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Soluble epoxide hydrolase inhibitory activity of anthraquinone components from *Aloe*

Ya Nan Sun [a], Jang Hoon Kim [b], Wei Li [c], A. Reum Jo [a], Xi Tao Yan [d], Seo Young Yang [a], Young Ho Kim [a,*]

[a] College of Pharmacy, Chungnam National University, Daejeon 305-764, Republic of Korea
[b] Virology Unit, Department of Horticultural Environment, National Institute of Horticultural and Herbal Science, RDA, Wanju-gun 440-310, Republic of Korea
[c] School of Biotechnology, Yeungnam University, Gyeongsan, Gyeongbuk 712-749, Republic of Korea
[d] Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Science, Northwest A & F University, Yangling 712100, Shaanxi, China

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ABSTRACT

Aloe is a short-stemmed succulent herb widely used in traditional medicine to treat various diseases and as raw material in cosmetics and heath foods. In this study, we isolated and identified two new anthraquinone derivatives, aloinoside C (**6**) and aloinoside D (**7**), together with six known compounds from an aqueous dissolved *Aloe* exudate. Their structures were identified by spectroscopic analysis. The inhibitory effects of the isolated compounds on soluble epoxide hydrolase (sEH) were evaluated. Compounds **1**–**8** inhibited sEH activity potently, with IC_{50} values ranging from 4.1 ± 0.6 to 41.1 ± 4.2 μM. A kinetic analysis of compounds **1**–**8** revealed that the inhibitory actions of compounds **1**, **6** and **8** were non-competitive, whereas those of compounds **2**–**5** and **7** were the mixed-type. Molecular docking increases our understanding of receptor–ligand binding of all compounds. These results demonstrate that compounds **1**–**8** from *Aloe* are potential sEH inhibitors.

1. Introduction

Aloe (Liliaceae) is a succulent herb distributed widely in Europe, Asia, and the southern parts of North America. It has a long history of use as a traditional herbal medicine for treating burns, psoriasis symptoms, and hyperlipidemia.[1] The *Aloe* leaf contains more than 200 nutritional substances, including vitamins, minerals, amino acids, and active enzymes, which work in synergy to bring about these biological and healing effects.[2] *Aloe* is also used as a food product and beverage ingredient. It is popularly used in functional foods and in nutraceuticals in China, Korea, Japan, and some European countries.[3]

The primary phytochemical constituents of *Aloe* are chromones,[4] anthraquinones,[5] and pyrones.[6] Some of these constituents have multiple biological properties, such as, anti-tumor,[7] antioxidant,[8] anti-inflammatory,[9] anti-aging,[10] and anti-diabetic properties.[11] The bioactive components of *Aloe*, called chromones from exhibit potent antioxidative, anti-inflammatory and mushroom tyrosinase inhibitory activities.[12,13] Anthraquinone derivatives have a cathartic effect and significant increased in the water content of the rat large intestine[14] and have strong antitumor activity against MCF-7 breast cancer and MDA-MB-231 cancer cells. The unusual malic acid acylated carbohydrates have effects on cell proliferation and the expression of proinflammatory cytokine genes, such as interleukin (IL)-6, IL-8 and intercellular adhesion molecule 1 (ICAM-1).[15–17] *Aloe* extract appeared to be an anti-diabetic and anti-lipidemic agent in streptozotocin-induced type 2 diabetic model rats.[18–21] However, the soluble epoxide hydrolase (sEH) inhibitory activities of the *Aloe* components have not been reported.

Soluble epoxide hydrolase (sEH) is a member of the epoxide hydrolase family and is found primarily in the cytosol and peroxisomes of mammalian tissues including the liver, kidneys, intestines and vascular tissues.[22–25] It catalyzes the hydrolysis of epoxyeicosatrienoic acids (EETs) into the corresponding dihydroxyeicosatrienoic acids (DHETs). Accumulating preclinical and epidemiological evidence suggests that the modulation of cytochrome P450 (CYP)-mediated eicosanoid metabolism is a novel therapeutic approach for treating chronic inflammatory and cardiovascular diseases.[26] EETs are epoxidized lipids derived from arachidonic acid (AA) by the action of cytochrome P450; they possess anti-inflammatory properties and are involved in vasodilatation and vasoprotection, and regulate of cardiac blood pressure.[27–29] These properties suggest that EETs are associated with pain modulation and psychosis. EETs also suppress the tonic component of seizure-related excitability by modulating gamma-aminobutyric acid (GABA) activity. Additionally, EETs are known

* Corresponding author. Tel.: +82 42 821 5933; fax: +82 42 823 6566.
E-mail address: yhk@cnu.ac.kr (Y.H. Kim).

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to play vital roles in calcium-activated potassium (BK) channel activities, preoxisome proliferator activated receptor (PPAR α and PPAR γ) activation, and nuclear factor kappa B (NF-κB) inhibition, which are believed to be inherently associated with anti-hypertensive and cardiovascular protective effects. Therefore, regulating of blood EET levels by inhibiting sEH has attracted considerable attention as a promising strategy for treating certain cardiovascular events.[30–33,22] Since EETs are converted into inactive DHETs by sEH, sEH inhibitors may be a useful therapy for these diseases. Potent urea-based sEH inhibitors developed in a previous pharmacology study exhibited poor solubility and relatively short durations of action. Therefore, structurally novel compounds possessing sEH inhibitory activity are needed.

2. Results and discussion

2.1. Identification of compounds 1–8

In the current study, two new (**6** and **7**) and six known anthraquinone derivatives (**1**–**5** and **8**) were isolated from an aqueous dissolved *Aloe* exudate (Fig. 1). Their structures were identified as follows: aloe emodin (**1**),[35] aloin A (**2**),[36] aloin B (**3**),[36] desoxyaloin (**4**),[37] aloinoside B (**5**),[38] aloinoside C (**6**), aloinoside D (**7**), and elgonica dimer A (**8**).[39]

Compound **6** was a yellow amorphous solid, $[\alpha]_D^{25}$: −17.6 (*c* 0.05, MeOH); its molecular formula was $C_{26}H_{30}O_{12}$ based on the HR-ESI-MS peak at *m*/*z* 557.1650 ($[M+Na]^+$, calcd for 557.1635). The ^{1}H NMR spectra of **6** (Table 1) revealed the presence of five aromatic protons that were grouped according to coupling and splitting. The signals showed one *meta*-coupled aromatic proton spin system: δ_H 7.03 (1H, br s, H-5) and 6.80 (1H, br s, H-7) were divided into an A ring; and three ortho-coupled aromatic protons signals at δ_H 6.81 (1H, d, J = 8.4 Hz, H-2), 7.47 (1H, dd, J = 8.4, 7.5 Hz, H-3), and 6.82 (1H, d, J = 7.5 Hz, H-4) were in the B ring. One methine signal at δ_H 4.60 (1H, s, H-10), and methylene signals at δ_H 4.64 (1H, d, J = 1.2 Hz, H-11) and 4.53 (1H, d, J = 1.2 Hz, H-11) were also seen in the ^{1}H NMR spectrum. Analyses of the ^{13}C NMR and DEPT spectrum of **6** showed 26 carbon resonances. There was one carbonyl signal at δ_C 195.7, one methine signal at δ_C 45.5, and twelve aromatic carbon signals between δ_C 115.9 and 163.6 in the ^{13}C NMR spectrum, indicating that this compound should have an oxanthrone skeleton. In addition, nine signals from δ_C 69.9 to 87.9 and other two signals at δ_C 101.1 and 18.2 indicated that compound **6** possessed two sugar moieties. After acid hydrolysis, these sugar units were identified as xylose and rhamnose compared with a reference.[38] Moreover, there was a methylene signals showed at δ_C 68.2 in the ^{13}C NMR spectrum. Methylene signals at δ_H 4.64 and 4.53 in the ^{1}H NMR spectrum the correlation of these signals with

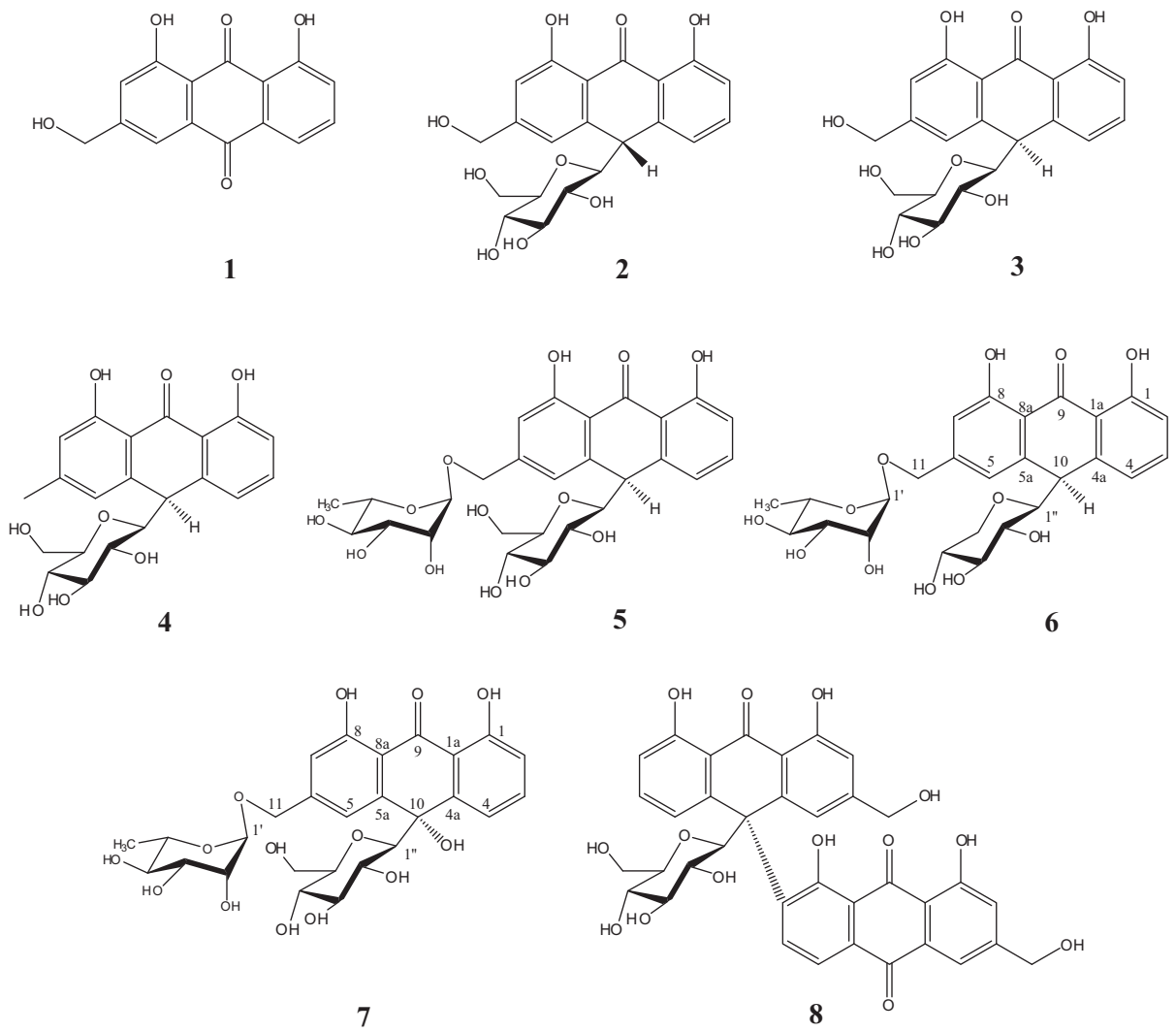

Figure 1. Structures of compounds **1**–**8** from *Aloe*.