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# Antiplasmodial activity of cucurbitacin glycosides from *Datisca glomerata* (C. Presl) Baill

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ABSTRACT

The traditionally used antimalarial plant, *Datisca glomerata* (C. Presl) Baill, was subjected to antiplasmodial assay guided fractionation. This led to the isolation of seven cucurbitacin glycosides, datiscosides I–O, along with two known compounds, datiscoside and datiscoside B, from the aerial parts of *D. glomerata*. Their structures and relative stereochemistry were determined on the basis of mass spectrometry, 1D and 2D NMR spectroscopic data. Antiplasmodial $IC_{50}$ values were determined for all isolated compounds against a chloroquine sensitive strain of *Plasmodium falciparum* (D10), which were also evaluated *in vitro* for their antileishmanial activity against *Leishmania tarentolae*. Cytotoxicity was evaluated against rat skeletal muscle cells (L6) and Chinese ovarian hamster cells (CHO). The antiplasmodial activity of the compounds was moderate and ranged from 7.7 to 33.3 μM. None of the compounds showed appreciable antileishmanial activity. The compounds displayed cytotoxicity against L6 but not CHO mammalian cells.


## 1. Introduction

Malaria is a devastating parasitic disease that causes over 200 million infections and 600,000 deaths a year (World Health Organization, 2011). Increased resistance to currently used antimalarial therapies signifies an urgent need to discover and develop novel drugs. Plants are widely used as a first line remedy for the infection in malaria-endemic areas (Bourdy et al., 2008) and many have served as a source of novel antimalarial compounds (Kaur et al., 2009). While malaria is not a present day concern in North America, it was once a major threat to the people of the continent who have historically turned to plants for treatment (Hasegawa, 2007). In a continuation of our ongoing investigation of traditionally used antimalarial plants of North America for novel antimalarial compounds (Grace et al., 2010; Graziose et al., 2011, 2012), the aim of this study was to evaluate the antiplasmodial activity of *Datisca glomerata* (C. Presl) Baill, commonly known as durango root.

*D. glomerata* (Datiscaceae), is a functionally androdioecious (Listen et al., 1990) perennial herb that inhabits riparian environments in California, Baja California and other parts of the southwestern United States (Davidson, 1973). *D. glomerata* was used by the Native Americans as an external wash for sores, as a sore throat remedy, and occasionally to treat fevers (Moerman, 2009). *Datisca cannibina*, the only other species of the family Datiscaceae, is found in central Asia and northern India (Davidson, 1973) and has been traditionally considered as a substitute to quinine (Bradley et al., 1799). During World War II, it was shown that a crude extract of *D. glomerata* had potent *in vivo* antimalarial properties in white leghorn chicks infected with *Plasmodium gallinaceum* (Spencer et al., 1947).

As a member of the cucurbitales, *D. glomerata* is known to produce chemical compounds of the cucurbitacin class, and previous reports have described unique cucurbitacin glycosides from *D. glomerata* aptly named the datiscosides (Kupchan et al., 1972; Sasamori et al., 1983). The first cucurbitacin reported from *D. glomerata*, named datiscoside (**1**), was isolated as an antileukemic principle in 1972 (Kupchan et al., 1972) and its molecular structure and absolute configuration were confirmed by X-ray crystallography (Restivo et al., 1973) (see Fig 1). Datiscoside (**1**) is the 16-*O*-(2′-*O*-acetyl-6′-deoxy-α-L-*gluco*-hex-3′-ulopyranoside) of cucurbitacin D. The unique structure of datiscoside (**1**) prompted a further investigation of the chemistry of *D. glomerata*, which yielded an

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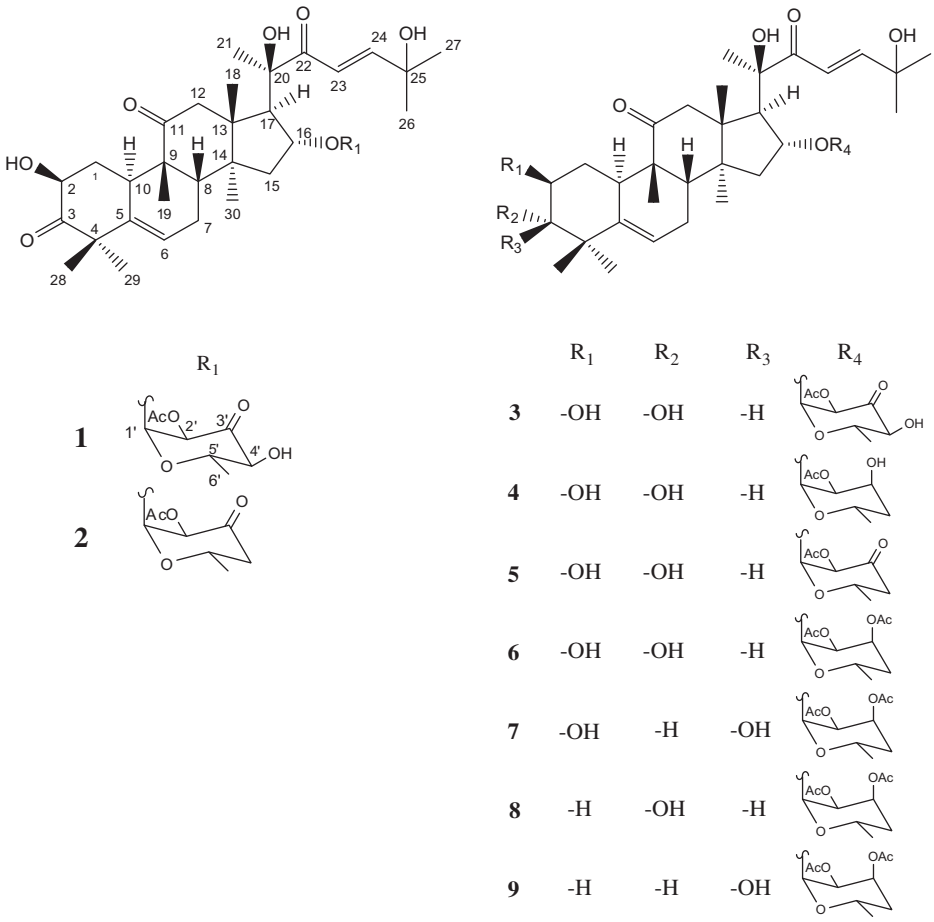


**Fig. 1.** Structures of the isolated compounds.

additional seven cucurbitacin glycosides, named datiscoside B-H-along with datiscoside (**1**) and the aglycones cucurbitacin D and F as well as cucurbitacin B (Sasamori et al., 1983).

Cucurbitacins are known to be cytotoxic (Chen et al., 2005), and there have been reports of livestock poisoning following consumption of *D. glomerata* (Galey et al., 1990). However, species of Cucurbitaceae have a long history of medicinal use for various ailments supporting the therapeutic value of cucurbitacins. Interestingly, few reports have been published assessing the antimalarial potential of cucurbitacins, despite the widespread traditional use of species of the cucurbitales to treat malaria (Bourdy et al., 2008).

This work describes the antiplasmodial assay guided fractionation of the aerial parts of *D. glomerata*. The present work yielded seven novel cucurbitacin glycosides, named datiscosides I–O (**2**, **4**–**9**) along with two known compounds, datiscoside (**1**) and datiscoside B (**3**). The isolation and structure elucidation as well as the antiplasmodial, antileishmanial and cytotoxic activity of these compounds is discussed.

## 2. Results and discussion

### 2.1. Compound characterization

The methanol extract of the dried aerial parts of *D. glomerata* was suspended in water and successively partitioned with hexane, ethyl acetate and 2-butanol. The ethyl acetate and 2-butanol fractions were combined and subjected to bioassay guided fractionation against the chloroquine sensitive strain *Plasmodium falciparum* (D10), which led to the isolation of nine cucurbitacin glycosides (**1**–**9**). Compounds **1** and **3** were identified as datiscoside and datiscoside B by comparing their spectroscopic data with the data reported in the literature (Kupchan et al., 1972; Restivo et al., 1973; Sasamori et al., 1983) (see Tables 1 and 2 and Fig 1).

Compound **2** was assigned a molecular formula $C_{38}H_{54}O_{11}$ based on its HR-ESI-TOFMS signal at *m*/*z* 709.3576 $[M+Na]^+$. The molecular weight of **2** was less than that of **1** by 16 mass units suggesting one less oxygen atom. The $^1H$ and $^{13}C$ NMR spectroscopic data showed eight methyl singlets, an olefinic proton, two *trans*-coupled olefinic protons, three carbonyls, and three oxygenated functions indicating a cucurbitacin triterpene-type structure, which was similar to cucurbitacin D, the aglycone of **1** (Sasamori et al., 1983). However, the NMR spectra suggested that **2** possessed a different sugar moiety. The downfield shifts of H-1′($\delta_H$ 5.29) and H-2′ ($\delta_H$ 5.18) in the $^1H$ NMR spectrum suggested that C-2′ was linked to an acetoxy group, similar to that of **1**. This was corroborated by the data obtained from the HMBC spectrum, which showed a correlation of H-2′ to the acetoxy carbonyl attached at C-2′. The coupling constant between H-1′ and H-2′ (4 Hz), suggested an equatorial (H-1′)-axial (H-2′) orientation (Bubb, 2003), similar to that of **1** (Sasamori et al., 1983). The HMBC spectrum also showed a correlation between both H-1′ and H-2′ and the C-3′ carbonyl group. The $^1H$ NMR spectrum displayed an upfield shift of H-4′ eq ($\delta_H$ 2.40) and H-4′ ax ($\delta_H$ 2.39), while H-5′ appeared slightly shifted downfield ($\delta_H$ 3.82) compared to **1**. In the $^{13}C$ NMR spectrum, the C-4′ was shifted upfield ($\delta_C$ 48.5), compared to that of **1** ($\delta_C$ 78.0), which, along with the DEPT NMR data confirmed that C-4′ was missing the hydroxyl group. Therefore, it was confirmed