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A new iridoid glycoside and a new cinnamoyl glycoside from *Scrophularia ningpoensis* Hemsl

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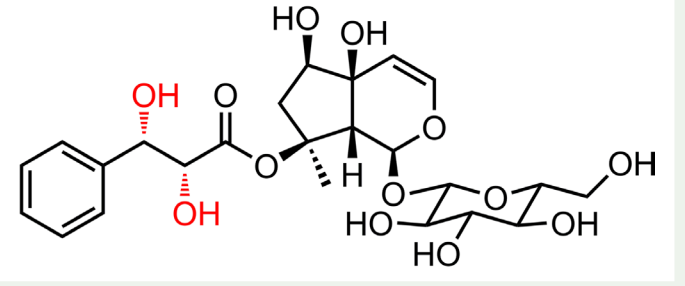
ABSTRACT

A new iridoid glycoside, namely 8-*O*-(*threo*-2, 3-dihydroxyl-3-phenyl-propionoyl)-harpagide (**1**), along with a new cinnamoyl glycoside named as *cis*-sibirioside A (**2**), were isolated from *Scrophularia ningpoensis* Hemsl. Their chemical structures were completely established by spectroscopic methods and comparison with related literatures. Compound **1** exhibited moderate antifouling effect against the settlement of *Balanus amphitrite* larvae with IC_{50} being 13.5 μg/mL and LC_{50} > 25 μg/mL.



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KEYWORDS
Scrophularia ningpoensis Hemsl; iridoid glycoside; cinnamoyl glycoside; antifouling

1. Introduction

The genus *Scrophularia* of the family *Scrophulariaceae*, versatile in metabolising varieties of iridoid glycosides being commonly considered as its chemotaxonomic markers (Ramunno et al. 2006; Venditti et al. 2016), encloses more than 300 species widely distributed in China. *Scrophularia ningpoensis* Hemsl., commonly known as 'Xuanshen' in Chinese, has been used in traditional Chinese medicine practice for over 2000 years, which is frequently utilised in combination with other herbs as a nutrient and a health strengthening agent (Sagare et al. 2001).

Previous chemical investigations have identified more than 30 iridoid glycosides and sugar esters from *S. ningpoensis* (Kajimoto et al. 1989; Qian et al. 1992; Li et al. 1999, 2000a,

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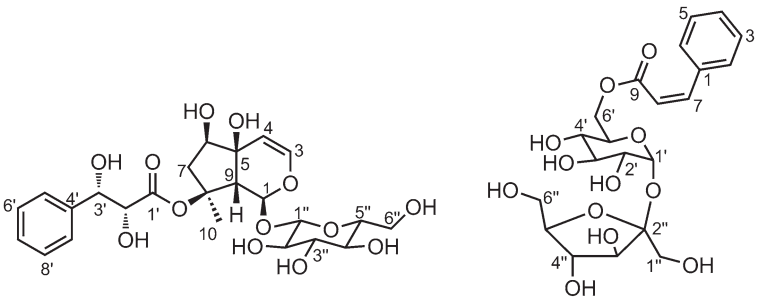

Figure 1. Chemical structures of compounds **1**–**2**.

2009; Zou & Yang 2000; Nguyen et al. 2005; Chen et al. 2007, 2008; Niu et al. 2009). Some of these compounds were found to exhibit antibacterial (Li et al. 2009), antioxidant (Li et al. 2000b), cytotoxic (Nguyen et al. 2005) and neuroprotective (Kim SR & Kim YC 2000; Kim et al. 2002; Wang et al. 2009) activities. In view of the herb's versatility in metabolising structurally and biologically interesting compounds, *S. ningpoensis* was selected and systematically explored by us, resulting in the isolation of three unusual zwitterionic alkaloids in our previous investigation (Zhang et al. 2015). Herein, we reported the isolation, structural elucidation and antifouling effect of a new iridoid glycoside, namely 8-*O*-(*threo*-2, 3-dihydroxyl-3-phenyl-propionoyl)-harpagide (**1**), along with a new cinnamoyl glycoside named as *cis*-sibirioside A (**2**) (Figure 1), from the other fraction of the same crude extract of *S. ningpoensis* as described previously.

2. Results and discussion

The 70% EtOH/H_2O crude extract of the dried root of *S. ningpoensis* was suspended in water and extracted subsequently with petroleum ether, EtOAc and *n*-BuOH. From the *n*-BuOH extract, a new iridoid glycoside (**1**) and a new cinnamoyl glycoside (**2**) were isolated by means of macroporous resin column chromatograph, silica gel column chromatography and preparative reversed-phase HPLC.

Compound **1** was obtained as an amorphous grayish powder. The molecular formula of **1** was determined to be $C_{24}H_{32}O_{13}$ by HR-ESI-MS, displaying ion peak $[M + Na]^+$ at *m/z* 551.1743 (calcd for $C_{24}H_{32}NaO_{13}^+$ at *m/z* 551.1741). The IR spectrum of compound **1** showed absorption bands for hydroxyl group (3373 cm^{-1}), carbonyl group (1719 cm^{-1}) and aromatic moiety (1648 cm^{-1}). Preliminary inspection of the ^1H NMR spectrum of **1** led to the identification of the following representative signals: δ_H 1.70 (3H, s, H-10), 2.09 (1H, dd, *J* = 15.0, 4.2 Hz, H-7a), 2.69 (1H, d, *J* = 15.0 Hz, H-7b), 3.76 (1H, s, H-9), 5.17 (1H, d, *J* = 6.0 Hz, H-4), 5.32 (1H, d, *J* = 9.0 Hz, H-1″), 6.69 (1H, s, H-1), 6.52 (1H, d, *J* = 6.0 Hz, H-3), as well as five aromatic protons δ_H 7.85 (2H, d, *J* = 7.8 Hz, H-5′, H-9′), 7.37 (2H, t, *J* = 7.5 Hz, H-6′, H-8′), 7.26–7.29 (1H, m, H-7′). On the basis of above information, compound **1** was assumed to be an iridoid glycoside, similar to harpagoside previously isolated from *Scrophularia buergeriana* Miq. (Kitagawa et al. 1967) and *Harpagophytum procumbens* DC. (Qi et al. 2006). This assumption was in good agreement with the ^{13}C NMR data of **1**, and further clearly supported by the detailed 2D NMR analyses involving ^1H-^1H COSY, HSQC and HMBC (Figure S1 in Supporting

Information, SI). The ^{1}H and ^{13}C NMR data (Table S1 in SI) of compound **1** were very similar to those of harpagoside with the major difference being that two olefinic signals of the cinnamoyl moiety in harpagoside were replaced by the signals of two oxygenated CH at δ_H 4.80 (1H, d, J = 7.5 Hz, H-2′)/δ_C (77.2, C-2′) and δ_H 5.35 (1H, d, J = 7.5 Hz, H-3′)/δ_C (75.8, C-3′), respectively, suggesting the presence of 2,3-dihydroxy-3-phenyl-propionoyl moiety in **1**, instead of cinnamoyl one. This assignment was unambiguously corroborated by the ^{1}H-^{1}H COSY displaying cross peak between H-2′ and H-3′, in combination with the diagnostic correlations from H-2′ to carbonyl carbon C-1′ (δ_C 173.5), and the H-3′ to aromatic carbon C-5′/C-9′ (δ_C 128.0) in HMBC (Figure S1 in SI). The relative configuration of the two hydroxyl groups at C-2′ and C-3′, respectively, was tentatively assigned to be *threo*, by the coupling constant of $J_{2',3'}$ = 7.5 Hz (~3.0/8.0 for *erythro*/ *threo*, respectively) (Hada et al. 1988; Sung et al. 2001). This assumption was consistent with the results expected from the ChemBio3D software, by which the dihedral angle between H-2′and H-3′ of the energy-minimised configuration was calculated to be 53° for *threo vs* 75° for *erythro* (Figure S2 in SI), leading to the rough assignment that the predicted $J_{2',3'}$ for *threo* was more close to the experimental data (7.5 Hz) than that for *erythro* according to Karplus equitation (Minch 1994). Consequently, compound **1** was assigned as 8-*O*-(*threo*-2, 3-dihydroxyl-3-phenyl-propionoyl)-harpagide.

Compound **2** was obtained as an amorphous brown powder. Its molecular formula $C_{21}H_{28}O_{12}$ was determined by HR-ESI-MS displaying ion peak at *m/z* 495.1453 $[M + Na]^+$ (calcd for $C_{21}H_{28}NaO_{12}^+$ at *m/z* 495.1478). After acid hydrolysis, fructose and glucose were detected by GC analysis. The IR spectrum suggested the presence of hydroxyl (3377 cm^{-1}) and conjugated ester groups (1700 cm^{-1}). The NMR data of **2** was similar to that of sibirioside A first isolated from the *Veronicastrum sibiricum* (L.) Pennell (Lin et al. 1995), with the major difference being that the signals of *trans* olefinic double bond in sibirioside A was replaced by the signals of the *cis* one. The ^{1}H NMR spectrum of **2** (Table S1 in SI) displayed typical signals arising from a monosubstituted benzene ring at δ_H 7.60–7.62 (2H, m, H-2/H-6), 7.33–7.36 (3H, m, H-3/H-4/H-5) and a *cis* CH = CH group at δ_H 7.04 (1H, d, J = 12.6 Hz, H-7), 6.03 (1H, d, J = 12.6 Hz, H-8), suggesting the presence of *cis*-cinnamoyl moiety in **2**, which was confirmed by the ^{1}H–^{1}H COSY correlations, together with the correlations from H-7 to C-9 (δ_C 167.8) and H-8 to C-1 (δ_C 136.2) in HMBC (Figure S1 in SI). In addition, the typical signal at δ_H 5.36 (1H, d, J = 3.3 Hz, H-1′) ascribing to the anomeric proton of the *α*-glycopyranose, together with the ^{13}C NMR spectrum of **2** exhibiting signals indicative of two anomeric carbons at δ_C 105.2 (C-2″) and 93.4 (C-1′) and three methylene groups at δ_C 64.6 (C-6′), 64.1 (C-1″) and 63.9 (C-6″), strongly suggested the presence of a sucrose moiety in **2**, which was consistent with the results of GC analyses and further supported by the HMBC correlation from H-1′ to C-2″. Furthermore, the diagnostic correlation from H-6′ (δ_H 4.44/4.25) to C-9 in HMBC, clearly indicated that the *cis*-cinnamoyl was connected to the sucrose moiety at C-6′ position. Therefore, compound **2** was elucidated to be 6-*O*-*cis*-cinnamoyl *β*-fructofuranosyl-(2→1)-*O*-*α*-glucopyranoside and named as *cis*-sibirioside A.

Marine biofouling, an undesirable accumulation of marine microorganisms, algae and animals on submerged substrates, has caused series of severe problems for maritime and aquaculture industries worldwide (Wang et al. 2015), being one of major concerns to scientists. With the global banning of organotin, one type of previously widely used antifoulant, from production and application in antifouling paint due to displaying toxicity to target and/or non-target marine organisms (Li et al. 2013), the search of effective and environmentally benign antifouling compounds is becoming an urgent need of marine coating

industries. Natural products have been proven to be a rich resource for identifying non-toxic and effective antifoulants (Huang et al. 2014; Zhang et al. 2014). Keeping this in mind, in this study, the isolates are evaluated for antifouling effect against the settlement of *Balanus amphitrite* larvae. Pleasingly, compound **1**, despite less potent than the positive control (IC_{50} = 3.2 μg/mL, LC_{50} > 25 μg/mL), exhibits moderate inhibitory effect with IC_{50} being 13.6 μg/mL and LC_{50} over 25 μg/mL, being a potent non-toxic antifoulant. Whereas, compound **2** shows no antifouling effect at the concentrations up to 25 μg/mL.

3. Experimental

3.1. General experimental procedures

Optical rotation was measured on JASCO P-2000 digital polarimeter (Jasco, Tokyo, Japan). UV spectrum was recorded on a Shimadzu UV2401PC spectrophotometer (Shimadzu, Kyoto, Japan). IR spectra were recorded on Perkin-Elmer 16 PC FT-IR spectrometer (Perkin–Elmer, Boston, USA). NMR experiments were measured on Varian Mercury VX 300 spectrometer (Varian, Japan) operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively, with TMS as internal standard and chemical shifts reported in ppm. High resolution mass spectra (HRMS) were performed on QSTAR XL mass spectrometry system (Applied Biosystems, USA). The preparative HPLC was performed on Waters systems (Waters, UK) involving Waters 2545 binary gradient module, Waters 2996 PDA detector, MassLynx V4.1 workstation and XBridge RP18 column (19 x 300 mm, 5 μm). Column chromatography (CC) was performed with silica gel (230–400 mesh, Merck, Germany) or macroporous absorptive resin D101 (250–300 μm, Tianjin Pesticide Factory, P.R. China). TLC was performed on aluminium sheet precoated with silica gel G_{60} (Merck, Germany). Spots were visualised under UV light or by spraying with 5% H_2SO_4 in EtOH followed by heating.

3.2. Plant material

Roots of *S. ningpoensis* were collected in August 2006 in Ningbo, Zhejiang province of China. The plant was identified by Dr. Guangmiao Fu and a voucher specimen (TCM-203) was deposited in the Biotechnology Research Institute of The Hong Kong University of Science and Technology.

3.3. Extraction and isolation

Dried roots of *S. ningpoensis* (4.3 kg) were crushed and extracted with 70% EtOH aqueous (3 x 10 L) for 2 h each time under refluxing condition. The combined extract solutions were concentrated *in vacuo* to give a residue (505 g), which was suspended in water (0.8 L), followed by successive extraction using petroleum ether (1 L x 3), EtOAc (1 L x 3) and *n*-BuOH (1 L x 3). The concentrated *n*-BuOH extract (126.4 g) was subject to macroporous absorptive resin D101 column chromatography (diameter 10 cm, height 60 cm) and eluted with solutions of EtOH/H_2O (0, 30%, 60%, 95%, each 3 L) to give 8 fractions (Frs. A-H). Fr. G (8.5 g) was subject to silica gel column chromatography (diameter 4 cm, height 20 cm), which was eluted with solutions of $CHCl_3$-MeOH-H_2O (5:95:0, 10:90:0.2, 15:85:0.5, 20:80:1, 25:75:2, 30:70:5, each 1 L) to give thirteen fractions (Frs. G1-G13). Fr. G4 (85 mg) was further purified by prep. RP-HPLC, which was eluted with 30% CH_3CN-H_2O to give compounds **1** (4.5 mg, t_R 13.5 min) and **2** (3.6 mg, t_R 10.2 min).

3.3.1. 8-O-(threo-2, 3-Dihydroxyl-3-phenyl-propionoyl)-harpagide (1)

Amorphous grayish powder; $[\alpha]_D^{25}$ − 10.4 (*c* = 0.19, CH_3OH); IR (film) ν_{max}: 3373, 2929, 1719, 1648, 1235, 1077 cm^{-1}; UV (CH_3OH): λ_{max} (log ε): 206 (2.45), 271 (1.86) nm; ^1H NMR (300 MHz, pyridine-d_5), δ_H: 6.69 (1H, s, H-1), 6.52 (1H, d, *J* = 6.0 Hz, H-3), 5.17 (1H, d, *J* = 6.0 Hz, H-4), 4.08 (1H, d, *J* = 4.2 Hz, H-6), 2.09 (1H, dd, *J* = 15.0, 4.2 Hz, H_a-7), 2.69 (1H, d, *J* = 15.0 Hz, H_b-7), 3.76 (1H, s, H-9), 1.70 (1H, s, H-10), 4.80 (1H, d, *J* = 7.5 Hz, H-2′), 5.35 (1H, d, *J* = 7.5 Hz, H-3′), 7.85 (2H, d, *J* = 7.8 Hz, H-5′, H-9′), 7.37 (2H, t, *J* = 7.5 Hz, H-6′, H-9′), 7.26–7.29 (1H, m, H-7′), 5.32 (1H, d, *J* = 9.0 Hz, H-1″), 3.99–4.04 (1H, m, H-2″), 4.28–4.29 (1H, m, H-3″), 4.27–4.29 (1H, m, H-4″), 3.99–4.02 (1H, m, H-5″), 4.53 (1H, d, *J* = 11.7 Hz, H_a-6″), 4.37 (1H, dd, *J* = 11.7, 4.8 Hz, H_b-6″); ^{13}C NMR (75 MHz, pyridine-d_5), δ_C: 93.9 (C-1), 141.6 (C-3), 108.4 (C-4), 73.2 (C-5), 77.0 (C-6), 44.9 (C-7), 88.2 (C-8), 55.0 (C-9), 22.3 (C-10), 173.5 (C-1′), 77.2 (C-2′), 75.8 (C-3′), 143.3 (C-4′), 128.0 (C-5′, C-9′), 128.1 (C-6′, C-8′), 127.5 (C-7′), 98.1 (C-1″), 74.6 (C-2″), 78.3 (C-3″), 71.3 (C-4″), 78.7 (C-5″), 62.3 (C-6″); HR-ESI-MS: *m/z* 551.1743 $[M + Na]^+$ (calcd for $C_{24}H_{32}NaO_{13}^+$: 551.1741).

3.3.2. cis-Sibirioside A (2)

Amorphous brown powder; $[\alpha]_D^{25}$ + 50.0 (*c* = 0.08, CH_3OH); IR (film) ν_{max}: 3377, 2930, 1700, 1633, 1056 cm^{-1}; UV (CH_3OH): λ_{max} (log ε): 203 (2.62), 216 (2.55), 279 (2.37) nm; ^1H NMR (300 MHz, CD_3OD), δ_H: 7.60–7.62 (2H, m, H-2, H-6), 7.33–7.36 (3H, m, H-3, H-4, H-5), 7.04 (1H, d, *J* = 12.6 Hz, H-7), 6.03 (1H, d, *J* = 12.6 Hz, H-8), 5.36 (1H, d, *J* = 3.3 Hz, H-1′), 3.38 (1H, dd, *J* = 9.6, 3.3 Hz, H-2′), 3.67–3.71 (1H, m, H-3′), 3.23–3.27 (1H, m, H-4′), 3.99–4.05 (1H, m, H-5′), 4.44 (1H, d, *J* = 11.7 Hz, H_a-6′), 4.25 (1H, dd, *J* = 11.7, 4.8 Hz, H_b-6′), 3.59–3.61 (1H, m, H-1″), 4.10 (1H, d, *J* = 8.4 Hz, H-3″), 3.96–4.02 (1H, m, H-4″), 3.77–3.93 (1H, m, H-5″), 3.73–3.79 (2H, m, H-6″); ^{13}C NMR (75 MHz, CD_3OD), δ_C: 136.2 (C-1), 130.9 (C-2, C-6), 129.1 (C-3, C-5), 130.1 (C-4), 144.8 (C-7), 120.1 (C-8), 167.8 (C-9), 93.4 (C-1′), 73.1 (C-2′), 74.5 (C-3′), 71.5 (C-4′), 71.9 (C-5′), 64.6 (C-6′), 64.1 (C-1″), 105.2 (C-2″), 79.1 (C-3″), 75.9 (C-4″), 83.9 (C-5″), 63.9 (C-6″); HR-ESI-MS: *m/z* 495.1475 $[M + Na]^+$ (calcd for $C_{21}H_{28}NaO_{12}^+$: 495.1478).

3.4. Acid hydrolysis

The acid hydrolysis of the glycoside was performed according to the literature (Nord & Kenne 1999). Briefly, The isolate **2** (1.0 mg) were hydrolysed in 2 M CF_3COOH (0.5 mL) at 120 °C for 1 h, respectively. Then the solvent was removed by blowing with N_2 to give a residue, to which 1 M NH_4OH (0.2 mL) was added, followed by the addition of the solution of $NaBH_4$ (4 mg) in 1 M NH_4OH (0.3 mL). The mixture then was reacted at 40 °C for 1 h. Excess $NaBH_4$ was quenched with 0.5 mL AcOH and the boric acid formed was removed by co-distillation with 10% AcOH in MeOH (3 x 0.5 mL) followed by MeOH (3 x 0.5 mL). The resulting alditols were acetylated using Ac_2O-Pyridine (1:1, 0.6 mL) at 120 °C for 40 min. Then the solvent was evaporated by blowing with N_2, the resulting residue was extracted with DCM (0.5 mL). The obtained DCM solution was subject to GC analysis under the following conditions: HP 6850 gas chromatograph equipped with an FID detector. Column: HP-1 column (30 m x 0.25 mm x 0.25 µm). Column temperature: 170 °C. Carrier gas: H_2 (2.0 mL/min). Injector and detector temperature: 220 °C/300 °C. Injection volume: 1µL. GC analysis showed the presence of glucose (t_R 12.44 min) and fructose (t_R 11.93 min and 12.44 min) in **2** with a

ratio of 1:1. Retention time of the authentic samples after being treated with the same procedure as that of **2**, were detected at 12.44 min for D-glucose, 11.93 min and 12.44 min for D-fructose.

3.5. Antifouling assay

The antifouling assay was evaluated according to the procedure reported previously (Zhang et al. 2014). Briefly, Fresh cyprids of the barnacle *Balanus amphitrite* were used in the testing. Larval settlement assays were examined using 24-well polystyrene plates with Sea-Nine 211^{TM} (4,5-dichloro-2-n-octyl-4-iso-thiazolin-3-one) being served as positive control. The tested samples and Sea-Nine 211^{TM} were dissolved with small amount of dimethyl sulfoxide (DMSO) and then diluted with 0.22 μm filtered seawater (FSW) to achieve the final concentrations of 25.0, 12.5, 6.25, 3.13 and 1.56 μg/mL. About 15–20 competent larvae were added to each well containing 1 mL of test solution in triplicate, with wells having only FSW, DMSO and larvae being served as negative control. The plates were incubated at 25 °C for 48 h, followed by being examined under a microscope to count settled, unsettled larvae and where appropriate, potential toxic effects were recorded. The number of settled larvae was expressed as a percentage of the total number of larvae per well. The EC_{50} was calculated as the concentration where 50% of the larval individuals were inhibited to settle as compared to the control, while LC_{50} was calculated as the concentration where 50% of the larval population was dead.

4. Conclusions

In summary, as part of our searching for bioactive metabolites from natural resources, the versatile herb *S. ningpoensis* was selected and chemically investigated, leading to the identification of one new iridoid glycoside, namely 8-*O*-(*threo*-2, 3-dihydroxyl-3-phenyl-propionoyl)-harpagide (**1**), along with a new cinnamoyl glycoside named as *cis*-sibirioside A (**2**). Structurally, compound **1**, containing a *threo*-2, 3-dihydroxyl-3-phenyl-propionoyl group which is unusual within natural products, is interesting, to the best of our knowledge, this is the first report of natural products containing this kind of group. Biologically, compound **1** exhibits moderate antifouling effect against the settlement of *Balanus amphitrite* larvae with IC_{50} being 13.5 μg/mL and LC_{50} > 25 μg/mL, being a potential lead compound for further investigation.

Disclosure statement

No potential conflict of interest was reported by the authors

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References

Chen X, Liu YH, Chen P. 2007. Iridoid glycosyl esters from *Scrophularia ningpoensis*. Nat Prod Res. 21:1187–1190.

Chen B, Liu Y, Liu HW, Wang NL, Yang BF, Yao XS. 2008. Iridoid and aromatic glycosides from *Scrophularia ningpoensis* Hemsl. and their inhibition of [Ca^{2+}] increase induced by KCl. Chem Biodivers. 5:1723–1735.

Hada S, Hattori M, Tezuka Y, Kikuchi T, Namba T. 1988. New neolignans and lignans from the aril of *Myristica fragrans*. Phytochemistry. 27:563–568.

Huang X, Xu Y, Zhang YF, Zhang Y, Wong YH, Han Z, Yin Y, Qian P. 2014. Nontoxic piperamides and their synthetic analogues as novel antifouling reagents. Biofouling. 30:473–481.

Kajimoto T, Hidaka M, Shoyama K, Nohara T. 1989. Iridoids from *Scrophularia ningpoesis*. Phytochemistry. 28:2701–2704.

Kim SR, Kim YC. 2000. Neuroprotective phenylpropanoid esters of rhamnose isolated from roots of *Scrophularia buergeriana*. Phytochemistry. 54:503–509.

Kim SR, Lee KY, Koo KA, Sung SH, Lee NG, Kim J, Kim YC. 2002. Four new neuroprotective iridoid glycosides from *Scrophularia buergeriana* roots. J Nat Prod. 65:1696–1699.

Kitagawa I, Nishimura T, Takei M, Yosioka I. 1967. On the iridoid constituent isolated from the roots of *Scrophularia buergeriana*. Chem Phar Bull. 15:1254–1256.

Li YM, Jiang SH, Gao WY, Zhu DY. 1999. Iridoid glycosides from *Scrophularia ningpoensis*. Phytochemistry. 50:101–104.

Li YM, Jiang SH, Gao WY, Zhu DY. 2000a. Phenylpropanoid glycosides from *Scrophularia ningpoensis*. Phytochemistry. 54:923–925.

Li YM, Han ZH, Jiang SH, Jiang Y, Yao SD, Zhu DY. 2000b. Fast repairing of oxidized OH radical adducts of dAMP and dGMP by phenylpropanoid glycosides from *Scrophularia ningpoensis* Hemsl. Acta Pharmacol Sin. 21:1125–1128.

Li J, Huang XY, Du XJ, Sun WJ, Zhang YM. 2009. Study of chemical composition and antimicrobial activity of leaves and roots of *Scrophularia ningpoensis*. Nat Prod Res. 23:775–780.

Li Y, Wu H, Xu Y, Shao C, Wang C, Qian P. 2013. Antifouling activity of secondary metabolites isolated from Chinese marine organisms. Mar Biotechnol. 15:552–558.

Lin WH, Wang TX, Cai MS, Shang EN. 1995. Structures of new cinnamoyl glucoside from the roots of *Veronicastrum sibiricum*. Acta Pharm Sin. 30:752–756.

Minch MJ. 1994. Orientational dependence of vicinal proton-proton NMR coupling constants: The Karplus relationship. Concept Magn Reson A. 6:41–56.

Nguyen AT, Fontaine J, Malonne H, Claeys M, Luhmer M, Duez P. 2005. A sugar ester and an iridoid glycoside from *Scrophularia ningpoensis*. Phytochemistry. 66:1186–1191.

Niu ZR, Wang RF, Shang MY, Cai SQ. 2009. A new iridoid glycoside from *Scrophularia ningpoensis*. Nat Prod Res. 23:1181–1188.

Nord L, Kenne L. 1999. Separation and structural analysis of saponins in a bark extract from *Quillja saponaria* Molina. Carbohydr Res. 320:70–81.

Qi J, Chen J, Cheng Z, Zhou J, Yu B, Qiu SX. 2006. Iridoid glycosides from *Harpagophytum procumbens* D.C. (devil's claw). Phytochemistry. 67:1372–1377.

Qian J, Hunkler D, Rimpler H. 1992. Iridoid-related aglycone and its glycosides from *Scrophularia ningpoensis*. Phytochemistry. 31:905–911.

Ramunno A, Serrilli AM, Piccioni F, Serafini M, Ballero M. 2006. Taxonomical markers in two endemic plants of Sardinia: *Verbascum conocarpum* and *Scrophularia trifoliata*. Nat Prod Res. 20:511–516.

Sagare AP, Kuo CL, Chueh FS, Tsay HS. 2001. De novo regeneration of *Scrophularia yoshimurae* Yamazaki (Scrophulariaceae) and quantitative analysis of harpagoside, an iridoid glucoside, formed in aerial and underground parts of in vitro propagated and wild plants by HPLC. Biol Pharm Bull. 24:1311–1315.

Sung SH, Huh MS, Kim YC. 2001. New tetrahydrofuran-type sesquilignans of *Saururus chinensis* root. Chem Pharm Bull. 49:1192–1194.

Venditti A, Frezza C, Riccardelli M, Foddai S, Nicoletti M, Serafini M, Bianco A. 2016. Secondary metabolites from *Scrophularia canina* L. Nat Prod Res. 30:1665–1669.

Wang H, Xu Y, Yan J, Zhao X, Sun X, Zhang Y, Guo J, Zhu C. 2009. Acteoside protects human neuroblastoma SH-SY5Y cells against beta-amyloid-induced cell injury. Brain Res. 1283:139–147.
Wang K, Xu Y, Lu L, Li Y, Han Z, Zhang J, Shao C, Wang C, Qian P. 2015. Low-toxicity diindol-3-ylmethanes as potent antifouling compounds. Mar Biotechnol. 17:624–632.
Zhang J, Liang Y, Liao X, Deng Z, Xu S. 2014. Isolation of a new butenolide from the South China Sea gorgonian coral *Subergorgia suberosa*. Nat Prod Res. 28:150–155.
Zhang J, Ip FCF, Tong EPS, Chan KW, Li L, Ng YP, Ip NY. 2015. Ningpoensines A-C: unusual zwitterionic alkaloids from Scrophularia ningpoensis. Tetrahedron Lett. 56:5453–5456.
Zou C, Yang X. 2000. A new iridoid glucoside from ningpo fig-wort (*Scrophularia ningpoensis*). Chin Tradit Herb Drugs. 31:241–243.