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Functionality of garlic sulfur compounds (Review)

TAIICHIRO SEKI and TAKASHI HOSONO

Department of Bioscience, College of Bioresource Sciences, Nihon University, Fujisawa, Kanagawa 252-0880, Japan

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Abstract. Garlic (*Allium sativum* L.), a perennial herbaceous edible plant, is classified in the Amaryllidaceae family and belongs to the Allium genus. It has a higher sulfur content than other plants. Garlic is extensively used worldwide as a spice and flavoring agent, and it generates a unique aroma during cooking. Garlic possesses various properties, including anti-thrombotic, antioxidant, blood cholesterol-lowering, anti-obesity and anti-dementia effects. These properties have been attributed to various garlic-derived sulfur-containing compounds, including *S*-allyl cysteine, allicin, allyl sulfides and ajoene. The present review provides an overview of the mechanisms that underlie the generation of odor compounds in garlic and discusses certain observed effects of garlic consumption.

Contents

Correspondence to: Professor Taiichiro Seki, Department of Bioscience, College of Bioresource Sciences, Nihon University, 1866 Kameino, Fujisawa, Kanagawa 252-0880, Japan
E-mail: seki.taiichirou@nihon-u.ac.jp

Abbreviations: AGE, aged garlic extract; AMS, allyl methyl sulfide; Aβ, amyloid-β; AD, Alzheimer's disease; CBS, cystathionine β-synthase; CHD, coronary heart disease; CSE, cystathionine γ-lyase; DADS, diallyl disulfide; DATS, diallyl trisulfide; DIO, diet-induced obese; GSH, glutathione; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SAC, *S*-allyl cysteine; PD, Parkinson's disease; TF, tissue factor; TNF-α, tumor necrosis factor-α; UCPs, uncoupling proteins; WAT, white adipose tissue

Key words: alliin, allicin, garlic, organosulfur compound, AGE, DATS

1. Introduction

Garlic (*Allium sativum* L.) is a perennial herbaceous edible plant in the Amaryllidaceae family and *Allium* genus that contains a high sulfur content compared with other plants (1). It is extensively used worldwide as a spice and flavoring agent, and it emanates a distinctive aroma during cooking. However, raw and intact garlic lacks substantial odor. This absence of odor can be attributed to the non-volatility of alliin, the precursor of garlic's odor compounds, and the localization of alliin and the enzyme alliinase (EC 4.4.1.4; https://www.genome.jp/dbget-bin/www_bget?ec:4.4.1.4), responsible for breaking down alliin into odor compounds, within intact garlic bulbs. Garlic exhibits favorable properties, including anti-thrombotic, anti-atherosclerotic, antioxidant, anticancer, anti-obesity and neuroprotective effects. These functional properties have been attributed to various sulfur-containing compounds derived from garlic. The present review provides an overview of the mechanisms that underlie the generation of odor compounds in garlic and discusses certain of the observed effects of garlic consumption (1,2).

2. Data collection

A comprehensive literature search was conducted using databases including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/home.uri) and Web of Science (https://www.webofscience.com). The search included keywords such as garlic, organosulfur compounds, health benefits and mechanisms of action. Studies published within the last 20 years were prioritized, with a focus on peer-reviewed articles from high-impact journals. Both *in vitro* and *in vivo,* as well as clinical studies were considered to provide a balanced synthesis of available evidence. This approach ensured the credibility and relevance of the data discussed in the present review.

3. Organosulfur compounds and their health effects

Mechanism of odor compound generation in garlic. The main component of garlic is *S*-allyl cysteine sulfoxide (alliin), a sulfur-containing amino acid that acts as the precursor for its characteristic odor. This non-volatile derivative of cysteine is stored in the cytoplasm of mesophyll storage cells within the bulb. Conversely, alliinase (C-S lyase), which catalyzes alliin, is localized in the vacuole of the vascular sheath cell of the bulb (3). When garlic tissues undergo disruption during cooking or processing, alliinase acts on alliin to cleave the sulfur-carbon bond. This enzymatic reaction results in the breakdown of alliin into allyl sulfenic acid and aminoacrylic acid. Allyl sulfenic acid is rapidly converted into the odorant allyl thiosulfinate (allicin) via dehydration, producing the distinctive odor of crushed garlic. Allicin, a highly reactive compound, generates various additional odor compounds through reactions with other compounds and self-decomposition (Fig. 1) (4,5). Heating non-crushed garlic inactivates alliinase, preventing allicin formation during cooking and facilitating alliin formation instead (Fig. 2A). Odor compounds generated by allicin (Fig. 2B) include allyl sulfides, allyl methyl sulfides (AMS) and ajoene (Fig. 2C and D). Diallyl disulfide (DADS), a typical allyl sulfide, is formed by non-enzymatic reactions with allyl mercaptan, a degradation product of allicin. Subsequently, DADS is converted to diallyl trisulfide (DATS) and diallyl tetrasulfide, which contain additional sulfur atoms, through autolysis and complex non-enzymatic reactions. These sulfides can be efficiently collected as essential oils by steam distillation of crushed garlic homogenate (Fig. 2C). Garlic produces sulfur-containing compounds during cooking and processing procedures. Ajoene, discovered in 1984, is generated by oil-based heating of crushed garlic and subsequent chemical reactions with three allicin molecules (Fig. 2D) (6). Unlike sulfides, ajoene undergoes minimal production during garlic crushing alone. All of these sulfur-containing compounds are lipophilic and have unique odors. Conversely, aged garlic extract (AGE), obtained by soaking untreated or sliced garlic in a water and alcohol solution for an extended period, contains water-soluble sulfur compounds, including *S*-allyl cysteine (SAC) and *S*-allyl mercapto-cysteine (7). In contrast to lipophilic sulfur compounds, these water-soluble compounds lack a strong odor (Fig. 2E).

Garlic consumption is presumed to aid in preventing lifestyle diseases, such as diabetes and atherosclerosis, through various sulfur-containing compounds derived from alliin. The following sections discuss the diverse effects of consuming garlic and its sulfur compounds. The physiological effects of garlic-derived sulfur compounds are summarized in Table I.

Cardiovascular health

Anti-platelet and anti-thrombotic activity of garlic. Platelet aggregation is a pivotal response in the hemostatic reaction to vascular damage. However, excessive platelet aggregation may indicate a prothrombotic condition. Therefore, suppression of excessive platelet aggregation could reduce the risk of thromboembolic diseases. Garlic intake can significantly inhibit platelet aggregation (8).

SAC-containing AGE reduces platelet adhesion to fibrinogen. This effect reportedly occurs through elevation of the intraplatelet cyclic adenosine monophosphate concentration and inhibition of the bond between the platelet surface adhesion molecule integrin αIIbβ3 and fibrinogen (8).

Various garlic extracts, prepared through diverse methods and conditions, have been tested against human platelets to assess their impacts on platelet aggregation. The results indicated that anti-platelet aggregation activity depends upon the allicin content of the extracts (9). Furthermore, heating of garlic for >10 min before cooking completely suppresses its anti-platelet aggregation activity. There is evidence that light crushing of garlic prior to cooking can preserve its anti-platelet aggregation activity after cooking. These results indicate that the compounds with anti-platelet activity are produced through reactions catalyzed by CS-lyase. Actually, DATS shows potent anti-platelet activity *in vitro* (10).

To comprehensively assess proteins with post-translational thiol modifications, the shotgun liquid chromatography-tandem mass spectrometry method was applied to Jurkat cells (a human acute T-cell leukemia cell line) that had been treated with allicin (11). The analysis revealed that various proteins, including those associated with the cytoskeleton and glycolysis, undergo oxidative modification by allicin (11). DATS also oxidatively modifies specific cysteine residues of the cytoskeletal protein tubulin (12). DATS exhibits greater reactivity with cysteine residues compared with its saturated structural analogue, dipropyl trisulfide; it also demonstrates potent platelet aggregation inhibitory effects (10). These findings suggest that certain physiological activities of garlic sulfur compounds, including platelet aggregation inhibition, can be attributed to the oxidative modification of cellular proteins (Fig. 3).

Tissue factor (TF) is an important coagulation factor in initiating the extrinsic coagulation pathway. Subendothelial TF is responsible for the initiation of fibrin formation at sites of vascular injury. Tumor necrosis factor-α (TNF-α) induced TF mRNA expression in human umbilical vein endothelial cells was suppressed by the inhibition of JNK signal. Therefore, the inhibition of the JNK pathway by DATS may inhibit the induction of TF by TNF-α. DATS inhibited not only TF activity but also TF mRNA and protein expression *in vitro* (13). Garlic is a promising food with anti-thrombotic function, which can suppress both primary and secondary clot formation. The anti-thrombotic effect of garlic is beneficial for patients who are allergic or intolerant to aspirin and is expected to be an alternative or complementary therapy to anti-platelet therapy.

A double-blinded placebo-controlled randomized study performed in 51 patients with coronary heart disease (CHD) to examine the effects of time-released garlic powder tablets on the values of 10-year prognostic risk of acute myocardial infarction and sudden death. The 12-month treatment with the garlic resulted in the significant decrease in cardiovascular risk by 1.5-fold in men, and by 1.3-fold in women. Thus, garlic may be crucial for the secondary prevention of atherosclerotic diseases in patients with CHD (14).

Blood pressure-lowering and myocardial protective effects. Hydrogen sulfide (H_2S), a hazardous and toxic gas, is produced in the human body from cysteine via enzymes, including cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). This compound functions as both a neurotransmitter and vasoactive agent, similar to well-known gaseous mediators such as nitric oxide and carbon monoxide (15,16). In addition to endogenously synthesized H_2S, garlic-derived sulfur-containing compounds have been reported to act as H_2S donors, contributing to blood pressure reduction through blood vessel dilation (17). A previous study showed that the addition of garlic extracts to erythrocytes *in vitro* resulted in H_2S release. Furthermore, application of sulfur-containing compounds from garlic to the aorta and cardiac vessels of rats led to vasodilation. The generation

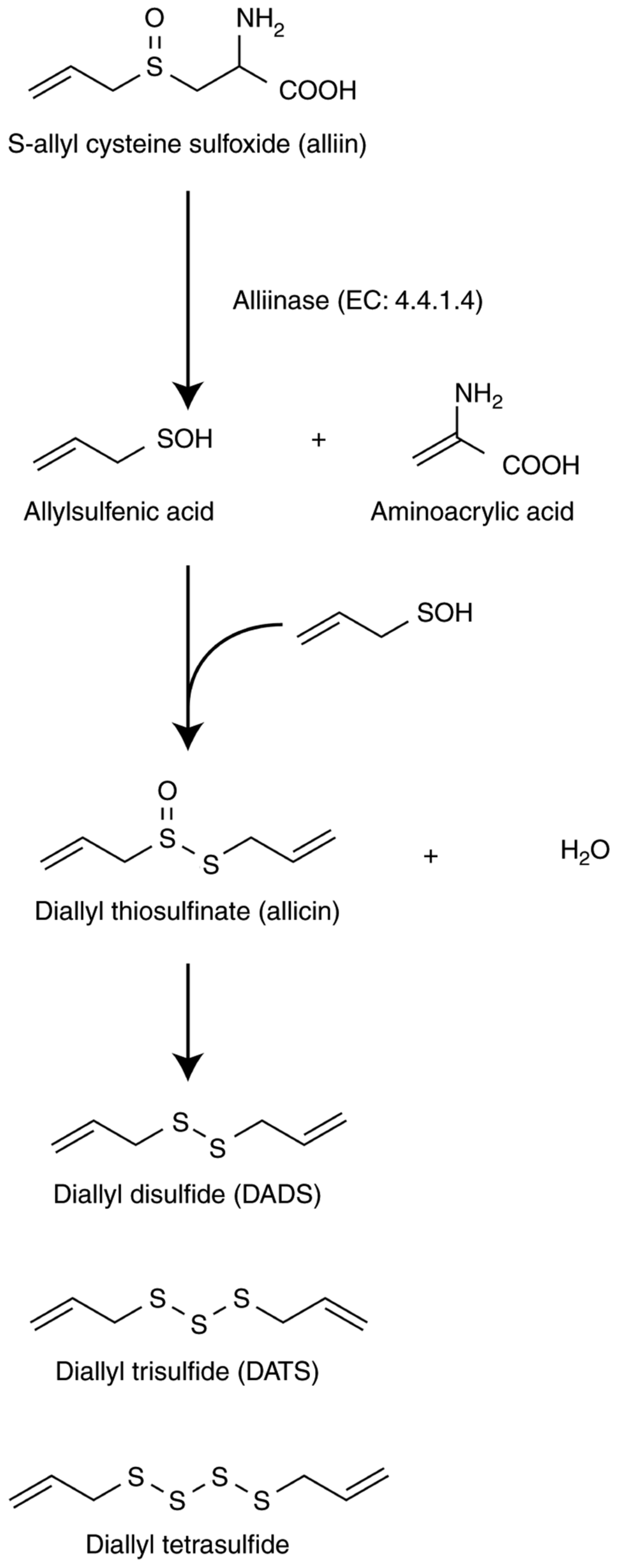

Figure 1. Mechanism of odor compound generation in garlic. When garlic tissue is disrupted through cooking or other methods, alliin in the cytoplasm of mesophyll storage cells reacts with alliinase in the vacuoles of vascular sheath cells, resulting in allyl sulfenic acid production. Allyl sulfenic acid is promptly converted into allicin, which is inherently unstable and undergoes non-enzymatic reactions that lead to the formation of various sulfides.

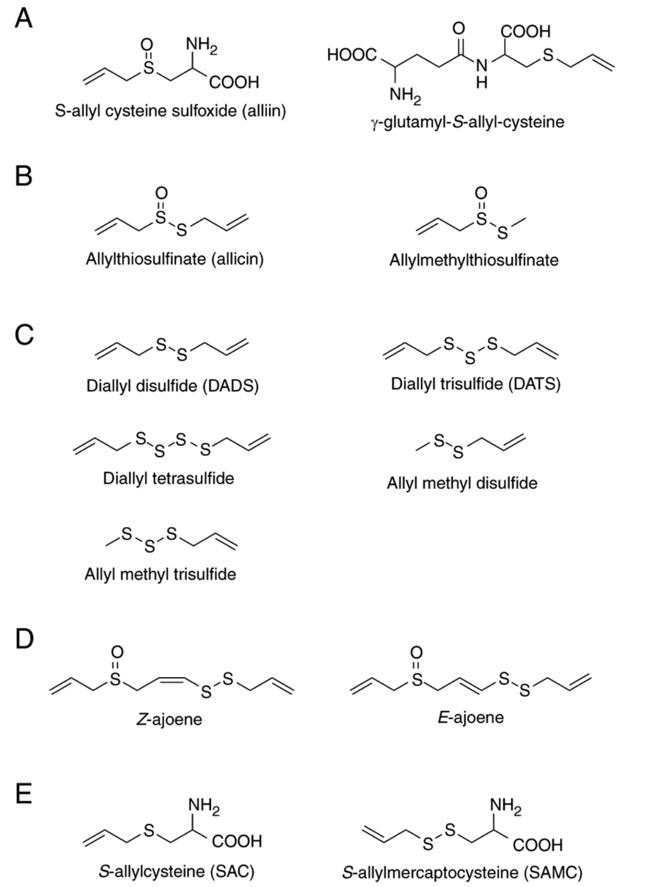

Figure 2. Chemical structures of garlic-derived compounds. Sulfur is stored as (A) amino acids, and major sulfur-containing compounds are produced through (B) crushing, (C) steam distillation, (D) heating in oil, and (E) prolonged alcohol treatment of garlic.

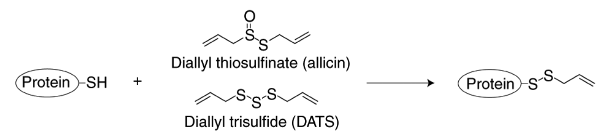

Figure 3. Post-translational protein modification by allicin and DATS. Allicin and diallyl trisulfide oxidatively modify specific SH groups of cysteine residues in proteins that regulate the functions of other proteins.

of H_2S by garlic-derived sulfur compounds is attributed to reactions with intracellular glutathione (GSH) and polysulfide compounds (18).

The role of H_2S in the healthy organism is well understood; decreased plasma H_2S concentrations or disturbances in its synthesis in some tissues have been described (19). It has also been reported that vascular diseases are closely related with the downregulation of the H_2S pathway. The decreased plasma H_2S concentrations are observed in patients with hypertension, heart failure or ischemic heart disease in comparison with the normal-control patients (20-23). Moreover, the plasma H_2S in the patients with vascular diseases was correlated with the severity of symptoms; it was significantly lower in acute myocardial infarction and unstable angina in comparison with a stable form of the disease (24). It has also been reported that marked reduction in plasma H_2S in both patients with chronic kidney disease (CKD) and animal CKD models (25-27). Moreover, it was found that low H_2S levels in type 2 diabetes mellitus patients showed a higher risk of cardiovascular disease (28). Thus, the garlic compounds

Table I. Functions of garlic-derived compounds described in the present review.

First author, year	Compound	Function	(Refs.)
Cavagnaro *et al*, 2007	Diallyl thiosulfinate	Anti-platelet	(9)
Chan *et al*, 2013	(Allicin)	Antioxidant	(31)
		Cardioprotection	
Lin *et al*, 2017		ABC transporter A1 upregulation	(34)
Morihara *et al*, 2010		CD36 scavenger receptor lowering effect	(35)
Kumar, 2015		Acetylcholinesterase inhibition	(50)
Nillert *et al*, 2017		Anti-brain inflammation, improves memory	(51)
Zhang *et al*, 2018		Anti-oxidative stress, improves cognitive function	(52)
Tedeschi *et al*, 2022		Anti-Alzheimer's disease	(55)
Hiebert and Werner, 2019		Antioxidant, hepatoprotective effect	(63)
Allison *et al*, 2012	S-allyl-cysteine	Anti-platelet	(8)
Chuah *et al*, 2007		Myocardial protective effect	(29)
		Hydrogen sulfide generation	
Zarezadeh *et al*, 2017		Anti-neuroinflammation,	(54)
		acetylcholinesterase inhibition	
Tedeschi *et al*, 2022		Anti-Alzheimer's disease	(55)
Sripanidkulchai, 2019			(58)
Morihara *et al*, 2016	Aged garlic extract	Cholesterol lowering effect	(33)
Kumar *et al*, 2018	Ajoene	Acetylcholinesterase inhibition	(49)
Xu *et al*, 2020	Diallyl disulfide	Anti-inflammation, improving brain function	(53)
Sripanidkulchai, 2019		Anticancer properties	(58)
Hosono *et al*, 2020	Diallyl trisulfide	Anti-platelet	(10)
Okue *et al*, 2022		Anti-coagulation	(13)
Tsai *et al*, 2015		Myocardial protective effect	(30)
Benavides *et al*, 2017		Hydrogen sulfide generation	(17)
Cai and Hu, 2017			(18)
Miura *et al*, 2021		Anti-obesity	(42)
Hosono *et al*, 2020		Anticancer properties	(12)
Farhat *et al*, 2021			(59)
Zhang *et al*, 2016		Antioxidant, hepatoprotective effect	(65)
Hosono-Fukao *et al*, 2009			(66)
Panyode *et al*, 2016	Allyl methyl disulfide	Antioxidant, hepatoprotective effect	(64)

may be contributing the amelioration of pathology of these diseases.

Furthermore, SAC administration increased the blood concentration of H_2S in a rat model of myocardial infarction due to elevated CSE activity in the left ventricle, revealing a myocardial protective effect (29). DATS also protected myocardial cells from high-glucose-induced apoptosis by enhancing CSE-derived H_2S production (30). These findings suggest that garlic can lower blood pressure and protect the myocardium by directly or indirectly increasing the blood concentration of H_2S.

Metabolic effects

Improvements in lipid abnormalities and anti-atherosclerotic effects. Lipid abnormalities, characterized by elevated levels of triglycerides and cholesterol, high concentrations of low-density lipoprotein (LDL) and low concentrations of high-density lipoprotein (HDL), are recognized as contributors to severe vascular complications including atherosclerosis and myocardial infarction. Consumption of garlic and its sulfur-containing compounds has been reported to improve lipid abnormalities and reduce cardiovascular disease risk by inhibiting LDL oxidation (31,32). AGE administration in apolipoprotein E-deficient mice on a high-fat diet, which serves as an atherosclerosis model, reduced plasma total cholesterol and triglyceride concentrations and suppressed lipid deposition within the vascular lumen, a characteristic of atherosclerotic lesions in the aortic arch (33). Allicin suppresses lipid accumulation, enhances ABC transporter A1 expression in macrophages, and promotes cholesterol efflux from cells by regulating peroxisome proliferator-activated receptor gamma/liver X receptor alpha signaling, which regulates lipid metabolism (34). Additionally, allicin inhibits the expression of the scavenger receptor CD36, responsible for oxidized lipoprotein uptake, and hinders oxidized LDL-induced monocyte differentiation into macrophages (35).

In patients with hyper-homocysteinemia-related coronary artery disease, allicin administration was associated with improved homocysteine levels and reduced carotid artery intima-media thickness (36). Furthermore, individuals with dyslipidemia experienced significant reductions in plasma cholesterol and LDL concentrations, with simultaneous increases in HDL concentrations, after the consumption of garlic powder tablets in the single-blind, placebo-controlled study (37). These findings suggest that garlic and its sulfur-containing compounds can improve lipid metabolism and prevent atherosclerosis by inhibiting macrophage foaming.

Anti-obesity and anti-diabetic effects. In recent years, obesity rates have increased due to altered social eating habits, dietary diversification and lack of exercise (38). Obesity is characterized by excessive body fat accumulation and constitutes a leading cause of metabolic syndrome, which results in lifestyle-related conditions such as diabetes, dyslipidemia and hypertension; it eventually causes severe complications, such as cardiovascular disease (39).

Several studies have indicated that the consumption of garlic and its sulfur-containing compounds may have beneficial effects on obesity and metabolic syndrome. Garlic powder consumption in high-fat diet-induced obese (DIO) mice prevented increases in body weight and adipose tissue mass while improving plasma lipid profiles. Additionally, garlic powder consumption increased the mRNA expression of uncoupling proteins (UCPs) in brown adipose tissue, liver, white adipose tissue (WAT) and muscle. Furthermore, the decrease in mouse body temperature was suppressed, even during exposure to cold temperatures (4˚C) (40). Our previous study revealed that oral administration of garlic oil to DIO rats, obtained through steam distillation of crushed garlic, suppressed weight gain while increasing the UCP expression in brown adipose tissue, thereby enhancing energy expenditure (41). These results indicated that UCPs may be involved in the anti-obesity effects of garlic. Furthermore, the anti-obesity potential of DATS was demonstrated in a rat model. Considering the emerging role of microRNAs (miRNAs) in lifestyle diseases, their roles in the anti-obesity effects of DATS were investigated. Transcriptomic analyses revealed that DATS downregulated miRNA-335 expression and normalized obesity-associated mRNA signatures in the epididymal WAT of obese rats (42).

In a rat model of streptozotocin-induced type 1 diabetes, crushed garlic administration suppressed the elevation of blood glucose, reduced glycated protein levels, increased blood insulin concentrations, and lowered lipid peroxide levels in the pancreas and liver (43). Additionally, raw crushed garlic has been reported to improve the pathological features of metabolic syndrome, including elevated blood glucose levels, impaired glucose tolerance, and fructose-induced dyslipidemia (44,45). Although alliin administration to DIO mice via drinking water did not affect body weight or energy expenditure, it enhanced insulin sensitivity and ameliorated hyperlipidemia (46). Similarly, SAC consumption was associated with enhanced insulin sensitivity (47). These findings suggest that garlic and its sulfur-containing compounds have the potential to ameliorate diabetes-associated pathological conditions, including obesity and glucose intolerance.

Neuroprotective effects: Anti-Alzheimer's disease (AD) and anti-Parkinson's disease (PD) effects. AD is a neurodegenerative disorder characterized by progressive memory loss, cognitive impairment and behavioral changes. It accounts for nearly 50% of all dementia cases and is associated with abnormal accumulation of amyloid-β (Aβ) and tau proteins, leading to neuronal damage and neurotransmitter depletion (48). A key pathological feature of AD is a significant reduction in acetylcholine levels due to the excessive activity of acetylcholinesterase (AChE), an enzyme that degrades acetylcholine in the nervous system. Therefore, AChE inhibitors are considered to be promising therapeutic agent for AD.

Several garlic-derived organosulfur compounds have demonstrated neuroprotective effects by targeting multiple pathological pathways of AD. For instance, ajoene and allicin have been reported to inhibit AChE activity, thereby preserving cholinergic function (49,50). Additionally, SAC and DADS exert anti-inflammatory and antioxidant effects by modulating microglial activation and reducing oxidative stress in AD models (51-54). Oral administration of AGE has been shown to suppress Aβ-induced neuroinflammation and improve cognitive function in animal models, suggesting its potential role in preventing AD progression (55).

Recent evidence also indicates that H_2S plays a critical role in neurodegenerative diseases. Studies have reported that plasma H_2S levels are significantly reduced in patients with AD, suggesting an impairment in endogenous H_2S metabolism (56). Similarly, PD, which is characterized by motor system dysfunction due to dopaminergic neuron loss, has been linked to decreased H_2S production in the substantia nigra, likely due to downregulation of CBS (57). Since garlic-derived sulfur compounds can enhance endogenous H_2S production, they may contribute to the amelioration of both AD and PD symptoms. Taken together, these findings highlight the multifaceted neuroprotective potential of garlic-derived sulfur compounds beyond their H_2S-mediated effects. AGE, SAC and DATS have been shown to attenuate oxidative stress, suppress neuroinflammation, and inhibit AChE activity, thereby preserving neuronal function and preventing cognitive decline (58). Given these mechanisms, garlic and its bioactive components hold promise as potential therapeutic agents for neurodegenerative diseases, including AD and PD.

Anticancer effects. Data from clinical studies suggest that garlic consumption may have effects on cancer prevention. The two main type of compounds that have been shown to have anticancer properties are lipid-soluble allyl sulfur compounds including DADS and DATS, and water-soluble compounds including SAC and *S*-allyl mercapto-cysteine (59). DATS has demonstrated significant anticancer effects across various cancer types by inhibiting proliferation, inducing apoptosis and autophagy, suppressing invasion and migration, and modulating the tumor microenvironment (60). These multifaceted actions contribute to its potential in both cancer prevention and treatment. Furthermore, DATS has been shown to enhance chemotherapy sensitivity by modulating drug-efflux pump proteins and increasing oxidative stress in resistant cells. Previous studies have identified common chemoresistance-associated genes that impact cancer survival, highlighting the importance of targeting these pathways to overcome resistance (61). Collectively, these findings suggest that DATS could serve as an adjunctive therapy in cancer treatment, particularly in overcoming chemoresistance (62).

4. Mechanisms of action: Anti-inflammatory and antioxidant effects

Reactive oxygen species-induced oxidative stress impairs the functions of cellular macromolecules, including DNA, proteins and lipids, contributing to lifestyle-related diseases such as cancer and diabetes. The human body maintains homeostasis by promptly responding to oxidative stress through nuclear factor erythroid 2-related factor 2 (Nrf2) and Kelch-like ECH-associated protein 1 (Keap1) (63). During oxidative stress, cysteine residues within Keap1 become oxidized, prompting the dissociation of Nrf2 from Keap1. Subsequently, Nrf2 translocates into the nucleus and acts as a transcription factor to activate antioxidant and drug-metabolizing enzymes that are involved in biological defense mechanisms. A common oxidative stress injury consists of liver damage induced by excessive drug intake. Garlic-derived sulfur-containing compounds have demonstrated protective effects against drug-induced liver damage. Oral administration of allicin to a mouse model of alcoholic fatty liver disease increased the expression of antioxidant enzymes, suppressed inflammatory cytokines, ameliorated fatty liver, and mitigated liver damage (64). Allyl methyl disulfide also exhibits protective effects against acetaminophen-induced acute liver damage by enhancing the expression of antioxidant enzymes and GSH, an antioxidant substance (65).

It was previously reported by the authors that oral administration of DATS exerts liver-protective effects by modulating the expression of antioxidant and drug-metabolizing enzymes in a rat model of carbon tetrachloride-induced acute liver injury (66,67). Several garlic-derived sulfur-containing compounds are suspected to stimulate antioxidant enzymes involved in the human defense system. These garlic compounds, acting as electrophilic agents, activate the Nrf2-Keap1 signaling pathway by oxidizing cysteine residues within the Keap1 molecule (68,69).

5. Side effects and toxicity for practical implications and the preparation methods

Garlic is considered to be safe for daily intake in our life; however, it may cause side effects such as burning sensations and diarrhea in sensitive individuals under excessive consumption of garlic. A randomized controlled trial was conducted to clarify the effect of high doses of raw garlic on an empty stomach and it showed changes in the intestinal flora, flatulence and gastrointestinal disturbances (70). Furthermore, dermatitis or burns can be observed by topical application of raw garlic (71). Prolonged intake of high doses of raw garlic leads to stomach ulcers as well as hemolytic anemia in laboratory animals. The primary toxicological mechanism can be attributed to oxidative hemolysis by sulfide derived from garlic characterized by methemoglobinemia and the Heinz body formation. A low dose of garlic is considered to be safe, but therapeutic dose may cause mild gastrointestinal disorder, while a higher dose of garlic may cause liver damage (72). The anti-thrombotic activity of garlic may influence the use of oral anti-coagulants; thus, there are concerns against surgery or contraindications of anticlotting medications such as warfarin in the medical field (73).

Allicin is a membrane-permeable compound that readily enters cells and interacts with sulfhydryl-containing molecules such as GSH and cysteine residues in proteins and enzymes. This interaction can lead to cytotoxic effects due to the oxidative modification of thiol groups. The processing method significantly influences the bioavailability and efficacy of garlic-derived sulfur compounds through the generation of allicin. Raw garlic contains alliin and alliinase, which react upon crushing to form allicin, a bioactive but highly unstable compound. To mitigate potential cytotoxicity and enhance stability, specific extraction and preparation techniques, such as alcohol soaking or heat treatment, can be employed to denature CS-lyase.

AGE is produced by prolonged extraction in alcohol, resulting in increased SAC content while minimizing allicin-related cytotoxic effects. SAC is well characterized for its safety and has <4% of the toxicity of allicin or DADS. Toxicological evaluations, including both acute and chronic toxicity studies, have confirmed the safety of AGE for long-term use (74).

Commercial garlic products vary widely in their processing methods, affecting their bioactive composition and stability. Acid-treated garlic products, such as pickled garlic, inactivate alliinase, preventing allicin formation. However, minced garlic exposed to acidic environments retains residual CS-lyase activity, leading to limited allicin production. Over time, allicin undergoes spontaneous conversion to allyl sulfides, including diallyl sulfide and DATS, which exhibit unique biological effects (75).

The bioavailability of allicin and its metabolites has been examined by measuring breath AMS, the primary volatile metabolite of allicin (76). Allicin bioavailability from enteric-coated garlic tablets ranged from 36-104%, but it was reduced to 22-57% when consumed with a high-protein meal due to slower gastric emptying. Regardless of meal composition, non-enteric tablets provided consistently high bioavailability (80-111%), while garlic powder capsules varied between 26-109%. Cooked or acidified garlic foods, which lack alliinase activity, exhibited lower but still significant allicin bioavailability: boiled (16%), roasted (30%), pickled (19%) and acid-minced (66%).

Given these variations, standardizing garlic processing methods is crucial for optimizing its health benefits. While there is no universally established daily intake of garlic, the German Commission E monograph (1988) recommends 1-2 cloves (~4 g) of fresh garlic per day as beneficial to human health (61). Further research is warranted to establish guidelines that maximize the therapeutic potential of garlic-derived sulfur compounds while minimizing variability in bioavailability.

6. Conclusions and future directions

Garlic-derived organosulfur compounds, including allicin, SAC and DATS, have shown promising antioxidative, anti-inflammatory and anticancer properties. However, despite extensive *in vitro* and *in vivo* studies, their precise molecular mechanisms in human physiology remain incompletely understood.

Future research should prioritize clinical validation (large-scale, placebo-controlled trials to evaluate long-term health effects), mechanistic studies (identifying specific signaling pathways influenced by garlic compounds), bioavailability and formulation (optimizing delivery methods to enhance therapeutic efficacy) and personalized nutrition approaches (investigating individual variations in response to dietary garlic intake, particularly in relation to the gut microbiome).

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Authors' contributions

TS was responsible for article selection and literature review. TS and TH wrote the manuscript. TH constructed figures. Data authentication is not applicable. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

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