, **14**, 1627-31.

Ali M, Thomson M, Afzal M (2000). Garlic and onions: their effect on eicosanoid metabolism and its clinical relevance. *Prostaglandins Leukot Essent Fatty Acids,* **62**, 55-73.

Arabbi PR, Genovese MI, Lajolo FM (2004). Flavonoids in vegetable foods commonly consumed in Brazil and estimated ingestion by the Brazilian population. *Agric Food Chem*, **52**, 1124-31.

Arora A, Shukla Y (2002). Induction of apoptosis by diallyl sulfide in DMBA-induced mouse skin tumors. *Nutr Cancer*, **44**, 89-94.

Avila MA, Velasco JA, Cansado J, Notario V (1994). Quercetin mediates the down-regulation of mutant p53 in the human breast cancer cell line MDA-MB468. *Cancer Res*, **54**, 2424-8.

Avila MA, Velasco JA, Harter KW, et al (1996). Quercetin as a modulator of the cellular neoplastic phenotype. *Adv Expl Biol*, **401**, 101-10.

Block E (1985). The chemistry of garlic and onions. *Sci Am*, **252**, 94-9.

Borek C (2001). Antioxidant health effects of aged garlic extract. *J Nutr*, **131**, 1010S-5S.

Boyle SP, Dobson VL, Duthie SJ, Kyle JA, Collins AR (2000). Absorption and DNA protective effects of flavonoid glycosides from an onion meal. *Eur J Nutr*, **39**, 213-23.

Brady JF, Ishizaki H, Fukuto JM, et al (1991). Inhibition of cytochrome P450 IIE1 by diallyl sulfide and its metabolites. *Chem Res Toxicol*, **4,** 642-7.

Caltagirone S, Raneletti FO, Rinelli A, et al (1997). Interaction with type II estrogen binding sites and antiproliferative activity of tamoxifen and quercetin in human non-small-cell lung cancer. *Am J Resp Cell Mol Biol*, **17**, 51-9.

Castillo MH, Perkins E, Campbell JH, et al (1989). The effects of the bioflavonoid quercetin on squamous cell carcinoma of head and neck region. *Am J Surg*, **158**, 351-5.

Challier B, Perarnau JM, Viel JF (1998). Garlic, onion and cereal fibre as protective factors for breast cancer: a French case-control study. *Eur J Epidemiol,* **14,** 737-47.

Choi JA, Kim JY, Lee JY, et al (2001). Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin. *Int J Oncology,* **19**, 837-44.

Csokay B, Prajda N, Weber G, Olah E (1997). Molecular mechanisms in the antiproliferative action of quercetin. *Life Sci*, **60**, 2157-63.

Darzynkiewicz Z (1995). Apoptosis in antitumor strategies: modulation of cell cycle or differentiation. *J Cell Biochem*, **58**, 151-9.

Davis W Lamson, MS ND, Matthew S (2000). Brignall, ND. *Altern Med Rev*, **5**, 196-208.

Dion ME, Agler M, Milner JA (1997). S-Allyl cysteine inhibits nitrosomorpholine formation and bioactivation. *Nutr Cancer*, **28**, 1-6

Dirsch VM, Gerbes AL, Vollmar AM (1998). Ajoene, a compound of garlic, induces apoptosis in human promyeloleukemic cells, accompanied by generation of reactive oxygen species and activation of nuclear factor kappaB. *Mol Pharmacol*, **53**, 402-7.

Divedi C, Rohlfs S, Jarvis D, Engineer FN (1992). Chemoprevention of chemically induced skin tumor development by diallyl sulfide and diallyl disulfide. *Pharm Res*, **9**, 1668-70.

Dorant E, van den Brandt PA, Golbohm RA (1995). Allium vegetable consumption, garlic supplement intake, and female breast carcinoma incidence. *Breast cancer Res Treat*, 33, 163-70.

Dorant E, van den Brandt PA, Goldbohm RA, Sturmans F (1996). Consumption of onions and a reduced risk of stomach carcinoma. *Gastroenterology*, **110,** 12–20.

Dorsch W, Ettl M, Hein G, et al (1987). Anti-asthmatic effects of onions: Inhibition of platelet-activating factor-induced bronchial construction by onion oils. *Int Arch Allergy Appl Immuno*l, **82**, 535–6.

Dorsch W, Wagner H, Bayer T, et al (1988). Antiasthmatic effects of onions: Alk(en)ylsulfinothic acid alk(en)ylesters inhibit histamine release, leukotriene and thromboxane biosynthesis in vitro and counteract PAF- and allergen-induced bronchial obstruction in vivo. *Biochem Pharmacol*, **37**, 4479–85.

Dwivedi C, John LM, Schmidt DS, Engineer FN (1998). Effects of oil-soluble organosulfur compounds from garlic on doxorubicin-induced lipid peroxidation. *Anticancer Drugs*, **9**, 291-4.

Fenwick GR, Hanley AB (1985). The genus Allium-Part 1. *Crit Rev Food Sci Nutr*, **22**, 199-271.

Fleischauer AT, Poole C, Arab L (2000). Garlic consumption and cancer prevention: metaanalyses of colorectal and stomach cancers. *Am J Clin Nutr,* **72**, 1047–52.

Fleischauer AT, Arab L (2001). Garlic and cancer: a critical review of the epidemiologic literature. *J Nutr*, **131**, 1032S-40S.

Fukushima S, Takada N, Hori T, Wanibuchi H (1997). Cancer prevention by organosulfur compounds from garlic and onion. *J Cell Biochem Suppl*, **27**, 100-5.

Fukao T, Hosono T, Misawa S, Seki T, Ariga T (2004). The effects of allyl sulfides on the induction of phase II detoxification enzymes and liver injury by carbon tetrachloride. *Food Chem -9 Toxicol*, **42**, 743.

Gao CM, Takezaki T, Ding JH, Li MS, Tajima K (1999). Protective effect of allium vegetables against both esophageal and stomach cancer: a simultaneous case-referent study of a high-epidemic area in Jiangsu Province, China. *Jpn J Cancer Res*, **90**, 614-21.

Guyonnet D, Siess MH, Le Bon AM, Suschetet M (1999). Modulation of phase II enzymes by organosulfur compounds from allium vegetables in rat tissues. *Toxicol Appl Pharmacol*, **154**, 50-8.

Haber-Mignard D, Suschetet M, Berges R, Astorg P, Siess MH (1996). Inhibition of aflatoxin B1- and N-nitrosodiethylamine-induced liver preneoplastic foci in rats fed naturally occurring allyl sulfides. *Nutr Cancer*, **25**, 61-70.

Hartwell LH, Kastan MB (1994). Cell cycle control and cancer. *Science* (Washington, DC), **266**, 1821-8.

Helen A, Rajasree CR, Krishnakumar K, Augusti KT, Vijayammal PL (1999). Antioxidant role of oils isolated from garlic (*Allium sativum* Linn) and onion (*Allium cepa* Linn) on nicotine induced lipid preoxidation. *Vet Hum Toxicol*, **41**, 316-9.

Hong JY, Smith T, Lee MJ, et al (1991). Metabolism of carcinogenic nitrosamines by rat nasal mucosa and the effect of diallyl sulfide. *Cancer Res*, **51**, 1509-14.

Hong JY, Wang ZY, Smith TJ, et al (1992) Inhibitory effects of diallyl sulfide on the metabolism and tumorigenicity of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)- 1-butanone (NNK) in A/J mouse lung. *Carcinogenesis*, **13**, 901-4.

Hsing AW, Chokkalingam AP, Gao YT, et al (2002). Allium vegetables and risk of prostate cancer: a population-based study. *J Natl Cancer Inst*, **94**, 1648-51.

Hu X, Singh SV (1997). Glutathione S-transferases of female A/J mouse lung and their induction by anticarcinogenic organosulfides from garlic. *Arch Biochem Biophys*, **340**, 279-86.

Ide N, Lau BHS (2001). Garlic compounds minimize intracellular oxidative stress and inhibit nuclear factor – KB activation. *J Nutr*, **131**, 1020S-6S.

Ioku K, Aoyama Y, Tokuno A, et al (2001). Various cooking methods and the flavonoid content in onion. *J Nutr Sci Vitaminol* (Tokyo), **47**, 78-83.

Ip C, Lisk DJ (1994a). Characterization of tissue selenium profiles and anticarcinogenic responses in rats fed natural sources of selenium-rich products. *Carcinogenesis*, **15,** 573-6.

Ip C, Lisk DJ (1994b). Enrichment of selenium in allium vegetables for cancer prevention. *Carcinogenesis*, **15**, 1881-5.

Jeitner TM, Delikatny EJ, Bartier WA, Capper HR, Hunt NH (1998). Inhibition of drug-naive and -resistant leukemia cell proliferation by low molecular weight thiols. *Biochem Pharmacol*, **55**, 793-802

Knowles LM, Milner JA (1997). Garlic constituents alter cell cycle progression and proliferation. *FASEB J*, **11**, A422(abs.).

Knowles LM, Milner JA (1998). Depressed p34cdc2 kinase activity and G2/M phase arrest induced by diallyl disulfide in HCT-15 cells. *Nutr Cancer*, **30**, 169-174.

Key TJ, Silcocks PB, davey GK, Appleby PN, Bishop DT (1997). A case-control study of diet and prostate cancer. *Br J cancer*, **76**, 678-87.

Koch HP, Lawson LD (eds) (1996). Garlic: The Science and Therapeutic Application of *Allium sativum* L and related species, **2d ed**. Baltimore: Williams and Wilkins, 62-4.

Larocca LM, Teofili L, Leone G, et al (1991). Antiproliferative activity of quercetin on normal bone marrow and leukaemic progenitors. *Br J Haematol*, **79**, 562-6.

Larocca LM, Teofili L, Sica S, et al (1995). Quercetin inhibits the growth of leukemic progenitors and induces the expression of transforming growth factor-B1 in these cells. *Blood*, **85**, 3654-61.

Lea MA, Ayyala UM (1997). Differentiating and growth inhibitory effects of diallyl disulfide on cancer cells. *Int J Oncol*, **11**, 181-5.

Lea MA, Randolph VM, Patel M (1999). Increased acetylation of histones induced by diallyl disulfide and structurally related molecules. *Int J Oncol*, **15**, 347-52.

Li G, Qiao CH, Lin RI, et al (1995). Anti-proliferative effects of garlic constituents in cultured human breast cancer cells. *Oncol Rep*, **2**, 787-91.

Malaveille C, Hautefeuille A, Pignatelli B, et al (1996). Dietary phenolics as anti-mutagens and inhibitors of tobacco-related DNA adduction in the urothelium of smokers. *Carcinogenesis*, **17**, 2193-200,

Meister A, Anderson ME (1983). Glutathione. *Annu Rev Biochem*, **52,** 711-60.

Milner JA (1996). Garlic: its anticarcinogenic and antitumorigenic properties. *Nutr Rev*, **54**, S82-6.

Milner JA (2001). A historical perspective on garlic and cancer. *J Nutr*, **131**, 1027S-31S.

Milner JA (2001). Mechanisms by which garlic and allyl sulfur compounds suppress carcinogen bioactivation. Garlic and carcinogenesis. *Adv Exp Med Biol*, **492**, 69–81.

Miodini P, Fioravanti L, Di Franzo G, Cappelletti V (1999). The two phytoestrogens genistein & quercetin exert different effects on oestrogen receptor function. *Br J Cancer*, **80**, 1150-5.

Molnar J, Beladi I, Domonkos K, et al (1981). Antitumor activity of flavonoids on NK/Lyascites tumor cells. *Neoplasma*, **28**, 11-8.

Mostafa MG, Mima T, Ohnishi ST, Mori K (2000). S-allylcysteine ameliorates doxorubicin toxicity in the heart and liver of mice. *Planta Med*, **66**, 148-51.

Myhrstad MCW, Carlsen H, Norstrom O, Blomhoff R, Moskaug JO (2002). Flavonoids increase the intracellular glutathione level by transactivation of the gamma-glutamylcysteine synthetase catalytical subunit promoter. *Free Rad Biol Med*, **32**, 386-93.

Nakagawa S, Kasuga S, Matsunna H (1989). Prevention of liver damage by aged garlic extract and its compounds in mice. *Phytother Res*, **3**, 50-3.

Nakajima H, Hori Y, Terano H, et al (1996). New antitumor substances, FR901463, FR901464 and FR901465. II. Activities against experimental tumors in mice and mechanism of action. *J Antibiot* (Tokyo), **49**, 1204-11.

Nishioka H, Imoto M, Sawa T, et al (1989). Screening of phosphatidylinositol kinase inhibitors from Streptomyces. *J Antibiot* (Tokyo), **42**, 823-5.

Nurse P (1990). Universal control mechanism regulating onset of M-phase. *Nature* (Lond.), **344**, 503-8.

Onstad D (1996). Whole Foods Companion: a Guide for Adventurous Cooks, Curious Shoppers & Lovers of Natural Foods. White River Junction, VT: Chelsea Green Co, 202-6.

O'Reilly JD, Mallet AI, McAnlis GT, et al (2001). Consumption of flavonoids in onions and black tea: lack of effect on F2-isoprostanes and autoantibodies to oxidized LDL in healthy humans. *Am J Clin Nut, 73*, 1040-4.

Pan J, Hong JY, Ma BL, et al (1993). Transcriptional activation of P-450 2B1/2 genes in rat liver by diallylsulfone, a compound derived from garlic. *Arch Biochem Biophys*, **302**, 337-42.

Pereira MA (1995). Chemoprevention of diethylnitrosamine-induced liver foci and hepatocellular adenomas in C3H mice. *Anticancer Res*, **15,** 1953-6.

Pereira MA, Grubbs CJ, Barnes LH, et al (1996). Effects of the phytochemicals, curcumin and quercetin, upon azoxymethane-induced colon cancer and 7,12-dimethylbenzy[a]anthracene-induced mammary cancer in rats. *Carcinogenesis*, **17**, 1305-11.

Perchellet JP, Perchellet EM, Abney NL, Zirnstein J A, Belman S (1986). Effects of garlic and onion oils on glutathione peroxidase activity, the ratio of reduced and oxidized glutathione and ornithine decarboxylase induction in isolated mouse epidermal cells treated with tumor promoters. *Cancer Biochem Biophys*, **8**, 299-312.

Pinto JT, Qiao C, Xing J, et al (1997). Effects of garlic thioallyl derivatives on growth, glutathione concentration, and polyamine formation of human prostate carcinoma cells in culture. *Am J Clin Nutr*, **66**, 398-405.

Prasad NS, Raghavendra R, Lokesh BR, Naidu KA (2004). Spice phenolics inhibit human PMNL 5-lipoxygenase. *Prostaglandins Leukot Essent Fatty Acids*, **70**, 521-8.

Reicks MM, Crankshaw DL (1996). Modulation of rat hepatic cytochrome P-450 activity by garlic organosulfur compounds. *Nutr Cancer*, **25**, 241-8.

Sakamoto K, Lawson LD, Milner J (1997). Allyl sulfides from garlic suppress the in vitro proliferation of human A549 lung tumor cells. *Nutr Cancer*, **29**, 152-6.

Scambia G, Raneletti FO, Panici PB, et al (1990). Synergistic antiproliferative activity of quercetin and cisplatin on ovarian cancer cell growth. *Anticancer Drugs*, **1**, 45-8.

Scambia G, Raneletti FO, Panici PB, et al (1991). Quercetin inhibits the growth of a multidrug-resistant estrogen-receptor-negative MCF-7 human breast-cancer cell line expressing type II estrogen-binding sites. *Cancer Chemother Pharmacol*, **28**, 255-8.

Scambia G, Raneletti FO, Panici PB, et al (1992). Inhibitory effect of quercetin on primary ovarian and endometrial cancers and synergistic activity with cis-diamminedichloroplatinum(II). *Gynecol Oncology*, **45**, 13-9.

Scambia G, Raneletti FO, Panici PB, et al (1993). Quercetin induces type-II estrogen-binding sites in estrogen-receptor-negative (MDA-MB231) and estrogen-receptor-positive (MCF-7) human breast-cancer cell lines. *Int J Cancer*, **54**, 462-6.

Scharfenberg K, Wagner R, Wagner KG (1990). The cytotoxic effect of ajoene, a natural product from garlic, investigated with different cell lines. *Cancer Lett*, **53**, 103-8.

Scharfenberg K, Ryll T, Wagner R, Wagner KG (1994). Injuries to cultivated BJA-B cells by ajoene, a garlic-derived natural compound: cell viability, glutathione metabolism, and pools of acidic amino acids. *J Cell Physiol*, **158**, 55-60.

Schaffer EM, Liu JZ, Green J, Dangler CA, Milner JA (1996). Garlic and associated allyl sulfur componenets inhibit N-

methyl-N-nitrosourea induced rat mammary carcinogenesis. *Cancer Lett*, **102**, 199-204.

Sendl A, Elbl G, Steinke B, et al (1992). Comparative pharmacological investigations of *Allium ursinum* and *Allium sativum*. *Planta Med*, **58**, 1-7.

Sengupta A, Ghosh S, Das S (2003). Tomato and Garlic can Modulate Azoxymethane Induced Colon Carcinogenesis in Rat. *European J Cancer Prevention*, **12**, 195-200

Sheen LY, Chen HW, Kung YL, Liu CT, Lii CK (1999). Effects of garlic oil and its organosulfur compounds on the activities of hepatic drug-metabolizing and antioxidant enzymes in rats fed high- and low-fat diets. *Nutr Cancer*, **35**, 160-6.

Shon MY, Choi SD, Kahng GG, Nam SH, Sung NJ (2004). Antimutagenic, antioxidant and free radical scavenging activity of ethyl acetate extracts from white, yellow and red onions. *Food Chem Toxicol*, **42**, 659-66.

Shukla Y, Arora A, Singh A (2002). Antitumorigenic potential of diallyl sulfide in Ehrlich ascites tumor bearing mice. *Biomed Environ Sci*, **15**, 41-7.

Siess MH, Le Bon AM, Canivenc-Lavier MC, Suschetet M (1997). Modification of hepatic drug-metabolizing enzymes in rats treated with alkyl sulfides. *Cancer Lett*, **120**, 195-201.

Sigounas G, Hooker JL, Li W, Anagnostou A, Steiner M (1997). S-Allylmercaptocysteine, a stable thioallyl compound, induces apoptosis in erythroleukemia cell lines. *Nutr Cancer*, **28**, 153-9.

Sigounas G, Hooker J, Anagnostou A, Steiner M (1997). S-Allylmercaptocysteine inhibits cell proliferation and reduces the viability of erythroleukemia, breast, and prostate cancer cell lines. *Nutr Cancer*, **27**, 186-91.

Singhal RL, Yeh YA, Prajda N, et al (1995). Quercetin down-regulates signal transduction in human breast carcinoma cells. *Biochem Biophys Res Comm*, **208**, 425-31.

Singh A, Shukla Y (1998). Antitumor activity of diallyl sulfide in two-stage mouse skin model of carcinogenesis. *Biomed Environ Sci*, **11**, 258-63.

Singh A, Shukla Y (1998). Antitumour activity of diallyl sulfide on polycyclic aromatic hydrocarbon-induced mouse skin carcinogenesis. *Cancer Lett*, **131**, 209-14.

Sparnins VL, Venegas PL, Wattenberg LE (1982). Glutathione S transferase activity: enhancement by compounds inhibiting chemical carcinogenesis and by dietary constituents. *J Natl Cancer Inst*, **68**, 493-6.

Sparnins VL, Barany G, Wattenberg LW (1988). Effects of organosulfur compounds from garlic and onion on benzo[a]pyrene-induced neoplasia and glutathione S-transferase activity in the mouse. *Carcinogenesis*, **9**, 131-4.

Sumiyoshi H, Wargovich MJ (1990). Chemoprevention of 1,2-dimethylhydrazine-induced colon cancer in mice by naturally occurring organosulfur compounds. *Cancer Res*, **50**, 5084-7.

Sundaram SG, Milner JA (1993). Impact of organosulfur compounds in garlic on canine mammary tumor cells in culture. *Cancer Lett*, **74**, 85-90.

Sundaram SG, Milner JA (1996). Diallyl disulfide induces apoptosis of human colon tumor cells. *Carcinogenesis*, **17**, 669-73.

Sundaresan S, Subramanian P (2003). S-allylcysteine inhibits circulatory lipid peroxidation and promotes antioxidants in N-nitrosodiethylamine-induced carcinogenesis. *Pol J Pharmacol*, **55**, 37-42.

Takeyama H, Hoon DS, Saxton RE, Morton DL, Irie RF (1993). Growth inhibition and modulation of cell markers of melanoma by S-allyl cysteine. *Oncology*, **50,** 63-9.

Takezaki T, Gao CM, Ding JH, et al (1999). Comparative study of lifestyles of residents in high and low risk areas for gastric cancer in Jiangsu Province, China; with special reference to allium vegetables. *J Epidemiol*, **9**, 297-305.

Tsuda H, Uehara N, Iwahori Y, et al (1994). Chemopreventive effects of beta-carotene, alpha-tocopherol and five naturally occurring antioxidants on initiation of hepatocarcinogenesis by 2-amino-3-methylimidazo[4,5-f]quinoline in the rat. *Jpn J Cancer Res*, **85**, 1214-9.

Virtanen AL, Matikkala EJ (1976). The isolation of S-methyl-L-cysteine sulphoxide and S-n-propyl-L-cysteine from onion (Allium cepa) and the antibiotic activity of crushed onion. *Acta Chem Scand*, **13**, 1898-900.

Wattenberg LW, Sparnins VL, Barany G (1989). Inhibition of N-nitrosodiethylamine carcinogenesis in mice by naturally occurring organosulfur compounds and monoterpenes. *Cancer Res*, **49**, 2689-92.

Weisberger AS, Pensky J (1958). Tumor inhibition by a sulfydryl-blocking agent related to an active principle of garlic (*Allium sativum*). *Cancer Res*, **18**, 1301-8.

Wei H, Wei L, Frenkel K, Bowen R, Barnes S (1993). Inhibition of tumor-promoter induced hydrogen peroxide formation by genistein *in vitro* and *in vivo*. *Nutr Cancer*, **20**, 1-12.

Welch C, Wuarin L, Sidell N (1992). Antiproliferative effect of the garlic compound S-allyl cysteine on human neuroblastoma cells in vitro. *Cancer Lett*, **63**, 211-9.

Yamasaki T, Li L, Lau BHS (1994). Garlic compounds protect vascular endothelial cells from hydrogen peroxide- induced oxidant injury. *Phytother Res*, **8**, 408-12.

Yin MC, Hwang SW, Chan KC (2002). Nonenzymatic antioxidant activity of four organosulfur compounds derived from garlic. *J Agric Food Chem*, **50**, 6143-7.

Yoshida M, Sakai T, Hosokawa N, et al (1990). The effect of quercetin on cell cycle progression and growth of human gastric cancer cells. *FEBS Letters*, **260**, 10-3.

Yoshida M, Yamamoto M, Nikaido T (1992). Quercetin arrests human leukemic T-cells in late G1 phase of the cell cycle. *Cancer Res*, **52**, 6676-81.

You WC, Blot WJ, Chang YS, et al (1989). Allium vegetables and reduced risk of stomach cancer. *J Natl Cancer Inst*, **81**, 162-4.

You WC, Zhang L, Gail MH, et al (1998). Helicobacter pylori infection, garlic intake and precancerous lesions in a Chinese population at low risk of gastric cancer. *Int J Epidemiol*, **27**, 941-4.

Zheng S, Yang H, Zhang S, et al (1997). Initial study on naturally occurring products from traditional Chinese herbs and vegetables for chemoprevention. *J Cell Biochem*, **Suppl 27**, 106-12

Ziegler DM (1985). Role of reversible oxidation-reduction of enzyme thiolsdisulfides in metabolic regulation. *Annu Rev Biochem*, **54**, 305-29.