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Iridoid glucosides of *Paederota lutea* and the relationships between *Paederota* and *Veronica*

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Abstract

In a chemical investigation of the water soluble compounds in *Paederota lutea* eight known iridoids were isolated together with a new one with a 8,9-double bond, namely paederotoside (10-*O*-benzoyl-6′-*O*-α-arabino(1 → 6)-β-glucopyranosyl arborescosidic acid) and the 6-hydroxy-flavone glucoside 4′-*O*-methylscutellarein 7-*O*-β-glucopyranoside. The known iridoid glucosides were 8-epiloganic acid, gardoside, aucubin, catalpol and the 6-*O*-esters of catalpol: veronicoside, catalposide, amphicoside and verproside. The compounds isolated show that *Paederota* has a glycoside content almost identical to that of a general *Veronica* species, and this is in good agreement with the results from recent investigations of the phylogeny of *Veronica* and its closest relatives, where *Paederota* is placed as a sister-group next to *Veronica*. In an analysis of the iridoid glucosides from some of these relatives, it is shown that *Veronica*, *Paederota*, *Picrorhiza* and *Veronicastrum* are all characterized by containing 6-*O*-esters of catalpol. Some less closely related taxa namely: *Lagotis*, *Wulfenia*, *Plantago*, *Aragoa* and *Globularia* instead contain 10-*O*-esters of catalpol or aucubin.

Keywords: Chemotaxonomy; *Paederota lutea*; Plantaginaceae; Veronicaceae; Iridoid glucosides; Paederotoside

1. Introduction

Paederota is a genus of two species from the south-eastern European Alps; *Paederota lutea* with yellow flowers and *P. bonarota* with blue flowers. It is included in that part of the former Scrophulariaceae that has recently been moved to Plantaginaceae (Angiosperm Phylogeny Group, 2003). The genus has its closest affinities with *Veronica*, in which it has at times been included (von Wettstein, 1895). Apart from the two European species, *P. lutea* and *P. bonarota*, the Caucasian species *P. pontica* was originally described in *Paederota* but later segregated in its own genus, *Paederotella*, by Kemularia-Nathadze (1952) and most recently has been found by DNA sequence data to be derived from within *Veronica*, well apart from *Paederota* (Albach et al., 2004). Analyses of DNA sequence data have also helped to elucidate the pattern of relationship between *Paederota* and *Veronica*. Analysis of nuclear ribosomal DNA sequences showed *Paederota* to be derived from within *Veronica* (Albach and Chase, 2001), whereas analysis of plastid DNA sequences revealed a sister-group relationship between the two genera (Albach and Chase, 2004). Incongruence tests favored the hypothesis that sampling errors had lead to the inclusion of *Paederota* in *Veronica* when using nuclear ribosomal DNA sequences.

So far the only chemical investigations of the genus are those of Grayer-Barkmeijer (1973, 1979) who in her wide-ranging paper chromatographic study of *Veronica* and its relatives also examined the two species of *Paederota*. Both species were reported to contain aucubin (**1**), catalpol (**2**) and the 6-*O*-catalpol esters veronicoside (**3**), catalposide (**4**) and amphicoside (**5**); *P. lutea* also contained verproside (**6**) as well as a so-called unidentified '*Veronica spicata* ester' (Grayer-Barkmeijer, 1973). Later, in the more comprehensive thesis (Grayer-Barkmeijer, 1979), both plants were also reported to contain a number of 6-hy-

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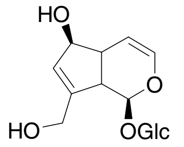
droxylated flavone 7-glycosides. We can now report on the isolation of the glycosides from *P. lutea*.

2. Results and discussion

The water-soluble part of an EtOH extract of *P. lutea* L. f. collected in Carinthia (Austria) in 2002, was subjected to reversed phase column chromatography and gave a number of known iridoid glucosides, namely 8-epiloganic acid (**7**), gardoside (**8**), **1** and **2** as well as the catalpol esters **3**–**6** previously detected in the plant. In addition a new iridoid glucoside which we have named paederotoside (**9**) and the known flavone glucoside 4′-*O*-methylscutellarein 7-*O*-β-glucopyranoside (**11**) was isolated.



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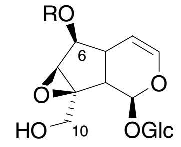
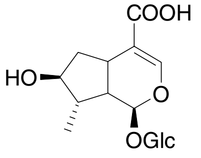


2 R = H
3 R = Benzoyl
4 R = 4-OH-Benzoyl
5 R = Vanilloyl
6 R = 3,4-di-OH-Benzoyl



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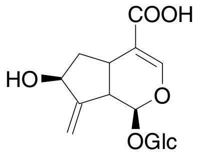

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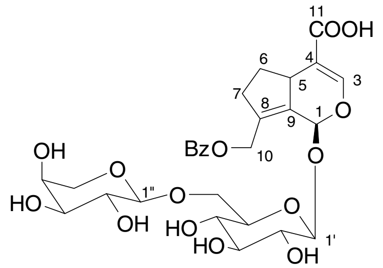

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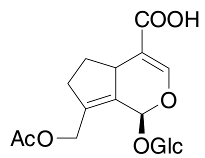

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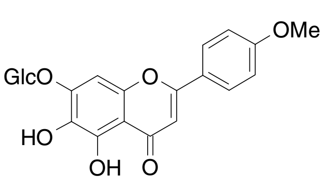

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Paederotoside (**9**) was isolated as a glass $[\alpha]_D^{20}$ −29° with the molecular formula $C_{28}H_{34}O_{15}$, as established by HRESIMS. In agreement with this, the ^{13}C NMR spectrum (Table 1) showed 28 signals; of these, 10 could be assigned to an iridoid aglucone very similar to that of alpinoside (**10**) (Jensen et al., 1996; Calis et al., 2001), except for the acetyl group in the latter. Seven signals could be assigned to a benzoyl group. Of the remaining 11 signals, six could be assigned to a β-glucopyranosyl moiety alkylated at the 6-*O*-position as seen by the low field shift of C-6, and another set of five signals could be assigned to an α-arabinopyranosyl moiety. In fact, when compared to the reported data of the α-L-arabinopyranosyl(1 → 6)-β-*D*-glucopyranosyl moiety of a known naphthopyranone glycoside (Piacente et al., 2001), a convincing correspondence was seen (Table 1) when allowing for the aromatic aglycone in the latter. The assignment of the ^1H NMR chemical shifts (Table 1) was partly based on DQF-COSY and HSQC spectra and was in full agreement with this analysis. Thus, the low field position of the singlet at δ 6.32 assigned to C-1 of the iridoid aglucone was indicative of the presence of an 8,9-double bond (Jensen et al., 1996). The C-3 peak, however, was found at an unusually high field (δ 7.24) when compared to the usual value for an iridoid (i.e. δ 7.5–7.6), but this is a known effect for iridoid acids, which are partly ionised (von Poser et al., 1998; Iavarone et al., 1983). The low field position of the signals assigned to the C-10 methylene group, an AB system centred at δ 5.03, indicated that this was the position of the benzoyloxy group, and a correlation between CO (δ 165.6) of the benzoyl group and the H-10 signals confirmed this. Likewise, a significant correlation was seen between the anomeric carbon atom C-1″ of the arabinosyl group (δ 105.5) and the H-6′-signals at δ 3.66 and 4.10, proving the position of the link between the two carbohydrate moieties.

A second sample of the plant collected from a different population in Carinthia in 2003 was similarly investigated. This collection, however, proved devoid of the iridoid acids **7**–**9**.

Aucubin (**1**) and catalpol (**2**) together with the catalpol esters **3**–**6** have been found to be present in most species of *Veronica* investigated (Grayer-Barkmeijer, 1973, 1979; Taskova et al., 2002). The two acid iridoids 8-epiloganic acid (**7**) and gardoside (**8**) are common metabolites in plants producing **1** and **2** (cf. Rønsted et al., 2000), but neither appears to have been isolated from *Veronica* before. However, 8-epiloganin has been reported from *V. triphyllos* (Grabias et al., 1995) and aromatic esters of **7** and **8** have been reported from *V. anagallis-aquatica* (Lahloub et al., 1993).

The finding of a new carbocyclic iridoid glucoside with an 8,9-double bond is more interesting. Compounds with this structural feature have a very limited distribution; they have been reported previously from

Table 1
NMR data in CD_3OD for paederotoside and model compounds

Atom	Paederotoside (**9**)[a]			Alpinoside[b] (**10**)	Naphthopyranone glycoside[c]
	^{1}H	^{13}C	HMBC correlations	^{13}C	^{13}C
Aglucone					
1	6.32 (*s*)	91.6	1′, 3, 5, 8	91.7	
3	7.24 (*br. s*)	149.4	1, 4, 5, 11	151.4	
4		115.6		115.0	
5	3.6 (*m*)	39.8		39.3	
6	2.61 (*m*), 1.51 (*m*)	32.2	7, 8, 9	32.1	
7	2.61 (2H, *m*)	35.2	5, 6, 8	35.1	
8		136.8		137.4	
9		135.8		134.6	
10	4.96 (*br. d*, 12.8) 5.10 (*d*, 12.8)	61.6	CO,7,8,9	60.9	
11		167.9		171.1	
Glc					
1′	4.72 (*d*, 8.1)	100.1	1, 5′	99.9	103.8
2′	3.19 (*t*, 8.3)	74.7	1′, 3′	74.7	75.2
3′	3.37 (*t*, 9.0)	77.9	2′, 4′	78.0	77.6
4′	3.30 (*t*, 9.0)	71.7	3′, 5′	71.5	71.4
5′	3.6 (*m*)	77.2		78.3	77.3
6′	3.66 (*dd*, 11.5, 4.7) 4.10 (*dd*, 11.5, 2.1)	69.5	1″, 4′, 5′	62.7	69.6
Ara					
1″	4.30 (*d*, 6.4)	105.5	6′, 3″, 5″		105.1
2″	3.59 (*dd*, 9.0, 6.4)	72.5	1″, 3″		72.5
3″	3.56 (*dd*, 8.9, 3.0)	74.1	2″		74.2
4″	3.77(*m*)	69.9	4″		69.3
5″	3.52 (*dd*, 12.4, 1.7) 3.84 (*dd*, 12.4, 3.0)	66.7	1″, 3″		66.4
Benzoyl					
1‴		131.3			
2‴/6‴	8.03 (2H, *d*, 7,9)	130.7	CO, 4‴		
3‴/5‴	7.50 (2H, *t*, 7.9)	129.7	1‴		
4‴	7.61 (*t*, 7.5)	134.4	2‴/6‴		
CO		165.6			

[a] Signals were assigned using COSY and HSQC spectra.
[b] Data from Calis et al. (2001).
[c] Data from Piacente et al. (2001); only the α-L-arabinopyranosyl(1 → 6)-β-D-glucopyranosyl part.

two species of *Veronica*, namely *V. anagallis-aquatica* (Lahloub, 1992a), *V. cymbalaria* (Taskova et al., 1999), from *Wulfenia carinthiaca* Jacq. (Arnold et al., 2002), and from all of the five species of *Globularia* investigated recently with proper techniques, namely *G. cordifolia* (Kirmizibekmez et al., 2003b), *G. davisiana* (Calis et al., 2002a), *G. dumulosa* (Kirmizibekmez et al., 2003a), *G. orientalis* (Calis et al., 2002b) and *G. trichosantha* (Calis et al., 2001). Finally, compounds of this type appear to be present in about half of the 50 *Plantago* species investigated for iridoid glucosides (Rønsted et al., 2003b). All these taxa are members of the new Plantaginaceae (Veronicaceae *sensu* Olmstead et al., 2001), which has recently been separated from Scrophulariaceae s. str., based on plastid DNA gene sequencing results (Olmstead et al., 2001). With this distribution pattern, iridoid glucosides with an 8,9-double bond are therefore potential taxonomic markers although they apparently only occur sporadically within each genus.

Comparing the aromatic esters of **1** and **2** known from *Paederota* and *Veronica* with those found in the remaining 10 taxa of the phylogram (Fig. 1), an interesting picture emerges. Regarding these genera, no chemical results have been reported for *Wulfeniopsis* and *Erinus*, but data exist for the remaining eight taxa. Thus, *Picrorhiza* has been extensively investigated due to its use in Ayurvedic and Chinese medicine. Roots of *P. kurrooa* have given a number of iridoids of which the main are **1** and **2** and in addition picroside I (6′-*O*-cinnamoyl-catalpol), amphicoside (**5**), minecoside (6-*O*-isoferuloyl-catalpol), veronicoside (**3**) and 6-*O*-feruloyl-catalpol (Stuppner and Wagner, 1989; Jia et al., 1999). From *P. scrophulariiflora* almost the same compounds has been isolated (Wang et al., 1993; Li et al., 1998).

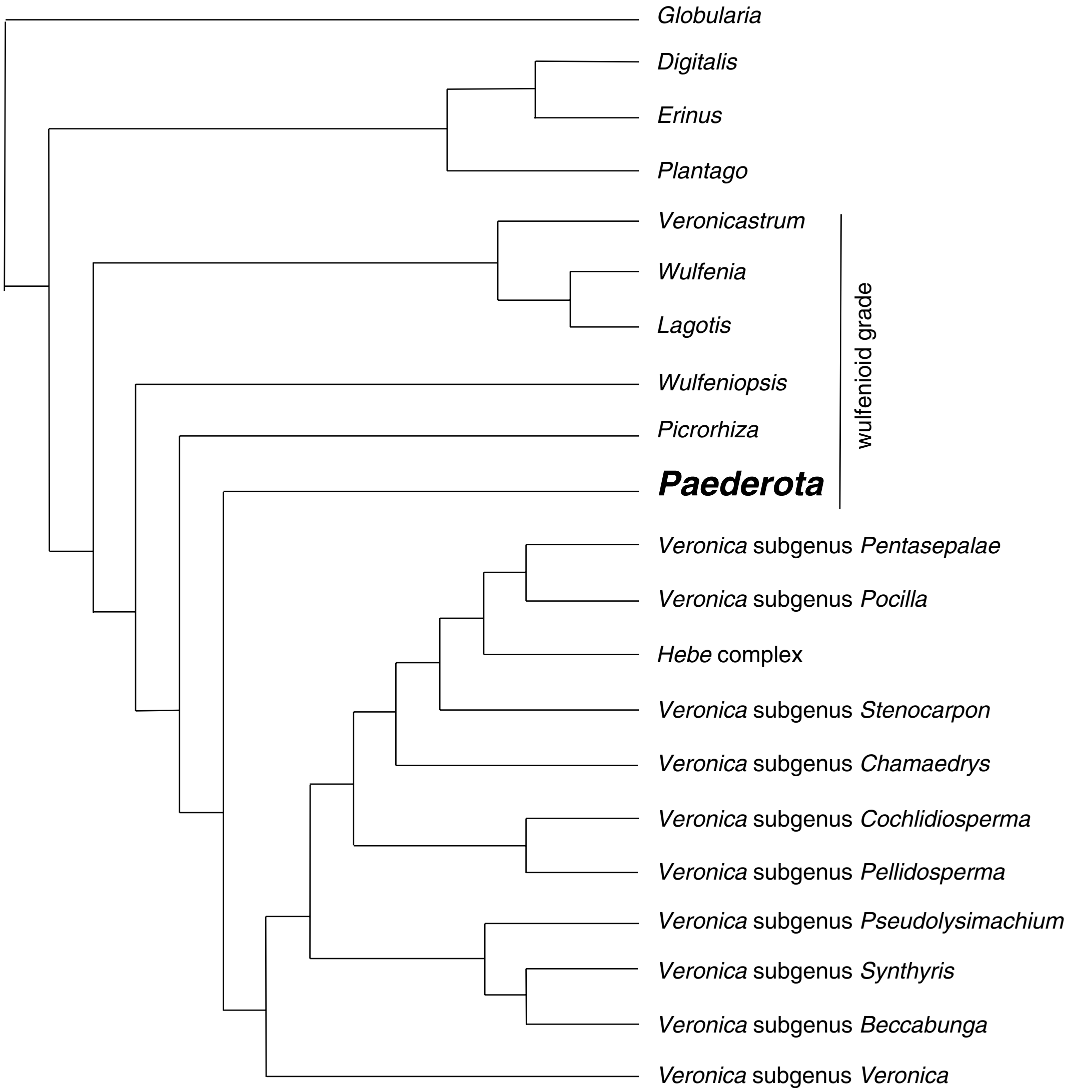

Fig. 1. Phylogenetic tree based on plastid rps16 DNA sequences, which shows the current best estimate for the relationships of *Paederota* and its relatives. Modified from Albach and Chase (2004). The position of *Aragoa* as a sister to *Plantago* (not shown in tree) is based on Bello et al. (2002).

The *Veronicastrum* clade has been fairly well investigated. Thus, three species of *Lagotis* have been reported to contain iridoid glycosides, namely *L. stolonifera* (Calis et al., 1991), *L. brevituba* (Zong and Che, 1995) and *L. yunnanensis* (Yang et al., 2003). Along with **1** and **2**, isoscrophularioside (10-*O*-cinnamoyl-aucubin) and globularin (10-*O*-cinnamoyl-catalpol) was reported; while the last species has given 10-*O*-(3,4-dimethoxycinnamoyl)-aucubin. The iridoids from *Wulfenia carinthiaca* Jacq. (Arnold et al., 2002) are, besides the 8,9-unsaturated compound noted above, the same type of esters, namely isoscrophularioside and globularin (in this case the most hydrophilic compounds were not isolated from the plant). From *Veronicastrum sibiricum*, the results are somewhat conflicting: Lee et al. (1987) found **1** and **2**, together with minecoside (6-*O*-isoferuloyl-catalpol) and 6-*O*-veratroyl-catalpol. But in a more recent investigation Lin et al. (1995) report the compounds 6-*O*-(3,4-dimethoxycinnamoyl)-myoporoside, scrophularioside (6′-*O*-cinnamoyl-aucubin) and 6-*O*-feruloyl-catalpol.

Of the remaining genera in the phylogram, *Digitalis* does not contain iridoids (Jensen et al., 1975), but the remaining genera *Plantago*, *Aragoa* and *Globularia* all have at least some species with globularin (10-*O*-cinnamoyl-catalpol) or 10-*O*-benzoyl-catalpol (Rønsted et al., 2003a,b), while 6-*O*-esters of catalpol are unknown from these relatively well-investigated genera.

Analysing the above findings, we can conclude that one group is characterized by almost consistently containing 6-*O*-esters of catalpol, namely *Veronica*, *Paederota*, *Picrorhiza* and *Veronicastrum*. The remaining taxa with iridoids present: *Lagotis*, *Wulfenia*, *Plantago*, *Aragoa* and *Globularia* often contain 10-*O*-esters of catalpol or aucubin. This is in very good agreement with the phylogram. However, it is intriguing that the *Veronica*-

strum clade appear to be inhomogeneous with regard to the iridoids present. Work is in progress to resolve this question by investigating more genera and species.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova-500 MHz or Mercury-300 MHz instruments in MeOH-d_4 using the solvent peak (δ 3.31 and 49.0, respectively) as the internal standard. LC-HR ESIMS was performed on an Agilent HP 1100 Liquid Chromatograph equipped with a BDS-C18 reversed phase column running a water-acetonitrile (50 ppm TFA in water) gradient. The LC was coupled to a LCT of a TOF MS (Micromass, Manchester, UK) operated in the positive electrospray ion mode using 5-leucineenkephalin as lock mass. The compounds isolated were identified by their NMR data; **1**, **2**, **7** and **8** by comparison with standards, **3**–**6** by comparison with published data (Sticher and Afifi-Yazar, 1979; El-Naggar and Doskotch, 1980; Lahloub, 1992b; Afifi-Yazar and Sticher, 1980). Only a ^{1}H NMR spectrum (in MeOH-d_4) was recorded of **11**, when the compound unfortunately was lost, and further characterisation was impossible).

3.2. Plant material

Material of *P. lutea* was collected in 2002 at Eisenkappler Hütte, Carinthia, Austria (Albach 209, WU) and in 2003 close to Torre die Disteis, northeastern Italy (Schneeweiss 9701, WU).

3.3. Work-up of Austrian sample (from 2002)

Dry plant (8.6 g) was brought to boiling with EtOH (50 ml), cooled and blended, and left to stand for seven days. After filtering, the extract was taken to dryness and partitioned in H_2O–Et_2O. Finally, the aqueous layer was concentrated to give the crude extract (850 mg). This was chomatographed on a Merck Lobar (RP-18) reverse-phase column (size B) eluting with H_2O–MeOH (25:1 to 1:1). This gave a sugar fraction ($\approx$200 mg; with $\approx$25% mannitol, as seen by ^{13}C NMR in D_2O), a fraction with gardoside and catalpol (**8** and **2**; 2:5; 30 mg), aucubin (**1**; 30 mg), 8-epiloganic acid (**7**; 20 mg), verproside (**6**; 30 mg), catalposide (**4**; 40 mg), amphicoside (**5**; 120 mg), veronicoside (**3**; 40 mg) and finally a 3:1 mixture of paederotoside and 4′-*O*-methylscutellarein 7-*O*-β-glucopyranoside (**9** and **11**; 40 mg). Rechromatography of the last fraction on a Merck HIBAR reverse-phase C18-column (7 μm; 250 × 25 mm) gave pure **9** (20 mg). Compound **11**, however, was not isolated in this case.

3.4. Work-up of Italian sample (from 2003)

Dry plant (4.0 g) was extracted as above to give the crude extract (320 mg). Chromatography gave first a fraction (100 mg) with sugars containing a trace of **2**, then **1** (30 mg), **6** (15 mg), **4** (20 mg), a mixture containing **4** and **5** (3:2; 50 mg), a fraction with mainly **3** (20 mg) and finally **11** (5 mg).

3.5. Paederotoside (*9*)

$[\alpha]_D^{20} = -29°$ (*c* 0.3, MeOH); LC-HR ESIMS *m/z*: 633.1773 $[M+Na]^+$ ($C_{28}H_{34}O_{15}Na$ requires 633.1795); NMR data in Table 1.

3.6. Stachannin A (scutellarein 4′-O-methylether 7-O-β-glucopyranoside; *11*)

^{1}H NMR (300 MHz, MeOH-d_4): δ 7.96 (*d*, $J = 8.6$ Hz, H-2′,6′), 7.07 (*d*, $J = 8.6$ Hz, H-3′,5′), 7.01 (*s*, H-8), 6.66 (*s*, H-3), 5.06 (*d*-like, $J = 7.0$ Hz, H-1″), 3.97 (*dd*, $J = 2.1$ and 12.1 Hz, H-6a″), 3.88 (*s*, 4′-OMe), 3.73 (*dd*, $J = 6.0$ and 12.1, H-6b″), 3.54–3.60 (3H, H-2″,3″,5″), 3,42 (*t*-like, $J = 9$ Hz, H-4″). Consistent with the published spectrum, allowing for a different solvent (Pütün and Özcan, 1992).

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