

Iridoid glucosides from *Pentas lanceolata* (Forssk.) Deflers growing on the Island of Sardinia

Alessandro Venditti · Laura Guarcini ·
Mauro Ballero · Armandodoriano Bianco

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Abstract The ethanolic extract of *Pentas lanceolata* (Forssk.) Deflers was investigated from a phytochemical point of view and in particular on the monoterpeneoid glucosides content. Iridoid glucosides have a taxonomic relevance, e.g., asperuloside and its derivative are characteristic of the Rubioideae subfamily where this species is comprised. In the light of earliest phylogenetic molecular study which proposed to merge *P. lanceolata* in the Spermaceae tribe, a phytochemical approach also becomes necessary for a correct classification of this species. A total of 12 compounds were identified in detail, ten of these are iridoid glucosides: asperuloside, asperulosidic acid, tudoside, *E*-uenfoside and *Z*-uenfoside previously identified in this genus; whereas, deacetyl-asperulosidic acid, ixoside, griselinoside, 6 β ,7 β -epoxysplendoside were recognized here for the first time from *P. lanceolata*. Among the non-iridoidic compounds ursolic acid and D-xylose were identified.

Keywords *Pentas lanceolata* · Rubiaceae · Iridoids · Chemotaxonomy

Introduction

Pentas lanceolata (Forssk.) Deflers (Egyptian star flower) is a shrub with developed branches which grows up to 90–100 cm. The leaves are dark green, wrinkled, lanceolate that arise rough to the touch, the flowering starts from spring and is characterized by the presence of numerous small star-shaped flowers of red, pink or white color, with umbrella inflorescences. This species belongs to Rubiaceae family, originating from East Africa to Arabia (Verdcourt 1976), it is widely used as decorative plant, principally for building of “Butterfly Garden”, because of the prolonged flowering period that reaches the autumn. Flowering plants are attractive to butterfly, bees and other insects. Some ethnobotanical uses of this plant in its place of origin are also known, mainly as anti-malarial (Wanyoike et al. 2004; Kigonde et al. 2001; Endale et al. 2012), against lung diseases (Van Puyvelde et al. 1994) and for wound-healing properties (Nayak et al. 2005). In this study, we report the analysis of the polar fraction obtained from the aerial parts of a sample collected from a spontaneous population growing in the Island of Sardinia.

In particular, we focused our attention on the iridoid glucosides content because this kind of substances is considered chemotaxonomic markers in the Rubiaceae family. Previous study on this species reported the identification of several iridoid glucosides, named tudoside, 13*R*-*epi*-garternoside, 13*R*-*epi*-epoxygarternoside and a mixture of two isomers *E*- and *Z*-uenfoside (Schripsema et al. 2007), together with asperuloside and asperulosidic acid which have been found to be characteristic of the Rubioideae subfamily (Bianco et al. 1978; Inouye et al. 1988; Bianco 1990; Vieira et al. 1999; Schripsema et al. 2007; Serrilli et al. 2008; Venditti et al. 2014). Since the systematic of this family is very complex, with division into subfamily

A. Venditti · L. Guarcini · A. Bianco
Department of Chemistry, University of Roma “La Sapienza”,
Piazzale Aldo Moro, 5, 00185 Rome, Italy

A. Venditti (✉)
Department of Environmental Biology, University of Roma
“La Sapienza”, Piazzale Aldo Moro, 5, 00185 Rome, Italy
e-mail: alessandro.venditti@uniroma1.it

M. Ballero
Dipartimento di Scienze Botaniche, Consorzio Interuniversitario
CoSMese, Università di Cagliari, Monserrato, Italy

and tribe, the aim of this study was to deepen the knowledge about the monoterpenoid glucosides pattern of this species and also to give some indications from a chemotaxonomic point of view for a correct classification of *P. lanceolata*. In the past the genus *Pentas* was placed in the Oldenlandieae, subfamily Cinchonoideae by Schumann (1897), but more recently this genus was moved into the Hedyotideae, subfamily Rubioideae by Verdcourt (1958) where is currently classified. Lately a revision of the subfamily Rubioideae was proposed on the basis of the phylogenetic analysis of molecular data which would include this genus in the tribe Spermaceae (Bremer and Manen 2000).

Materials and methods

General

NMR spectra were recorded on Varian Mercury 300 MHz and/or on Bruker Avance 400 MHz instrument using CD₃OD or D₂O as deuterated solvents; the chemical shift was expressed in ppm from TMS.

MS spectra were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source, that operated in the negative and/or positive ion mode. The flow rate of sample infusion was 10 µL/min with 100 acquisitions per spectrum. Data were analyzed by using the MassLynx software developed by Waters.

Solvents of RPE grade were purchased from Sigma Aldrich or Carlo Erba Reagenti, silica gel 60 (70–230 mesh ASTM) from Fluka.

Plant materials

Plant materials were collected in Sardinia and the botanical identification was performed by one of us (M.B). A sample of the studied plant is stored in our laboratory under the accession number PLF200709CA.

Extraction and isolation of polar compounds

The dried plant materials (55.4 g) were exhaustively extracted four times using 96 % ethanol (0.35 L each, for 48 h). The extracts were collected and the ethanol was eliminated at reduced pressure until a water suspension was obtained. The suspension was frozen and then lyophilized, to preserve temperature-sensitive compounds, obtaining 4.32 g of crude extract. A preliminary purification by CC over silica gel (40.0 g) was performed on 2.01 g of the crude extract using butanol saturated with water as eluting solvent. From this separation step a low

polarity fraction (Fr. 1–3) was recovered where the presence of low polarity compounds was evidenced by ¹H-NMR. The (Fr. 6) fraction contained a mixture (~2:1) (8.7 mg) of *E*-uenfoside (5) and *Z*-uenfoside (6) (Schripsema et al. 2007) with a minor presence of a third compound (7) which might be also an iridoidic compound on the basis of the resonances visible in the ¹H-NMR spectra. tudoside (4) (20.1 mg) was eluted as pure compound (Fr. 11–13), followed by fractions where different mixture of iridoids were contained (Fr. 21–25 and Fr. 32–58). The more polar fractions (Fr. 60–82), where sugars were the main compounds, resulted positive to vanillin/HCl test evidencing also the presence of iridoidic compounds. These last ones (Fr. 60–82) (286.4 mg) were added with activated charcoal until no reaction to vanillin/HCl reagent. The obtained suspension, stratified on a sintered Gooch funnel, was first washed with water to remove the saccharides, then was eluted with methanol 30 % in water recovering a mixture of iridoids very similar to (Fr. 32–58) which was gathered with (Fr. 32–58) for further purification. By desorbing the charcoal with 70 % methanol in water griselinoside (9) (2.0 mg) (Ono et al. 2006) was eluted. Fractions (Fr. 95–100) contained a mixture of saccharides of which d-xylose (12) (30.3 mg) (Breitmaier and Voelter 1990) was the main component. The low polarity fractions (Fr. 1–3) (590 mg) was purified on silica gel (18.0 g) using a different eluting mixture. The chromatographic run started with chloroform/methanol (98:2, v/v) and the polarity was gradually increased to 95:5, v/v and then to 9:1, v/v. This separation allowed to recover ursolic acid (11) (25.4 mg) (Gnoatto et al. 2008) as pure compound, among waxes and long chain fatty acids. The remaining fractions, containing mixtures of iridoids, were gathered in one (Fr. 21–58) (347 mg) and re-chromatographed on silica gel (12.0 g) using chloroform/methanol as mobile phase. The column was conditioned with chloroform/methanol 9:1, v/v and the chromatographic run started with 8:2, v/v mixture, then the polarity was gradually increased to 7:3 and finally to 6:4, v/v. The following compounds were eluted: asperuloside (1) (Fr. 15–18) (15.2 mg) (Inouye et al. 1964, 1970), 6β,7β-Epoxysplendoside (10) (Fr. 22–23) (2.2 mg) (Jensen and Nielsen 1982), asperulosidic acid (2) (Fr. 26–30) (4.8 mg) (Bianco et al. 1978, 1981), deacetyl-asperulosidic acid (3) (Fr. 38–42) (6.2 mg) (Inouye et al. 1969; Bianco et al. 1978, 1981), ixoside (8) (Fr. 50–56) (3.1 mg). All the isolated compounds were identified by comparison with literature data and/or direct comparison with standard compounds available in our laboratory.

Asperuloside (1): ¹H-NMR, CD₃OD, 300 MHz, δ 7.30 (1H, bs, H-3), 5.96 (1H, bs, H-7), 5.73 (1H, bs, H-1), 5.51 (1H, d, *J* = 6.0 Hz, H-6), 4.80 (partially overlapped with HDO signal, H1'), 4.66 (2H, d, *J* = 12.3 Hz, H-10), H-5

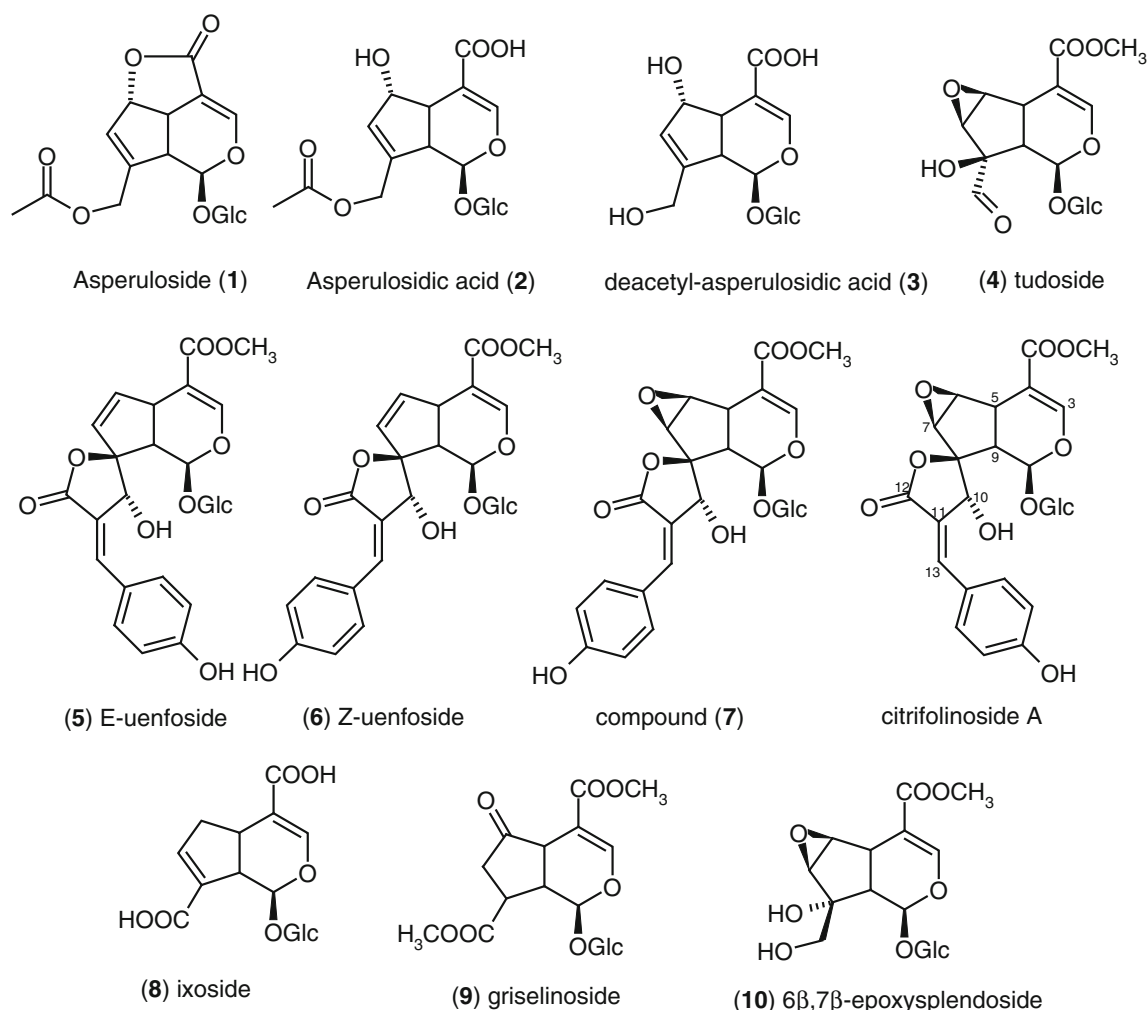


Fig. 1 Iridoid glucosides from *P. lanceolata*

and H-9 overlapped with sugar signals, 2.14 (3H, s, $\underline{CH_3}$ -CO). HR-ESI-MS: m/z 437.09 [M+Na]⁺.

Asperulosidic acid (2): ¹H-NMR, D₂O, 400 MHz, δ 7.44 (1H, d, J = 2.2 Hz, H-3), 6.07 (1H, d, J = 2.0 Hz, H-1), 5.84 (1H, bs, H-7), 4.89 (1H, d, J = 8.0 Hz, H-1'), 4.74 (partially overlapped with HDO signal a 4.78 ppm, H-6), 3.09 (1H, t, J = 3 Hz, H-9), 2.75 (1H, t, J = 8.2 Hz, H-5), 2.15 (3H, s, $\underline{CH_3}$ -CO). ESI-MS: m/z 431.26 [M-H]⁻; m/z 455.05 [M+Na]⁺.

Deacetyl-asperulosidic acid (3): ¹H-NMR, CD₃OD, 300 MHz, δ 7.56 (1H, s, H-3), 5.90 (1H, bs, H-7), 5.31 (1H, bs, H-1), 5.10 (1H, d, J = 8.7 Hz, H-6), 4.76 (1H, d, J = 7.7 Hz, H-1'), 4.22 (2H, bd, J = 13 Hz, H-10), 3.02 (1H, bt, J = 6.5 Hz, H-9), 2.55 (1H, bt J = 7.7 Hz, H-5). ESI-MS: m/z 413.28 [M+Na]⁺.

Tudoside (4) : ¹H-NMR (300 MHz, CD₃OD) δ 9.54 (1H, s, H-10), 7.35 (1H, s, H-3), 5.76 (1H, s, H-1), 3.74 (3H, s, $\underline{OCH_3}$), 3.39 (overlapped, H-5), 2.44 (1H, d, J = 8.4 Hz, H-9). ¹³C-NMR (75 MHz, CD₃OD) δ 201.99

(C-10, aldehyde), 168.54 (C-11), 154.66 (C-3), 107.28 (C-4), 99.84 (C-10 Hydrated aldehyde), 98.31 (C-1'), 93.92 (C-1), 82.06 (C-8), 78.22 (C-3'), 77.87 (C-5'), 74.44 (C-2'), 71.47 (C-4'), 62.83 (C-6'), 51.68 ($\underline{OCH_3}$), 46.80 (C-9), 33.30 (C-5). ESI-MS: m/z 473.17 [M+Na]⁺.

E-Uenfoside (5): ¹H-NMR (400 MHz, CD₃OD) δ 7.69 (2H, d, J = 8.7 Hz, H-2', H-6'), 7.61 (1H, s, H-13), 7.47 (1H, d, J = 1.6 Hz, H-3), 6.89 (2H, d, J = 8.6 Hz, H-3', H-5'), 6.46 (1H, dd, J = 5.8, 2.3 Hz, 7-H), 6.10 (1H, dd, J = 5.8, 2.5 Hz, H-6), 5.21 (1H, d, J = 6.1 Hz, H-1), 4.61 (1H, d, J = 8.0 Hz, H-1''), 3.92 – 3.86 (1H, m, H-5), 3.75 (3H, s, $\underline{OCH_3}$), 2.55 (1H, dd, J = 6.9, 6.5 Hz, H-9). ESI-MS: m/z 546.78 [M-H]⁻; m/z 570.78 [M+Na]⁺.

Z-Uenfoside (6) : ¹H-NMR (400 MHz, CD₃OD) δ 7.98 (2H, d, J = 8.7 Hz, H-2', H-6'), 7.50 (1H, d, J = 1.7 Hz, H-3), 7.08 (1H, d, J = 2.2 Hz, H-13), 6.80 (2H, d, J = 8.8 Hz, H-3'; H-5'), 6.39 (1H, dd, J = 5.8, 2.4 Hz, H-7), 5.88 (1H, dd, J = 5.7, 2.4 Hz, H-6), 5.45 (1H, d, J = 5.5 Hz, H-1), 5.31 (1H, d, J = 1.8 Hz, H-10), 4.75

(1H, d, $J = 7.8$ Hz, H-1''), 3.87 (1H, m, H-5), 3.75 (3H, s, $-\text{OCH}_3$), 2.78 (1H, dd, $J = 7.3, 5.6$ Hz, H-9). ESI-MS: m/z 546.78 $[\text{M}-\text{H}]^-$; m/z 570.78 $[\text{M}+\text{Na}]^+$.

Compound (7) : $^1\text{H-NMR}$ (400 MHz CD_3OD) δ 8.06 (2H, d, $J = 8.6$ Hz, H2'', H6''), 7.59 (1H, s, H13), 7.46 (1H, d, $J = 3.2$ Hz, H3), 6.82 (2H, d, $J = 8.6$ Hz, H3'', H5''), 5.14 (1H, s, H10), 2.78 (1H, dd, $J = 7.0, 5.9$ Hz, H9). ESI-MS: m/z 562.75 $[\text{M}-\text{H}]^-$; m/z 586.73 $[\text{M}+\text{Na}]^+$.

Ixoside (8) : $^1\text{H-NMR}$ (300 MHz, D_2O) δ 7.53 (1H, bs, H-3), 7.03 (1H, m, H-7), 5.76 (1H, d, $J = 4.6$ Hz, H-1), 3.20 (1H, overlapped with sugar signals, H-9), 3.04 (1H, bt, $J = 5.6$ Hz, H-5), 2.69–2.46 (2H, m, H-6). ESI-MS: m/z 411.20 $[\text{M}+\text{Na}]^+$.

Griselinoside (9) : $^1\text{H-NMR}$ (300 MHz, D_2O) δ 7.64 (1H, bs, H-3), 5.34 (1H, d, $J = 6$ Hz, H1), 3.81 (3H, s, $-\text{OCH}_3$), 3.74 (3H, s, $-\text{OCH}_3$), 3.51 (overlapped with sugar signal, H-5), 2.76 (partially overlapped with sugar signal, H-9), 2.20–1.97 (2H, m, H-7). $^{13}\text{C-NMR}$ (75 MHz, D_2O) δ 211.8 (C-6), 175.8 (C-10), 169.0 (C-11), 153.8 (C-3), 104.5 (C-4), 99.1 (C-1'), 96.6 (C-1), 76.3 (C-3'), 75.5 (C-5'), 72.6 (C-2'), 69.3 (C-4'), 62.5 (C-6'), 52.1 ($-\text{OCH}_3$), 45.12 (C-9), 39.5 (C-8), 38.1 (C-7). ESI-MS: m/z 431.09 $[\text{M}-\text{H}]^-$; m/z 455.16 $[\text{M}+\text{Na}]^+$.

6 β ,7 β -Epoxy splendoside (10) : $^1\text{H-NMR}$ (300 MHz, D_2O) δ 7.52 (1H, bs, H-3), 5.65 (1H, bd, $J = 6.9$ Hz, H-1), 4.89 (1H, d, $J = 7.8$ Hz, H-1'), 4.01 (1H, bd, $J = 3.0$ Hz, H-6), 3.75 (3H, s, $-\text{OCH}_3$), 3.18 (1H, partially overlapped with sugar signals, H-5), 2.58 (1H, bt, $J = 7.2$ Hz, H-9). ESI-MS: m/z 433.19 $[\text{M}+\text{Na}]^+$.

Ursolic acid (11) : $^1\text{H-NMR}$ (400 MHz CD_3OD) δ 5.23 (1H, t, $J = 3.6$ Hz, H-12), 3.15 (1H, dd, $J = 11.2, 5.0$ Hz, H-3), 2.20 (1H, d, $J = 11.0$ Hz, H-18), 2.04 (1H, td, $J = 13.4, 4.1$ Hz, H-15a), 1.93 (1H, dd, $J = 8.7, 3.7$ Hz, H-16a), 1.12 (3H, s, H-27), 0.98 (3H, s, H-23), 0.97 (3H, d, $J = 6.8$ Hz, H-29), 0.96 (3H, s, H-26), 0.88 (3H, d, $J = 6.5$ Hz, H-30), 0.85 (3H, s, H-24), 0.78 (3H, s, H-25). $^{13}\text{C-NMR}$ (101 MHz, MeOD) δ 181.74 (C-28), 139.68 (C-13), 126.95 (C-12), 79.76 (C-3), 56.79 (C-5), 54.42 (C-18), 49.21 (C-17), 48.63 (C-9), 43.29 (C-14), 40.83 (C-4), 40.47 (C-19), 40.46 (C-20), 40.05 (C-1), 39.88 (C-8), 38.15 (C-10; C-22), 34.38 (C-7), 31.81 (C-21), 29.26 (C-23), 28.82 (C-2), 27.94 (C-15), 25.37 (C-16), 24.41 (C-27), 24.14 (C-11), 21.62 (C-30), 19.52 (C-6), 17.86 (C-29), 17.69 (C-24), 16.43 (C-26), 16.07 (C-25). ESI-MS: m/z 455.05 $[\text{M}-\text{H}]^-$; m/z 479.04 $[\text{M}+\text{Na}]^+$.

d-Xylose (12) : $^1\text{H-NMR}$ (300 MHz, D_2O) δ 5.2 (1H, d, $J = 3$ Hz, H1 α), 4.62 (1H, d, $J = 8.8$ Hz, H1 β), 4.14–3.18 overlapped CH signals. $^{13}\text{C-NMR}$ (75 MHz, D_2O) δ 96.02 (C1 β), 92.21 (C1 α), 75.88 (C3 β), 74.27 (C2 β), 72.89 (C3 α), 72.54 (C3 β), 71.25 (C2 α), 69.78 (C4 α), 69.74 (C4 β), 67.05 (C5 β), 60.87 (C5 α). ESI-MS: m/z 173.12 $[\text{M}+\text{Na}]^+$.

Results and discussion

The analysis of the ethanolic extract obtained from the aerial parts of *P. lanceolata* led mainly to isolation of iridoid glucosides (Fig. 1). Ursolic acid and a monosaccharide, d-xylose (Fig. 2) were also identified in minor amount. Compounds (1) asperuloside and (2) asperulosidic acid were already identified in *P. lanceolata* (Inouye et al. 1988) while compound (3), deacetyl-asperulosidic acid, was recognized for the first time in this study. These derivatives (1,2,3) are considered chemotaxonomic markers for the subfamily Rubioideae. Tudoside (4) resulted the main iridoidic component as well as in the previous analyses of this species (Schripsema et al. 2007). We also evidenced a notable amount of a mixture (~2:1) composed of *E*-uenfoside (5) and *Z*-uenfoside (6) and a minor quantity of a third component (7). This compound (7), could be an iridoidic substance featured with a spironolactone functionality and provided with a *para*-hydroxybenzene moiety (evidenced by two sets of doublets in the aromatic region at 6.82 ppm and relative to H3'' and H5'' and the more deshielded at 8.06 ppm relative to H2'' and H6'', both coupling constants of 8.6 Hz). A singlet at δ 7.59 which could be assigned to H13, a doublet at δ 7.46 (1.9 Hz) for H3, a singlet at δ 5.14 for H10 and a double doublets δ 2.78 (7.0/5.9 Hz) for H9 were also evident. Probably there is no double bond between C6 and C7, but reasonably an epoxide function, which causes a shift effect on the H6 and H7 signals to about 4.0–3.8 ppm might be hypothesized in these positions. All these signals, compared with the respective signals of citrifolinolide A (Sang et al. 2001), seemed to be shifted in the same manner as in the couple of epimers *E*- and *Z*-uenfoside. In particular, the doublet relative to H2'' and H6'' resulted more deshielded in the *Z*-isomer, whereas the doublet of H3'' and H5'' resulted shifted at higher field in the *Z*-isomer; H9 has also a similar deshielding effect in the *Z*-isomer. All these data seemed to be in accordance with the presence of the *Z*-epimer of citrifolinolide A, of which we could hypothesize the presence, also on the basis of corresponding mass

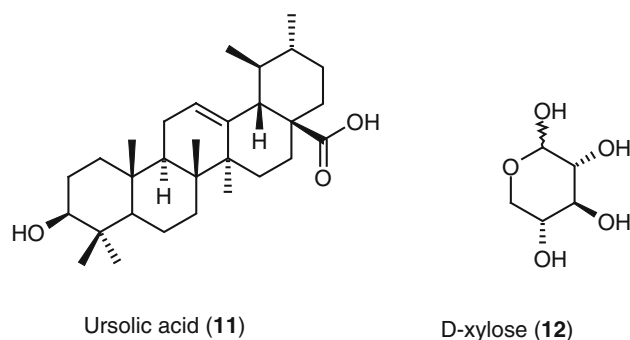


Fig. 2 Non-iridoidic compounds isolated from *P. lanceolata*

spectrometric signals both in negative and positive ionization mode (m/z 562.75 $[M-H]^-$; m/z 586.73 $[M+Na]^+$). Surely, further study on this aspect should be conducted to confirm or not this hypothesis. From both, chemical and chemotaxonomic point of view, compounds (**5**) and (**6**) [and also compound (**7**) if confirmed] are very particular substances due to their spironolactone functionality which is a very rare feature among iridoids isolated from the Rubiaceae family. Similar compounds have been previously recognized in *Morinda citrifolia* (citrifolinoside A), (Sang et al. 2001) and in *M. coreia* (yopaoside A and B, structures not reported) (Kanchanapoom et al. 2002). Recently the structures of yopaoside A and B were revised in particular for the configuration at C-8 and C-10. NMR data for yopaoside A were found to be identical to those reported for citrifolinoside, whereas yopaoside B was revised to citrifolinoside A (Schripsema et al. 2006).

Morinda citrifolia and *M. coreia* are comprised in the Psychotria tribe of Rubioideae, a tribe very near to Spermaceae where *P. lanceolata* should be placed on the basis of the earliest phylogenetic analysis of molecular data (Bremer and Manen 2000).

Ixoside (**8**) firstly isolated by Takeda (1975) is an iridoid characteristic of the genus *Ixora* which is comprised in the subfamily Ixoroideae of Rubiaceae, but was also isolated from *Tarenna kotoensis* (Takeda et al. 1976) which belongs to a different subfamily (Cinchonoideae). Considering the occurrence of this compound this is the first report on isolation of ixoside (**8**) from a genus belonging to Rubioideae subfamily. Ixoside (**8**) was also recognized in species belonging to different families as *Dolichandrone serriculata* (Bignoniaceae) (Sinaphet et al. 2006) and *Leonotis nepetaefolia* (Takeda et al. 1999) (Lamiaceae), both families, as Rubiaceae, are comprised in the Subclass Asteridae.

Particularly interesting was the identification of compound (**9**) griselinoside, because this substance was mainly isolated from *Verbena* spp. (Verbenaceae) (Damtoft et al. 1979; Pagani 1984; Ono et al. 2006) and from *Toricellia angulata* (Cornaceae) (Wu et al. 2000), and is reported here for the first time from a Rubiaceae species.

6 β ,7 β -Epoxy splendoside (**10**) was primarily recognized in *Fouquieria* spp. (Ericales) (Jensen and Nielsen 1982) and lately was isolated also from *M. citrifolia* (Sang et al. 2002). This compound has an epoxy group at C6–C7 in the same configuration of tudoside (**4**), the major compound recognized in *P. lanceolata*.

The last two isolated compounds, ursolic acid (**11**) and d-xylose (**12**), have no particular importance from a chemosystematic point of view since pentacyclic triterpenes are widely distributed in the plant kingdom as the monosaccharides, but were recognized here for the first time in *P. lanceolata*.

In conclusion, regarding the presence of iridoid glycosides, we documented a composition quite similar to those reported in previous studies, but the presence of minor compounds never identified in this species was evidenced. The presence of the same compounds among different species, as compounds (**8**), (**9**) and (**10**), is an evidence of common biochemical pathways and may also reveal their taxonomical proximity. On the other hand, these differences could also have arisen from the different pedological and climatic conditions in which the studied samples have grown. In fact the Sardinian climate and soil are very different with respect to the native places of this species where a tropical climate is present. In support of this last hypothesis, the influence of the Sardinian environment on the phenotype expression, we have previously recognized some particular iridoidic pattern in Rubiaceae species (*Galium*) from Sardinia (Serrilli et al. 2008).

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