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Natural phosphodiesterase-4 inhibitors from the leaf skin of *Aloe barbadensis* Miller

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ABSTRACT

The ethanolic extract of *Aloe barbadensis* Miller leaf skin showed inhibitory activity against phosphodiesterase-4D (PDE4D), which is a therapeutic target of inflammatory disease. Subsequent bioassay-guided fractionation led to the isolation of two new anthrones, 6′-*O*-acetyl-aloin B (**9**) and 6′-*O*-acetyl-aloin A (**11**), one new chromone, aloeresin K (**8**), together with thirteen known compounds. Their chemical structures were elucidated by spectroscopic methods including UV, IR, 1D and 2D NMR, and HRMS. All of the isolates were screened for their inhibitory activity against PDE4D using tritium-labeled adenosine 3′,5′-cyclic monophosphate (^{3}H-cAMP) as substrate. Compounds **13** and **14** were identified as PDE4D inhibitors, with their IC_{50} values of 9.25 and 4.42 μM, respectively. These achievements can provide evidences for the use of *A. barbadensis* leaf skin as functional feed additives for anti-inflammatory purpose.

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1. Introduction

Aloe barbadensis Miller, also known as “true aloe”, is a medicinal and edible plant widely distributed in Europe, Asia and southern parts of North America [1,2]. In general, its leaf can be divided into three major parts, the outer green leaf skin, the inner clear pulp and the bitter yellow exudate secreted by vascular bundles [3]. The pulp (aloe gel) is widely used for cosmetics, beverage and nutraceutical [4], and the exudate composed of phenolic compounds [5] has a long history of medical use such as being a laxative [6], anti-oxidant [7] and anti-cancer agents [8]. Instead, it seems that the leaf skin part of *A. barbadensis* is regarded as solid waste generated during the processing. Excitingly, recent studies and our preliminary experiments have demonstrated that *A. barbadensis* leaf skin extract could serve as functional feed additives for immunity enhancement and anti-inflammatory purposes [9], which makes it possible to turn trash into treasure. However, the compositions of *A. barbadensis* leaf skin have rarely been reported. For further studies, it is urgent to clarify its chemical constituents and corresponding bioactivity.

The phosphodiesterases (PDEs) are a superfamily of enzymes that catalyze the hydrolysis of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [10]. Among the eleven PDE families categorized by the human genome encoding, the cAMP-specific PDE4, which is mainly distributed

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in immune and inflammatory cells, has gained increasing attention [11]. PDE4 is involved in inflammatory responses and is proven as targets for the treatments of chronic obstructive pulmonary disease (COPD), asthma and central nervous system (CNS) disease [12–14]. Recent research also demonstrated that PDE4 is bound up with anti-aging, reducing stroke risk, and treating memory loss associated with Alzheimer's disease [15–17], which make it a research hotspot.

Our previous report indicated that *A. barbadensis* extract and several compounds possessed anti-inflammatory properties through inhibiting the activity of PDE4D [18]. In continuation, it was found that the ethanolic extract of *A. barbadensis* leaf skin showed similar effects as well. Subsequent phytochemical investigation led to the isolation of two new anthrones (**9** and **11**), one new chromone (**8**), together with thirteen known compounds (Fig. 1). All of the isolates were screened for their inhibitory activity against PDE4D. As a result, compounds **13** and **14** were identified as PDE4 inhibitors, with their IC_{50} values less than 10 μM. Herein, the details of the isolation, structural elucidation and the PDE4 inhibitory activity assay of these compounds are described.

2. Experimental

2.1. General

Optical rotations were measured on a Rudolph Autopol I automatic polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA) with MeOH as solvent. UV spectra were recorded on a Shimadzu UV2457 spectrophotometer (Kyoto, Japan) and IR spectra were obtained with a Bruker Tensor 37 FT-IR spectrophotometer (Bruker Optics Inc., Billerica, MA, USA) with KBr pellets. NMR spectra were acquired using a Bruker AVANCE 400 spectrometer (Bruker Biospin GmbH, Rheinstetten, Germany) and chemical shifts (δ) were given in ppm with TMS as internal standard. ESIMS data were determined on a TSQ Quantum mass spectrometer (Thermo Finnigan LLC, San Jose, CA, USA) and high-resolution mass spectra (HRMS) were obtained on a Shimadzu LCMS-IT-TOF hybrid mass spectrometer (Kyoto, Japan). Semi-preparative RP-HPLC was performed on a Shimadzu LC-20AT liquid chromatography system (Kyoto, Japan) equipped with two LC-20AT pumps and a dual wavelength UV-VIS detector monitoring at 300 and 355 nm. A semi-preparative ODS-A column (250 × 10 mm i.d., 5 μm, YMC Co., Ltd., Kyoto, Japan) was employed for the separation at a flow rate of 3.0 mL min^{-1}. Reversed-phase flash chromatography (RP-FC) was achieved on a Biotage Isolera flash purification system (Biotage AB, Uppsala, Sweden) coupled with an Eyela glass column (300 × 20 mm i.d., Tokyo, Japan) packed with RP-C_{18} gel (20–40 μm, Fuji Silisia Chemical Ltd., Nagoya, Japan). Silica gel (300–400 mesh) used for column chromatography was produced by Qingdao Marine Chemical Co., Ltd. (Qingdao, China). Thin layer chromatography (TLC) was carried out on silica gel G precoated plates (Qingdao Marine Chemical Co., Ltd., Qingdao, China) and spots were visualized under UV 254 and/or 365 nm or by spraying with

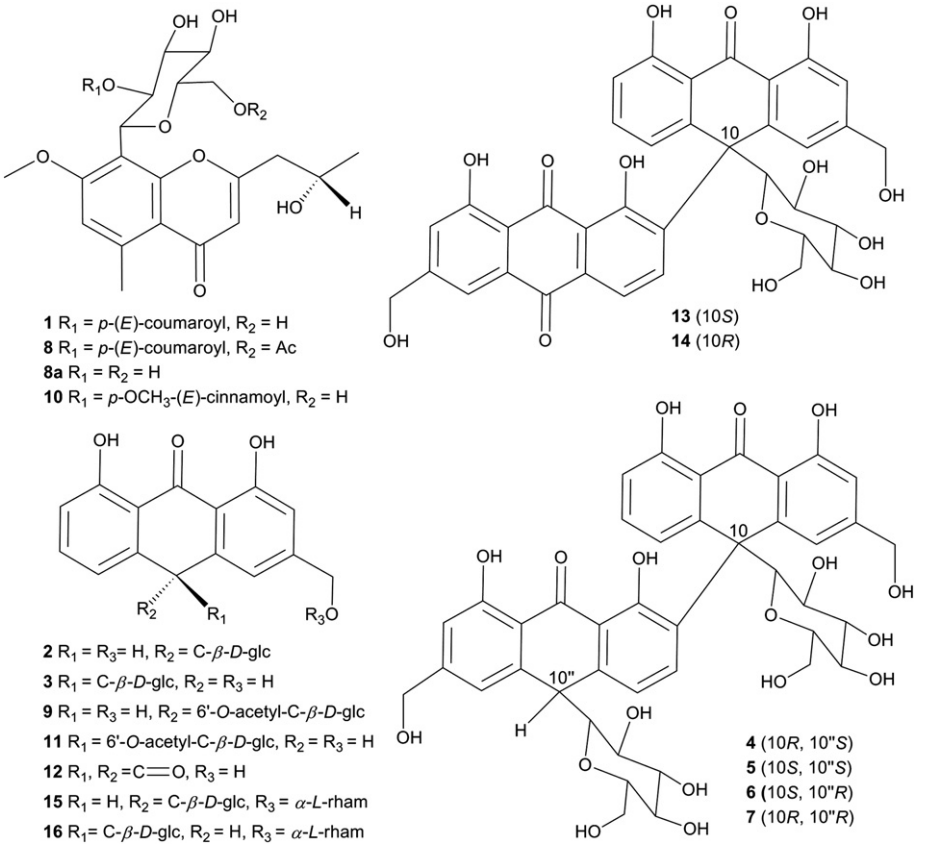

Fig. 1. Chemical structures of compounds **1**–**16**.

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