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An ellagitannin, *n*-butyl gallate, two aryltetralin lignans, and an unprecedented diterpene ester from *Pelargonium reniforme*

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Abstract

The structural diversity of the metabolic pool of *Pelargonium reniforme* was extended by the characterization of the $^1C_4$-glucose based ellagitannin pelargoniin E, gallic acid *n*-butyl ester, (−)-4,4′,9′-trihydroxy-3′,5′-dimethoxy-2,7′-cyclolignan 9-*O*-β-glucopyranoside and reniformin, a diterpene ester comprised of a diterpene acid with an uncommon –$(CH_2)_2$– bridging element linked to 2-(4-hydroxyphenyl)ethansulfonic acid. These metabolites were associated with the known (α,β)-3,4-di-*O*-galloyl-glucopyranoside, 4,6-dihydroxy-2β-glucopyranosyloxyacetophenone, 1-*O*-galloylglycerol, 6′-*O*-galloylsalidroside and (+)-isolariciresinol-9′-*O*-β-glucopyranoside. All structures were established on the basis of spectroscopic methods.

Keywords: *Pelargonium sidoides*; Ellagitannin; Pelargoniin E; Diterpene; Reniformin; Butyl gallate; Aryltetralin lignans

1. Introduction

The pink-flowered *Pelargonium reniforme* CURT. (Geraniaceae), mainly distributed in coastal regions of southern Africa, is an attractive erect shrub and has a long tradition as herbal medicine (Watt and Breyer-Brandwijk, 1962; Hutchings, 1996). Following its therapeutic use in traditional and modern phytomedicine for the treatment of upper respiratory tract infections (Kolodziej and Kiderlen, 2007), this medicinal plant continues to be the subject of extensive studies to identify the underlying active principle(s). The metabolic pool of. *P. reniforme* exhibited remarkable diversity and complexity. Our recent systematic examination has revealed the presence of a notable wealth of highly oxygenated simple coumarins (Latté et al., 2000), ellagitannins with a $^1C_4$ glucose core (Latté and Kolodziej, 2000) and *O*-galloyl *C*-glycosylflavones (Latté et al., 2002). The coumarins and phenolic constituents are of particular interest, displaying moderate antibacterial and fairly high immunomodulatory properties (Kayser and Kolodziej, 1997; Kayser et al., 2001). In our continuing work on this plant, we have discovered three new phenolic metabolites, the corilagin-based ellagitannin pelargoniin E (**1**), *n*-butyl gallate (**2**), and (−)-4,4′,9-trihydroxy-3′,5′-dimethoxy. 2,7′-cyclolignan 9-*O*-β-glucopyranoside (**3**) from the aerial parts, and a novel diterpene ester, reniformin (**5**), from the roots of *P. reniforme*. The former metabolites were associated with five rarely reported compounds (**4**, **6**–**9**). The current paper reports the isolation and structure elucidation of the new natural products.

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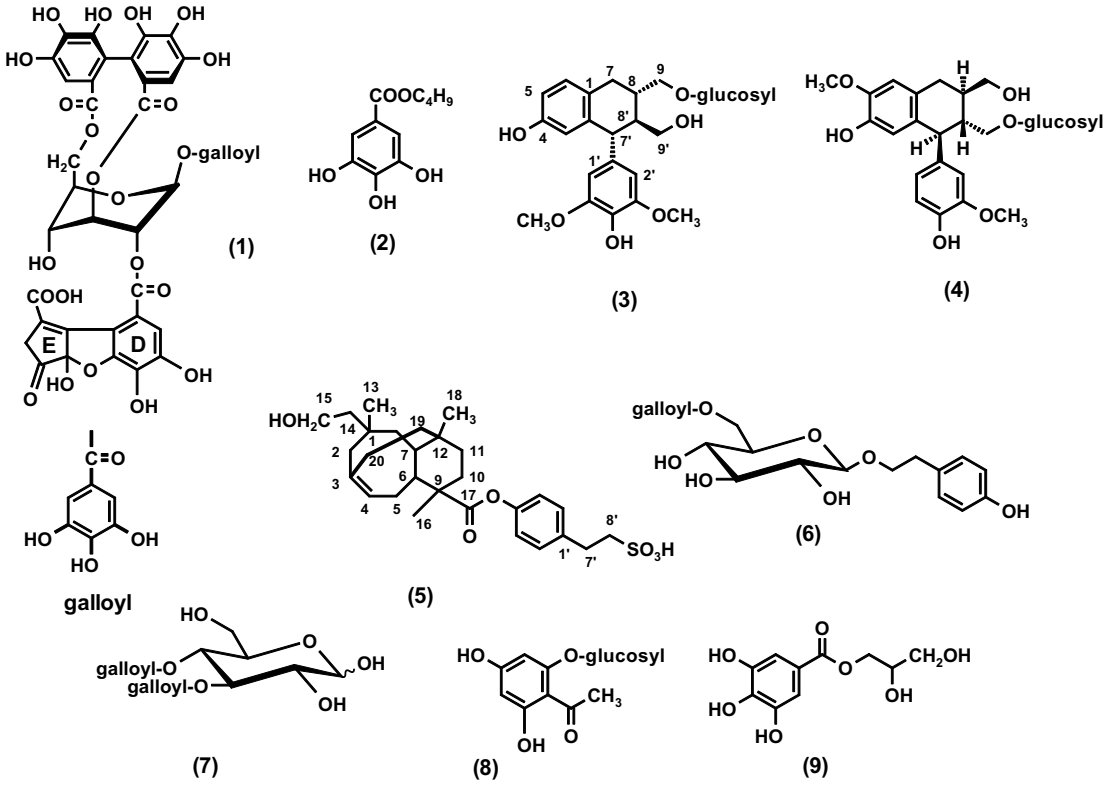

2. Results and discussion

An aqueous acetone extract of the aerial parts of *P. reniforme* was successively extracted with petroleum ether, chloroform and ethyl acetate. The ethyl acetate soluble portion was subjected to repeated chromatography on Sephadex LH-20 using water-methanol gradients. Final purification by semi-preparative HPLC yielded three new natural products, the ellagitannin pelargoniin E (**1**), *n*-butyl gallate (**2**), and the aryltetralin lignan **3** along with five known compounds (**4**, **6**–**9**) obtained for the first time from this plant source.

Compound **1** was readily shown to be an ellagitannin by the characteristic coloration with $FeCl_3$ (blue), potassium iodate (pink) (Haslam, 1965) and sodium nitrite/acetic acid (blue) (Bate-Smith, 1972). Its FAB-MS showed an $[M+Na]^+$ peak at *m/z* 947, reminiscent of pelargoniin A and phyllantusiin C, representing oxidatively modified metabolites of geraniin (Latté and Kolodziej, 2000; Yoshida et al., 1992). Confirmation of the presence of a corilagin moiety was obtained from the fragment at *m/z* 633 and the familiar ^1H resonances of a galloyl group (δ 7.06 *s*, 2xH), a hexahydroxydiphenoyl (HHDP) moiety (δ 6.67 and 6.83, each *s*, 2x1H), and signals characteristic of a $^1C_4$ glucopyranose core (δ 6.44–4.26, 7xH; $J \leqslant 4$ Hz for H-1, H-2, H-3 and H-4). The location of the galloyl group at C-1 followed from a significant downfield shift of the anomeric proton (δ 6.44), assigned with the aid of ^1H–^1H shift correlation spectra, while the *R*-configuration at the chiral HHDP group was evidenced by the negative Cotton effect at 242 nm in the CD spectrum of **1** (Okuda et al., 1995). Besides these signals attributable to a corilagin unit, the ^1H NMR spectrum of **1** showed an isolated methylene function [δ 3.04, br *s*, H_2-3′ (ring E)] and an isolated aromatic proton [δ 7.28, *s* (ring D)], suggesting the presence of an oxidatively modified DHHDP moiety. Given the molecular mass of **1** at *m/z* 924 and the established corilagin moiety in the molecule, the remaining substructure was evidently represented by a $C_{13}H_7O_8$ fragment, compatible with the ion at *m/z* 291 in the EI-MS. Although lack of sufficient sample quantity excluded ^{13}C NMR analysis, comparison of chemical shift data (CD_3OD) with those of the structurally related pelargoniins and realization of a carboxylic proton from an acetone-d_6 spectrum as previously demonstrated for pelargoniin D (Latté and Kolodziej, 2000) in conjunction with close examination of the mass fragmentation of **1** facilitated definition and placement of the modified DHHDP residue. The position of this acyl residue at C-2 was readily inferred from the conspicuous downfield position of H-2 of the glucose moiety (δ 5.23, *d*, $J = 4.0$ Hz) relative to that of corilagin (δ 3.98), while the relatively upfield position of just H-4 Glc (δ 4.45) reflected the only non-acylated position of the carbohydrate residue. The ion at *m/z* 308 indicated the 2-acyloxy fragment resulting from cleavage between the corilagin and the DHHDP moieties. Based on the above evidence, the structure of compound **1** was identified as depicted in its formula. In analogy to the series of structurally related ellagitannins from the same plant source, trivially named pelargoniins A–D (Latté and Kolodziej, 2000), this new analogue was designated as pelargoniin E.