Antitumor Allium Sulfides

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We examined the sulfides in onion (Allium cepa L.), Welsh onion (A. fistulosum L.), and garlic (A. sativum L.), and obtained three new thiolane-type sulfides (onionins A1–A3) from onion; two new thiabicyclic-type sulfides (welsonins A1, A2), together with onionins A1–A3, from Welsh onion; and six new acyclic-type sulfides (garlicnins L-1–L-4, E, and F), ten new thiolane-type sulfides (garlicnins A, B1–B4, C1–C3, K1, and K2), and three new atypical cyclic-type sulfides (garlicnins G, I, and J) from garlic. Acetone extracts showed the potential of these sulfides in inhibiting the polarization of M2 activated macrophages that are capable of suppressing tumor-cell proliferation. The effect of the thiolane-type sulfide of a major component, onionin A1, on tumor progression and metastasis in both osteosarcoma and ovarian cancer-bearing mouse models was then examined. Tumor proliferation was depressed, and tumor metastasis was controlled by regulating macrophage activation. These results showed that onionin A1 is an effective agent for controlling tumors in both in vitro and in vivo models, 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. Based on these findings, pharmacological investigations will be conducted in the future to develop natural and healthy foods and anti-cancer agents that can prevent or combat disease.

Key words Allium cepa; Allium fistulosum; Allium sativum; thiolane-type; thiabicyclic-type; antitumor effect

1. Introduction

Onion (Allium cepa L.), garlic (Allium sativum L.), and Welsh onion (Allium fistulosum L.) belong to the genus Allium. In particular, garlic is ranked at the top of the list of designer foods showing anticancer effects by the National Cancer Institute. Generally, the biological activities of onion and garlic can be classified into 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.1–5

The chemistry of Allium sulfides began with the discovery of alllicin (1944)7 and alllii (1951)8 in garlic. In 1971, two kinds of vinylthiin derivatives9 were identified as thermal decomposition compounds by the GC analysis of alllicin. In 1984, Block and Ahmad determined the structure of azoene in the ether fraction.10 It was found that volatile garlic oils contain many sulfur compounds such as diallysulfide, (Z and E)-azoene, 1,3-vinylthiin, and 1,2-vinylthiin produced by the decomposition of thiosulfates.11 It was revealed that isoalliin was a precursor12–14 to the sulfides in onion. This was

![Fig. 1. Structures of Thiolane-Type Sulfides, Onionins A1 (I), A2, and A3](image-url)

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converted to thiosulfinate and (Z)-propanthial-S-oxide—a lachrymatory factor—via alkenesulfenic acid by the action of allinase, which furthermore produce thiosulfonate derivatives, sulfide analogs, and twiebelane. Dipropylsulfide was detected in the volatile oils of Welsh onion. Unexpectedly, there are few clarified sulfides obtained from the *Allium* species. Therefore, we started this investigation aiming at the isolation, structural characterization, and pharmacological analysis of the *Allium* sulfides that show antitumor activity.

2. Extraction, Separation and Structural Determination of *Allium* Species

Acetone was selected as the extracting solvent because it was expected to prolong the life-times of allylsulfenic acid (or 1-propenesulfenic acid) and allylthiosulfenic acid (or 1-propenethiosulfenic acid)-derived easily by the decomposition of allicin-owing to the electron inductive interaction between acetone and the sulfenic acids. Onion (640 g) and Welsh onion (1.1 kg), cultivated at Kumamoto Prefecture in Japan, and Chinese garlic (1.0 kg) were independently chopped and

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**Chart 1. Hypothetical Pathway to Onionins A₁ (I), A₂, and A₃**

**Chart 2. Hypothetical Pathway to Welsonin A₁ (2)**
blended with acetone in a mixer. We used Chinese garlic, which is the same species as Japanese garlic, as the crude material for extraction since it is popular on the market and the occurrence of various sulfides (due to long drying storage) is expected. The respective mixtures were then soaked in acetone for 3 d at room temperature. During this time, the sulfenic acid analogs might undergo chemical changes such as cyclization and artificial reactions to produce new sulfides. We would like to obtain stable cyclic sulfides possess antitumor activity, even though they might not be genuine compounds present in *Allium* species. Next, the filtrate was evaporated at 40°C in vacuum to obtain a residue that was partitioned between ethyl acetate and water. The resulting respective residues, the ethyl acetate layer and aqueous layer, were examined separately and their abilities in inhibiting macrophage activation were examined separately and their abilities in inhibiting macrophage activation were examined separately. The extracts (750 mg from onion; 200 mg from Welsh onion; 5.9 g from garlic) were then separated by chromatography on silica gel with *n*-hexane–acetone mixtures (6 : 1→5 : 1→4 : 1→3 : 1→2 : 1) to yield a) three new compounds named onionins A₁ (1, 42.2 mg), A₂ (23.5 mg), and A₃ (16.2 mg),¹⁹,²⁰ from onion; b) two new sulfides named welsonins A₁ (2, 18.9 mg) and A₂ (15.8 mg),²¹ together with three sulfides identical to onionin A₁ (34.2 mg),¹⁹ onionin A₂ (22.1 mg), and onionin A₃ (16.4 mg),²⁰ from Welsh onion; and c) twenty-one new sulfides named garlicnins A (48.2 mg),²² B₁ (3, 52.0 mg), B₂ (47.2 mg), B₃ (19.8 mg), B₄ (19.3 mg), C₁ (26.4 mg), C₂ (23.4 mg), C₃ (14.6 mg), D (105.0 mg),²³,²⁴ L₁ (47.2 mg), L₂ (19.8 mg), L₃ (19.3 mg), L₄ (23.4 mg), E (14.6 mg), F (15.2 mg),²⁵ K₁ (23.5 mg), K₂ (16.2 mg), H₁ (12.1 mg),²⁶ G (17.2 mg), I (17.4 mg), and J (12.4 mg)²⁷ together with a known sulfide, (E)-ajoene (279.7 mg),¹⁰,²³ from garlic. The structures of the obtained sulfides were elucidated using high-resolution fast atom bombardment mass spectroscopy (HR-FAB-MS), ¹H-NMR, ¹³C-NMR, ¹H–¹H-NMR correlation spectroscopy (COSY), ¹H-detected heteronuclear correlation through multiplet quantum coherence (HMOC), heteronuclear multiple bond correlation (HMBC), and nuclear Overhauser effect spectroscopy (NOESY). The method of aromatic solvent-induced NMR shifts was applied²⁸,²⁹ to determine the relative steric configurations of the cyclic sulfides.

### 3. Structures of Isolated Sulfides from Onion, Welsh Onion and Garlic, and Hypothetic Pathways of Their Sulfides

#### 3.1. Onion

Three new compounds named onionins A₁ (1), A₂, and A₃ were obtained from onion. The structure of onionin A₁ (1) was characterized as 3,4-dimethyl-2-sulfenic acid-5-(prop-1-en-1-yl)thiolan-1-iium-1-olate, and other analogous onionins A₂ and A₃ were steric isomers of 1 as shown in Fig. 1. They have the unique thiolan-1-iium-1-olate (tetrahydrothiophen-1-oxide) skeleton substituted with a sulfenic acid.
moiety at C-2 and a propenyl group at C-5. They were also obtained as major sulfides from Welsh onion and correspond to garlicnins B₁, B₂, B₃, and B₄, later described. These thiolane-type sulfides are isomers that differ only in the propenyl substitution and hence are the predominant compounds obtained by extraction of Allium species with acetone.

The formation of onionins A₁ (1), A₂, and A₃ is proposed as shown in Chart 1: allicin was firstly derived from S-allyl L-cysteine, next allicin was transformed into 1-propenyl 1-propenethiosulfinate via double-bond rearrangement and was then converted to 2,3-dimethylbutanedithial 1-oxide via [3,3]-sigmatropic rearrangement. Next, the generated compound was ring-closed to form a thiophene derivative that was attached with 1-propenesulfenic acid or/and allyl thiosulfenic acid derived from allicin to finally produce the thiolane-type sulfides, onionins A₁, A₂, and A₃ as illustrated in Chart 1.

3.2. Welsh Onion Two new sulfides named welsonin A₁ (2) and A₂ were obtained together with three thiolane-type sulfides identical with onionins A₁, A₂, and A₃ from onion.

Welsonin A₁ (2) and A₂ were obtained together with three thiolane-type sulfides identical with onionins A₁, A₂, and A₃ from onion. They have a new thia-bicyclo-nonane framework coupled with a cyclic sulfoxide and a lactone ring entirely different from those of the thiolane-type sulfides such as onionins A₁, A₂, and A₃ from onion, and Welsh onion, and garlicnins B₁, B₂, B₃, and B₄ from garlic. The structures of welsonin A₁ (2) and A₂ were characterized as 8-(prop-1-en-1-yldisulfanyl)-1,5-dihydroxy-9-methyl-3-oxa-7-thia-bicycle[4.3.0]-nonane-2-one-7-oxide, respectively, as shown in Fig. 2.

Notably, the production of welsonins A₁ (2) and A₂ might originate from the coupling of 1-propenyl sulfenic acid derived from allicin (Chart 2), and d-xylonic acid. This differs from the production of thiolane-type sulfides such as onionins A, garlicnins B, and garlicnins C groups. The production of the first pentacyclic sulfoxide ring could be interpreted as follows. First, the elimination of the hydroxyl group of d-xylonic acid exposes the carbonium ion, where the sulfur on 1-propenyl sulfenic acid attacks to form a new bond. This double bond then transfers to the sulfonium ion in sulfenic acid, and the next bonding between the resulting carbonium ion on the sulfenic acid and the methine carbon on d-xylonic acid takes place as illustrated in Chart 2. This was further attacked by 1-propenyl thiosulfenic acid to produce the bicyclo-nonane derivative.

3.3. Chinese Garlic Twenty-one new sulfides named garlicnins were obtained along with (E)-ajoene from garlic. The above garlicnins were divided into three type groups; first is acyclic-type sulfides, L-1, L-2, L-3, L-4, E, and F second is thiolane-type sulfides, garlicnins A, B₁ (3), B₂, B₃, B₄, C₁, C₂, C₃, K₁, and K₂, similar with those of onionins A₁, A₂, and A₃, and third is atypical cyclic-type sulfides, garlicnins G, I and J, different from the above thiolane-type sulfides. The structures of garlicnins L-1, L-2, L-3, and L-4, were characterized as (E)-5-thiaocta-6-ene 4-methyl-2,5-dioxide, E-2,6,7-trithiadeca-4,9-
diene 2-oxide, Z-4,5,9,10-tetrathiatrideca-1,7,12-triene, and E-6,7-dithiadieca-2,9-diene-2-methyl-1-oxide, respectively (Fig. 3). Next, the structures of thiolane-type sulfides, garlicins B₁, B₂, B₃, and B₄, were also characterized as 3,4-dimethyl-2-sulfenic acid-5-(prop-2-en-1-yl) thiolan-1-ium-1-olates (Fig. 4). Garlicins B₁, B₂, B₃, and B₄ are isomers
obtained by shifting the double bond of the 1-propenyl group of the onionins A series to the 2-propenyl group in the garlic-nins B series, with substitution at C-5. The structures of thiolane-type sulfides, garlicnins C₁, C₂, and C₃, were deduced to be 3,4-dimethyl-2-(prop-2-en-1-ylsulfinyl)-5-(prop-1-enylsulfinyl)-thiolan-1-ium-1-olates (Fig. 5). Garlicnins C₁, C₂, and C₃ have the same thiolane-type sulfide backbone as onionins A and garlicnins B groups, and they are steric isomers of each other. However, they differ in the substitutions of 1-propenyl-sulfinyl at C-5 and allylthiosulfanyl at C-2.

Finally, the structures of atypical cyclic-type sulfides, garlicnins G, I, and J were represented as 4-(prop-2-en-1-yl)-3-(prop-2-ene-1-sulfinyl)-1,2-dithiolane, 5-methyl-2-(prop-2-en-1-ylsulfinyl)-3-[(prop-2-en-1-ylsulfinyl)methyl]thiolan-1-ium-1-olate, and 6-methyl-2,3-bis(prop-2-en-1-ylsulfinyl)thian-1-ium-1-olate, respectively (Fig. 6).

The first acyclic-type sulfides would be produced by arrangement and combination of 1-propenyl sulfenic acid and
allyl thiosulfenic acid derived from allicin (Chart 3). In the production of the second thiolane-type sulfides, the garlicnins B and C series, the ring-closed thiolane compound produced via 1-propenyl 1-propenethiosulfinate by double bond migration and 2,3-dimethylbutanedithial 1-oxide by 3,3-sigmatropic rearrangement derived from allicin was attacked with allyl thiosulfenic acid to yield the garlicnins B series and, conversely the thiolane compound was combined with allyl thiosulfenic acid and 1-propenyl sulfenic acid to generate the garlicnins C series, as illustrated in Chart 4. In the production of the third atypical cyclic-type sulfides, the first stages were triggered by the combination of the C-1 on allyl sulfenic acid and the C-2 on allylthiosulfenic acid in garlicnin G (Chart 5), the combination of the C-2 on allyl sulfenic acid and the C-1 on 1-propenyl sulfenic acid in garlicnin I (Chart 6), and the combination of the C-1 on 1-propenyl sulfenic acid and the C-3 on allyl sulfenic acid in garlicnin J (Chart 7). All of these methods differ from the production of the garlicnins B and C series including the bond formation between the C-2 and C-2’ by 3,3-sigmatropic rearrangement on 1-propenyl-1-propene thiosulfinate giving 2,3-dimethylbutanedithial 1-oxide (Chart 4). The formation of the pathways to three types of garlicnins is summarized in Chart 8.

4. Effect on Macrophage Activation and Antitumor Activity of Thiolane-Type Sulfide (Onionin A₁)

Since the thiolane-type sulfides such as onionins A₁–A₃ from onion and Welsh onion, and garlicnins B₁–B₄, and C₁–C₃, from garlic are common compounds among these three Ali-lium species and are included as major sulfides, we examined the effects on macrophage activation and the antitumor activity of the onionin A₁, which is representative of the thiolane-type sulfides.

4.1. Ability of Thiolane-Type Sulfide (Onionin A₁) to Suppress M2 Macrophage Activation

Macrophages that infiltrate cancer tissues are referred to as tumor-associated macrophages (TAMs) and are closely involved in the development of the tumor microenvironment. TAMs are categorized as alternatively activated macrophages (M2) because of their anti-inflammatory functions. Normally, the presence of TAMs in certain types of tumors is associated with a poor prognosis for the tumor-bearing patients. Furthermore, inhibition of M2-macrophage polarization is known to suppress tumor cell proliferation. The incubation of human monocyte-derived macrophages (5×10⁴ cells per well of a 96-well plate) were incubated with the indicated amount of onionin A₁ (ONA) for 24 h after treatment with IL-10 (20 nmol/L) for 2 d, followed by the determination of CD163 expression by cell enzyme-linked immunosorbent assay (Cell-ELISA) (A). Human monocyte-derived macrophages (5×10⁴ cells per well of a 96-well plate) were incubated with ONA (30 μmol/L) for 24 h after treatment with tumor culture supernatant (TCS) for 2 d, followed by the determination of CD163 expression by Cell-ELISA (B). Human monocyte-derived macrophages (5×10⁴ cells per well of a 96-well plate) were stimulated with LPS (100 ng/mL) for 24 h after incubation with ONA (30 μmol/L) for 24 h in the presence of TCS, followed by determination of the levels of IL-10 and IL-12 secretion using ELISA (C). The data are presented as the means (standard deviation (S.D.)). *p<0.01, **p<0.001 vs. IL-10.

Fig. 7. Onionin A₁ (ONA) Changes M2 Polarization to M1 Polarization in Human Macrophages
CD163, indicating their capability for suppressing M2 macrophage polarization. Based on these results, we can assume that the ingredients of Frs. 1 and 2 may show similar potential for the suppression of tumor cell proliferation by regulating macrophage activation. Next, we isolated a new compound named onionin A₁ (ONA) from these fractions, and revealed that onionin A₁ significantly inhibited CD163 expression in a dose-dependent manner using a cell enzyme-linked immunosorbent assay (Cell-ELISA) (Fig. 7A). It is well known that tumor culture supernatant (TCS) upregulates CD163 expression and induces M2 polarization.⁴⁸ We found that onionin A₁ inhibited the CD163 overexpression induced by TCS derived from SKOV3 cells, a human ovarian cancer cell line (Fig. 7B). TCS also increased IL-10 (M2 marker) secretion (Fig. 7C) and decreased IL-12 secretion (M1 marker) (Fig. 7C), whereas onionin A₁ significantly reversed the IL-10 upregulation and IL-12 downregulation induced by TCS treatment (Fig. 7C). These data suggest that onionin A₁ inhibits macrophage polarization into the M2 phenotype. Human monocyte-derived macrophages (5×10⁴ cells per well of a 96-well plate) were incubated with the fractions (100 µg/mL) for 24 h after treatment with IL-10 (20 nM) for 2 d, followed by the determination of CD163 expression by cell-ELISA.

4.2. Thiolane-Type Sulfide (Onionin A₁) Suppressed Protumoral Functions of Macrophages As it is well known that activated M2 macrophages accelerate tumor cell proliferation, we hypothesized that onionin A (I) also inhibits cell–cell interactions between macrophages and tumor cells. The proliferation of mouse osteosarcoma LM-8 cells increased significantly when co-cultured with macrophages, and this protumoral macrophage function was suppressed by onionin A treatment (Fig. 8), thus indicating that onionin A (I) inhibits tumor proliferation by regulating macrophage activation.

4.3. Effect of Thiolane Type Sulfide (Onionin A₁) on Tumor Progression and Metastasis in Tumor Injected Mice We also examined the effects of onionin A₁ (ONA) on tumor progression and metastasis in mouse osteosarcoma and an ovarian cancer-bearing mice model. Administration of onionin A₁ (I) significantly suppressed both subcutaneous tumor development and lung metastasis in the mouse osteosarcoma (LM-8)-bearing mice model (Fig. 9A). Furthermore, onionin A₁ also significantly suppressed tumor progression in the mouse ovar-
ian cancer (iMOC)-bearing mouse model (Fig. 9B), suggesting that onionin A₁ can be an orally available small molecule for anti-cancer therapy.¹⁹,²⁰ 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.

5. Conclusion

The identification and characterization of these novel sulfides isolated from onion, Welsh onion, and garlic would contribute to the accumulation of information on new chemicals and pharmaceutical compounds in the Allium sulfide group. Among the thiolane type of major sulfides from Allium origins, garlicin B₁ (3) (Fig. 10) is expected to be developed as a novel anticancer agent, as it has a high yield, representing approximately 0.1% of that of Chinese garlic, and is a synthesizable target because of its structural simplicity. Based on these findings, pharmacological investigations are expected to be conducted in the future to develop natural and healthy foods and anti-cancer agents containing these compounds that can prevent or combat disease.

Conflict of Interest The authors declare no conflict of interest.

References and Notes

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