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Anti-inflammatory steroidal glycosides from the berries of *Solanum nigrum* L. (European black nightshade)

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ABSTRACT

Seven previously undescribed steroidal glycosides, along with three known congeners were isolated from the unripe berries of *Solanum nigrum* L. (Solanaceae). Their structures were elucidated on basis of 1D and 2D NMR, HR-ESI-MS spectroscopic data and GC analysis after acid hydrolysis. The potential inhibitory effects on nitric oxide (NO) production induced by lipopolysaccharide in RAW 264.7 cell line and the anti-proliferative activities against five cancer cell lines (HL-60, U-937, Jurkat, K562 and HepG2) were evaluated. Seven compounds exhibited inhibition activities on NO production with IC_{50} values ranging from 11.33 to 49.35 μM. Structure-activity relationships of the isolated compounds were also discussed.

1. Introduction

Solanum nigrum L. (Solanaceae, also named European black nightshade) is native to Eurasia, which distributes mainly in temperate, subtropical, and tropical areas of China and India, as well as in Americas, Australasia, and South Africa (Jimoh et al., 2010; Wang and Tang, 1980). In China, the whole plants are widely used as folk medicine for their anti-pyretic and diuretic effects. Previous studies have found that this plant have remarkable antitumor effects, such as anti-proliferation, induced apoptosis or autophagy (Ding et al., 2013; Hsu et al., 2009; Huang et al., 2010; Jeong et al., 2007; Yang et al., 2010). Recent studies reported that the water extract of *S. nigrum* had hepatoprotective (Hsu et al., 2009), hypolipidemic and hypoglycemic activities (Hou et al., 2013; Sohrabipour et al., 2013). Previous phytochemical work on *S. nigrum* has resulted in the identification of steroidal saponins, phenolic, anthocyanin and polysaccharides (Ding et al., 2013; Li et al., 2009, 2010; Wang et al., 2017a; Zhou et al., 2006). However, most of these work focused on the whole plants, leaves or ripe berries of *S. nigrum*, there are few reports about the bioactive ingredients of its unripe berries (Eltayeb et al., 1997; Jagadeeshan et al., 2017).

Inflammation is a biological response of the host to foreign challenge or tissue injury and can be classified as either an acute or a chronic response depended on the time of onset (Lawrence et al., 2002). Chronic inflammation plays key role in the initiation and progression of several chronic conditions including cancer, arteriosclerosis, diabetes, obesity, and even neurodegenerative diseases (Chung et al., 2009; Sun et al., 2016). Nitric oxide (NO) is a signaling molecule which plays a key role in the pathogenesis of inflammation and considered as a pro-inflammatory mediator that induces inflammation due to over production in abnormal situations. Inhibitors of NO production represent potential therapeutic agents for inflammatory diseases (Sharma et al., 2007).

As part of our ongoing program to seek bioactive components from medicinal plants, fruits, and vegetables, our previous studies on the unripe berries of *S. nigrum* led to the isolation of nine previously undescribed steroidal saponins along with seven known congeners, and most of the isolated compounds exhibited pronounced inhibitory effects on the LPS induced NO production (He and Liu, 2007; Wang et al., 2016, 2013, 2017b). In continuing our study on the unripe berries, ten additional steroidal glycosides including seven previously undescribed compounds were obtained, and their potent anti-inflammatory and anti-proliferative activities were also evaluated *in vitro*.

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2. Results and discussion

2.1. Structure elucidation

The 70% methanol aqueous extract of the berries of *S. nigrum* was chromatographed on D101 macroporous resin, followed by silica gel and ODS column chromatography, and finally purified by RP-HPLC to afford ten steroidal glycosides, including seven previously undescribed compounds **1**–**6**, **9**. Their chemical structures were summarized in Fig. 1.

Acid hydrolysis of each compound followed by GC analysis of the sugar derivatives (see experimental section) revealed the presence of D-glucose, D-galactose, and L-rhamnose for compounds **1**, **5**, **6**, D-glucose and L-rhamnose for compounds **2**, **3**, **4**, and D-glucose, D-galactose for **9**. The β-anomeric configuration for glucose and galactose in their pyranose form was determined from their $^{3}J_{1,2}$ coupling constants ($J = 7.4–7.9$ Hz) and the α-anomeric configuration of rhamnose in its pyranose form was determined from its broad singlet ($J = 1.0$ Hz) as observed in the ^{1}H NMR spectra.

Compound **1** was isolated as white amorphous powder, $[\alpha]^{14}_{D}$ −87.1 (*c* 0.50, MeOH). Its molecular formula was deduced to be $C_{51}H_{82}O_{23}$ on the basis of the positive-ion HR-ESI-MS at m/*z* 1080.5616 $[M+NH_4]^+$ (calcd for $C_{51}H_{86}NO_{23}$, 1080.5591) as well as its ^{13}C NMR data (Tables 2–4). The IR spectrum showed the characteristic absorption of hydroxyl group at 3400 cm^{-1} and two

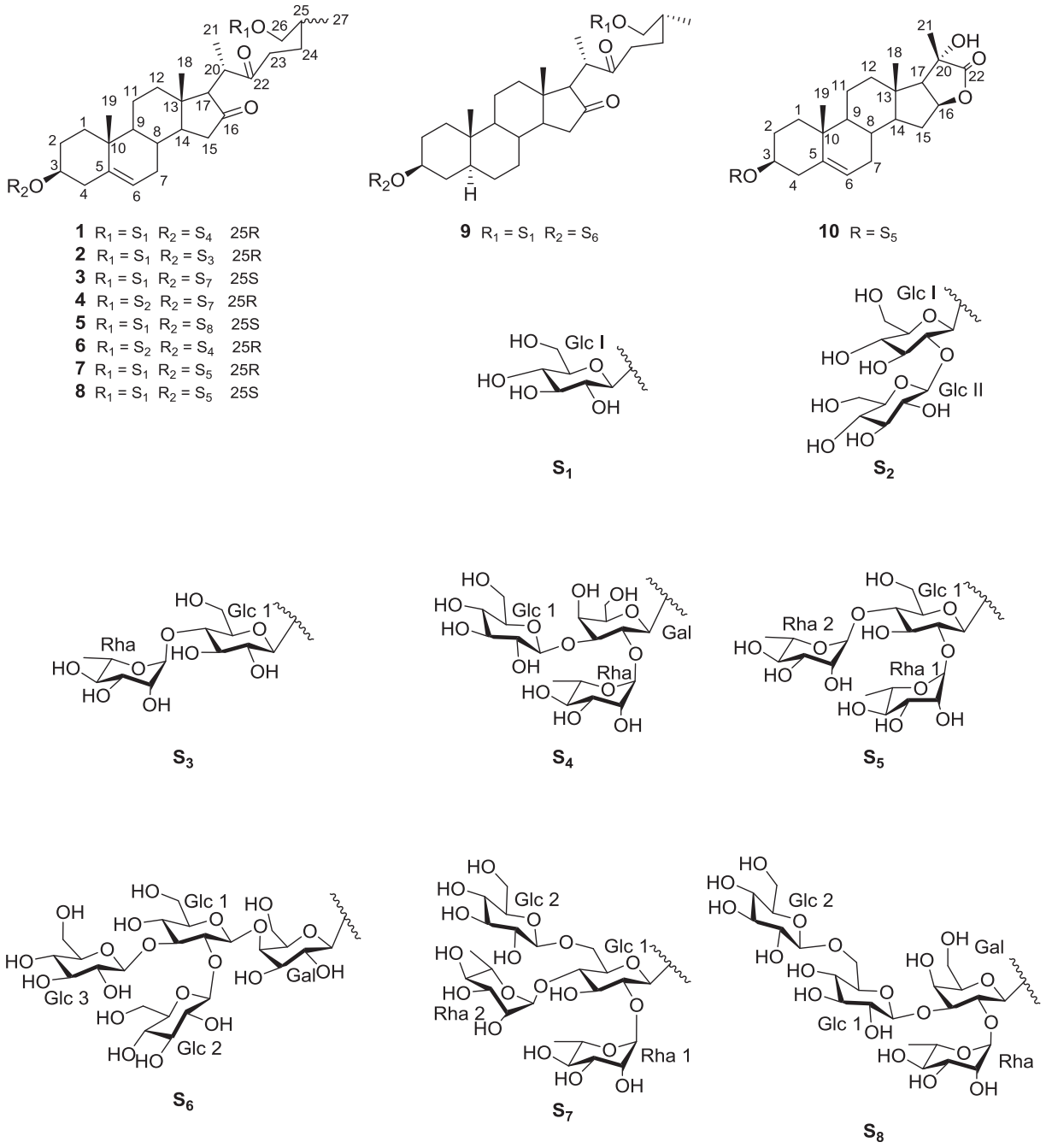

Fig. 1. Structures of the isolated compounds **1**–**10.**