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Review

Molecular mechanisms for the anti-cancer effects of diallyl disulfide

Lan Yi, Qi Su *

Cancer Research Institute, University of South China, Hengyang 421001, Hunan Province, China

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ABSTRACT

Considerable evidence in recent years suggests that garlic has anti-proliferative effects against various types of cancer. Garlic contains water-soluble and oil-soluble sulfur compounds. Oil-soluble compounds such as diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS) and ajoene are more effective than water-soluble compounds in protection against cancer. DADS, a major organosulfur compound derived from garlic, can decrease carcinogen-induced cancers in experimental animals and inhibit the proliferation of various types of cancer cells. Its mechanisms of action include: the activation of metabolizing enzymes that detoxify carcinogens; suppression of the formation of DNA adducts; antioxidant effects; regulation of cell-cycle arrest; induction of apoptosis and differentiation; histone modification; and inhibition of angiogenesis and invasion. These topics are discussed in depth in this review.

Contents

1. Introduction

Large epidemiologic studies have suggested that garlic plays an important role in the reduction of the prevalence of cancer. Galeone et al. (2006) showed an inverse relationship between the frequency of garlic intake and the risk of several common cancers (including cancer of the oral cavity and pharynx, esophageal cancer, colorectal cancer, laryngeal cancer, breast cancer, ovarian cancer, prostate cancer, and renal cell cancer) in southern Europe. It has been reported, in studies in populations in China, Japan, Uruguay, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and the UK, that increasing the consumption of garlic can lead to a significant reduction in the risk of contracting

Abbreviations: OSCs, organosulfur compounds; DAS, diallyl sulfide; DADS, diallyl disulfide; DATS, diallyl trisulfide; MNU, testosterone- and *N*-methyl-*N*-nitrosourea; NDEA, *N*-nitrosodiethylamine; MPN, methyl-n-pentylnitrosamine; TPA, 12-O-tetradecanoylphorbol-13-acetate; ODC, ornithine decarboxylase; QR, quinone reductase; GT, glutathione transferase; GSH, glutathione; rGSTA5, glutathione S-transferase A5; rAFAR1, aflatoxin B1 aldehyde reductase 1; AOM, azoxymethane; NDEA, nitrosodiethylamine; NAT, N-acetyltransferase; 2-AAF, N-acetyl-2-aminofluorene; MAP, Mitogen-activated protein; Rac2, Ras-related C3 botulinum toxin substrate 2; NAC, N-acetyl cysteine; PARP, poly(adenosine diphosphate-ribose) polymerase; NF-κB, nuclear factor-kappa B; ER, endoplasmic reticulum; CTX, cyclophosphamide; HDAC, Histone deacetylase; MMPs, matrix metalloproteinases; (TNF)α, tumor necrosis factor; MIF, migration inhibitory factor; SSH, suppressive subtractive hybridization.

* Corresponding author. Tel./fax: +86 734 8281547.
E-mail address: suqi1@hotmail.com (Q. Su).

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gastric cancer (You et al., 1989; De Stefani et al., 2001; Hirohata and Kono, 1997; Gonzalez and Riboli, 2006). Garlic intake was significantly related to a low risk of gastric cancer in a case-control study of 102 patients with gastric cancer and 204 non-cancer controls in Nis, Serbia (Lazarevic et al., 2010). In addition, garlic is significantly related to a lower risk of colorectal adenoma (Millen et al., 2007) Karagianni et al. (2010) suggested that garlic intake was inversely related to the prevalence of colorectal polyps in 52 cases with colorectal polyps and 52 healthy controls in a Greek population. A case-control study of 166 patients with polyps in the large bowel showed that garlic intake had a strong protective effect against large-bowel polyps in a Bulgarian population (Kotzev et al., 2008). A cohort study of breast-cancer survivors showed that a significant number of African–American breast-cancer survivors were using garlic as a complementary and alternative medicine (CAM) (Adams-Campbell, 2011). Galeone et al. (2009) observed a moderate protective role of garlic on the risk of endometrial cancer in a case-control study of 454 endometrial cancer cases and 908 controls in an Italian population. Garlic intake has been associated with enhanced immune function, antibacterial, antifungal and antivirus activities, the prevention of platelet aggregation, and a reduction in the detrimental properties of cholesterol and triglycerides. Moreover, some of the organosulfur compounds (OSCs) in garlic inhibit carcinogen activation, boost phase-II detoxifying processes, cause cell-cycle arrest; induce apoptosis, increase histone acetylation, influence intercellular communication in the gap junction, modulate the cellular redox state, and participate in the development of multidrug resistance (Iciek et al., 2009).

Garlic contains water-soluble and oil-soluble OSCs. Oil-soluble OSCs such as diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS) and ajoene. DADS is an organosulfur compound derived from garlic and a few other genus Allium plants. Along with diallyl trisulfide and diallyl tetrasulfide, it is one of the principal components of the distilled oil of garlic. It is a yellowish liquid which is insoluble in water and has a strong garlic odor. It is produced during the decomposition of allicin, which is released upon crushing garlic and other plants of the Alliaceae family. Diallyl disulfide can be readily oxidized to allicin with hydrogen peroxide or peracetic acid. Allicin in turn can hydrolyze giving diallyl disulfide and trisulfide. Reaction of DADS with liquid sulfur gives a mixture containing diallyl polysulfides with as many as 22 sulfur atoms in a continuous chain (Wang et al., 2013).

For the past few years, investigators have focused attention on DADS (a major OSC derived from garlic) because it has been shown to decrease the formation of carcinogen-induced cancers and to inhibit the proliferation of various types of cancer cells (Druesne et al., 2004a,b; Liao et al., 2009; Huang et al., 2011; Nakagawa et al., 2001; Lei et al., 2008; Hui et al., 2008; Wu et al., 2005; Xiang et al., 2005; Yuan et al., 2004; Wen et al., 2004; Arunkumar et al., 2006a,b; Gunadharini et al., 2006; Yi et al., 2010a,b). The actions of DADS include activation of the metabolizing enzymes that detoxify carcinogens, suppression of the formation of DNA adducts, antioxidant formation, regulation of cell-cycle arrest, induction of apoptosis and cell differentiation, histone modification, and inhibition of angiogenesis and cell invasion (Miroddi et al., 2011; Tsubura et al., 2011; Herman-Antosiewicz and Singh, 2004; Milner, 2006).

2. Inhibition of carcinogen-induced activity

Studies in experimental animals have provided convincing evidence that DADS can afford protection against cancer induced by various chemical carcinogens by inhibition of carcinogen activation through modulation of cytochrome P450-dependent monooxygenases and/or acceleration of carcinogen detoxification *via* induction of phase-II enzymes.

Research has shown that DADS can decrease testosterone- and *N*-methyl-*N*-nitrosourea (MNU) induced carcinogenesis in the prostate gland of rats (Arunkumar et al., 2006a,b), and reduce the incidence of tumor formation in MNU-induced carcinogenesis in mammary glands through inhibition of DNA alkylation as well as formation of O(6)-methylguanine adducts and N(7)-Methylguanine adducts (Schaffer et al., 1996). DADS inhibits the activity of cytochrome P4501 in human hepatoma cells, suggesting that the protective mechanism may be related to the modulation of CYP1-mediated bioactivation in reducing benzo[*a*]pyrene-induced carcinogenesis; DADS is the most efficient OSC in reducing benzo(*a*)pyrene genotoxicity in HepG2 cells (Chun and Choi, 2001; Belloir et al., 2006). Guyonnet et al. found that DADS reduced the promotional activity of phenobarbital in *N*-nitrosodiethylamine (NDEA) induced hepatocarcinogenesis in rats (Guyonnet et al., 2004). DADS was found to inhibit the formation of stomach tumors by >90% in *N*-nitrosodiethylamine-induced carcinogenesis in mice (Wattenberg et al., 1989). DADS was found to lower the prevalence of ductal carcinoma and to decrease the total number of tumors in 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced carcinogenesis in rat mammary glands, suggesting that DADS could be a chemopreventive agent against cancer in this tissue (Mori et al., 1999). A low dose (200 mg/kg) of DADS decreased the level of CYP2E1 protein in the liver by 25%, and this inhibition was sustained after 1, 4 and 8 weeks of treatment in chemically induced development of colon cancer in rats (Davenport and Wargovich, 2005). DADS can inhibit CYP2E1 levels in rats and humans as well as CYP2A3 levels in rats in methyl-n-pentylnitrosamine (MPN)-induced carcinogenesis (Morris et al., 2004). DADS has shown potent inhibitory effects in 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ornithine decarboxylase (ODC) activity in mouse epidermal 308 cells (Lee and Pezzuto, 1999). DADS has been shown to induce the formation of ethoxyresorufin O-deethylase, methoxyresorufin O-demethylase and pentoxyresorufin O-dependentylase, as well as to decrease levels of nitrosodimethylamine N-demethylase and erythromycin N-demethylase; these actions were accompanied by an increase in the activities of CYP 2B1/2 and a decrease in the activities of CYP 2E1 and phase-II enzymes. These findings suggest a possible protective effect of DADS in the first step of carcinogenesis *via* modulation of the enzymes involved in carcinogen metabolism (Siess et al., 1997).

There is evidence that DADS can protect against cancer in humans through induction of phase-II detoxification enzymes. In rats, DADS is a potent inducer of phase-II enzymes *via* an increase in the tissue activities of quinone reductase (QR) and glutathione transferase (GT). DADS may be important in the anti-cancer action of garlic (Munday and Munday, 2001). DADS increases the tissue activities of QR and GT in the gastrointestinal tract of the rat; significant increases in QR activity were observed at a dose of only 0.3 mg/kg/day (Munday and Munday, 1999). DADS can effectively enhance the glutathione (GSH) content of the intestinal mucosa and liver (Chittezhath and Kuttan, 2006). DADS is a potent inducer of glutathione S-transferase A5 (rGSTA5) and aflatoxin B1 aldehyde reductase 1 (rAFAR1). The induction of rGSTA5 and rAFAR1 is probably the main mechanism by which DADS elicits protection against aflatoxin B1 (AFB(1))-induced carcinogenesis (Guyonnet et al., 2002). DADS induces overexpression of GST (particularly mGSTM1 and mGSTM4 genes) in the stomach and small intestine of mice (Andorfer et al., 2004). A positive correlation between the induction of mGSTP1-1 in the liver and forestomach by DADS and its effectiveness in preventing BP-induced neoplasia in the forestomach in mice has been noted (Hu et al., 1997; Srivastava et al., 1997). Analogously, DADS inhibited azoxymethane (AOM)-induced colon carcinogenesis in male F344 rats, and may be associated with the increased activities of GST, NAD(P)H-dependent QR, and uridine 5'-diphospho-glucuronosyltransferase (Reddy et al., 1993).