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Review

Sulfur-containing compounds from leaves of *Allium* plants, *A. fistulosum, A. schoenoprasum* var. *foliosum,* and *A. sativum*

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ABSTRACT

Allium plants are known worldwide as medicinal foodstuffs. A number of sulfur-containing compounds have been isolated from *Allium* plants, including allicin and ajoene, which are known for their biofunctional activities, such as anticancer activity. In the course of studies of sulfur-containing compounds, sulfur-containing multiple-ring compounds and thiolane-type compounds were isolated from the leaves of *Allium fistulosum*, *Allium schoenoprasum* var. *foliosum*, and *Allium sativum*. The chemical structures of these compounds were elucidated on the basis of physicochemical evidence. In addition, the biosynthetic pathways for these compounds were proposed. In this paper, studies on sulfur-containing compounds from the leaves and the whole plants of *A. fistulosum* 'kujou', *A. schoenoprasum* var. *foliosum*, and *A. sativum* and their proposed biosynthetic pathways are reviewed.

Key words: *Allium fistulosum*, *Allium schoenoprasum* var. *foliosum*, *Allium sativum*, sulfur-containing compound, tetrahydrothiophene

1. Introduction

Allium species are well-known foodstuffs that are widely used worldwide. Approximately 800 species, including leek (*A. fistulosum*), garlic (*A. sativum*), and onion (*A. cepa*), are known (Rose et al., 2005). Since ancient times, *Allium* plants have been used not only as foodstuffs but also for the purpose of treating diseases. *A. fistulosum* leaves have been used to treat cold symptoms, such as fever and pain, as well as severe diarrhea in traditional Chinese medicine. The biofunctional activities of *Allium* plants have been extensively studied. The extracts of *Allium* plants have been reported to exhibit such biological activities as anticancer (Kinjo et al., 2016; Matsuura et al., 2006), antidiabetic (Eidi et al., 2006; Elosta et al., 2016), platelet aggregation inhibitory (Hiyasat et al., 2009), antibacterial (Cellini et al., 1996), antiviral (Weber et al., 1992), and anti-obesity activities (Sung et al., 2011), as well as to prevent cognitive function decline (Ray et al., 2011). Sulfur-containing compounds are the characteristic constituents of *Allium* plants (Figure 1). The isolation of allicin from garlic (*A. sativum*) in 1944 (Cavallito and Bailey, 1944; Cavallito et al., 1944) was followed by the isolation of alliin from garlic (*A. sativum*) in the 1950s (Stoll and Seebeck, 1951); acyclic sulfur-containing compounds, such as ajoene, from garlic and onion (*A. cepa*) in the 1970s and 1980s (Block et al., 1980; Block and Ahmad, 1984; Brodnitz and Pascale, 1971); and cyclic sulfur-containing compounds from onion (*A. cepa*) in the 2010s (Aoyagi et al., 2011; Block et al., 2018; El-Aasr et al., 2010, 2011; Kubec et al., 2018; Nohara, 2012, 2013, 2014, 2015, 2016, 2018a, 2018b; Ono et al., 2017; Stefanova et al., 2019). In the 1990s, volatile sulfur-containing compounds were detected in welsh onion (*Allium fistulosum* var. *maichuon*) and shallot (*Allium fistulosum* var. *caespitosum*) (Kuo et al., 1990). Other constituents, namely, flavonoids, steroidal saponins, cinnamic acid derivatives, and pyrazine derivatives, were isolated from *Allium* plants as well. Sulfur-containing compounds from *Allium* plants exhibit various biological activities. In particular, allicin and ajoene, two typical sulfur-containing compounds from *Allium* plants, possess anticancer activity (Arditti et al., 1991; Oommen et al., 2004), anti-inflammatory activity (Dirsch et al., 1998), anti-oxidant activity (Prasad et al., 1995), and antibacterial activity (Cañizares et al., 2004), and prevent cardiovascular disease (Benavides et al., 2007; Zoccali et al., 2009). It was recently reported that cyclic sulfur-containing compounds isolated from onion show antitumor activity (El-Aasr et al., 2010). Thus, sulfur-containing compounds from *Allium* plants are important for the development of innovative medicines. In this review, we summarize the isolation and structure determination sulfur-containing compounds from

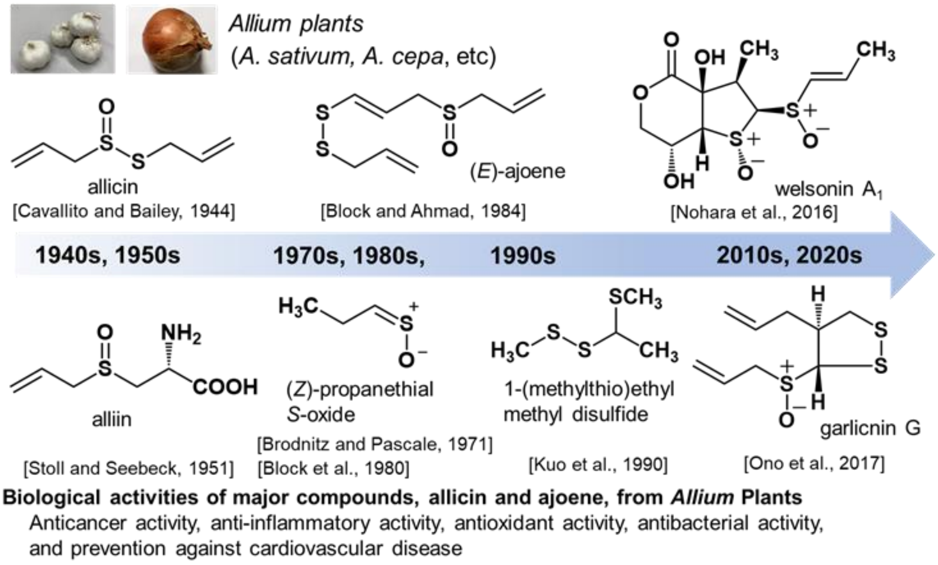


Figure 1. Sulfur-containing compounds in *Allium* plants.

the leaves and/or the whole plants of *A. fistulosum* 'kujou', *A. schoenoprasum* var. *foliosum*, and *A. sativum*, and present the proposed biosynthetic pathways for the compounds.

2. Sulfur-containing compounds in *Allium* plants and their biosynthesis (production process)

The reaction sequence for the formation of sulfur-containing compounds, such as allicin and ajoene, in *Allium* plants is shown in Figure 2. *Allium* plants possess sulfur-containing amino acids (cysteine sulfoxides), such as alliin and isoalliin (Kubec et al., 2000). When plant tissues are destroyed by external factors, cysteine sulfoxides are converted into allylsulfenic acid, 1-propenesulfenic acid, etc. by intracellular degrading enzymes, such as alliinase, stored in other cells. Next, *E*/*Z*-ajoene, 2-vinyl-4*H*-1,3-dithiin 3-vinyl-4*H*-1,2-dithiin, and propanethial *S*-oxide (tear component in onion) are obtained via unstable sulfur-containing compounds such as allicin through a subsequent chemical reaction and/or enzymatic reaction (Block et al., 1986; Imai et al, 2002; Schmidt et al., 1996). From the above, sulfur-containing compounds in *Allium* plants are secondarily produced by an enzymatic reaction and chemical reactions using cysteine sulfoxides as the starting material. Therefore, when isolating sulfur-containing compounds from *Allium* plants, it is important to examine the extraction conditions for *Allium* plants.

3. Isolation of kujounins and allium sulfoxides from *A. fistulosum* 'kujou'

The isolation of sulfur-containing compounds from *A. fistulosum* 'kujou' was examined. At first, the extraction conditions for the leaves, namely, the extraction solvent, the extraction temperature, and the extraction time, were investigated for the purpose of isolating sulfur-containing

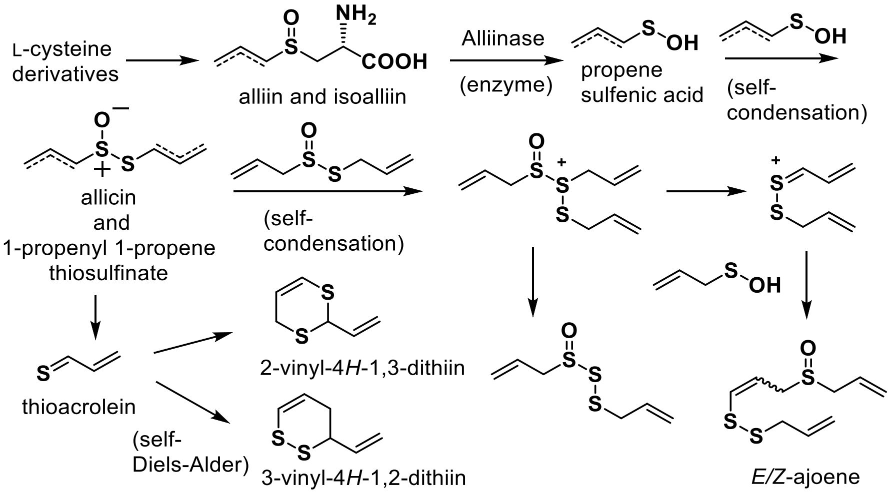


Figure 2. Reaction sequence for the formation of ajoene from alliin.

compounds produced by enzymatic reactions and chemical reactions (Figure 3). When water was used as the extraction solvent, it was unsuitable because the yields of sulfur-containing compounds on the HPLC analysis were low. When methanol, ethanol, acetone, and 80% aqueous acetone were used as solvent, acetone and 80% aqueous acetone was confirmed to contain diverse components although significant difference was not observed on the HPLC analysis. On the other hand, when the plants were extracted at 60–80˚C using several solvents, the formation of complex mixture by decompose was confirmed on HPLC analysis. Therefore, the extraction was performed at room temperature. Finally, the optimal conditions for the extraction were cutting fresh plants, using acetone or 80% acetone solution as the extraction solvent, and extracting at room temperature for 72–96 hours. Fresh leaves (white parts) of *A. fistulosum* ‘kujou’ (11 kg) were chopped and blended in a mixer with acetone. The mixture was extracted with acetone for 72 hours at room temperature. The acetone extract was partitioned between EtOAc and water. The EtOAc fraction was subjected to normal- and reversed-phase column chromatography and HPLC to obtain polycyclic sulfur-containing compounds, kujounins A_1 (**1**, 1.4×10^{-6}%, isolation yield from plants), A_2 (**2**, 1.7×10^{-6}%), A_3 (**3**, 3.6×10^{-7}%), B_1 (**4**, 3.1×10^{-7}%), B_2 (**5**, 2.6×10^{-7}%), and B_3 (**6**, 2.8×10^{-7}%), and monocyclic sulfur-containing compounds, allium sulfoxides A_1 (**7**, 3.1×10^{-7}%), A_2 (**8**, 3.2×10^{-7}%), and A_3 (**9**, 2.6×10^{-7}%) (Fukaya et al., 2018, 2019a) (Figure 4).

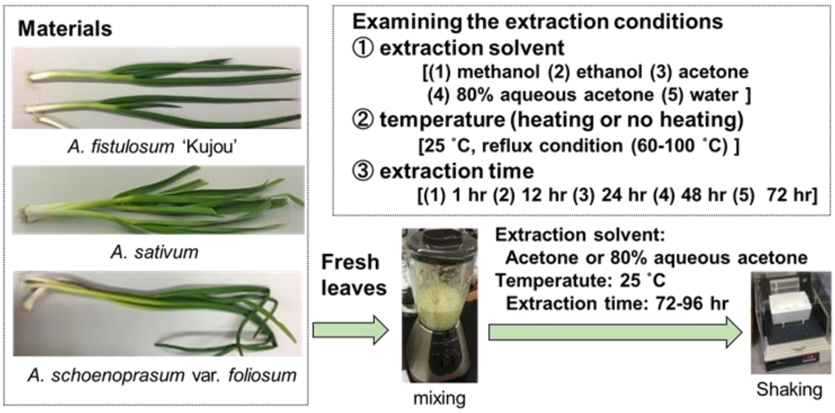


Figure 3. Determination of the optimum extraction conditions for the isolation of sulfur-containing compounds from *A. fistulosum* ‘Kujou’.

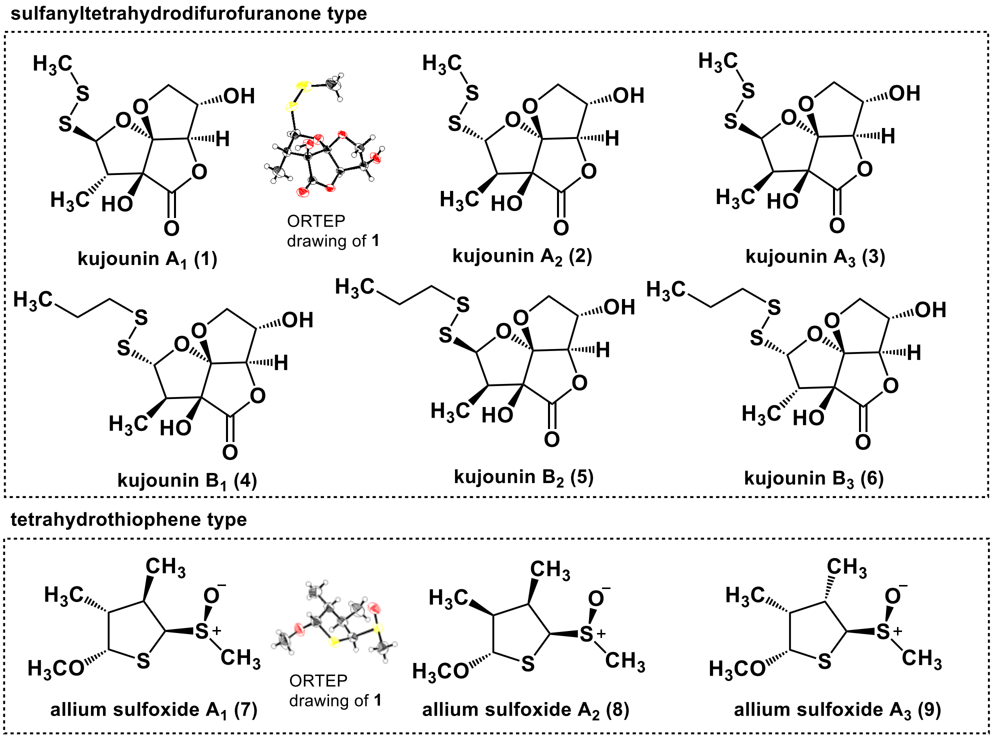


Figure 4. Sulfur-containing compounds, kujounins and allium sulfoxides, from *A. fistulosum* ‘kujou’.

4. Structure determination of kujounin A_1 isolated from *A. fistulosum* ‘kujou’

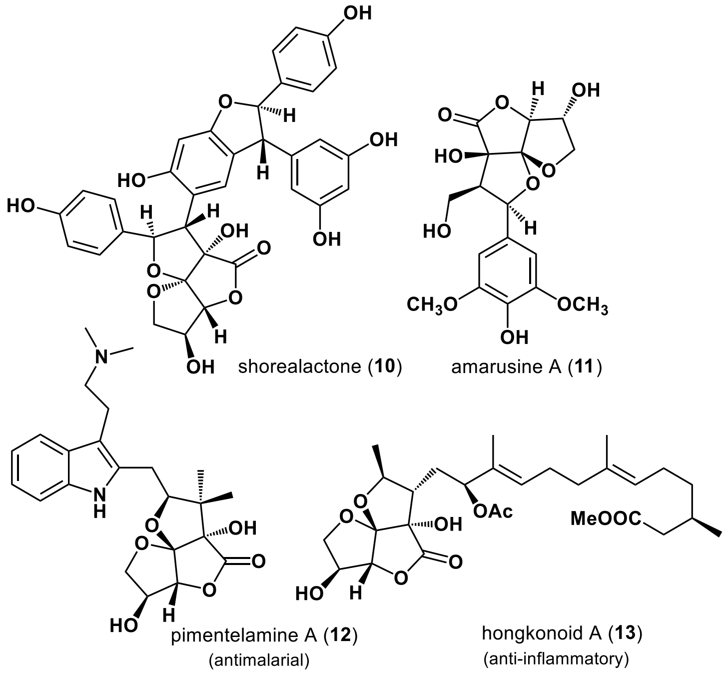
Kujounin A_1 (**1**) was isolated as colorless crystals and displayed a positive optical rotation ($[\alpha]^{25}_D$ +61.1, $c = 0.1$, in MeOH). In the ESI (electrospray ionization) MS measurement, the pseudo-molecular ion peak $[M + Na]^+$ was observed at *m/z* 317. Its molecular formula was $C_{10}H_{14}O_6S_2$, which was determined on the basis of the HR (high resolution) ESI-MS peak at *m/z* 317.0120 and ^{13}C NMR data. The planar structure of **1** was estimated from the HMBC and DQF-COSY spectra. In addition, the relative configurations were revealed by the NOESY spectrum. Compound **1** was obtained as a monocrystal in EtOAc : MeOH : H_2O (about 1 : 1 : 1), and Cu-Kα X-ray diffraction measurement clarified its absolute configuration to be 3*S*, 3a*R*, 5a*S*, 6*S*, 7*R*, and 8a*R*. Consequently, the chemical structure of kujounin A_1 (**1**) was determined to be (3*S*,3a*R*,5a*S*,6*S*,7*R*,8a*R*)-3,5a-dihydroxy-6-methyl-7-(methyldisulfanyl)tetrahydro-2*H*-difuro[3,2-b:2',3'-c]furan-5(5a*H*)-one. Compound **1** has a tetrahydrodifurofuranone skeleton that is rarely reported in natural products. To the best of our knowledge, there are four examples with the tetrahydrodifurofuranone skeleton: shorealactone (**10**) (Ito et al., 2003), amarusine A (**11**) (Sun et al., 2014), pimentelamines (**12**) (Robertson et al., 2017), and hongkonoids (**13**) (Zhao et al., 2018), and these compounds show several biological activities, such as antimalarial and anti-inflammatory activities (Figure 5). In this regard, further investigation of the biofunctional activities should be carried out.

5. Structure determination of allium sulfoxide A_1 (7) obtained from *A. fistulosum* ‘kujou’

Allium sulfoxide A_1 (**7**) was isolated as colorless crystals and displayed a positive optical rotation ($[\alpha]^{25}_D$ +5.4, $c = 0.1$, in MeOH). In the ESI-MS measurement, the pseudo-molecular ion peak $[M + Na]^+$ was observed at *m/z* 231. Its molecular formula was $C_8H_{16}O_2S_2$, which was determined on the basis of the HR-ESI-MS peak at *m/z* 231.0484 and ^{13}C NMR data. The structure of **7** including the relative configurations was estimated from the HMBC, DQF-COSY, and NOESY spectra. In addition, allium sulfoxide A_1 (**7**) was obtained as a monocrystal in EtOAc and methanol (about 1 : 1), and Cu-Kα X-ray diffraction indicated that its absolute configuration was 2*S*, 3*R*, 4*R*, 5*R*. Consequently, the chemical structure of allium sulfoxide A_1 (**7**) was determined to be (2*S*,3*R*,4*R*,5*R*)-2-methoxy-3,4-dimethyl-5-[(*S*)-methylsulfinyl]tetrahydrothiophene.

6. Isolation of folionins from fresh whole plants of *A. schoenoprasum* var. *foliosum*

The isolation of sulfur-containing compounds from the whole plant of *A. schoenoprasum* var. *foliosum*, which is endemic to Japan and used as a Japanese spice and a medicinal plant for its antibacterial activity and appetite-enhancing effect, was investigated. Fresh whole plants of *A. schoenoprasum* var. *foliosum* (19 kg) were chopped and blended in a mixer with acetone. The mixture was extracted with acetone for 72 hours at room temperature. The acetone extract was partitioned between EtOAc and water and the EtOAc fraction was subjected to normal- and reversed-phase column chromatography and HPLC to obtain folionins A_1 (**14**,


shorealactone (**10**)

amarusine A (**11**)

pimentelamine A (**12**)
(antimalarial)

hongkonoid A (**13**)
(anti-inflammatory)

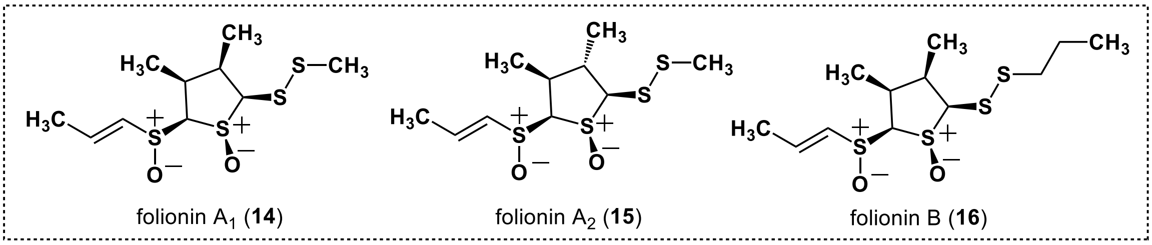
Figure 5. Compounds with tetrahydro-2*H*-difuro[3,2-*b*:2’,3’-*c*]furan-5(5a*H*)-one skeleton.

2.1 × 10^{-7}%, isolation yield from whole plant), A_2 (**15**, 1.8 × 10^{-7}%), and B (**16**, 1.7 × 10^{-7}%) (Fukaya et al., 2019b). The planar structures of compounds **14**–**16** were determined from the 1D and 2D NMR spectra. These compounds have the 2,3-dimethyltetrahydrothiophene skeleton and are highly sulfurized. The relative configurations of **14**–**16** except the relative configuration of the sulfoxide moiety were revealed from the NOESY spectrum. To determine the relative configuration of the sulfoxide moiety in tetrahydrothiophene sulfoxide, an aromatic-solvent-induced NMR shift was used (Ronayne and Williams, 1967). The ^{1}H NMR spectra measured in $CDCl_3$ and C_6D_6 were compared. The ^{1}H NMR spectrum of **14** measured in C_6D_6 showed an upfield shift of the peaks at H-2 (–0.51) and H-5 (–0.57), suggesting that the sulfoxide moiety in tetrahydrothiophene sulfoxide had an axial conformation because the aromatic solvent and the axial conformer formed a collision complex. As regards compounds **15** and **16**, the relative configurations of the sulfoxide were similarly estimated. Consequently, the chemical structures of folionins A_1 (**14**), A_2 (**15**), and B (**16**) were determined (Figure 6). In addition, sulfur-containing compounds with the same planar structures as **14** and **15,** called allithiolanes, were isolated from the bulbs of processed onion (*A. cepa*) (Kubec et al., 2018).

7. Isolation of foliogarlic di- and trisulfanes, from leaves of *A. sativum*

The isolation of sulfur-containing compounds from the leaves of *A. sativum* was carried out. Fresh leaves of *A. sativum* (15.0 kg) were blended in a mixer with water. Then, acetone was added into the mixture to make an 80% acetone solution. The mixture was extracted for 96 hours at room temperature (25˚C). The extract was partitioned between EtOAc and water and the EtOAc fraction was subjected to normal- and reversed-phase column chromatography and HPLC to obtain foliogarlic disulfanes A_1 (**17**, 1.3 × 10^{-4}%, isolation yield from plants), A_2 (**18**, 2.1 × 10^{-4}%), and A_3 (**19**, 0.9 × 10^{-4}%) and foliogarlic trisulfanes A_1 (**20**, 1.5 × 10^{-4}%) and A_2 (**21**, 0.8 × 10^{-4}%) (Fukaya et al., 2020). The chemical structures of these compounds were elucidated on the basis of physicochemical evidence including 1D and 2D NMR data and MS data (Figure 6). Compounds **17**–**21** have a tetrahydro-2*H*-difuro[3,2-*b*:2',3'-*c*]furan-5(5a*H*)-one skeleton with a methyl group at 6-position and a 2-propenyl disulfane or 2-propenyl trisulfane group at 7-position. Particularly, foliogarlic trisulfanes **20** and **21** are rare compounds derived from medicinal plants.

Sulfur-containing compounds from the fresh whole plants of *A. schoenoprasum* var. *foliosum*



Sulfur-containing compounds from the leaves of *A. sativum*

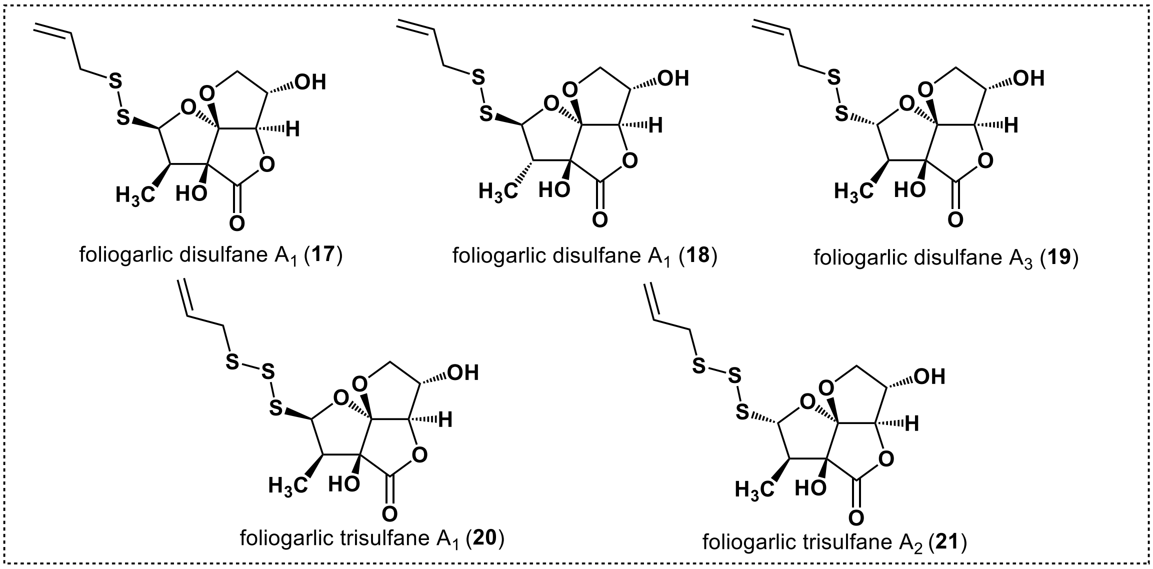


Figure 6. Folionins and foliogarlic di- and trisulfanes isolated from fresh whole plants of *A. schoenoprasum* var. *foliosum* and leaves of *A. sativum.*

8. Hypothetical biosynthetic pathways for kujounins and foliogarlic di- and trisulfanes

A biosynthetic pathway for kujounins **1**–**6** and foliogarlic di- and trisulfanes **17**–**21** is proposed (Figure 7). Allicin and 1-propenyl 1-propenethiosulfinate are generated from alliin and isoalliin by the enzyme alliinase when plant tissues are broken. Then, allicin and 1-propenyl 1-propenethiosulfinate are converted into disulfane and trisulfane via unstable intermediates by self-condensation and hydrolysis. Finally, the tetrahydro-2*H*-difuro[3,2-*b*:2',3'-*c*]furan-5(5a*H*)-one skeleton is formed from semidehydroascorbate by cyclization and sulfane formation. Consequently, kujounins **1**–**6** and foliogarlic di- and trisulfanes **17**–**21** are obtained. In 2018, kujounin A_2 was synthesized from ascorbic acid using a stereoselective Tsuji-Trost reaction and ozonolysis by biosynthesis-inspired approach (Burtea and Rychnovsky, 2018).

9. Hypothetical biosynthetic pathways for allium sulfoxides and folionins

A biosynthetic pathway for allium sulfoxides **7**–**9** and folionins **14**–**16** is proposed (Figure 8). 1-Propenyl 1-propenethiosulfinate is converted into 2,3-dimethyl-butanedithial 1-oxide via a [3,3]-sigmatropic rearrangement (Block et al., 2018). The intermediate undergoes ring closure, oxidation, methylation, and sulfane formation, in that order, to produce allium sulfoxides **7**–**9** and folionins **14**–**16**.

10. Conclusion

Several sulfur-containing compounds having a tetrahydrodifurofuranone skeleton and tetrahydrothiophenes were isolated from the leaves and/or the whole plants of *A. fistulosum* ‘kujou’, *A. schoenoprasum* var. *foliosum*, and *A. sativum.* It was clarified that the major sulfur-containing compounds exhibited differences in their basic skeletons

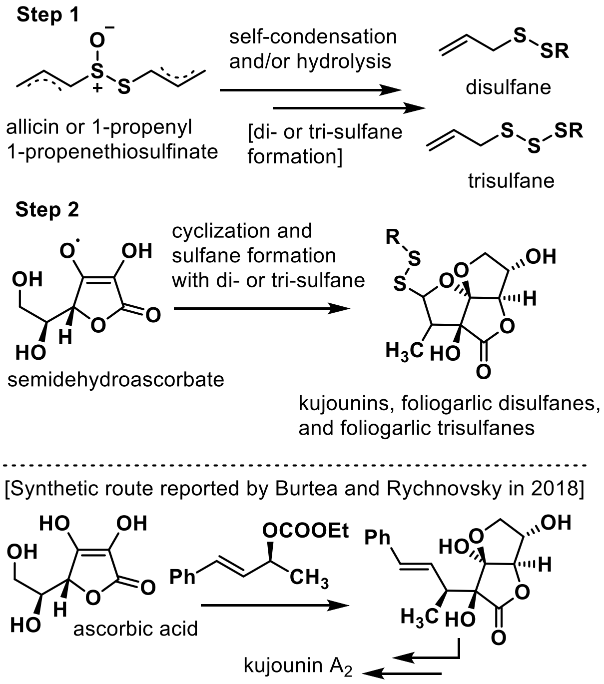


Figure 7. Proposed biosynthetic pathways for kujounins, foliogarlic disulfanes, and foliogarlic trisulfanes.

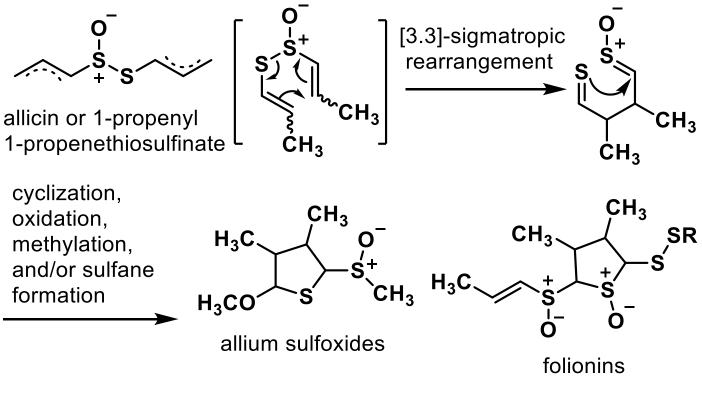


Figure 8. Proposed biosynthetic pathways for allium sulfoxides and folionins.

even if the extraction method was the same. The sulfur-containing compounds displayed several biofunctional activities, such as anticancer activity. In this regard, sulfur-containing compounds from *Allium* plants are important for the development of innovative medicines. The biofunctional activities should be studied in the future.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

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