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Anti-cancer activities of *S*-allylmercaptocysteine from aged garlic

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[ABSTRACT] While most types of malignancies remain recalcitrant to treatment, application of natural products or their analogs in daily life has offered some hopes as an effective prophylaxis against cancer onset and progression in the past decades. Emerging evidence supports a link between garlic consumption and decreased cancer incidence. Notably, aged garlic extract (AGE) exhibits stronger anti-cancer activities than that of fresh garlic, by virtue of enrichment of several AGE-specific organosulfur compounds, including *S*-allylmercaptocysteine (SAMC). In this review, we summarize the up-to-date mechanistic pathways associated with the anti-proliferative, anti-metastatic and pro-apoptotic effects of SAMC in various cancer models. Based upon the proven safety and improved understanding on its anti-neoplastic properties, SAMC has gained recognition as a promising daily food supplement for cancer prevention or management.

[KEY WORDS] Aged garlic; *S*-allylmercaptocysteine; Cancer; Molecular pathway; Reactive oxygen species

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Introduction

Allium sativum, commonly known as garlic, is a bulbous plant of the onion genus (*Allium*). It has a long history of being utilized as a foodstuff and an effective medicinal substance for centuries in countries such as Egypt and China [1-2]. Like other members of *Allium*, garlic has been valued for its broad effects in helping maintain the human body's metabolic balance against vulnerability. Indeed, extensive experimental evidence from cell and animal models indicates that several garlic-derived organosulfur compounds are efficacious in reducing blood pressure, hyperlipidemia, and oxidative stress, while promoting cardiovascular and hepatic functions, prostanoids synthesis, and immune-regulation [3-4]. Recent epidemiological studies also demonstrate that garlic consumption is negatively associated with incidence of various cancer types, including stomach, colorectal, lung, prostate, and skin cancers [5-7].

Pharmacologically, garlic can yield distinctly enriched preparations by a variety of processing methods. In the market, besides fresh garlic, there are mainly four types of commercially available garlic products, including aged garlic extract (AGE), dehydrated garlic powder, garlic oil and garlic oil macerate [8]. AGE is a processed product from aging garlic what is sliced and then extracted by water or ethanol. It mainly contains several water-soluble allyl amino acid derivatives (such as SAC, SAMC and *N*-fructosyl arginine) and a small amount of oil-soluble compounds [9] (Fig. 1). AGE has been considered to possess immune-enhancing, hepato-protective, antioxidant and anticancer properties with proven safety [1].

Pharmacokinetic studies suggest that SAC and SAMC may be the main active ingredients in AGE, since allicin, vinyldithiins, ajoene, and diallyl disulfide (DADS) are not detected in the blood and urine after treatment [1]. SAMC (*S*-allylmercaptocysteine, chemical formula: CH_2=CH-CH_2-S-S-CH_2-$CHNH_2$-COOH) is a stable nonvolatile sulfur-containing compound of AGE. It can be prepared in a rapid spontaneous reaction between L-cysteine and allicin in aqueous solution (PH 6) (Fig. 2), with very high yield (93%) [10]. Since the pharmacological features and therapeutic perspectives of SAC have been extensively studied and reviewed [11-12], we focused on the beneficial effects of SAMC in this article.

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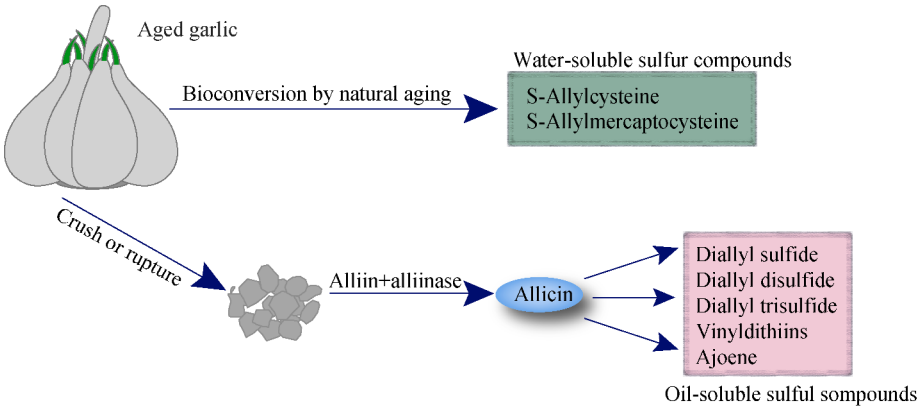

Fig. 1 Major components derived from aged garlic

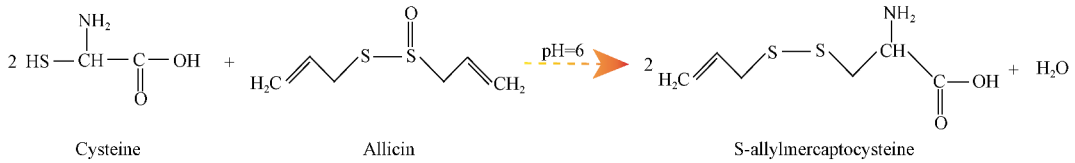

Fig. 2 Chemical synthesis reactions of SAMC during garlic aging process

To date, the health-promoting effects of SAMC have been amply demonstrated in several disease models. For example, overuse of gentamicin, an aminoglycoside type of antibiotic widely used for treating bacterial infections, can give rise to adverse effects, including inner ear and kidney dysfunctions. In a gentamicin-induced rat kidney injury model, excessive production of reactive oxygen species (ROS), including superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$), and nitrosative stress from renal mitochondria were frequently observed, resulting in severe glomerular and tubular damages. Pre-treatment with SAMC significantly attenuated such tissue injury by upregulating the expression of antioxidant enzymes (e.g. GPx, GR, CAT and Mn-SOD) [13]. As an eye treatment, administration of SAMC into the corneas of rabbits decreased intraocular pressure without affecting pupil diameter. Further research revealed that SAMC caused a marked increase in atrial natriuretic peptide (ANP) concentration in the aqueous humor of rabbit, which partially explained the mechanism of SAMC-induced ocular hypotension [14]. Furthermore, we characterized the hepato-protective mechanisms of SAMC in carbon tetrachloride (CCl_4)-or acetaminophen (APAP)-induced acute liver injury and high fat diet-induced non-alcoholic fatty liver disease (NAFLD) in rodent models [15-19]. SAMC potently alleviated hepatic injuries, by reducing symptoms such as inflammation, necro-apoptosis, fibrosis, lipid metabolism dysfunction, and oxidative stress. SAMC achieves this primarily through its anti-inflammatory, antioxidant and autophagic regulatory actions [15, 20].

Indeed, most studies on the beneficial effects of SAMC focused on its potential anti-cancer application. In a variety of cancer types, SAMC has been shown to exert potent and specific anti-cancer effects on different regulating pathways (Table 1).

Liver cancer

The occurrence of liver cancer is mainly caused by cirrhosis, which is associated with viral infections and chronic alcohol consumption. Recent computational findings suggest that SAMC has high docking score for the oncogene Kras (RAS) in HepG2 cells, which is a small GTPase with functional importance in regulating cytoskeleton dynamics, and cell growth and tissue development. However, the complex formed by SAMC and RAS is not stable, suggesting that SAMC may not have an effect on Ras activity strong or long enough for SAMC to prevent liver tumorigenesis [35]. In addition, transforming growth factor-beta (TGF-β) signaling was reported to be important in SAMC-induced hepatoma cell apoptosis *in vitro*. Specifically, SAMC treatment potently activated TGF-β1, TβRII, p-smad2/3, smad4 and smad7 signaling, as well as the intrinsic apoptotic pathways (e.g. Bim and Bcl-2) in HepG2 cells, which was different from TGF-β alterations in colon cancer cell (SW620) [36].

Gastric cancer

Frequently asymptomatic in its early stage, gastric cancer progressively alters the micro-environment to favor tumorigenesis. This insidious nature helps ensure gastric cancer as a malignancy with the second highest fatal ratio of cancer-related diseases in the world. In experimental models, when cultured with SAMC, SGC7901 gastric cancer cells showed marked morphological changes, such as apoptosis-related atrophy, shrinkage, fragmentation and reduced cell connections. The MAPK, and intrinsic and extrinsic apoptotic pathways were

reportedly involved in these processes [31, 42]. Similarly, studies in SNU-1 gastric cancer cells confirmed the pro-apoptotic activities of SAMC [31]. SNU-I after treatment of SAMC showed a mitochondrial cytochrome c activation and an *in vitro* caspase-3 activity [10]. In a nude mice model implanted with tumors of human KMN-45 gastric cancer cells, SAMC administration was found to suppress tumor growth and induce apoptosis in tumor cells via Bcl-2 family-related pathways [32].

Table 1 Summary of anti-neoplastic mechanisms of SAMC

Cancer type	Models	Treatment and dosage	Proposed mechanisms	Ref.
Colon	Cells and mice	SW-480 and HT-29 cells treated with 300 μmol·L^{-1} SAMC alone or in combination with sulindac sulfide for 24 h. SAMC at 300 mg·kg^{-1}·day^{-1} in mice by gavage feeding for 16 d.	Activation of JNK1 pathway; microtubule depolymerization; mitochondrial membrane depolarization	[5, 21-24]
Prostate	Cells and mice	0−200 μmol·L^{-1} SAMC-treated LNCaP cell or SAMC-treated PC-3, DU145 cells for 24 h. Mice were orogastrically fed of different doses of SAMC for 28 d.	Rescue of GSH deficits; alteration of prostate biomarker expression and testosterone utilization; restoration of E-cadherin expression	[25-30]
Gastric	Cells and mice	0−400 μmol·L^{-1} SAMC-treated SNU-1 cells and SGC 7901 cells for 24 h, SAMC treated mice by 100 or 300 mg·kg^{-1} daily orogastric feeding for 24 d.	Cytochrome c release and caspase-3 activation; activation of MAPK and Bcl-2 family-related pathways	[10, 31-32]
Breast	Cells	0−800 μmol·L^{-1} SAMC in MCF-7 and MDA-MB-231 cells for 24 to 72 h.	Caspase-3/9 activation; pro-apoptotic proteins Bax, p53 and p21 up-regulation; anti-apoptotic protein Bcl-2 and Bcl-XL down-regulation	[26, 33-34]
Liver	Cells	HepG2 cells tested with 800 μmol·L^{-1} SAMC alone or in combination with MAPK inhibitors for 8 h.	Potent activation of TGF-β1, TβRII, p-smad2/3, smad4 and smad7 signaling	[35-36]
Bladder	Cells	0−200 μmol·L^{-1} SAMCtreated stable Id-1-expressing and si-Id-1 transfectants in RT112 and MGH-U1 cells for 24 h	Id-1 as a potential target of SAMC mediated treatment	[7]
Thyroid	Cells	8305C (HPACC) was treated with 100, 300 μmol·L^{-1}, and 500 μmol·L^{-1} SAMC for 48 h.	Induction of apoptosis by inhibiting telomerase activity	[37]
Ovarian	Cells and mice	HO8910, SKOV3 and HO8910PM cells treated with 300 μmol·L^{-1} SAMC for 2 to 8 h. Mice were given intragastric administration of 0.3 mg·g^{-1}·d^{-1} of SAMC for 21 days.	Restoration of E-cadherin expression	[29, 38]
Lung	Cells	A549 cells were either pre-treated or co-treated with 1 μmol·L^{-1} B(a)P and either 10 or 50 μmol·L^{-1} SAMC for 24 h.	Inhibition of ROS formation, DNA damage, and NF-κB activation	[39]
Erythroleukemia	Cells	SAMC treated OCIM, HEL and DS19 cells in the dosage of 46, 93, 25 μmol·L^{-1}for 24 h respectively.	Induction of histone acetylation	[26, 40-41]

Colon cancer

Among cancer types, colon cancer has been extensively studied to characterize the mechanistic roles of SAMC in cancer treatment. SAMC challenge (200 μmol·L^{-1}) markedly inhibited cell growth, arrested G_2/M cell cycle phases, induced apoptosis, and suppressed invasion of the colon cancer cell lines SW-480 and HT-29. The observed phenotypes were accompanied by activation of caspase-3 and JNK1 signaling and induced GSH upregulation [21]. Other studies also unveiled several mechanistic pathways by which SAMC exerts its suppressive effects in colon cancer cells. Firstly, SAMC modulates normal cellular functions by altering cytoskeleton dynamics. *In vitro* immunofluorescence study showed that treatment of SW-480 cells or NIH3T3 fibroblasts with SAMC leads to rapid microtubule depolymerization, microtubule cytoskeleton disruption, Golgi dispersion, centrosome fragmentation, and spindle assembly disruption in mitotic cells. While co-treated with β-mercaptoethanol (β-ME), a reducing agent with one -SH/molecule, significantly reduced the effect of SAMC on microtubule polymerization [5]. SAMC could also inhibit *de novo* tubulin polymerization to induce microtubule depolymerization [5]. Secondly, SAMC selectively perturbs signal transduction pathways important for stress response and control of cell death/survival. Of note, activation of JNK1 and subsequent caspase seems to be critical for PARP-mediated apoptosis, since JNK1 knockout or selective JNK inhibitor SP600125 application blocked the apoptosis induced by SAMC in the early phase (24 h) but not the late phase (48 h). Other MAPK family members, such as ERK1/2 and p38 MAPK, were found to be not involved in SAMC-induced SW-480 apoptosis. When cells were pre-treated with specific inhibitors of ERK1/2 (PD98059) or p38 MAPK (SB203580) prior to SAMC incubation in SW-480 cells at concentrations sufficient for suppressing ERK1/2 or p38 phosphorylation, neither compound had an effect on SAMC-induced apoptosis. These data confirm that SAMC can induce apoptosis in colon cancer cells primarily via JNK-dependent pathway in the first 24 h [5, 23]. Thirdly, SAMC can directly target mitochondria to initiate apoptosis in cancer cells. SAMC treatment (300 μmol·L^{-1}) strongly induced the loss of mitochondrial membrane potential in SW480 cells, leading to the cytochrome crelease from inner membrane of mitochondria, to induce cellular apoptosis via the intrinsic apoptotic pathway [22].

Liang *et al.* constructed a stable luciferase expression system of colon cancer cell line (SW620-Fluc) to establish a xenograft mice model, which was convenient in viewing the *in vivo* anti-tumor effect of SAMC *via* bioluminescence imaging technique. They found that the fluorescence intensity of tumor in SAMC-treated group were significantly weaker than that in the untreated group at day 12 and 16 after cell implantation. Histopathological results revealed that SAMC directly triggers cell apoptosis within tumor by activated caspase 3 and cleaved PARP1 [24], without causing toxic symptoms in vital organs (e.g. heart and liver).

Prostate cancer

Prostate cancer is one of the most common male cancers, whose symptoms are generally elusive in the initial stage. Investigation on androgen-dependent human prostate carcinoma cells (LNCaP) found that SAMC exhibited potent effects on (1) inhibition of cell growth, (2) testosterone catabolism rate, and (3) induction of well-known biomarkers' expression in LNCaP cells including prostate specific antigen (PSA) and prostate specific membrane antigen (PSMA) [25-27]. Furthermore, studies on androgen-independent prostate carcinoma cell lines, including PC3, DU145 and 22Rv1, found that SAMC inhibited colony formation, increased apoptosis *in vitro* and suppressed CWR22R-formed xenograft tumor growth *in vivo* [28].

Cancer metastasis refers to the spread of cancer cells from one organ or part of the body to another, which is the principal cause for cancer-related death. Based on colony-forming, wound-closure and Matrigel-invasion assays in potentially invasive androgen-independent prostate cancer (PCa) cells, SAMC was found to suppress PCa cell proliferation and invasive abilities [29]. In a fluorescent orthotopic prostate cancer SCID mouse model constructed with a green fluorescent protein-expressing PC-3 cell line, results also indicate that SAMC could inhibit tumor growth and dissemination, without obvious toxicity *in vivo* [30]. Further mechanistic investigation showed that SAMC suppressed tumor cell invasiveness by inducing E-cadherin expression and by inhibiting the activation of its transcriptional suppressor Snail [28-29]. In addition, SAMC has properties that increase the chemical sensitivity of prostate cancer cells. Docetaxel is a recently introduced new agent against hormone refractory prostate cancer (HRPC). Clinically, it has made a modest but significant improvement on patients' survival. When applied in co-treatment with SAMC, the anti-cancer activities of docetaxel were significantly potentiated in *in vitro* assays with PC3, DU145 and 22Rv1 cells, as assessed in terms of colony forming inhibition, apoptosis induction and G_2/M phase arrest [30].

Breast cancer

Breast cancer is a malignancy that commonly occurs in women with a multifactorial etiology including genetic inheritance, obesity and hormone abnormalities. SAMC exhibited potent effects on cell growth/invasion retardation, cell cycle arrest, and apoptosis induction of both estrogen receptor (ER)-positive MCF-7 cell and ER-negative MDA-MB-231 cell. Alterations of the intrinsic apoptotic pathway, including caspase-3/9 activation, pro-apoptotic proteins (e.g. Bax, p53 and p21) up-regulation, and anti-apoptotic protein (e.g. Bcl-2 and Bcl-XL) down-regulation were the main mechanisms underlying SAMC actions [26, 33].

Estrogen receptor (ER) is a transcription factor responsible for modulating the biological activities of estrogen. Recently, evidence indicates that ER activity was closely related to the occurrence of breast cancer. Indeed, suppressing the activity of ER to rectify hormonal balance has been raised as a treatment option for breast cancer. Strong hydrogen bonding between Glu353/Arg394 of ER and SAMC may partially explain how SAMC inhibits ER-dependent growth of breast cancer cells [34].

Bladder cancer

Over-expression of inhibitor of differentiation-1 (Id-1) is often deemed a disease marker in bladder cancer for its roles in promoting neoplasm, metastasis and resistance to therapy. In a study comparing the response to SAMC by a bladder cancer cell line (RT112) with low endogenous Id-1 expression and another cell line (MGH-U1) with high endogenous Id-1 expression, it was found that Id-1 level was negatively associated with the positive effect of SAMC on cell survival. It is also worth noting that knock-down of Id-1 augments cellular susceptibility to SAMC. Overall, evidence suggests that Id-1 may be a potential target of SAMC mediated treatment of bladder cancer [7].

Thyroid cancer

A recent study examined the effects of SAMC on anaplastic thyroid cancer (ATC), a rare and rapidly fatal endocrine malignancy [37]. The human anaplastic thyroid cancer cell line 8305C (HPACC) was subjected to SAMC challenge. In transmission electron microscopy (TEM) analysis of cellular ultrastructures, pervasive effects of SAMC were revealed, which included typical apoptotic characteristics such as cell atrophy, shrinkage, blurred contour, fragmentation and even lysis into small pieces. In cell assays, SAMC also significantly inhibited cell proliferation of HPACC-8305C, arrested the cells in G_2/M phase, induced apoptosis and inhibited telomerase activity [37]. Nevertheless, detailed anti-cancer mechanisms of SAMC actions in thyroid cancer warrant further exploration.

Lung cancer

Benzo(a)pyrene [B(a)P] is one of the most potent carcinogens, which promotes the development and metastasis of lung cancer through inducing DNA intercalation, oxidative damage, mutations, chromosomal aberrations, and overt tumorigenesis. Wang *et al.* investigated whether SAMC can prevent B(a)P-induced precancerous carcinogenesis in the human lung cell

line A549. Both pre-treatment and co-treatment of SAMC significantly reversed B(a)P-induced A549 cell proliferation, ROS formation, DNA damage, NF-κB activation and cell cycle alteration *in vitro*, suggesting the therapeutic potential of SAMC in managing B(a)P-induced human lung cancer [38].

Ovarian cancer

By using several established human cell lines (HO8910, HO8910PM, and SKOV3), Wu *et al.* investigated the effects of SAMC on ovarian cancer cells. *In vivo* and *in vitro* experiments showed that SAMC induced apoptosis and restored E-cadherin expression in SKOV3 and HO8910 cells, which agrees with earlier findings [28, 39]. However, HO8910PM cells, a line with high metastatic potential, showed markedly higher resistant to SAMC effect in colony formation, cells migration, invasion, and tumor growth in a xenograft mice model. Further study revealed that the survivin gene was highly expressed in HO8910PM cells. Pre-treatment with specific survivin siRNA resensitized HO8910PM cells to SAMC [39]. These results suggest that downregulation of survivin expression/activity in conjunction with SAMC treatment could be a possible approach to managing this malignant cancer, where survivin is highly expressed.

Erythroleukemia

Studies on the anti-proliferative potential of SAMC in the erythroleukemia cell lines HEL and OCIM-1 have provided evidence that SAMC can induce dose-dependent inhibition of cell growth, G_2/M phase arrest, and apoptosis initiation [26, 40]. In DS19 mouse erythroleukemia cells, SAMC (25 mmol·L^{-1}) blunted cell proliferation and induced histone acetylation. In further validation with Caco-2 human colon cancer cells and T-47D human breast cancer cells, SAMC also triggered histone acetylation, suggesting a general epigenetic response. The mechanism by which SAMC induces histone acetylation currently remains poorly understood, though it may be partially related to SAMC's catabolic product allyl mercaptan, which can act as a competitive HDAC inhibitor to promote rapid and sustained histone hyperacetylation in human cancer cells [41].

Conclusion

As most malignancies are costly and far from tractable in the clinic, early prevention and management by everyday intake of food supplements with anti-cancer potential has emerged as a cogent and practicable idea in the past decades. Numerous lines of evidence in basic and clinical research have confirmed the medicinal benefits of garlic constituents in cancer prevention or treatment, including AGE-derived organosulfur compounds [43]. The ability of SAMC to remove ROS and up-regulate antioxidant enzymes may explain one of the main reasons to anti-cancer [13]. Current researches provide compelling evidence that SAMC possess anti-tumor property mainly through activating MAPK, scavenging active oxygen and resisting inflammation [43]. SAMC induces Bcl-2 family imbalance to cause apoptosis of tumor cell through modulation of MAPK pathway and mitochondrial cytochrome c release. Meanwhile, SAMC also can inhibit tumor cell proliferation by inducing histone acetylation and inhibiting microtubule polymerization. Besides, mechanistic studies showed that SAMC induced E-cadherin to suppress tumor cell invasiveness (Fig. 3). Apart from direct anti-neoplastic

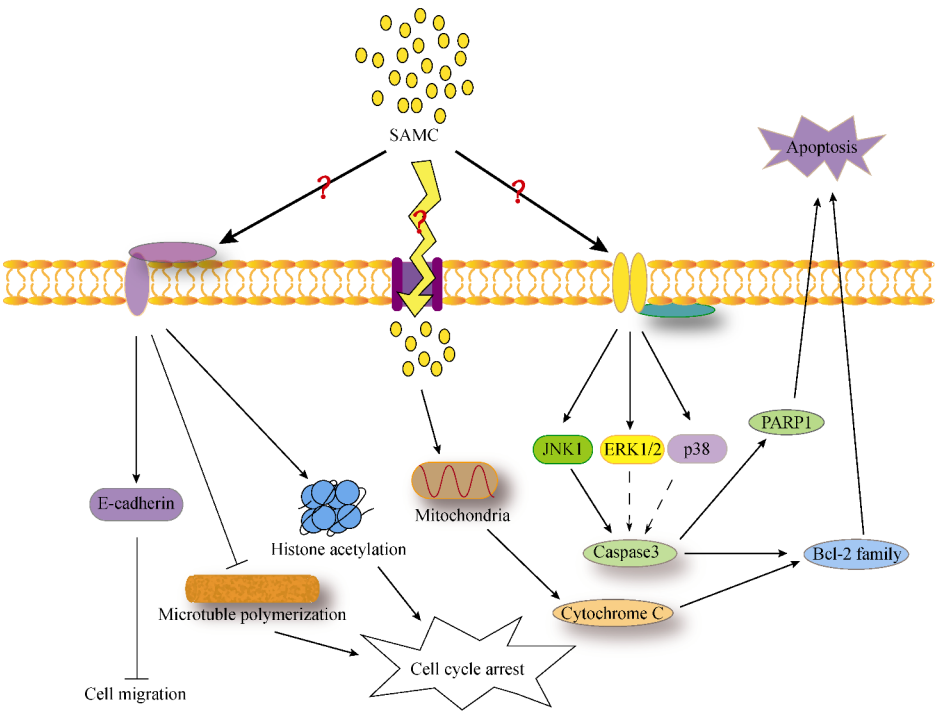

Fig. 3 Signaling pathways involved in SAMC mediated cancer inhibition

properties, SAMC has been found to increase the chemosensitivity of cancer cells. In a nude mice model implanted with the HRPC cell line CWR22R, combined treatment of docetaxel and SAMC yielded synergistic anti-tumor outcomes, which included reduced tumor growth, downregulation of Bcl-2 and upregulation of E-cadherin, with no obvious adverse effects. SAMC can significantly enhance the ability of rapamycin inducing colon cancer cell apoptosis and inhibiting tumor growth in xenograft nude mice [44]. In another study, co-administration of sulindac sulfide (SS) with SAMC in human colon cancer cell lines (SW-480 and HT-29) led to a significantly enhanced capacity to inhibit cell proliferation and induce apoptosis, as compared with SS alone [21].

Indeed, there remain several research gaps in our understanding on SAMC-mediated cancer inhibition. First, even though SAMC is considered as a novel anti-cancer candidate compound, the pharmacokinetics of SAMC is unestablished. Second, potential pharmacological interactions between SAMC and other garlic-derived organosulfur compounds (e.g. SAC and allicin) are largely unclear, though some commercial AGE formulations may come as a mixture of those compounds. Third, the direct interacting proteins/molecular targets of SAMC in cells are unknown. Whether SAMC interacts with membrane receptors to transduce anti-cancer signals in cancer cells remains to be clarified. Fourth, although garlic is generally safe for most people when taken appropriately via the oral route, it can elicit a number of side effects in some people, including nausea, vomiting, body odor, bleeding and diarrhea [45]. Lastly, clinical study on the anti-cancer therapeutic efficacy is needed to further prove the availability of SAMC as a novel and safe drug. Thus, development of novel drug forms is critical for the safe daily use of SAMC or AGE in preventing or managing cancer.

Abbreviation — Full name

AGE	Aged garlic extract
SAMC	*S*-allylmercaptocysteine
ROS	Reactive oxygen species
ER	Estrogen receptor
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
ATC	Anaplastic thyroid cancer

References

[1] Amagase H, Petesch BL, Matsuura H, *et al*. Intake of garlic and its bioactive components [J]. *J Nutr*, 2001, **131**(3s): 955S-962S.

[2] Borek C. Antioxidant health effects of aged garlic extract [J]. *J Nutr*, 2001, **131**(3s): 1010S-1015S.

[3] Yeh YY, Liu L. Cholesterol-lowering effect of garlic extracts and organosulfur compounds: human and animal studies [J]. *J Nutr*, 2001, **131**(3s): 989S-993S.

[4] Aggarwal BB, Shishodia S. Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: reasoning for seasoning [J]. *Ann N Y Acad Sci*, 2004, **1030**(1): 434-441.

[5] Xiao DH, Pinto JT, Soh JW, *et al*. Induction of apoptosis by the garlic-derived compound S-allylmercaptocysteine (SAMC) is associated with microtubule depolymerization and c-Jun NH2-terminal kinase 1 activation [J]. *Cancer Res*, 2003, **63**(20): 6825-6837.

[6] Pinto JT, Krasnikov BF, Cooper AJ. Redox-sensitive proteins are potential targets of garlic-derived mercaptocysteine derivatives [J]. *J Nutr*, 2006, **136**(3 Suppl): 835S-841S.

[7] Hu H, Zhang XP, Wang YL, *et al*. Identification of a novel function of Id-1 in mediating the anticancer responses of SAMC, a water-soluble garlic derivative, in human bladder cancer cells [J]. *Mol Med Rep*, 2011, **4**(1): 9-16.

[8] Tanaka S, Haruma K, Yoshihara M, *et al*. Aged garlic extract has potential suppressive effect on colorectal adenomas in humans [J]. *J Nutr*, 2006, **136**(3): 821s-826s.

[9] Chu Q, Lee DT, Tsao SW, *et al*. S-allylcysteine, a water-soluble garlic derivative, suppresses the growth of a human androgen-independent prostate cancer xenograft, CWR22R, under *in vivo* conditions [J]. *BJU Int*, 2007, **99**(4): 925-932.

[10] Lee Y. Induction of apoptosis by S-allylmercapto-L-cysteine, a biotransformed garlic derivative, on a human gastric cancer cell line [J]. *Int J Mol Med*, 2008, **21**(6): 765-770.

[11] Sathibabu Uddandrao VV, Brahmanaidu P, Saravanan G. Therapeutical perspectives of S-allylcysteine: effect on diabetes and other disorders in animal models [J]. *Cardiovasc Hematol Agents Med Chem*, 2016, **15**(2): 71-77

[12] Colin-Gonzalez AL, Santana RA, Silva-Islas CA, *et al*. The antioxidant mechanisms underlying the aged garlic extract- and S-allylcysteine-induced protection [J]. *Oxid Med Cell Longev*, 2012, **2012**: 907162

[13] Pedraza-Chaverri J, Barrera D, Maldonado PD, *et al*. S-allylmercaptocysteine scavenges hydroxyl radical and singlet oxygen *in vitro* and attenuates gentamicin-induced oxidative and nitrosative stress and renal damage *in vivo* [J]. *BMC Clin Pharmacol*, 2004, **4**: 5.

[14] Chu TC, Han P, Han G, *et al*. Intraocular pressure lowering by S-allylmercaptocysteine in rabbits [J]. *J Ocul Pharmacol Ther*, 1999, **15**(1): 9-17.

[15] Sumioka I, Matsura T, Kasuga S, *et al*. Mechanisms of protection by S-allylmercaptocysteine against acetaminophen-induced liver injury in mice [J]. *Jpn J Pharmacol*, 1998, **78**(2): 199-207.

[16] Sumioka I, Matsura T, Yamada K. Therapeutic effect of S-allylmercaptocysteine on acetaminophen-induced liver injury in mice [J]. *Eur J Pharmacol*, 2001, **433**(2-3): 177-185.

[17] Xiao J, Liong EC, Ling MT, *et al*. S-allylmercaptocysteine reduces carbon tetrachloride-induced hepatic oxidative stress and necroinflammation *via* nuclear factor kappa B-dependent pathways in mice [J]. *Eur J Nutr*, 2012, **51**(3): 323-333.

[18] Xiao J, Ching YP, Liong EC, *et al*. Garlic-derived S-allylmercaptocysteine is a hepato-protective agent in non-alcoholic fatty liver disease *in vivo* animal model [J]. *Eur J Nutr*, 2013, **52**(1): 179-191.

[19] Xiao J, Guo R, Fung ML, *et al*. Garlic-derived S-allylmercaptocysteine ameliorates nonalcoholic fatty liver disease in a rat model through inhibition of apoptosis and enhancing autophagy [J]. *Evid Based Complement Alternat Med*, 2013, **2013**: 642920.

[20] Yang L, Yang M, Li S, *et al*. S-allylmercaptocysteine attenuates

posaconazole-induced adverse effects in mice through antioxidation and anti-inflammation [J]. *Int Immunopharmacol*, 2018, **58**: 9-14.

[21] Shirin H, Pinto JT, Kawabata Y, *et al*. Antiproliferative effects of S-allylmercaptocysteine on colon cancer cells when tested alone or in combination with sulindac sulfide [J]. *Cancer Res*, 2001, **61**(2): 725-731.

[22] Xiao D, Pinto JT, Gundersen GG, *et al*. Effects of a series of organosulfur compounds on mitotic arrest and induction of apoptosis in colon cancer cells [J]. *Mol Cancer Ther*, 2005, **4**(9): 1388-1398.

[23] Liang D, Qin Y, Zhao W, *et al*. S-allylmercaptocysteine effectively inhibits the proliferation of colorectal cancer cells under *in vitro* and *in vivo* conditions [J]. *Cancer Lett*, 2011, **310**(1): 69-76.

[24] Zhang Y, Li HY, Zhang ZH, *et al*. Garlic-derived compound S-allylmercaptocysteine inhibits cell growth and induces apoptosis *via* the JNK and p38 pathways in human colorectal carcinoma cells [J]. *Oncol Lett*, 2014, **8**(6): 2591-2596.

[25] Pinto JT, Qiao C, Xing J, *et al*. Effects of garlic thioallyl derivatives on growth, glutathione concentration, and polyamine formation of human prostate carcinoma cells in culture [J]. *Am J Clin Nutr*, 1997, **66**(2): 398-405.

[26] Sigounas G, Hooker J, Anagnostou A, *et al*. S-allylmercaptocysteine inhibits cell proliferation and reduces the viability of erythroleukemia, breast, and prostate cancer cell lines [J]. *Nutr Cancer*, 1997, **27**(2): 186-191.

[27] Pinto JT, Qiao C, Xing J, *et al*. Alterations of prostate biomarker expression and testosterone utilization in human LNCaP prostatic carcinoma cells by garlic-derived S-allylmercaptocysteine [J]. *Prostate*, 2000, **45**(4): 304-314.

[28] Chu Q, Ling MT, Feng H, *et al*. A novel anticancer effect of garlic derivatives: inhibition of cancer cell invasion through restoration of E-cadherin expression [J]. *Carcinogenesis*, 2006, **27**(11): 2180-2189.

[29] Howard EW, Ling MT, Chua CW, *et al*. Garlic-derived S-allylmercaptocysteine is a novel *in vivo* antimetastatic agent for androgen-independent prostate cancer [J]. *Clin Cancer Res*, 2007, **13**(6): 1847-1856.

[30] Howard EW, Lee DT, Chiu YT, *et al*. Evidence of a novel docetaxel sensitizer, garlic-derived S-allylmercaptocysteine, as a treatment option for hormone refractory prostate cancer [J]. *Int J Cancer*, 2008, **122**(9): 1941-1948.

[31] Lee Y, Kim H, Lee J, *et al*. Anticancer activity of S-allylmercapto-L-cysteine on implanted tumor of human gastric cancer cell [J]. *Biol Pharm Bull*, 2011, **34**(5): 677-681.

[32] Yan JY, Tian FM, Hu WN, *et al*. Apoptosis of human gastric cancer cells line SGC 7901 induced by garlic-derived compound S-allylmercaptocysteine (SAMC) [J]. *Eur Rev Med Pharmacol Sci*, 2013, **17**(6): 745-751.

[33] Hung TC, Lee WY, Chen KB, *et al*. Investigation of estrogen receptor (ESR1) for breast cancer from traditional Chinese medicine [J]. *Biomed Res Int*, 2014, **2014**: 321486.

[34] Zhang H, Wang K, Lin G, *et al*. Antitumor mechanisms of S-allyl mercaptocysteine for breast cancer therapy [J]. *BMC Complement Altern Med*, 2014, **14**: 270.

[35] Tong D, Qu H, Meng X, *et al*. S-allylmercaptocysteine promotes MAPK inhibitor-induced apoptosis by activating the TGF-beta signaling pathway in cancer cells [J]. *Oncol Rep*, 2014, **32**(3): 1124-1132.

[36] Hung TC, Lee WY, Chen KB, *et al*. An investigation of small GTPases in relation to liver tumorigenesis using traditional Chinese medicine [J]. *Biomed Res Int*, 2014, **2014**: 428210.

[37] Liu Y, Yan J, Han X, *et al*. Garlic-derived compound S-allylmercaptocysteine (SAMC) is active against anaplastic thyroid cancer cell line 8305C (HPACC) [J]. *Technol Health Care*, 2015, **23 Suppl 1**: S89-93.

[38] Wu J, Zhao S, Zhang J, *et al*. Over-expression of survivin is a factor responsible for differential responses of ovarian cancer cells to S-allylmercaptocysteine (SAMC) [J]. *Exp Mol Pathol*, 2016, **100**(2): 294-302.

[39] Wang K, Wang Y, Qi Q, *et al*. Inhibitory effects of S-allylmercaptocysteine against benzo(a)pyrene-induced precancerous carcinogenesis in human lung cells [J]. *Int Immunopharmacol*, 2016, **34**: 37-43.

[40] Sigounas G, Hooker JL, Li W, *et al*. S-allylmercaptocysteine, a stable thioallyl compound, induces apoptosis in erythroleukemia cell lines [J]. *Nutr Cancer*, 1997, **28**(2): 153-159.

[41] Lea MA, Rasheed M, Randolph VM, *et al*. Induction of histone acetylation and inhibition of growth of mouse erythroleukemia cells by S-allylmercaptocysteine [J]. *Nutr Cancer*, 2002, **43**(1): 90-102.

[42] Zhu X, Jiang X, Li A, *et al*. S-allylmercaptocysteine suppresses the growth of human gastric cancer xenografts through induction of apoptosis and regulation of MAPK and PI3K/Akt signaling pathways [J]. *Biochem Biophys Res Commun*, 2017, **491**(3): 821-826.

[43] Nicastro HL, Ross SA, Milner JA. Garlic and onions: their cancer prevention properties [J]. *Cancer Prev Res (Phila)*, 2015, **8**(3): 181-189.

[44] Li S, Yang G, Zhu X, *et al*. Combination of rapamycin and garlic-derived S-allylmercaptocysteine induces colon cancer cell apoptosis and suppresses tumor growth in xenograft nude mice through autophagy/p62/Nrf2 pathway [J]. *Oncol Rep*, 2017, **38**(3): 1637-1644.

[45] Borrelli F, Capasso R, Izzo AA. Garlic (*Allium sativum* L.): adverse effects and drug interactions in humans [J]. *Mol Nutr Food Res*, 2007, **51**(11): 1386-1397.

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