Thiolane-type sulfides from garlic, onion, and Welsh onion

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Abstract
In this paper, we review our work in the last 10 years wherein we examined the sulfides in the acetone extracts of garlic (*Allium sativum*), onion (*A. cepa*), and Welsh onion (*A. fistulosum*), obtained and characterized the structures of new sulfides, three 3,4-dimethylthiolane-type sulfides from onion and Welsh onion, respectively, and four acyclic-type, nine 3,4-dimethylthiolane-type, four 2-methylthiolane (and thiane)-type, two 1,2-dithiolane-type, and two 2-oxothiolane-type sulfides, together with (E)-ajoene and one kujounin-type sulfide from garlic. During this process, structural corrections were made in onionin A group, garlicin A, and garlicin B group in some 3,4-dimethylthiolane-type sulfides. Next, hypothetical pathways for the production of the aforementioned sulfides were proposed. Furthermore, it was revealed that a typical 3,4-dimethylthiolane-type sulfide, onionin A1 obtained from onion, having the isomeric structure of garlicnin B1 obtained from garlic, decreased tumor proliferation and controlled tumor metastasis. These results showed that onionin A1 is an effective agent for controlling tumors, and that the antitumor effects observed in vivo are likely caused by reversing the antitumor immune system. Activation of the antitumor immune system by onionin A1 might be an effective adjuvant therapy for patients with osteosarcoma, ovarian cancer and other malignant tumors.

Keywords Garlic · Onion · Welsh onion · 3,4-dimethylthiolane-type · Onionin A1 · Garlicnin B1 · Antitumor effect

Introduction
Garlic (*Allium sativum* L.) is ranked at the top of the list of designer foods showing anti-cancer effects by the National Cancer Institute [1]. Generally, the biological activity of garlic is distinguished in two categories: cardiovascular disease prevention and cancer prevention. Activities in the former category include the inhibition of cholesterol synthesis, platelet aggregation, and arterial smooth muscle cell proliferation, as well as anti-inflammatory, antioxidant, and hydrogen sulfide-mediated vasodilatory effects. The activities in the latter category include the effects on carcinogen metabolism, i.e., enhanced cellular glutathione synthesis that induces cell cycle arrest and apoptosis, and prevention of *Helicobacter pylori* infection, gastric cancer, and colorectal cancer [2–6].

The chemistry of *Allium* sulfides began with the discovery of allicin and alliin in 1944 [7] and 1951 [8], respectively, in garlic. In 1971, two types of vinylthiin derivatives [9] were identified as thermally decomposed compounds by GC analysis of allicin. In 1984, Block and Ahmad determined the structure of ajoene in ether fraction [10]. It was also found that volatile garlic oils contained many sulfur compounds, such as diallylsulfide, (Z and E)-ajoene, 1,3-vinylthiin, and 1,2-vinylthiin, produced by the decomposition of thioureas [11]. Unexpectedly, there were few clarified sulfides from garlic; in particular, cyclic sulfides before our study. Therefore, we had started the investigation for aiming at the isolation, structural characterization, and antitumor activity of the cyclic sulfides (sulfur-containing compounds including sulfoxides) from garlic, onion (*A. cepa*), and Welsh...
onion (*A. fistulosum*). The present review provides a brief description of the above-mentioned study.

**Extraction and separation of garlic**

Acetone was selected as the extracting solvent because it was expected to prolong the lifetime of allyl (or 1-propenyl) sulfenic acid and allyl thiosulfenic acid, which are derived easily by the decomposition of allicin. The acyclic and cyclic sulfides are stabilized by the electron-inductive interaction between acetone and sulfenic acids, and between acetone and cyclic sulfide. Chinese garlic was used, which is the same as Japanese garlic, because it was readily available and the occurrence of various sulfides, due to long drying storage, was expected. Chinese garlic (1.0 kg) was chopped and blended with acetone in a mixer. The mixtures were then soaked in acetone for 3 days at room temperature. During this time, sulfenic acid analogs might undergo chemical changes, such as cyclization and artificial reactions, to produce new sulfides. In particular, we intended to obtain stable cyclic sulfides possessing antitumor activity. Next, the

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Fig. 1  Corrected structures of onionin A₁ (1) and garlicnin B₁ (2)

![Corrected structures of onionin A₁ (1) and garlicnin B₁ (2)](image)

Fig. 2  Structures of onionin A₁ (1), garlicnin B₁ (2), and garlicnin A (3)

![Structures of onionin A₁ (1), garlicnin B₁ (2), and garlicnin A (3)](image)
Table 1  Structures of garlicins and onionins isolated from garlic

i. Acyclic-Type

Garlicin L-1  Garlicin L-2  Garlicin L-3  Garlicin L-4

ii. 3,4-Dimethylthiolane-Type

Garlicin A  Garlicins B_1, B_2, B_3, B_4  Garlicins C_1, C_2, C_3  Garlicin M

iii. 2-Methylthiolane (thiane)-Type

Garlicin I_1, I_2  Garlicin J_2  Garlicin J_1

iv. 1,2-Dithiolane-Type

Garlicin G  Garlicin P

v. 2-Oxothiolane-Type

Onionin B_1  Onionin B_2
filtrate was concentrated at 40 °C in vacuum to obtain the extract in a small volume that was partitioned between ethyl acetate and water. The ethyl acetate extractive (5.9 g) was separated by column chromatography on silica gel eluting with n-hexane: acetone (from 6: 1 to 2: 1) to yield 21 new sulfides named garlicnins A (48.2 mg) [12], B1 (242.0 mg), B2 (47.2 mg), B3 (29.8 mg), B4 (19.3 mg), C1 (26.4 mg), C2 (23.4 mg), C3 (14.6 mg) [13, 14], G (17.2 mg), I1 (17.4 mg) [15], I2 (15.6 mg) [16], J1 (17.4 mg) [15], J2 (19.4 mg) [17], L-1 (47.2 mg), L-2 (19.8 mg), L-3 (19.3 mg), L-4 (23.4 mg) [18], M (21.1 mg) [16], P (18.4 mg) [17], and onionins B1 (27.4 mg), and B2 (26.2 mg) [19], together with the known sulfide, (E)-ajoene (279.7 mg) [10], and kujounin A1 derivative (22.1 mg), which related to kujounin A1 obtained from Allium fistulosum by Matsuda et al. [20]. The structures of the obtained sulfides were characterized using high-resolution fast atom bombardment mass spectroscopy (HRFABMS), 1H-NMR, 13C-NMR, 1H–1H NMR correlation spectroscopy (COSY), 1H-detected heteronuclear correlation through multiplet quantum coherence (HMOC), heteronuclear multiple bond correlation (HMBFC), and nuclear Overhauser effect spectroscopy (NOESY). To determine the relative steric configuration of the cyclic sulfides, aromatic solvent-induced NMR shifts were applied [21, 22].

**Extraction and separation of onion and Welsh onion**

Similarly, the extraction and separation of onion (A. cepa) and Welsh onion (A. fistulosum) were performed. From onion bulbs (640 g), onionin A1 (42.2 mg) [23], onionin A2 (23.5 mg), onionin A3 (16.2 mg) [24], onionin B1 (16.4 mg), and B2 (20.5 mg) [19], were obtained, and from Welsh onion leaves (1.1 kg), onionin A1 (34.2 mg), onionin A2 (22.1 mg) and onionin A3 (16.4 mg) [24] were obtained.

**Structures of isolated sulfides from garlic, onion, and Welsh onion**

The above garlicnins and onionins were divided into five types: acyclic-type sulfides including garlicnins L-1, L-2, L-3, and L-4; major sulfides, 3,4-dimethylthiolane-type sulfides including garlicnins A, B1, B2, B3, B4, C1, C2, C3, and M, onionins A1, A2, and A3; 2-methylthiolane (and thiane)-type sulfoxides including garlicnins I1, I2, J1 and J2; 1,2-dithiolane-type sulfoxides including garlicnins G and P; and 2-oxothiolane-type sulfides including onionins B1 and B2. The structures of acyclic-type sulfides, that is, garlicnins L-1, L-2, L-3, and L-4, were characterized as E-5-thiaocta-4,6-diene-2,5-dioxide, E-2,6,7-trithiaedeca-4,9-diene 2-oxide, Z-4,5,9,10-tetraathiatriedeca-1,7,12-triene, and E-6,7-dithiadeca-2,9-diene 2-methyl-1-oxide, respectively. Regarding the 3,4-dimethylthiolane-type sulfides, we determined the structure of onionin A1, prior to the structure determination of garlicnin B group from garlic, as 3,4-dimethylthiolane S-oxide (1’) in 2010 as shown Fig. 1, based on the 1H-1H COSY analysis that included the correlation between H-5 and H-1’, the proton assignments of H-2 and H-2 at C-2, and determination of the relative configuration by the aromatic solvent-induced NMR shifts [21, 22]. In relation to the structure of onionin A1, we determined the structure of garlicnin B1 (2’) isolated from garlic in 2012. However, in 2018, Block et al. corrected the structure of garlicnin B1 as 3,4-dimethyl-5-allylsulfynylthiolane-2-ol (2) [25] as shown in Fig. 1. This correction was made because the proposed continuity of nine carbons was not observed in the 13C-13C NMR incredible natural abundance double quantum transfer experiments (INADEQUATE). In 2019, Kubec et al. corrected onionin A1 as (E)-3,4-dimethyl-5-(1-propenylsulfonyl)thiolane-2-ol (1) as shown in Fig. 1, and he only corrected the part of structure and retained the names onionin A and garlicnin B [26]. Here, we reconfirmed the validity of their claims and we reformed the structures of onionin A1 (1) and garlicnin B1 (2), and determined the absolute configuration [27] of garlicnin B1 as shown in Fig. 2 by the Mosher method [28, 29] and NOESY analysis of 2. Simultaneously, the absolute configurations of onionin A1 and garlicnin A (3) were also deduced because their proton chemical shifts of H-2, H-3, H-4, CH3 at C-3, and CH3 at C-4, and their carbon chemical shifts of C-2, C-3, C-4, CH3 at C-3, and CH3 at C-4 approximated to those of garlicnin B1 (2) as shown in Fig. 2.

The structures of garlicnins C1, C2, and C3 were determined to be 2-(allyldisulfanyl)-5-(1-propenylsulfonyl)-3,4-dimethylthiolan-S-oxide. Garlicnins C1, C2, and C3 are steric isomers. The structure of garlicnin M was determined to be 2,5-bis(allylsulfanyl)-3,4-dimethyl-thiolane-5-oxide. Next, the structures of 2-methylthiolane-type

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(Fig. 3) Structures of (E)-ajoene and kujounin A1 derivative.
sulfoxides, that is, garlicnins I₁ and I₂ were determined to be 5-methyl-2-(allyldisulfanyl)-3-(allyldisulfanyl)-methyl]-thiolane-S-oxides, and the structures of 2-methylthiane-type sulfoxides; garlicnins of J₁ and J₂ were determined to be 6-methyl-2,3-bis(allyldisulfanyl)-thiane-S-oxide and 6-methyl-4-(allyl-disulfanyl)-thiane-S-oxide, respectively. The structures of 1,2-dithiolane-type sulfoxides; garlicnins G and P were determined to be 4-(allyl)-3-(allylsulfinyl)-1,2-dithiolane, and 3-methyl-2,7,8-trithia-bicyclo[3.3.0]octan-2-oxide, respectively. The structures of the above garlicnins and onionins are summarized in Table 1, together with (E)-ajoene and kujounin A₁ derivative as shown in Fig. 3.

**Hypothetic pathways to respective sulfides**

The first acyclic-type sulfides were produced by the arrangement and combination of allyl (or 1-propenyl) sulfinic acid, and allyl thiosulfenic acid derived from allicin (Fig. 4, Fig. 5). In the case of garlicnins L-1 and L-2, vinyl (ethenyl) and methyl sulfinic acid, respectively, were used in the first step of their synthesis. Moreover, on the basis of garlicnin L-2 formation, it was hypothesized that allyl (or 1-propenyl) sulfinic acid would be involved in hydroxylation for oxidative reaction, of which example were observed in the pathway to onionin B group. In the case of garlicnin L-2 formation, 1-propenyl sulfinic acid was likely involved in the dehydroxylation for reductive reaction, for which instances were observed in the pathways to garlicnins L-3, M, I₁, I₂, J₂, and onionin B group. Formation of garlicnin B group was proposed as shown in Fig. 6: allicin was firstly derived from S-allyl L-cysteine, next allicin was transformed into 1-propenyl 1-propene-thiosulfinate via double-bond rearrangement and was then converted to 2,3-dimethylbutanethial 1-oxide via [3,3]-sigmatropic rearrangement [30]. The generated intermediate was subsequently ring-closed to form a thiolane derivative that reacted with allyl sulfinic acid to finally produce the 3,4-dimethylthiolane-type sulfides, garlicnins B₁, B₂, B₃ and B₄. On the other hand, the above thiolane derivative was once hydroxylated on S in the thiolane framework to give thiolane S-oxide, and next reacted with allyl thiosulfenic acid and 1-propenyl sulfinic acid to generate the garlicnin C group, as shown in Fig. 6. The hypothetical
pathway for the production of garlicnin M is shown in Fig. 7. In the production of the 2-methylthiolane(and thiane)-type sulfoxides, the combination of C-2 on allyl sulfenic acid and C-1 on 1-propenyl sulfenic was triggered in the pathways to garlicnins I₁ and I₂ as shown in Fig. 8, and the combination between the C-1 on 1-propenyl sulfenic acid and C-3 on allyl sulfenic acid occurred for the formation of garlicnin J₁ as shown in Fig. 9. In the production of 1,2-dithiolane-type sulfoxides, the first stage was initiated by the combination of C-1 on allyl sulfenic acid and C-2 on allyl thiosulfenic acid in the case of garlicnin G. To produce garlicnin P, the dehydroxylation of allyl thiosulfenic acid resulted in successive rearrangements between allyl thiosulfenic acid and 1-propenyl sulfenic acid to yield garlicnin P as shown in Fig. 10. The 2-oxothiolane-type sulfoxides, onionins B₁ and B₂ were produced following hydroxylation to C-2 on the thiolane framework. This method differed from garlicnins C group, in which the hydroxylation to the S atom on the thiolane framework occurred as shown in Fig. 6. Furthermore, allyl sulfenic acid preferred hydroxylation at C-2 and 1-propenyl sulfenic acid may participate in dehydroxylation at C-4 as shown in Fig. 11.

**Effect of 3,4-dimethylthiolane-type sulfide [onionin A₁ (1)] on tumor progression and metastasis in tumor injected mice**

3,4-Dimethylthiolane-type sulfides, such as onionins A₁–A₃ from onion and Welsh onion, and garlicnins A, B₁–B₄, C₁–C₃, and M from garlic are common compounds among these *Allium* species and are regarded as major sulfides. Therefore, to examine the antitumor activity, onionin A₁ (1) [23], which is representative of the 3,4-dimethylthiolane-type sulfides, was investigated. Onionin A₁ is an isomer of garlicnin B₁, with an allylsulfanyl group instead of a 1-propenylsulfanyl group at C-5 on the core 3,4-dimethylthiolane 2-ol framework. Therefore, if onionin A₁ is active for anti-tumor effects then garlicnin B₁ also expected to be active. We used onionin A₁ available at this time for antitumor examination. The effects of onionin A₁ on tumor progression and metastasis in mouse osteosarcoma and ovarian cancer-bearing mouse models were investigated. Administration of onionin A₁ significantly suppressed both subcutaneous...
tumor development and lung metastasis in a mouse osteosarcoma (LM-8)-bearing mouse model (A in Fig. 12). Furthermore, onionin A1 significantly suppressed (in promotion stage) tumor progression in a mouse ovarian cancer (iMOC)-bearing mouse model (B in Fig. 12), suggesting that onionin A1 is an orally available small molecule for anti-cancer therapy [31, 32]. The antitumor effects observed in vivo are likely caused by reversal of the antitumor immune system. Activation of the antitumor immune system by onionin A1 might be an effective adjuvant therapy for patients with osteosarcoma, ovarian cancer and other malignant tumors.

**Conclusion**

The identification and characterization of novel sulfides isolated from garlic, onion, and Welsh onion have contributed to the identification of new chemicals and pharmaceutical compounds. Among the 3,4-dimethylthiolane-type of major sulfides, garlicnin B1 (Table 1, Fig. 13) is expected to be developed as a novel anti-cancer agent, as it is readily isolated in high yield, representing approximately 0.05% of Chinese garlic, and is also a synthesizable target because of its structural simplicity. Based on these findings,
Fig. 8 Hypothetical pathway to 2-methylthioline-type sulfoxides, garlicnins I₁ and I₂

Fig. 9 Hypothetical pathway to 2-methylthiane-type sulfoxides, garlicnins J₁ and J₂
Fig. 10 Hypothetical Pathway to 1,2-dithiolane-type sulfoxides, garlicinins G and P

Fig. 11 Hypothetical pathway to 2-oxothiolane-type sulfides, onionins B₁ and B₂
pharmacological investigations will be conducted to develop healthy foods and anti-cancer agents that can prevent or combat disease.

Declarations

Conflict of interest The authors declare no conflict of interest.

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Fig. 12 Effect of 3,4-Dimethylthiolane-type sulfide (onionin A1; ONA) on tumor progression and metastasis in tumor injected mice Onionin A1 (ONA) (20 mg/kg) was administered orally before and after the subcutaneous implantation of LM8 cells in the C3H mice (n=20, each group) for 3 weeks, followed by determination of the subcutaneous tumor weight and presence of lung metastasis (A). As a murine ovarian cancer model, C57B6 mice were injected in the right ovary with iMOC cells and were administered ONA (20 mg/kg) for 3 week, followed by determination of the subcutaneous tumor weight (B).

Fig. 13 Garlicnin B1 (2)
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