Recent Research Progress on Garlic (大蒜 dà suàn) as a Potential Anticarcinogenic Agent Against Major Digestive Cancers

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Abstract

Garlic (大蒜 dà suàn; the bulb of Allium sativum), bestowed with an array of organosulfur compounds finds its application in treating many ailments including cardiovascular problems, common cold, bacterial and fungal infections and cancer. Numerous epidemiological evidences document the beneficial effects of various bioactive organosulfur compounds of garlic against different types of cancer. Studies involving the animal and cell models indicate garlic bioactive compounds could be effective in treating all the stages of cancer. This review gives an update on the recent pre-clinical and clinical trials, carried out to evaluate the efficacy of various garlic bioactive compounds along with the mechanism of action pertaining to major digestive cancers including liver, gastric and colorectal cancers. The major anti-carcinogenic mechanisms are caspase dependent and/or independent induction of apoptosis, anti-proliferative, anti-metastasis, anti-oxidant and immunomodulative properties. Form the clinical trials an increase in the garlic consumption of 20 g/day reduced the risk of gastric and colorectal cancer. In summary, increased uptake of garlic in diet may prevent the incidence of digestive cancers.

Keywords: Liver cancer, Gastric cancer, Colorectal cancer, Garlic, Anticarcinogenic agent

Introduction

Cancer is a leading cause of death worldwide and accounted for nearly 13% of all deaths every year. Stomach cancer is the second leading cause of cancer death (738 000 deaths, 9.7% of the total) followed by liver cancer (696 000 deaths, 9.2% of the total) and colorectal cancer (608 000 deaths, 8% of total) worldwide (Ferlay et al., 2010). These major digestive cancers cause nearly one-fourth (27%) of all the cancer related deaths. Some of the advanced stages as in the liver cancer have no effective systemic chemotherapy options (Ng et al., 2012). Complementary alternative medicine (CAM) may be a choice to rely for a viable solution to overcome this limitation. Allium vegetables catch our attention on a cursory glance on list of herbs CAM.

Garlic (大蒜 dà suàn; the bulb of Allium sativum), a member of Liliaceae family is an important spice consumed globally and is bestowed with immense medicinal benefits. Numerous research findings have attributed these health benefits mainly to the organo-sulfur components like allin, γ-glutamylcysteine and their derivatives. Besides these organo sulfur compounds, garlic are rich in trace elements (zinc, magnesium, copper, selenium and iodine), protein content, dietary fibre, tocopherols, ascorbic acid, polyphenols. Historically almost all the civilizations in the world had knowledge of the medicinal
properties of garlic and have been used in treating a variety of ailments including leprosy, diarrhoea, constipation, infections (Hahn, 1996). However the garlic as a potent anticarcinogen came to light in the late 1950s after Weisberger and Pensky (1958) demonstrated thiosulfonates extracted from garlic possessed anti-tumor properties. Realizing the potential and with the advent of modern analytical techniques, there has been a surge in garlic research by many research groups around the world.

To explore the therapeutic potential and unravel the mechanisms of garlic extracts or compounds in digestive cancers numerous researchers focused on these areas. Most prominent among these are the studies pertaining to anticarcinogenic properties by pre-clinical trials using the cell lines and animal models. This review is an attempt to update the recent research progress related to garlic research against liver, gastric and colorectal cancers carried out in the recent years.

**Bioactive Compounds and Chemistry of Garlic**

The beneficial biological and medicinal properties of garlic have been attributed to the organosulfur compounds (Augusti and Mathew, 1974). The most important and predominant components in an intact garlic bulb are alliin (S-allyl-L-cysteine sulfoxide) and γ-glutamyl-S-allyl-L-cysteines; and traces of S-methylcysteine sulfoxide (methiin), S-(trans-1-propenyl)-L-cysteine sulfoxide, and S-2-carboxypropylglutathione and S-allylcysteine (Amagase, 2006). When the clove is damaged by crushing or cutting, an enzyme allinase present in the vacuole rapidly transforms alliin to allicin and this allicin is the main component of freshly prepared garlic homogenate (Lanzotti, 2006). However allicin being an unstable compound is easily converted to oil-soluble plosylsulfides like diallyl sulphide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS) and diallyl tetrasulfide. Ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide) is generated via allicin S-thiolation and 2-propenesulfenic acid addition. Another process of garlic extract contains ajoene (Block et al., 1984) in addition to 2-vinyl-4-H-1,3-dithiin, 3-vinyl-4-H-1,2-dithiin. Products like the heat treated garlic and garlic powder contain alliin as the major sulphur containing compound devoid of allicin since the enzyme allinase is inactivated by heating.

Out of different garlic extracts, the “aged garlic extract” (AGE) is prominent one. Due to the prolonged extraction under 15-20% ethanol at room temperature, compounds responsible for characteristic flavor, and pungent and toxic components are naturally transformed into stable and safe sulfur compounds. AGE contains most of all water-soluble sulfur compounds, S-allyl cysteine and S-allyl mercaptocysteine, and small amounts of oil-soluble allyl sulfides. These water-soluble sulfur compounds, formed during garlic extract aging, have huge antioxidant potential (Corzo-Martinez et al., 2007). Another commercially available product is the steam distilled garlic essential oil. Normally they are sold at concentration of 1 per cent blended with vegetable oils as capsules. Steam distilled garlic essential oil contains DADS, DATS, allyl methyl trisulfide, allyl methyl disulfide, diallyl tetrasulfide, allyl methyl tetrasulfide, dimethyl trisulfide, diallyl sulphide without the water soluble fraction and alliin devoid of allicin (Iciek et al., 2009). However the composition of these ingredients may be varying slightly based on the method employed to extract and garlic cultivars. A list of the predominant organo-sulfur compounds in the commercially available garlic products (Figure 1) is presented in Table 1.

**Evidences of Garlic as Anticarcinogenic Agent - Preclinical Trials**

The anticarcinogenic mechanisms of the purified active compounds of garlic or garlic extracts on various cancers types have been elucidated targeting cancer cell lines. Taking these cues of the biological process the compounds/extracts are tested using *in vivo* (animal models) to get a holistic idea of the mechanisms.

**In vitro studies**

**Gastric cancer**
Dose-dependent apoptosis was detected in ABGE-treated cells in SGC-7901 human gastric cancer cells in addition to the antioxidative and immunomodulating effects (Wang et al., 2012a). Allicin induces apoptosis in gastric SGC-7901 cancer cells through activation of both intrinsic mitochondrial and extrinsic Fas/FasL-mediated pathways and inhibited proliferation (Zhang et al., 2010). Garlic oil treatment on human gastric adenocarcinoma SGC7901 cells inhibits cancer cell proliferation by inhibiting cyclin E expression and the TGFalpha autocrine and paracrine loops (Liang et al., 2007). The effect of DADS in human gastric adenocarcinoma AGS cells (Park et al., 2011) exhibited inhibitory effects on cell motility and invasiveness were correlated with increased tightness of the tight junctions mediated by the increase in transepithelial electrical resistance. Activities of matrix metalloprotease (MMP)-2 and -9 in AGS cells were dose-dependently inhibited by treatment with 0-70 μM DADS. Additionally, repressed the levels of claudin proteins (claudin-2, -3, and -4), major components of TJs that play key roles in control and selectivity of paracellular transport. DADS (50, 100, 200, and 400 μM) decreased the viability of gastric adenocarcinoma AGS cell lines, and induced apoptosis in a dose-dependent manner regulated by increased expressions of Fas, caspase-3, Bax and decreased Bcl-2 expression (Lee et al., 2011a).

Some researchers have focused on evaluating the biotransformed garlic derivatives or the synergistic effects of garlic bioactive compounds along with other compounds. (Zheng and Li, 2008) found that garlic oil in combination with resveratrol synergistically induced the apoptosis of gastric cancer cell line MGC-803 with concomitant increase in the expression of Fas protein and bax gene and decrease of bcl-2 gene expression. The effect of SAMC on the growth of human gastric cancer SNU-1 cells featured a concentration-dependent inhibition of cell proliferation and cells developed many of the hallmark features of apoptosis, including DNA fragmentation and an increase in the sub-diploid population suggesting caspase-3 dependent effect of SAMC on gastric cancer SNU-1 cells may be connected with caspase-3 activation through the induction of Bax and p53, rather than Bcl-2 and p21 (Lee, 2008).

**Colorectal cancer**

Huang et al. (2011) studied the anti-proliferative activity of DADS and differentially expressed genes induced by DADS in human colon HT-29 cancer cells. A dose-and time-dependent growth inhibition and anti-proliferative effects were observed and concluded the plausible mechanisms to be transduction, cell proliferation/growth/apoptosis and secreted/extracellular matrix proteins. Garlic organosulfur compounds are also reported to affect migration and invasion. Using colo 205 human colon cancer cells it was shown that 10 and 25 μM of DAS, DADS, and DATS inhibited the migration and invasion in the order of DATS < DADS < DAS by inducing downregulation expression of PI3K, Ras, MEKK3, MKK7, ERK1/2, JNK1/2, and p38 and then lead to the inhibition of MMP-2, -7, and -9. The cell proliferation was also arrested by NF-kappaB and COX-2 inhibition (Lai et al., 2011). DADS afford greater benefit when supplied with other favorable dietary factors (short chain fatty acids/polysaccharides) that likewise reduce colonic tumor development (Altonsy and Andrews, 2011) in colorectal adenocarcinoma HT-29 cells by decreasing cellular proliferation, translocation of phosphatidylinerse to the plasma-membrane outer-layer, activation of caspase-3 and -9, genomic DNA fragmentation, and G2/M phase cell-cycle arrest.

Allicin exerted a time-and dose-dependent cytostatic effect on colon cancer cell lines HCT-116, LS174T, HT-29, and Caco-2 at concentrations ranging from 6.2 to 310 μM (Bat-Chen et al., 2010). While the allicin (62 μM) exerts cytotoxic effects on HCT-116 and induces apoptosis via a mechanism associated with transactivation of the transcription factor Nrf2 (Bat-Chen et al., 2010), DADS (200 μM) inhibits cell proliferation in HCT-116 cell lines by inducing ROS-mediated cell cycle arrest in G2/M phase through increase of cyclin B1, without p53 activation and mitochondrial ROS-mediated apoptosis accelerated by activation of p53 (Jo et al., 2008; Song et al., 2009). Another property of allyl sulfides, are the modulation of histone deacetylase activity. DADS is metabolized to allyl mercaptan (AM) within 30 min (Sheen et al., 1999) in primary rat hepatocytes, is important considering the fact that AM is more effective than its precursors (DADS, SAMC) at inhibiting histone deacetylase activity in cell-free conditions (Druesne et
al., 2004). In HT29 cells, inhibition of HDAC activity by AM coincided with increased global histone acetylation, as well as localized hyperacetylation of histone H3 on the P21WAF1 promoter. Recruitment of Sp3 to the P21WAF1 promoter occurred within 4 h of AM exposure and was followed by the subsequent binding of p53 to the distal enhancer region. Induction of p21 was both rapid and sustained and was associated with a dose-dependent G1 arrest in AM treated HT29 cells (Nian et al., 2008).

A study on DAS against Colo320 DM colon cancer cells elucidated the chemoprevention mechanisms to cell cycle arrest at G2/M phase, induction of apoptosis, antiproliferative, upregulated NF-kappaB, expression of caspase-3 and suppression of Extracellular Regulatory Kinase-2 (ERK-2) activity (Sriram et al., 2008) and also to induce STAT1 mediated apoptosis in colo 205 human colon cancer cells (Lu et al., 2007). Chen et al. (2012) explored the early Ca\(^{2+}\) signaling events in human colorectal cancer cells SW480 in response to DADS treatment suggesting DADS induced a significant rise in (Ca\(^{2+}\))i in SW480 colon cancer cells by stimulating both extracellular Ca\(^{2+}\) influx and thapsigargin-sensitive intracellular Ca\(^{2+}\) release and the mechanism of the later has not been elucidated.

Liver cancer

The effects of varying concentrations SAC (0 – 40 mM) on the proliferation and metastasis of hepatocellular carcinoma in HCC cell line MHCC97L exhibited anti-proliferative property attributable to significant suppression of proliferation markers, Ki-67 and proliferating cell nuclear antigen (PCNA) and the induction of cell cycle at S/G2 transition (Ng et al., 2012). Up-regulation of E-cadherin and down regulation of VEGF inhibited colony-forming abilities. Also, SAC significantly down regulated anti-apoptotic proteins (Bcl-xL and Bcl-2) thereby inducing caspase-3 and caspase-9 mediated apoptosis and necrosis. Additionally SAC down regulated cdc25c, cdc2 and cyclin B1 inducing the S phase arrest of MHCC97L cells. DATS exhibited the highest biological activities like anti-proliferation and caspase-3 mediated apoptotic induction in HepG2 cells among DAS, DADS and DATS (Iciek et al., 2012). DATS did not affect the activity of sulfur-transferases and lowered sulfane sulfur level in HepG2 cells and propose that sulfane sulfur containing DATS to be bioreduced in cancer cells to hydroperthiol leading to hydrogen peroxide generation, thereby influencing transmission of signals regulating cell proliferation and apoptosis. Similar results were observed by our group using human liver tumor cells (J5) to evaluate the efficacy of DAS, DADS and DATS in cell viability and cell cycle. Cell viability significantly decreased at DATS (50 or 100 \(\mu\)M) in dose and time dependent manner. Cell cycle studies showed arrest in G2/M phase on 100 \(\mu\)M DADS, 10, 50 or 100 \(\mu\)M DATS treatment. DATS was more effective in arresting cells in G2/M phase than DADS and DATS which was related to the decrease in the cyclin-dependent kinase (Cdks)-Cdk7 and increase in cyclin B1 protein levels this controlling action might relate to the sulfuric atom numbers in the structures of all these alkyl sulfides (Wu et al., 2004). An alk(en)yl thiosulfate, sodium n-propyl thiosulfate (NPTS), from garlic imparts hepato protection by inducing Phase II detoxification enzymes in rat hepatoma H411E cells (Chang et al., 2010).

When compared to the oil-soluble garlic extract DADS, water-soluble garlic extracts had pronounced effect in HepG2 cells (De Martino et al., 2006). Water-soluble extracts induced p53/p21-dependent cell cycle arrest in G2/M phase and apoptosis by the activation of c-Jun-NH(2) terminal kinase (JNK)/c-Jun phosphorylative cascade. Also DADS/DATS were effective in GSTP expression mediated through JNK-AP-1 and ERK-AP-1 signaling inducing phase II detoxification system (Tsai et al., 2007). DADS affects cell proliferation activity and viability and induces apoptosis. Temporary activation of MAPKs in HepG2 hepatoma cells and phospho-p38 and phospho-p42/44 regulated cell apoptosis were reported (Wen et al., 2004). Belloir et al. (2006) assessed the antigenotoxic potential of purified garlic compounds like allicin, DAS, DADS, S-allyl cysteine (SAC) and allyl mercaptan (AM) in the human hepatoma cell line HepG2and found them to protect human hepatic cells against the genotoxicity induced by indirect-and direct-acting genotoxic agents primarily by the inhibition of CYP enzymes and induction of phase II enzymes.
One of the mechanisms of the cytoprotective effects of chemopreventive agents is perceived to be the induction of antioxidant enzymes. Ajoene treatment activated Nrf2 in HepG2 cells, as indicated by increased phosphorylation and nuclear accumulation of Nrf2, decreased interaction with Kelch-like ECH-associated protein-1, and decreased Nrf2 ubiquitination inducing the antioxidant system, GCL induction, and the cellular GSH concentration rendering protection from oxidative stress (Kay et al., 2010).

In vivo studies

Gastric cancer

Wang et al. (2012a) tested the effects of aged black garlic extracts on gastric cancer against an in vivo model (Kunming mice inoculated with murine fore-gastric carcinoma cell line). In vivo studies on the mice were treated with various doses of ABGE (0, 200, 400 and 800 mg/kg, intraperitoneally) for 2 weeks. In tumor-bearing mice, significant antitumor effects of ABGE were observed, such as growth inhibition of inoculated tumors. They reason this for the increased indices of spleen and thymus serum superoxide dismutases, glutathione peroxidase, interleukin-2 and presume the anticarcinogenic action of ABGE may be partly due to its antioxidant and immunomodulatory effects. The biotransformed allyl sulfides also possess anti-tumorigenesis property. (Lee et al., 2011b) evaluated one such allyl-mercapto-glutathione S-conjugate, S-allylmercapto-L-cysteine(SAMC) at 100 mg/kg and 300 mg/kg on implanted tumors of human gastric cancer cell lines in nude mice and found the tumor inhibiting property attributed to the apoptotic characteristics regulated by bcl-2 and bax transcript levels.

Colorectal cancer

Chihara et al. (2010) evaluated the scavenging capacity of boiled garlic powder (BGP) on 1, 2-dimethylhydrazine-induced mucin-depleted foci (MDF) and aberrant crypt foci (ACF), preneoplastic lesions, in the rat colorectum by supplementing the diets of F344 rats with 5% or 1% BGP for 5 weeks. The numbers of MDF decreased significantly in a dose-dependent manner, compared with the DMH and basal diet value but the numbers of ACF showed a non-significant tendency to decrease. Further to test the effect of 10% BGP on the formation of DMH-induced O6-methylguanine (O6-MeG) DNA adducts, they conducted an animal trial on F344 rats by injecting DMH. Dietary administration of BGP significantly inhibited the O6-MeG DNA adduct levels in the colorectal mucosa, compared with the controls. Though the authors have not probed into the detailed mechanisms, they attribute the suppression of DMH induced MDF and O6-MeG DNA adduct formation partly to the hydroxyl radical scavenging action of the heat stable alliin in BGP. In the BGP used, alliin (27.0 mg/g dry weight) was detected and allicin producing potential was absent. Tumor volume and total hemoglobin in CT26 cancer cells implanted allograft BALB/c mice treated with 50 mg/kg bw DATS intraperitoneally once in four days prior to 4 weeks of cell inoculation significantly reduced (Wu et al., 2011). High temperature-and pressure-treated garlic (HTPG) at 1% or 3% imparts chemopreventive effects against colon carcinogenesis in the initiation stage of 1,2-dimethylhydrazine (DMH)-induced mucin-depleted foci (MDF) and aberrant crypt foci (ACF), preneoplastic lesions in Male F344 colorectum. Further dietary administration of 10% HTPG significantly reduced the adduct levels in the colorectal mucosa and liver. HTPG significantly reduced the activity of cytochrome P450 (CYP) 2E1, and significantly enhanced the activities of phase 2 enzymes, quinone reductase (QR) and glutathione S-transferase (GST), in rat liver (Chihara et al., 2009). DATS (5-40 μM) induced morphological changes and induced apoptosis inhibited CT26 cancer cells in vivo on a murine allograft animal model through the increase of the sub-G1 cells in the mouse colon carcinoma CT26 cells (Wu et al., 2011).

Liver cancer

Ng et al., (2012) proved the therapeutic potential of SAC individually (1 mg SAC/kg/day) and in combination with cisplatin (1 mg SAC/kg/day plus 1 mg cisplatin/kg/day) in an in vivo orthotopic
xenograft liver tumor model by demonstrating that SAC single or combined with cisplatin treatment inhibited the progression and metastasis of HCC tumor through the anti-proliferative property SAC. Zhang et al. (2012) investigated the protective effects of garlic oil (20 or 40 mg/kg) against N-nitrosodiethylamine (NDEA)-induced hepatocarcinoma in Wistar and observed decrease in nodule incidence, improved hepatocellular architecture, a dose-dependent manner reduction in NDEA-induced elevation of serum biochemical indices, decreased mRNA and protein levels of Bcl-2, Bcl-xl, β-arrestin-2 and increased Bax and caspase-3 and attributed this to the antioxidant activity and the induction of apoptosis. However the protective mechanisms of S-allylcysteine are mediated by modulating lipid peroxidation, GST stimulation, and by increasing the antioxidants (Sundaresan and Subramanian, 2008). Hepatocarcinogenesis induced by 7,12-dimethyl benz(a)anthracene (DMBA) in Swiss albino mice was effectively protected by DAS at 250 or 500 μg/mouse against oxidative stress (Prasad et al., 2008).

Another compound from garlic, scordinin (600 ppm) protected F344 rats from diethylnitrosamine (DEN)- and phenobarbital (PB)-induced hepatocarcinogenesis by decreasing glutathione S-transferase placental form-positive foci and nucleolar organizer regions’ protein (AgNORs) / nucleus in hepatocellular adenoma and carcinoma in the initiation or promotion phase. Scordinin significantly decreased the mean number of nucleolar organizer regions’ protein (AgNORs) / nucleus in hepatocellular adenoma and carcinoma (Watanabe et al., 2001). Aged garlic extract (2, 5, and 10 mL/kg) significantly decreased GST-P-positive foci in diethylnitrosamine (DEN)-induced neoplasia of the liver in male F344 rats (Uda et al., 2006).

**Clinical Trials**

**Gastric cancer**

Meta-analysis performed on the consumption of Allium vegetables and gastric cancer on the research papers from 1966 to 2010 indicated that increased consumption of garlic was found to be associated with a reduced gastric cancer risk odds ratio 0.53 and 95% confidence intervals, 0.40–0.65 (Zhou et al., 2011). Three hospital-based case-control studies, 8 population based case-control studies and 1 cohort study indicated that increased consumption of garlic was found to be associated with a reduced gastric cancer risk with odds ratio of 0.53; 95% confidence intervals, 0.40–0.65. Separate analysis of the hospital-based case-control studies (OR, 0.57; 95% CI, 0.34–0.80), and population-based case-control studies (OR, 0.52; 95% CI, 0.37–0.67) yielded similar results except for cohort studies (OR, 1.28; 95% CI, 0.45–3.66). The estimated summary OR for an increment of 20 g/day of Allium vegetables consumed (approximately the average weight of 1 garlic bulb) was 0.91 (95% confidence interval, 0.88-0.94), based on case-control studies from the dose-response meta-analysis.

In another cohort-study in European prospective investigation into cancer and nutrition (EPIC) analysis, an inverse association between total intake of vegetables, onion and garlic, and risk of intestinal gastric cancer was reported (Gonzalez et al., 2006). The same group reanalyzed the effect of fruit and vegetables, based on a longer follow-up and twice the number of GC cases with increased subjects of 477,312 men and women mostly aged 35 to 70 years participating in the EPIC cohort, including 683 gastric adenocarcinomas with 11 years of follow-up (Gonzalez et al., 2012). The inverse association between leafy vegetables, onion and garlic intake and risk of intestinal GC was no longer present. However in this study the garlic was not analyzed separately. Kim and Kwon (2009) evaluated the scientific evidence from 19 human studies for garlic intake with respect to the risk of different types of cancer using the US Food and Drug Administration's evidence based review system for the scientific evaluation of health claims. Limited evidence supports the relation between garlic consumption and reduced risk of colon cancer. A 14.7 yr follow-up for gastric cancer incidence to oral supplementation with garlic extract and steam-distilled garlic oil for 7.3 yr was associated with non-statistically significant reduction in gastric cancer (Ma et al., 2012).

**Colorectal cancer**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3942895/?report=printable
Ngo et al. (2007) systematically reviewed the scientific evidence of studies that examined effects of garlic on colon rectal cancer. One randomized controlled trial reported a statistically significant 29% reduction in both size and number of colon adenomas in patients taking aged garlic extract. Further they found five of 8 case control/cohort studies indicated a protective effect of high intake of raw/cooked garlic. Meta-analysis studies confirmed an inverse association of garlic consumption and relative risk with a 30% reduction. Eleven animal studies demonstrated a significant anticarcinogenic effect of garlic and/or its active constituents. There is consistent scientific evidence derived from randomized controlled trial of animal studies reporting protective effects of garlic on colon rectal cancer despite great heterogeneity of measures of intakes among human epidemiological studies.

Liver cancer

A randomized double blind 6 month clinical trial to evaluate the effects of Aged Garlic Extract (AGE – 500 mg/day) to advance staged cancer patients improved natural-killer (NK) cell activity but no improvement in quality of life (Ishikawa et al., 2006). In this trial, 84% of the patients were with liver cancer.

Garlic anti-cancer mechanisms on digestive cancers

Carcinogenesis is a multi-factor, multi-step and complex process involving five distinguishable but closely inter-linked stages. The mechanism of garlic's anticarcinogenic efficacy is dependent on many factors and it is difficult to precisely pinpoint a particular mechanism. The mechanism depends mainly on the (i) the type of cancer investigated (ii) the model system used (iii) the garlic compound used (iv) the stage of the cancer investigated. But we can generalize the garlic anti-cancer mechanisms and are summarized in Figure 2. For example, DATS exerts chemoprevention through the ER stress and the mitochondrial pathways in BCC (Wang et al., 2012b) but imparts different mechanism in digestive system. Prominent mechanisms prevalent in the animal experimental models are the hydroxyl scavenging action, anti-proliferative mechanism, anti-oxidant property, immunomodulutive functions (Wu et al., 2002) and induced apoptotic characteristics. In the cell models described here, garlic compounds inhibited cellular proliferation, inhibited G2/M and S-phase transition, attenuated of peroxide formation and DNA strand, ROS inhibition, induction of cell cycle at S/G2 transition, caspase mediated apoptosis induction, necrosis induction, inhibition of cell motility, inhibition of cell invasiveness, cell cycle arrest at the G0/G1 phases, caspase independent apoptosis, calcium signaling and p38 activation. DADS caused Ca2+ signal in a concentration dependent manner by evoking phospholipase C-independent Ca2+ release from ER and also by causing extracellular Ca2+ influx. These signaling effects may play a crucial role in the physiological action of DADS (Chen et al., 2012).

Apart from possessing anticarcinogenic properties, garlic is found to influence the multidrug resistance in vivo and in vitro by affecting the gene expression of the multidrug resistance in colo 205 human colon cancer cells in vitro and in vivo (Lai et al., 2012) and this can overcome the major obstacle of treatment and management of malignant cancers.

Conclusion

In summary, there has been a considerable increase in research papers on the efficacy of garlic compounds employing in vivo and in vitro studies. The garlic compounds targets multiple pathways, inclusive of the cell cycle, apoptotic cell death and angiogenic pathway, which confer their anticarcinogenic activities. However, very few studies take into consideration the parameters like half-life period, absorption rate, transport rate, permeability which influences the bioavailability of the compound. More critical information on the application of garlic as anticarcinogenic agent could be generated if such parameters are considered.
How much garlic or garlic extracts should we consume daily to get the beneficial chemopreventive properties? These are the intricate questions posed by the public, doctors and researchers. However, prevention is better than cure based on the results from recent clinical studies. Considering the fact of an increase in Allium vegetable consumption of 20 g/day (approximately the average weight of 1 garlic bulb) was associated with a statistically significant 9% decreased risk of gastric cancer (Zhou et al., 2011), and an increment in garlic consumption (>28.8 g/week) reduced the risk against colorectal and gastric cancers (Fleischauer et al., 2000). Garlic oil and AGE are the heavily researched garlic products and a clinical study indicated AGE at 500 mg/day improved natural-killer cell activity in advanced liver cancer patients. The advantage with AGE is that it is less odoriferous.

Although the innumerable preclinical studies have evidenced garlic or its constituents as potential anticarcinogenic agent; however, with few exceptions, the epidemiological studies are inconclusive on the cure of cancer by garlic. This may be due to the diversity in the stages of cancer, living style or food habits. For the practical application, it is important to evaluate if the dosages tested in cell models or animal systems are clinically achievable to impart anticancer activity in humans. Therefore, further research focusing on the pharmacokinetics aspects will be a worthwhile task to help the “traditional medicine” garlic to establish as a “potential anticarcinogenic agent” with strong scientific evidence.

References


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Figures and Tables
Figure 1

Commercial garlic products and their major organo-sulfur compounds
Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>Structure</th>
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<tr>
<td>1</td>
<td>Allicin (Diallyl thiosulfinate)</td>
<td>C₆H₁₀OS₂</td>
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<td>Allyl methane sulfinate</td>
<td>C₄H₈OS₂</td>
<td>136.23</td>
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<tr>
<td>3</td>
<td>Alliin (S-Allyl-L-cysteine sulfoxide)</td>
<td>C₆H₁₁NO₃S</td>
<td>177.22</td>
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<td>C₆H₁₁NO₂S</td>
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<td>126.26</td>
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</tr>
</tbody>
</table>
Structures of predominant organo-sulphur compounds present in commercial garlic preparations:

13. Diallyl sulfide \( \text{C}_6\text{H}_{10}\text{S} \) 114.21

14. 2-vinyl-4-H-1,3-dithiin \( \text{C}_6\text{H}_8\text{S}_2 \) 144.26

15. 3-vinyl-4-H-1,2-dithiin \( \text{C}_6\text{H}_8\text{S}_2 \) 144.26

16. E-ajoene \( \text{C}_9\text{H}_{14}\text{OS}_3 \) 234.40

17. Z-ajoene \( \text{C}_9\text{H}_{14}\text{OS}_3 \) 234.40
Figure 2

Anti-carcinogenic effect of garlic bioactive compounds in different stages of cancer progression

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