Potential Anticancer Effects of Aged Garlic Extract and its Water-soluble Organosulfur Compounds

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Review Article

ABSTRACT

Background: Cancer is among the leading causes of morbidity and mortality globally; it often leads to a steep rise in healthcare expenses. It is a known fact that various dietary ingredients such as aged garlic is an active anticancer agent, and its extracts do not have a strong odor and pungent taste.
Purpose: This review summarizes the potential beneficial effects of aged garlic extract (AGE) and its water-soluble organosulfur compounds on the cancer incidences, and in the prevention and improvement of malignancy factors.
Methods: The study utilizes systematic reviews on publications of previous studies obtained from scholarly journal databases including PubMed, Medline, Ebsco Host, Google Scholar and Cochrane. The study utilizes secondary information based on the studies conducted in cancer cell lines, animal and humans as there are increasing evidence of the efficacy of AGE and AGE-derived water-soluble organosulfur compounds in cancer and other malignancies.
Conclusion and Recommendation: Although animal and laboratory results were mostly consistent, there is variable evidence from human studies. The overall findings suggest that consumption of AGE and AGE-derived organosulfur compounds can offer significant protection against cancer. In our review, we found that there are shortcomings in various studies. Therefore, we recommend that more investigations are necessary to establish whether aged garlic extract could be considered for cancer prevention.

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Graphical Abstract
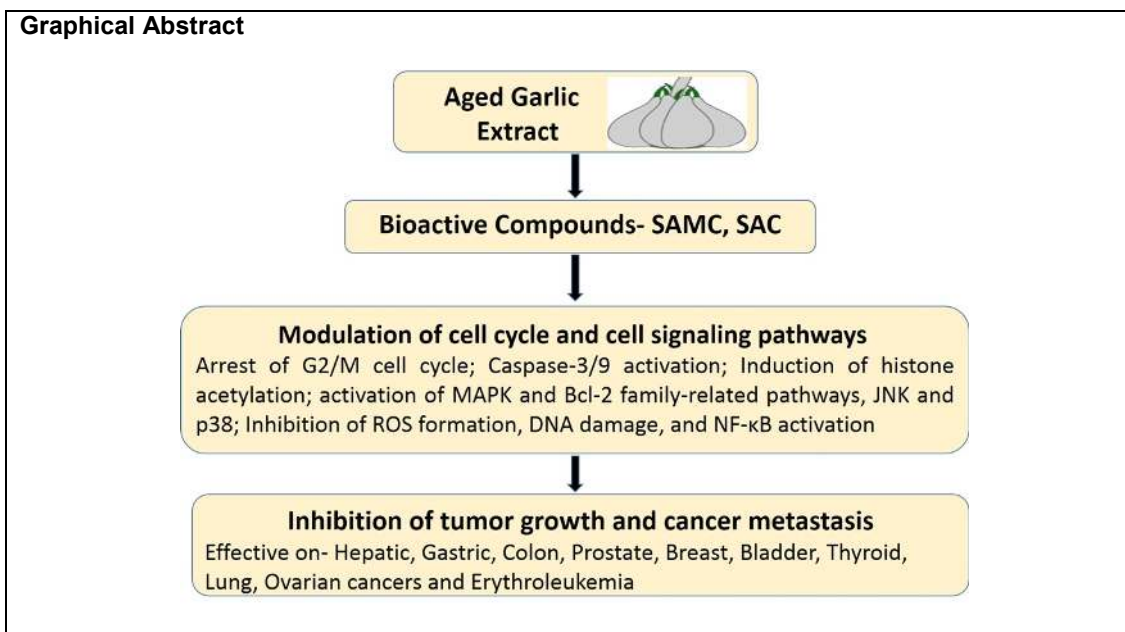
Keywords: Garlic; organosuphur; cancer; tumour; malignancy; anticancer.

ABBREVIATIONS

AGE   : Aged Garlic Extract
LDL   : Low Density Lipoprotein
SAMC   : S-allyl Mercapto Cysteine (SAMC)
SAC   : S-allyl Cysteine
ER   : Oestrogen Receptor

1. INTRODUCTION

Cancer is now widely recognized as a global problem that unfortunately lacks a global solution. The latest global cancer statistics report estimates 18.1 million new cancer cases and 9.4 million deaths [1]. An increased economic burden due to cancer is an area of concern for governments, healthcare practitioners, physicians, financial establishments and society [2]. Furthermore, the extent of the cancer burden increases significantly with remote location of the treating hospitals and socioeconomic background of individuals [3]. There are reports of therapeutic failure of the conventional chemotherapeutic agents, thereby requiring new strategies for treating cancer successfully. Diet and nutrition have been considered to play an important role in the pathogenesis and treatment of carcinogenesis.

Garlic (*Allium sativum* Linn) is used in abundance in the Asian region, especially in cooking. However, this is not where its use ends:

It has been used for more than 4 millennia for treatment of various illnesses and their prevention [4], and this idea of the use of herbs for the treatment of diseases, is a practice that has been employed for many years (e.g., for the treatment and prevention of cancer/obesity/heart disease). Application of garlic is known to have been a particularly popular method for the treatment of headaches, tumours, and heart problems (the Egyptian *Codex Ebers*, 1550 BC); there are artworks dedicated to the vegetable being engraved into the tombs of Ancient Egypt as far back as 3700 BC. Ideas such as these were not only present in Egypt: garlic has been utilised as an antiseptic for ulcers and injuries, as a tea (alongside onion) for headaches, cholera, fever, and dysentery [5], and as a stimulant for enhanced athletic performance in India, China, and Greece respectively. To bring this to the present day, Dolara et al. also note that those people who consume a notable amount of vegetables and fruits tend to see a reduction in their risk of contracting cancer [6].

Favorable biological and pharmacological effects of garlic preparations consumption have been documented in the *in-vivo* animal models and *in-vitro* cultured cell lines. Garlic is known as a useful material in decreasing blood pressure and cholesterol, inhibiting low density lipoprotein (LDL) oxidation, inhibiting platelet aggregation, and increasing nitric oxide production [7]. Many

studies showed a low incidence of stomach, colorectal, prostate, esophagus cancers, and female breast carcinoma in societies with high Allium vegetable consumption [8,9].

The advantages of garlic consumption have been mostly attributed to its immunity enhancing tendencies [10], prevention of nuclear factor kappa β (NF-kβ) activation triggered by receptor agonists (e.g., tumour necrosis factor-alpha [TNF-α]; lipopolysaccharide [LPS]), strong antioxidant impact [11], and, according to Youn et al., its containment of receptor-level Toll-Like Receptors (TLRs)-mediated signalling pathway [12].

However, it is essential to note that there are many health issues related to the eating of raw garlic [13]—usually concerning issues with digestion and the stomach— despite the wealth of advantages that also comes with this—not to mention the fact that a number of individuals would find the vegetable's pungent scent and taste to be enough of a deterrent for consuming it in raw form. Four significant garlic formulations that are available in the market are as follows: garlic powder, aged garlic extract (AGE), garlic oil macerate, and garlic essential oil [14].

The objective of current review was to summarize the potential effects of aged garlic extract (AGE) and its water-soluble organosulfur compounds (SAMC and SAC) on the cancer incidences, prevention and improvement of malignancy factors.

2. METHODS

The study utilizes systematic reviews on publications of previous studies obtained from scholarly journal databases including PubMed, Medline, Ebsco Host, Google Scholar and Cochrane. The study utilizes secondary information based on the studies conducted in cancer cell lines, animal, and humans, where there are increasing evidence of the efficacy of aged garlic extract (AGE) and AGE-derived water-soluble organosulfur compounds in cancer and other malignancies.

3. FRESH GARLIC AND AGE's CHEMICAL COMPONENTS

According to Santhosha et al., fresh garlic is comprised of approximately 28% carbohydrates (fructans), 2% proteins (alliinase), 1.5% fibre, 63% water, 2.3% organosulfur compounds, and 1.2% free amino acids (arginine) [15]. AGE's

higher biological activity is thought to be a result of fermentation that, in turn, leads to the phytochemical compound conversion process. According to Corzo-Martinez et al., odoriferous and cytotoxic alkyl alkane-thiosulfates (e.g., allicin) are formed as a result of the breakdown of cytotoxic cysteine sulfoxides (alliin) by alliinase [16]. This occurs once the garlic has been administered (e.g., after slicing/chewing/crushing), or dehydration has occurred. Alliin—which embodies the strong flavour of the garlic—is produced after γ-glutamyl cysteines [17], present in high concentration in garlic, has been hydrolysed and oxidised; it is formed at a cool temperature during garlic storage. This allicin—amongst its neighbouring thiosulfates—are then broken down into Diallyl Disulphide (DADS), dithiins, Diallyl Sulphide (DAS), Diallyl Trisulfide (DATS), and ajoene [16]. S-allyl cysteine (SAC) is another compound that is responsible for the overall positive health impacts of garlic (i.e., its anti-diabetic, anti-inflammatory, and anti-oxidant pursuits) [18]. According to Choi et al., S-allyl cysteine (SAC) is synthesized from γ-glutamyl cysteines through its catabolic pathway [19].

Complex chemical components present in AGE are mostly comprised of water-soluble allyl amino acid derivatives like stable lipid-soluble allyl sulphides, saponins, organosulfur content, flavonoids, and crucial micro- and macronutrients, and their synthesis is also highly reliant on the process by which they are formed. According to Wei & Lau, S-allyl mercapto cysteine (SAMC) (possessing antioxidant activity) and water-soluble S-Allyl Cysteine (SAC) are the key organosulfur compounds present in aged garlic extract (AGE) (Fig. 1)-and the pharmacokinetics studies performed in animals have indicated that these compounds are absorbed with ease in the gastrointestinal tract, and also disperse easily amongst the relevant organs (e.g., liver; plasma) [11]. Here, according to Nagae et al., SAC, after oral administration, had 98% bioavailability in rats [20].

According to Horie et al., antioxidant effect can also be found within the AGE derived lipid-soluble organosulfur compounds like DADS, diallyl polysulfide, and DAS—amongst others (e.g., *N*-fructosyl glutamate [21]; selenium; allicin [22]; *N*-fructosyl arginine, organosulfur compounds; and 5-HMF [23]. Furthermore, according to Hwang et al., the number of fructans were observed to be reduced while the fresh garlic converted to AGE [24].
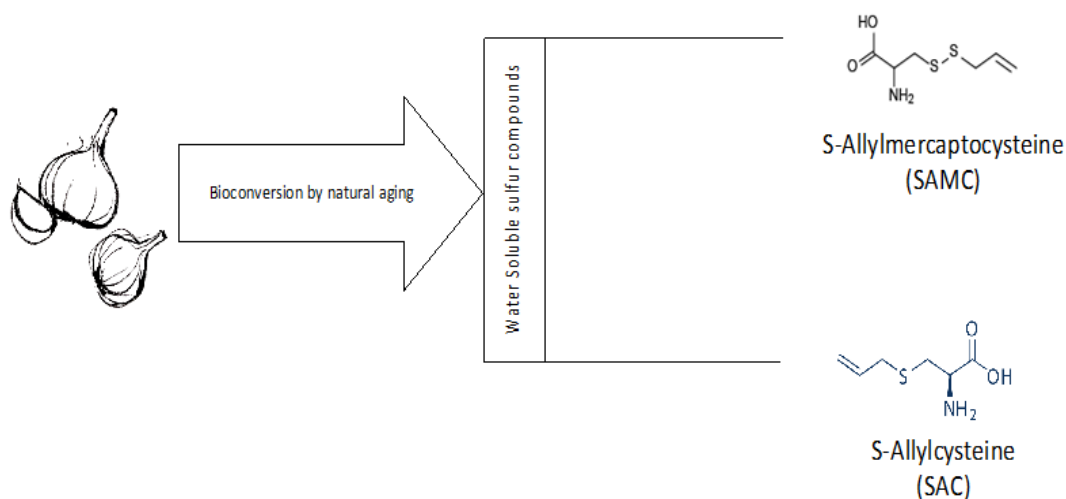
Fig. 1. Aged garlic extract and its water soluble sulfur compounds

Fig. 2. Aged garlic during the fermentation process (Left to Right)

3.1 Aged Garlic Extract (AGE)

According to Park et al., aged garlic extract (AGE) is fresh garlic (*Allium sativum L.*) that has been fermented in an environment where there are high temperature and humidity, and the texture of cloves turn dark, reminiscent of jelly, providing them with a syrupier flavour (Fig. 2) [25]. As a result of the decreased presence of allicin (allicin being changed to flavonoid compounds and bioactive alkaloids [26]), the final product does not possess a pungent taste. Furthermore, this production/fermentation process varies in terms of the time taken to complete such a process, being highly reliant on the creators, usage, and cultures present.

4. THERAPEUTIC USES OF AGE

As explored above, AGE is created by the fermentation of raw garlic at high humidity and temperature, and is amongst the garlic group that possesses no smell [25]. According to Park et al. and Kim et al., the Designer Foods Program tellingly considered garlic to be the most effective of ingredients when it comes to combatting cancer in 1990—and, in line with this, AGE's anti-allergen, inflammation, oxidant, diabetic, and carcinogenic impact has been highly appreciated in a variety of medical studies [25,27].

4.1 Cancer Growth Prevention

Elusive growth, allowing of recurring immortality, practiced invasion and metastasis, continuous multiplying signals, cell death opposition, and vascular creation activation are six of the cancer defining traits during human tumour growth—and, with this in mind, Hanahan & Weinberg concluded that certain foods can put a stop to such traits [28].

4.1.1 Hepatic cancer

According to Purev et al., human hepatocarcinoma HepG2 cell lines show a reduction in cytotoxicity as a result of treatment with the 70% w/v ethanol extract of AGE (500 µg/mL) [29]. While cirrhosis is linked with chronic alcohol consumption and viral infections, it is also understood to be the most common factor leading to hepatic cancer. Glutathione *S*-transferase placental form (GST-P)-positive foci were found to be impeded by SMC (*S*-

Methylcysteine) and AGE treatment; Glutathione *S*-transferase placental form (GST-P)-positive foci are the most effective markers for diethyl nitrosamine initiated hepatocellular lesions. SMC treatment leads to a variety of impacts: it reduces the number of hepatocytes showcasing a proliferating cell nuclear antigen; represses decarboxylase action; triggers the prompt replying to c-jun mRNA transcriptions and proto-oncogenes via down-regulation; and the reduction of GST-P-positive foci numbers when given during the promotion and initiation of tumour development stages [30].

According to Dion & Milner, a variety of studies have indicated the role of S-Allylcysteine (SAC) in effectively preventing DNA adduct formation, effectively inhibiting nitrosomorpholine's (NMOR) and liver carcinogen upstarting and formation, and also possess the ability to alter the cell model [31]. According to Ng et al., HCC cell line MHCC97L's hepatocellular carcinoma is impacted by the treatment with differing concentrations of SAC (0 – 40 mM) in terms of the metastasis and proliferation of cancer [32]. The anti-proliferative action of SAC was confirmed by analysing the display of proliferation markers' suppression, the Proliferating Cell Nuclear Antigen (PCNA) and Ki-67, and the upstarting of the cell cycle with the S/G2 shift. SAC notably downregulates anti-apoptoptic proteins (Bcl-xL and Bcl-2) and therefore triggers Caspase-9 and Caspase-3 dependent necrosis and apoptosis. Meanwhile, the aptitude of colony-creation was blocked with VEGF's downregulation, and E-cadherin's up-regulation. Furthermore, according to Iciek et al., MHCC97L cell arrest occurs as a result of SAC's downregulation of cdc2, cyclin B1, and cdc25c [33].

Recent computational studies recommend that SAMC has high docking potential for the oncogene Kras (RAS) in HepG2 cells. Notwithstanding, the formed complex of SAMC and RAS is unstable, which infers that SAMC may not show an effect on Ras activity, and is not strong or long enough for SAMC to attenuate hepatic tumorigenesis [34]. Furthermore, *in vitro* investigations on SAMC-induced hepatoma cells suggest that transforming growth factor-beta (TGF-β) signaling is vital for the induction of apoptosis. Especially, SAMC treatment prompts not only activation of TGF-β1, TβRII, p-smad2/3, smad4, and smad7 signaling, but also the intrinsic apoptotic pathways (e.g., Bim and Bcl-2) in HepG2 cells, which was not the same as TGF-

β alterations in the colon cancer cell (SW620) [35].

4.1.2 Gastric cancer

As a result of the fact that early gastric cancer possesses no identifiable symptoms that inevitably leads to a significant delay in its diagnosis, and therefore, gastric cancer currently possesses the second-highest death ratio of all cancerous diseases. Wang et al. uncovered that, once 100 mg/mL AGE is administered, apoptosis is triggered within SGC-7901 gastric cancer cell lines [36]. Meanwhile, when SAMC was used in the *in-vitro* studies, transformational alterations were witnessed within the SGC7901 gastric cancer cells (e.g., shrinkage; decreased cell association; atrophy; fragmentation). Further, once SAMC was used in SNU-I cells, *in-vitro* caspase-3 functioning and mitochondrial cytochrome c activation were observed, verifying SAMC's pro-apoptotic functioning [37]. In another study, murine foregastric caricinoma cell lines were incolated in Kunming mice for a duration of seven days, and subsequently, doses of 200, 400, and 800 mg/kg of AGE were injected. It was observed that AGE treatment enhanced the levels of glutathione peroxidase and serum superoxide dismutase, as well as reduced the weight and volume of the tumour [36]. Similarly, Yan et al. found that SAMC triggered tumour cell apoptosis through pathways related to Bcl-2 and thereby reduced the tumour development in the mice that were injected with KMN-45 gastric cancer cells [38].

In a similar vein, Lee et al. found Bcl-2-regulated apoptosis and bax transcription, as well as tumour prevention, after administering 100 mg/kg and 300 mg/kg SAMC to nude mice with human gastric cancer cell line tumours [37].

4.1.3 Colon cancer

Phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt) signal transduction pathway play a key role in the progression of colon cancer, and AGE has shown to repress the PI3K/Akt signal transduction pathway. Therefore, AGE, with the aid of cell cycle arrest and apoptosis, represses cell growth of HT29 colon cancer cells, thereby demonstrating cancer prevention capabilities within these cells. Furthermore, according to Dong et al., AGE represses the downstream target 70-kDa ribosomal protein S6 kinase 1 protein and mRNA levels, downregulates p-Akt

and Akt performance, and upregulates PTEN [39].

Furthermore, SAC treatment resulted in enhanced glutathione S-transferase (GST) activity in the liver, along with upping isozymes' levels of GST-α, GST-*μ,* and GST. In the same vein, Dion & Milner (1997) documented the prevention of colon cancer in female CF-1 mice post-SAC treatment, as well as that of and 6-OH-hydroxychlorzoxazone (6-OHCZX) and chlorzoxazone (CZX) metabolite with AGE [31].

In another study, apoptosis activation, colon cancer invasion hindering, significant suppressing of cell growth, and the stoppage of the G2/M cell phases, were all observed when SW-480 and HT-29 colon cancer cell lines were treated with SAMC (200 μmol/L). The observed phenotypes were complemented by activation of caspase-3 and JNK1 signaling and induced GSH upregulation [40]. In the same vein, it has also been found that there are a variety of ways in which SAMC goes about such cancer cell repression—namely by adjusting standard cellular activities via the changing of cytoskeleton dynamics. Along these lines, microtubule cytoskeleton impediment, the disintegration of centrosomes, quick-paced microtubule depolymerisation, Golgi distribution, and mitotic cell spindle assembly interference were all noted once NIH3T3 fibroblasts or SW-480 cells were administered with SAMC, which was determined by *in-vitro* immunofluorescence investigation.

According to Xiao et al., SAMC has the potential to trigger microtubule depolymerisation by repressing de novo tubulin polymerisation; the same researchers also noted that SAMC treatment resulted in a significantly lesser impact on such microtubule polymerisation when administered alongside β-mercaptoethanol (β-ME) [41]. It is also worth noting that essential signal transduction pathways that govern the cell life cycle and the stress response are systematically suspended by SAMC. It was noted that activation of JNK1 and subsequent caspase seems to be crucial for PARP-mediated apoptosis, because JNK1 knockout or selective JNK inhibitor SP600125 application blocked the apoptosis induced by SAMC in the early phase (24 h) but, the same was not observed in 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. These findings confirm that SAMC induces apoptosis in colon cancer cells primarily by JNK-

dependent pathway in the early phase (24 h) [41,42]. In addition to this, according to Xiao et al., cellular apoptosis is triggered through the intrinsic apoptotic pathway as a result of the release of cytochrome c from the mitochondrial inner membrane, which in turn was triggered by SW480 cells' loss of mitochondrial membrane potential post-SAMC treatment (300 μmol/L) [43]. From this, we can see that SAMC specifically focuses on mitochondria to upstart the cancer cell apoptosis.

With the aim of introducing a xenograft mice model, Liang et al. created a colon cancer cell line (SW620-Fluc) with robust luciferase expression system, which was ultimately helpful in assessing SAMC's impact in preventing tumours *in-vivo* with the help of bioluminescence imaging technique [42]. When compared with the control group, it was noted that the tumour was significantly lessened in terms of its fluorescence post-SAMC administration after 12 and 16 days of cell injection [44]. Furthermore, according to Liang et al., histopathological results indicated that SAMC cleaves PARP1 and triggers caspase-3, which ultimately leaves the vital organs (e.g., liver; heart) unharmed instead of upstarting the tumour's cell apoptosis [42].

4.1.4 Prostate cancer

Initially showing no symptoms, prostate cancer is frequently contracted in men. Here, SAMC is observed to reduce the activity and secretion of the Androgen-Responsive Human Prostate Carcinoma Cells' (LNCaP) membrane antigen and prostate-specific antigen. Furthermore, according to Tanaka et al., a specific reaction with ornithine decarboxylase at its nucleophilic thiol moiety, or a rise in the creation of Reduced Glutathione (GSH), leads to SAMC being disruptive to ornithine decarboxylase (the polyamine-synthesising enzyme) [30]. Indeed, changed polyamine concentrations, the triggering of prostate cancer biomarkers (e.g., Prostate-Specific Antigen [PSA]/Prostate-Specific Membrane Antigen [PSMA] expression in LNCaP cells), and cell growth reduction, can all be attributed to SAMC.

According to Sigounas et al., Pinto et al., and Pinto et al., the rate of testosterone catabolism, triggering of commonly known biomarkers' expression in LNCaP cells (e.g., Prostate-Specific Antigen [PSA]; Prostate-Specific Membrane Antigen [PSMA]), and cell growth repression, can all be attributed to the strong

impacts of SAMC—as concluded by a study centred on Androgen-Dependent Human Prostate Carcinoma Cells (LNCaP) [45-47].

Further, Chu et al. also concluded that SAMC treatment results in enhanced apoptosis *in-vitro* , repressed CWR22R-formed xenograft tumour growth, and colony creation stoppage; this was concluded after the analysis of data arising from the study that centred on the Androgen-Independent Prostate Carcinoma Cell lines (e.g., DU145; 22Rv1; PC3) [48]. Meanwhile, according to Howard et al., SAMC represses PCa's invasion and cell proliferation abilities, which in turn was concluded on the evidence of wound-closure, Matrigel-invasion assays, and the creation of colonies in the Androgen-Independent Prostate Cancer (PCa) cells that possess the capability to invade [49]. Notably, 'cancer metastasis' can be roughly defined as the dispersion of cancer cells to different parts of the body, and often it proves to be fatal. Howard et al. further stipulated that SAMC has the potential to prevent tumour dissemination and development without creating any apparent harm in-vivo; this conclusion was derived based on the experiments performed in the fluorescent orthotopic prostate cancer SCID mouse model with an integrated protein-expressing PC-3 cell line [49]. Furthermore, according to Howard et al. and Chu et al., SAMC's ability to repress the invasion of tumour cells was further demonstrated via the inhibition of its transcriptional suppressor snail, and E-cadherin expression induction [48,49].

Docetaxel is a new drug that inhibits the progression of Refractory Prostate Cancer (HRPC). When docetaxel is provided with SAMC, that possesses a range of other features built into its very make-up, it leads to enhanced chemical sensitivity of the prostate cancer cells Howard et al. stated that elements such as the upstarting of apoptosis, G2M phase stoppage in the in-vitro assays (possessing DU145, 22Rv1, and PC3 cells), and the repression of colony creation, were all observed upon the administration of docetaxel alongside SAMC [50]. Indeed, this has been seen to make small-scale yet influential progress on patient health.

4.1.5 Breast cancer

Breast cancer is most commonly associated with females possessing multifaceted aetiology (e.g., obesity; hormonal issues; genetic inheritance), and the cancer is malignant. It was observed that

cell life cycle stoppage, the upstarting of Oestrogen Receptor (ER)-Positive MCF-7 cell and ER-negative MDA-MB-231 cell apoptosis, and cell invasion/development issues were all impacted significantly by SAMC. According to Hung et al. and Sigounas et al., the critical activities of SAMC were concerned with the changes made to the intrinsic apoptotic pathways (i.e., the increased governing of pro-apoptotic proteins [e.g., Bax, p53 and p21]; the reduced governing of anti-apoptotic protein [e.g., Bcl-2 and Bcl-XL]; the kickstarting of caspase-3/9) [45,51].

Recently garnered investigations suggest that the occurrence of breast cancer and Oestrogen Receptor (ER)—the entity that oversees oestrogen's activities—activity have a strong link. Therefore, repression of ER repressive tendencies can solve the hormonal inequity and, therefore, it has also been put forward as a possible solution for breast cancer. Indeed, according to Zhang et al., SAMC treatment has the potential to repress the ER-reliant breast cancer cells via the formation of a robust hydrogen bond with residues Glu353/Arg394 of the ER [23].

4.1.6 Bladder cancer

Due to its influential role in increasing metastasis, treatment opposition, and neoplasm, the over-expression of the inhibitors of differentiation-1's (Id-1) are frequently acknowledged as signals of a bladder cancer illness. 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 [52]. Further, it was additionally deduced that Id-1's elimination enhanced the sensitivity of the cells to SAMC, leading to the general conclusion that, when it comes to treating bladder cancer, SAMC may direct much of its focus on Id-1.

4.1.7 Thyroid cancer

In an attempt to assess the impact cast on Anaplastic Thyroid Cancer (ATC)—an oftentimes-fatal and rarely contracted endocrine ailment—by SAMC, Liu et al. applied SAMC to

line 8305C (HPACC)—the anaplastic thyroid cancer cell in question—and observed a variety of impacts—namely reduction in size, fragmentation, atrophy, unclear contour, and lysis—via the Transmission Electron Microscopy (TEM) analysis of the cells [53]. In addition to these findings, they additionally noted that SAMC treatment leads to the stoppage of the G2/M stage in cells, the stoppage of telomerase functioning, the stoppage of HPACC-8305C's cell proliferation, and the kickstarting of apoptosis, within cell assays.

4.1.8 Lung cancer

It is known that treatment with B(a)P can induce lung cancer. A study was conducted to establish SAMC's potential in hindering B(a)P mediated carcinogens within the lung cell line A549, before developing full cancer Wang et al. found that the creation of ROS, the kickstarting of NF-κB, the elimination of B(a)P-induced A549 cell proliferation, the harming of DNA, and the changing of the *in-vitro* cell cycle, all occurred with SAMC administration [54]. This led to the conclusion that SAMC could effectively help treat B(a)P-induced lung cancer.

4.1.9 Ovarian cancer

In an attempt to establish SAMC's impact on ovarian cancer cells, Wu et al. took advantage of the likes of HO8910PM, SKOV3, and HO8910 cell lines, ultimately concluding—in support of Howard et al.—that SAMC revives E-cadherin expression and kick-start apoptosis in HO8910 and SKOV3 cells [49,55]. Whereas, in the xenograft mice model of HO8910 cells, no significant effect of SAMC was observed in terms of cell migration, tumour development, colony creation, and invasion. Furthermore, it was also observed that HO8910PM cells were reduced due to higher susceptibility to SAMC when treated with a particular surviving siRNA. Therefore, we can garner that a highly probable success rate in terms of addressing cancer could be achieved through simultaneously administering of SAMC and the downregulation of any continuous activity/expression.

When SAC was administered with special attention to timespan and concentration (16.25 mmol/L and 5.25 mmol/L at 48 h and 72 h in IC50), an observed inhibition was observed to A2780 cells [56]. The administration of SAC additionally triggers the revival of DKN1A's proteins and mRNA, as well as the reduction of

DNMT activity, DNMT1's protein levels, and DNA methylation within A2780 cells, 5-methylcytosine levels, and mRNA [57].

4.1.10 Erythroleukemia

Tanaka et al. and Sigounas et al. examined several investigations and concluded that SAMC's anti-proliferative capabilities within erythroleukemia cell lines are ensured by stopping the G2/M stage, kickstarting apoptosis, and stopping cell development [30,58]. It is also supported by the research into T-47D human breast cancer cells and Caco-2 human colon cancer cells (which conclude SAMC triggers an epigenetic reaction), where SAMC (25 mmol/L) was found to trigger histone acetylation and reduce cell proliferation within DS19 mouse erythroleukemia cells. Still, there is a poor understanding through which SAMC induces histone acetylation. However, 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 [59].

5. SUMMARY

Summary of the anti-cancer studies is presented in Table 1 by cancer type, treatment (AGE, SAMC, SAC) and proposed mechanisms.

A variety of investigations have supported the notion that certain ingredients—here, aged garlic extract and its organosulfur constituents — decrease one's chance of contracting cancer and endows a range of health benefits [62]. According to Pedraza-Chaverri et al. (2004), an essential approach to preventing cancer is using SAMC, considering its ability to upregulate antioxidants and eliminate ROS [63]. Additionally, Nicastro et al. (2015) have concluded that SAMC possesses elements that could effectively prevent cancer by inhibiting inflammation, reactive oxygen species, and by triggering MAPK. SAMC additionally halts the proliferation of tumour cells by stopping the microtubule polymerisation process and by upstarting histone acetylation and also triggers imbalance within the Bcl-2 family as a result of its upstarting of the tumour cell apoptosis via the changes in the MAPK pathway [62]. Furthermore, SAMC appears to enhance cancer cell chemosensitivity, as well as to increase rapamycin's effectiveness in colon cancer cell apoptosis (in turn stopping xenograft nude's tumour development) [64].

Table 1. Summary of the anti-cancer performed by treatment with AGE, SAMC, and SAC

Cancer type	Treatment	Proposed mechanisms	References
Bladder	0−200 µmol·L−1 SAMC treated 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	Matsuura et al. [60]. Jikihara et al. 2015.
Breast	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; antiapoptotic protein Bcl-2 and Bcl-XL downregulation	Xiao et al. [41], Shirin et al. [40], Xiao et al. [43], Liang et al. [42], Zhang Y, Li HY, Zhang ZH, et al. [44].
Colon	AGE: Colorectal cancer cell lines (SW480 and SW620) ECV304 cells DLD-1 human colon cancer cells (ATCC CCL-221)	Decreasing invasive activity Inhibiting cell proliferation Decreasing invasive activity Inhibiting cell motility Down regulating the expression of cyclin B1 and CDK1 Inhibiting of activation of NF-KB	Pinto et al. [46], Sigounas et al. [45], Pinto et al. [47], Chu et al. [48], Howard et al. [49], Howard et al. [50].
Erythroleukemia	SAMC treated OCIM, HEL and DS19 cells in the dosage of 46, 93, 25 µmol·L−1for 24 h respectively.	Induction of histone acetylation	Sigounas et al. [58]
Gastric	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	Tong et al. [34], Xiao et al. [61].
Liver	HepG2 cells treated with 800 µmol·L−1 SAMC alone or in combination with MAPK inhibitors for 8 h. Hepatoma cell lines (Hep3B and Huh-7)	Potent activation of TGF-β1, TβRII, psmad2/ 3, smad4 and smad7 signaling Regulating JNK and p38 MAPK pathways	Hu et al. [52].
Lung	AGE: the transformed rat lung endothelial cells	Inhibiting the tube formation of endothelial cells	Liu et al., [53].
Lung	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	Xu et al. [57].
Ovarian	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	Howard et al. [49].
Prostate	0−200 µmol·L−1 SAMC- SAC treated LNCaP cell or SAMC-treated PC-3, DU145 cells for 24 h. Mice were oro-gastrically 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	Wang et al. [54].
Thyroid	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	Liu et. al [53].

Meanwhile, Shirin et al. (2001) found that treatment with a combination of SAMC and Sulindac Sulphide (SS) within human colon cancer cell lines (SW-480 and HT-29) resulted in higher levels of initiation of apoptosis and stoppage of cell proliferation than the experiment where when the SS was administered alone [40].

6. CONCLUSION

One key area that has been neglected in the prior research concerns the medical benefits of the majority of organosulfur compounds derived from garlic, as well as water-soluble organophosphorus compounds. Although, AGE-derived compounds may be already be present in some currently advertised medications. Furthermore, the pharmacokinetics of such compounds have been left unidentified, as have the nature of the interaction between these compounds and proteins/intracellular molecular targets; indeed, how the signal transduction occurs within the cancer cells is still unknown. Finally, the side-effects of garlic consumption (e.g., diarrhoea; sickness; bleeding) should be made more publicly known. Further, additional investigations are required concerning the abilities of water-soluble organophosphorus compounds as being a new and reliable medication to prevent cancer. Hence, when it comes to solving/preventing cancer, many studies support the use of AGE's water-soluble organophosphorus compounds as medication. Despite all of the above advancements in our understanding, further research is required when it comes to grasping the role of water-soluble organophosphorus compounds in cancer prevention.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
    DOI:10.3322/caac.21492.

2. Paul C, Boyes A, Hall A, Bisquera A, Miller A, O'Brien L. The impact of cancer diagnosis and treatment on employment, income, treatment decisions and financial assistance and their relationship to socioeconomic and disease factors. Support Care Cancer. 2016;24(11):4739-46.
    DOI:10.1007/s00520-016-3323-y

3. Teng AM, Atkinson J, Disney G, Wilson N, Blakely T. Changing socioeconomic inequalities in cancer incidence and mortality: Cohort study with 54 million person-years follow-up 1981-2011. Int J Cancer. 2017;140(6):1306-16.
    DOI: 10.1002/ijc.30555

4. Block E. The chemistry of garlic and onions. Sci Am. 1985;252(3):114-9.
    DOI: 10.1038/scientificamerican0385-114

5. Ali M, Thomson M, Afzal M. Garlic and onions: their effect on eicosanoid metabolism and its clinical relevance. Prostaglandins Leukot Essent Fatty Acids. 2000;62(2):55-73.
    DOI: 10.1054/plef.1999.0124

6. 6.Dolara P, Bigagli E, Collins A. Antioxidant vitamins and mineral supplementation, life span expansion and cancer incidence: a critical commentary. Eur J Nutr. 2012;51(7):769-81.
    DOI: 10.1007/s00394-012-0389-2

7. 7.Singh VK, Singh DK. Pharmacological effects of garlic (Allium sativum L.). Annual Review of Biomedical Sciences. 2008;10(1).

8. Fleischauer AT, Arab L. Garlic and cancer: a critical review of the epidemiologic literature. J Nutr. 2001;131(3s):1032S-40S.
    DOI: 10.1093/jn/131.3.1032S

9. Milner JA. A historical perspective on garlic and cancer. J Nutr. 2001;131(3s):1027S-31S.
    DOI: 10.1093/jn/131.3.1027S

10. Reeve VE, Bosnic M, Rozinova E, Boehm-Wilcox C. A garlic extract protects from ultraviolet B (280-320 nm) radiation-induced suppression of contact hypersensitivity. Photochem Photobiol. 1993;58(6):813-7.

DOI: 10.1111/j.1751-1097.1993.tb04975.x

11. Wei Z, Lau BHS. Garlic inhibits free radical generation and augments antioxidant enzyme activity in vascular endothelial cells. Nutr Res. 1998;18(1):61-70.

Available:https://doi.org/10.1016/S0271-5317(97)00200-5.

12. Youn HS, Lim HJ, Lee HJ, Hwang D, Yang M, Jeon R, et al. Garlic (*Allium sativum*) extract inhibits lipopolysaccharide-induced Toll-like receptor 4 dimerization. Biosci Biotechnol Biochem. 2008;72(2):368-75.

DOI: 10.1271/bbb.70434.

13. Butt MS, Sultan MT, Butt MS, Iqbal J. Garlic: Nature's protection against physio-logical threats. Crit Rev Food Sci Nutr. 2009;49(6):538-51.

DOI: 10.1080/10408390802145344.

14. Amagase H. Clarifying the real bioactive constituents of garlic. J Nutr. 2006;136(3 Suppl):716S-25S.

DOI: 10.1093/jn/136.3.716S.

15. Santhosha SG, Jamuna P, Prabhavathi SN. Bioactive components of garlic and their physiological role in health maintenance: A review. Food Biosci. 2013;3:59-74.

Available:https://doi.org/10.1016/j.fbio.2013.07.001

16. Corzo-Martínez M, Corzo N, Villamiel M. Biological properties of onions and garlic. Trends Food Sci Technol. 2007;18(12):609-25.

17. Amagase H, Petesch BL, Matsuura H, Kasuga S, Itakura Y. Intake of garlic and its bioactive components. J Nutr. 2001;131(3s):955S-62S.

DOI: 10.1093/jn/131.3.955S.

18. Colin-Gonzalez AL, Ali SF, Tunez I, Santamaria A. On the antioxidant, neuroprotective and anti-inflammatory properties of S-allyl cysteine: An update. Neurochem Int. 2015;89:83-91.

DOI: 10.1016/j.neuint.2015.06.011.

19. Choi IS, Cha HS, Lee YS. Physicochemical and antioxidant properties of black garlic. Molecules. 2014;19(10):16811-23.

DOI: 10.3390/molecules191016811

20. Nagae S, Ushijima M, Hatono S, Imai J, Kasuga S, Matsuura H, et al. Pharmacokinetics of the garlic compound S-allylcysteine. Planta Med. 1994;60(3):214-7.

DOI: 10.1055/s-2006-959461.

21. Horie T, Awazu S, Itakura Y, Fuwa T. Identified diallyl polysulfides from an aged garlic extract which protects the membranes from lipid peroxidation. Planta Med. 1992;58(5):468-9.

DOI: 10.1055/s-2006-961517.

22. Ide N, Lau BH. Aged garlic extract attenuates intracellular oxidative stress. Phytomedicine. 1999;6(2):125-31.

DOI: 10.1016/S0944-7113(99)80047-6

23. Zhang H, Wang K, Lin G, Zhao Z. Antitumor mechanisms of S-allyl mercaptocysteine for breast cancer therapy. BMC Complement Altern Med. 2014;14:270.

DOI: 10.1186/1472-6882-14-270

24. Hwang IG, Kim HY, Woo KS, Lee J, Jeong HS. Biological activities of Maillard reaction products (MRPs) in a sugar–amino acid model system. Food Chem. 2011;126(1):221-27.

25. Park C, Park S, Chung YH, Kim GY, Choi YW, Kim BW, et al. Induction of apoptosis by a hexane extract of aged black garlic in the human leukemic U937 cells. Nutr Res Pract. 2014;8(2):132-7.

DOI: 10.4162/nrp.2014.8.2.132.

26. Yuan H, Sun L, Chen M, Wang J. The Comparison of the Contents of Sugar, Amadori, and Heyns Compounds in Fresh and Black Garlic. J Food Sci. 2016;81(7):C1662-8.

DOI: 10.1111/1750-3841.13365

27. Kim TH, Shin YJ, Won AJ, Lee BM, Choi WS, Jung JH, et al. Resveratrol enhances chemosensitivity of doxorubicin in multidrug-resistant human breast cancer cells via increased cellular influx of doxorubicin. Biochim Biophys Acta. 2014;1840(1):615-25.

DOI: 10.1016/j.bbagen.2013.10.023.

28. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

DOI: 10.1016/j.cell.2011.02.013.

29. Purev U, Chung MJ, Oh DH. Individual differences on immunostimulatory activity of raw and black garlic extract in human primary immune cells. Immunopharmacol Immunotoxicol. 2012;34(4):651-60.

DOI: 10.3109/08923973.2011.649288.

30. Tanaka S, Haruma K, Yoshihara M, Kajiyama G, Kira K, Amagase H, et al. Aged garlic extract has potential suppressive effect on colorectal adenomas in humans. J Nutr. 2006;136(3 Suppl): 821S-26S.
DOI: 10.1093/jn/136.3.821S.

31. Dion M, Milner J. Garlic inhibits cytochrome P450 2E1 mediated chlorzoxazone metabolism. FASEB J. 1997:2144-44.

32. Ng KT, Guo DY, Cheng Q, Geng W, Ling CC, Li CX, et al. A garlic derivative, S-allylcysteine (SAC), suppresses proliferation and metastasis of hepato-cellular carcinoma. PLoS One. 2012;7(2): e31655.
DOI: 10.1371/journal.pone.0031655.

33. Iciek M, Kwiecien I, Chwatko G, Sokolowska-Jezewicz M, Kowalczyk-Pachel D, Rokita H. The effects of garlic-derived sulfur compounds on cell proliferation, caspase 3 activity, thiol levels and anaerobic sulfur metabolism in human hepatoblastoma HepG2 cells. Cell Biochem Funct. 2012;30(3):198-204.
DOI: 10.1002/cbf.1835.

34. Tong D, Qu H, Meng X, Jiang Y, Liu D, Ye S, et al. S-allylmercaptocysteine promotes MAPK inhibitor-induced apoptosis by activating the TGF-beta signaling pathway in cancer cells. Oncol Rep. 2014;32(3): 1124-32.
DOI: 10.3892/or.2014.3295.

35. Hung TC, Lee WY, Chen KB, Chan YC, Chen CY. An investigation of small GTPases in relation to liver tumorigenesis using traditional Chinese medicine. Biomed Res Int. 2014;2014:428210.
DOI: 10.1155/2014/428210.

36. Wang X, Jiao F, Wang QW, Wang J, Yang K, Hu RR, et al. Aged black garlic extract induces inhibition of gastric cancer cell growth in vitro and in vivo. Mol Med Rep. 2012;5(1):66-72.
DOI: 10.3892/mmr.2011.588.

37. Lee Y, Kim H, Lee J, Kim K. Anticancer activity of S-allylmercapto-L-cysteine on implanted tumor of human gastric cancer cell. Biol Pharm Bull. 2011;34(5):677-81.
DOI: 10.1248/bpb.34.677.

38. Yan JY, Tian FM, Hu WN, Zhang JH, Cai HF, Li N. Apoptosis of human gastric cancer cells line SGC 7901 induced by garlic-derived compound S-allylmercapto-cysteine (SAMC). Eur Rev Med Pharmacol Sci. 2013;17(6):745-51.

39. Dong M, Yang G, Liu H, Liu X, Lin S, Sun D, et al. Aged black garlic extract inhibits HT29 colon cancer cell growth via the PI3K/Akt signaling pathway. Biomed Rep. 2014;2(2):250-54.
DOI: 10.3892/br.2014.226.

40. Shirin H, Pinto JT, Kawabata Y, Soh JW, Delohery T, Moss SF, et al. Antiproliferative effects of S-allylmercaptocysteine on colon cancer cells when tested alone or in combination with sulindac sulfide. Cancer Res. 2001;61(2):725-31.

41. Xiao D, Pinto JT, Soh JW, Deguchi A, Gundersen GG, Palazzo AF, et al. Induction of apoptosis by the garlic-derived compound S-allylmercaptocysteine (SAMC) is associated with microtubule depolymerization and c-Jun NH(2)-terminal kinase 1 activation. Cancer Res. 2003; 63(20):6825-37.

42. Liang D, Qin Y, Zhao W, Zhai X, Guo Z, Wang R, et al. S-allylmercaptocysteine effectively inhibits the proliferation of colorectal cancer cells under in vitro and in vivo conditions. Cancer Lett. 2011;310(1):69-76.
DOI: 10.1016/j.canlet.2011.06.019.

43. Xiao D, Pinto JT, Gundersen GG, Weinstein IB. Effects of a series of organosulfur compounds on mitotic arrest and induction of apoptosis in colon cancer cells. Mol Cancer Ther. 2005;4(9):1388-98.
DOI: 10.1158/1535-7163.MCT-05-0152.

44. Zhang Y, Li HY, Zhang ZH, Bian HL, Lin G. Garlic-derived compound S-allylmercaptocysteine inhibits cell growth and induces apoptosis via the JNK and p38 pathways in human colorectal carcinoma cells. Oncol Lett. 2014;8(6):2591-96.
DOI: 10.3892/ol.2014.2579.

45. Sigounas G, Hooker J, Anagnostou A, Steiner M. S-allylmercaptocysteine inhibits cell proliferation and reduces the viability of erythroleukemia, breast, and prostate cancer cell lines. Nutr Cancer. 1997;27(2):186-91.
DOI: 10.1080/01635589709514523.

46. Pinto JT, Qiao C, Xing J, Rivlin RS, Protomastro ML, Weissler ML, et al. Effects of garlic thioallyl derivatives on

growth, glutathione concentration, and polyamine formation of human prostate carcinoma cells in culture. Am J Clin Nutr. 1997;66(2):398-405.

DOI: 10.1093/ajcn/66.2.398.

47. Pinto JT, Qiao C, Xing J, Suffoletto BP, Schubert KB, Rivlin RS, et al. Alterations of prostate biomarker expression and testosterone utilization in human LNCaP prostatic carcinoma cells by garlic-derived S-allylmercaptocysteine. Prostate. 2000;45(4):304-14.

DOI:10.1002/1097-0045(20001201)45:4<304::aid-pros4>3.0.co;2-9.

48. Chu Q, Ling MT, Feng H, Cheung HW, Tsao SW, Wang X, et al. A novel anticancer effect of garlic derivatives: inhibition of cancer cell invasion through restoration of E-cadherin expression. Carcinogenesis. 2006;27(11):2180-9.

DOI: 10.1093/carcin/bgl054.

49. Howard EW, Ling MT, Chua CW, Cheung HW, Wang X, Wong YC. Garlic-derived S-allylmercaptocysteine is a novel in vivo antimetastatic agent for androgen-independent prostate cancer. Clin Cancer Res. 2007;13(6):1847-56.

DOI: 10.1158/1078-0432.CCR-06-2074.

50. Howard EW, Lee DT, Chiu YT, Chua CW, Wang X, Wong YC. Evidence of a novel docetaxel sensitizer, garlic-derived S-allylmercaptocysteine, as a treatment option for hormone refractory prostate cancer. Int J Cancer. 2008;122(9):1941-8. DOI: 10.1002/ijc.23355.

51. Hung TC, Lee WY, Chen KB, Chan YC, Chen CY. Investigation of estrogen receptor (ESR1) for breast cancer from traditional Chinese medicine. Biomed Res Int. 2014;2014:321486.

DOI: 10.1155/2014/321486.

52. Hu H, Zhang XP, Wang YL, Chua CW, Luk SU, Wong YC, 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. Mol Med Rep. 2011;4(1):9-16.

DOI: 10.3892/mmr.2010.380.

53. Liu Y, Yan J, Han X, Hu W. Garlic-derived compound S-allylmercaptocysteine (SAMC) is active against anaplastic thyroid cancer cell line 8305C (HPACC). Technol Health Care. 2015;23 Suppl 1:S89-93.

DOI: 10.3233/thc-150936.

54. Wang K, Wang Y, Qi Q, Zhang F, Zhang Y, Zhu X, et al. Inhibitory effects of S-allylmercaptocysteine against benzo(a)pyrene-induced precancerous carcinogenesis in human lung cells. Int Immunopharmacol. 2016;34:37-43.

DOI: 10.1016/j.intimp.2016.02.017.

55. Wu J, Zhao S, Zhang J, Qu X, Jiang S, Zhong Z, et al. Over-expression of survivin is a factor responsible for differential responses of ovarian cancer cells to S-allylmercaptocysteine (SAMC). Exp Mol Pathol. 2016;100(2):294-302.

DOI: 10.1016/j.yexmp.2016.02.003.

56. Xu Y, Su D, Zhu L, Zhang S, Ma S, Wu K, et al. S-allylcysteine suppresses ovarian cancer cell proliferation by DNA methylation through DNMT1. J Ovarian Res. 2018;11(1):39.

DOI: 10.1186/s13048-018-0412-1.

57. Xu YS, Feng JG, Zhang D, Zhang B, Luo M, Su D, et al. S-allylcysteine, a garlic derivative, suppresses proliferation and induces apoptosis in human ovarian cancer cells in vitro. Acta Pharmacol Sin. 2014;35(2):267-74.

DOI: 10.1038/aps.2013.176.

58. Sigounas G, Hooker JL, Li W, Anagnostou A, Steiner M. S-allylmercaptocysteine, a stable thioallyl compound, induces apoptosis in erythroleukemia cell lines. Nutr Cancer. 1997;28(2):153-9.

DOI: 10.1080/01635589709514568.

59. Lea MA, Rasheed M, Randolph VM, Khan F, Shareef A, desBordes C. Induction of histone acetylation and inhibition of growth of mouse erythroleukemia cells by S-allylmercaptocysteine. Nutr Cancer. 2002;43(1):90-102.

DOI: 10.1207/S15327914NC431_11.

60. Matsuura Y, Kawagoe T, Toki N, Tanaka M, Kashimura M. Long-standing complications after treatment for cancer of the uterine cervix--clinical significance of medical examination at 5 years after treatment. Int J Gynecol Cancer. 2006;16(1):294-7.

DOI:10.1111/j.1525-1438.2006.00354.x.

61. Xiao J, Xing F, Liu Y, Lv Y, Wang X, Ling MT, et al. Garlic-derived compound S-allylmercaptocysteine inhibits hepatocarcinogenesis through targeting

LRP6/Wnt pathway. Acta Pharmaceutica Sinica B. 2018;8(4):575-86.

Available:https://doi.org/10.1016/j.apsb.2017.10.003

62. Nicastro HL, Ross SA, Milner JA. Garlic and onions: their cancer prevention properties. Cancer Prev Res (Phila). 2015;8(3):181-9.

DOI: 10.1158/1940-6207.CAPR-14-0172

63. Pedraza-Chaverri J, Barrera D, Maldonado PD, Chirino YI, Macias-Ruvalcaba NA, Medina-Campos ON, 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. BMC Clin Pharmacol. 2004;4:5.

DOI: 10.1186/1472-6904-4-5

64. Li S, Yang G, Zhu X, Cheng L, Sun Y, Zhao Z. 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. Oncol Rep. 2017;38(3):1637-44.

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